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Doxazosin and hydrochlorothiazide equally affect arterial wall thickness in hypertensive males with hypercholesterolaemia (the DAPHNE study)

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ABSTRACT

Background: Observational studies suggest a synergistic effect of hypertension and hyperlipidaemia on the progression of atherosclerosis. The α-blocker doxazosin has favourable effects on plasma lipids, insulin resistance and blood pressure, while the diuretic hydrochlorothiazide (HCTZ) principally affects blood pressure and increases insulin resistance.

Methods: A randomised double-blind study over 36 months was performed to compare the effects of doxazosin and HCTZ on fasting lipids and on progression of peripheral atherosclerosis. Eighty males (45 to 70 years) with peripheral atherosclerotic disease and increased cholesterol levels (5.2-8.0 mmol/l) were treated for essential hypertension with either doxazosin (n=41) or HCTZ (n=39). Main outcome measures were arterial intima-media thickness (IMT) of the carotid and femoral arteries and fasting lipid parameters.

Results: In the doxazosin-treated group, significant changes were observed in the concentration of triglycerides (-13.7%, p<0.01), HDLc (+25.7%, p<0.05) and IDLc (-30.1%, p<0.05). In the HCTZ-treated group no significant changes in plasma lipid levels were observed. On follow-up visits systolic blood pressure in the doxazosin-treated group was 6 mm higher than in the HCTZ group. Nevertheless, the groups treated with doxazosin or HCTZ showed no differential effect on IMT after three years of treatment (p=0.81). A significant reduction of the IMT of combined carotid and femoral arterial walls was shown in both treatment groups (p<0.005).

Conclusions: Hypertension treatment with doxazosin or HCTZ resulted in a comparable change in arterial IMT after three years, in spite of differences in effect on plasma lipids. The study emphasises the importance of blood pressure control in patients with peripheral vascular disease and hypercholesterolaemia.

INTRODUCTION

Hypertension and hyperlipidaemia are major risk factors for atherosclerotic disease. Observational studies have demonstrated a synergistic effect of risk factors for vascular disease:[1] the individual with moderate hypertension without other risk factors is at lower risk for atherosclerosis than a person with other risk factors such as hypercholesterolaemia.[2] Major clinical trials have demonstrated that treatment with diuretics reduces the risk of cardiovascular disease.[3-5] These drugs are effective in the treatment of hypertension, but their use has been questioned since they exert adverse effects on lipids and lipoproteins.[6,7] It is not known to what extent these changes in plasma lipids affect the atherosclerotic risk in hypertensive patients. Doxazosin, a selective α_1-antagonist, is as effective as diuretics in the treatment of hypertension.[8,9] Additionally doxazosin has favourable effects on serum lipid concentrations, lowering triglycerides (TG) and increasing high-density lipoprotein cholesterol (HDLc).[10-12] If cardiovascular risk and hyperlipidaemia in patients with hypertension are

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associated, doxazosin could be an important agent to prevent vascular disease in patients with hypertension. Doxazosin has antiatherogenic properties in animal models.[13,14] As cardiovascular risk reduction is the ultimate goal of antihypertensive therapy, the effect of doxazosin on various forms of cardiovascular disease needs to be studied.
The Doxazosin Atherosclerosis Progression study in Hypertensives in the Netherlands (DAPHNE) is a three-year study in males with mild hypertension, hypercholesterolaemia and peripheral atherosclerosis designed to compare the effects of doxazosin and the diuretic hydrochlorothiazide (HCTZ) on lipid profile and atherosclerosis progression. For the detection of atherosclerosis progression quantitative B-mode ultrasound measurements of the arterial intima-media thickness (IMT) were used.[15,16]

PATIENTS AND METHODS

Study population and design

Eighty male patients, 45 to 70 years of age, with essential hypertension were recruited from the vascular surgical outpatient facilities of the University Hospital Dijkzigt Rotterdam and the St. Antonius Hospital Nieuwegein, in the Netherlands. Besides the presence of essential hypertension, the major inclusion criteria were the presence of peripheral atherosclerosis and mild hypercholesterolaemia. To be included, the diastolic blood pressure (DBP) readings had to be between 95-115 mmHg, measured twice in supine position on three separate occasions after five minutes rest. Mild hypercholesterolaemia was defined as a plasma cholesterol concentration between 5.2-8.0 mmol/l while on a cholesterol-lowering diet for at least six weeks. Peripheral artery disease was defined as intermittent claudication or peripheral vascular surgery because of atherosclerosis. The major exclusion criteria were systolic blood pressure (SBP) above 200 mmHg, secondary hypertension, symptomatic coronary heart disease or myocardial infarction within three months prior to the study, diabetes mellitus, and apolipoprotein E_2/E_2 genotype. The medical ethics committee of the University Hospital Dijkzigt approved the study; all participants gave written informed consent. All patients were given single-blind placebo medication for the first six weeks of the study, followed by a double-blinded treatment. Patients were randomised to one of two treatment arms: doxazosin or HCTZ, and were started on the lowest possible dose, which was increased in two weekly intervals, until the goal DBP of 90 mmHg was achieved. Dose adjustment was allowed during the rest of the study when DBP was consistently above 90 mmHg. For doxazosin the regimen was 1 mg, 2 mg, 4 mg, 8 mg and 16 mg once a day; for HCTZ the dosing was 12.5 mg, 25 mg, 50 mg and 100 mg once a day. At each visit compliance with treatment was checked by tablet count. At randomisation (baseline) 6, 12, 24 and 36 months the following investigations were carried out. Fasting (≥8 hours) blood samples were taken and carotid and femoral artery walls were assessed by means of B-mode ultrasound examinations. Electrocardiograms were carried out to identify left ventricular hypertrophy (LVH).
The primary objective of DAPHNE was to determine the effectiveness of doxazosin compared with HCTZ on the change in the maximum arterial wall thickness of twenty combined segments, over three years. The effect of doxazosin versus HCTZ on plasma lipids and lipid parameters was studied as a secondary objective.

Lipids and lipoprotein analysis

Fasting blood samples were drawn into tubes containing 1.5 mg/ml Na_2EDTA. Plasma was prepared from blood within two hours and immediately stored at -80°C until analysis. For the separation of lipoproteins, plasma was stored at 4°C and used within 24 hours. Cholesterol and triglycerides were determined by enzymatic methods (Boehringer test kit combinations, Mannheim, Germany). Plasma HDL was measured after precipitation of VLDL and LDL by addition of manganese chloride.[17] Apolipoprotein B was estimated by an immunoturbidimetric method using commercially available kits from DAKO (Glostrup, Denmark). Lipoproteins were separated by flotation during sequential ultra-centrifugation at densities of 1006 g/ml (VLDL), 1019 g/ml (IDL) and LDL 1063 g/ml. All runs were for 18 hours at 15°C and 40,000 rpm in a Ti 50.3 Beckman rotor in quick seal poly-alomere tubes. The recovery of cholesterol after centrifuge was >90% and of triglycerides >8%. As described, Apo E isoforms were determined by genotyping.[18]

B-mode ultrasound imaging, off-line video image analysis

B-mode ultrasound scans were taken using an ACUSON 128 ultrasound system equipped with an L7384 7 MHz linear array transducer (ACUSON Corporation; Mountain View, CA). At each ultrasound visit, six carotid and four femoral arterial segments were investigated. The B-mode ultrasound imaging and analysis includes the right and left common carotid (CCA) and the right and left bulb (BUL) arterial segments, the right and left internal carotid (ICA), the left and right common femoral (CFA) and the right and left superficial femoral (SFA) arterial segments. The length of measurement along the arterial wall is kept as close to 1 cm as practically possible, but is prone to differ between sites and patients due to individual anatomy and interference in the ultrasound image. Each arterial segment has a near wall (the wall proximate to the transducer) and a far wall (the wall distant from the transducer). Consequently, 20 longitudinal arterial wall segments were investigated per patient in each of the five ultrasound visits. A max IMT is defined as the maximum δ between two lines. The max IMT is the average over the 20 maximum IMT values of the segments. Segment images of each arterial

wall were stored on S-VHS tape. The video images were analysed off-line. Licensed PROSOUND image analysis software as developed in cooperation with Robert Selzer was used.[19-21] The study was quality controlled by repeated measurement procedure.[22] On a per subject basis, the SD of the means of the paired intrasonographer IMT measurements calculated according to Bland and Altman was 0.04 mm.[23] The co-efficient of variation of IMT measurements, defined as {(SD of the mean difference √(2) x 100}/ pooled means of IMT values), was 3%.[24]

Statistical analysis and definitions

The analysis was performed on an intention-to-treat basis. For the missing values in the ultrasound measurements the strategy as described by Espeland was used.[25] The significance of the change from baseline within a group was assessed using paired t-tests. To estimate the difference between doxazosin and HCTZ in treatment effect for an outcome variable, all patients with a baseline measurement and at least one follow-up measurement available were used in a repeated measurement analysis (SAS PROC MIXED).[26] We used an appropriate covariance structure, the follow-up data as outcome and the baseline measurement, treatment, visit number (categorical) and, if significant, the interaction between visit number and treatment as covariables. If the interaction was not significant, the mean difference between doxazosin and HCTZ during the total follow-up period was regarded as the difference in treatment effect. Variables with a skewed distribution were log-transformed, and then the corresponding treatment effect is expressed as the ratio of doxazosin/HCTZ. For the ultrasound measurements the interaction term was always included in the model and the mean difference between the treatments at the last visit was regarded as the treatment effect. Data are presented as mean ± standard deviation, unless stated otherwise.

RESULTS

Baseline characteristics

Eighty male patients were selected to participate in the study. The mean age was 59.1 ± 7.2 years, 24 patients were between 44 to 54 years, 35 patients between 55 to 64 years and 21 patients older than 65 years of age. The mean body mass index was 26 ± 3 kg/m². Diastolic blood pressure (DBP) was 101 ± 5 mmHg ranging from 95-117 mmHg, systolic blood pressure (SBP) 163 ± 17 mmHg ranging from 130-200 mmHg. Left ventricular hypertrophy was present in 11% of the patients. At randomisation 37 (46%) of the patients admitted smoking. During the trial 40 (50%) patients smoked cigarettes, with a median of ten cigarettes a day. The mean total cholesterol concentration was 6.0 ± 0.9 mmol/l. The median triglycerides concentration was 2.0 mmol/l, varying between 0.6-6.0 mmol/l.

Distribution of the most frequent apolipoproteins E genotype was 75% ApoE_3/E_3 and 17% Apo E_3/E_4.
The distributions of age, blood pressure, body mass index, symptomatic vascular disease, IMT of the arterial walls, plasma lipid concentrations and other metabolic variables at baseline were similar for the two treatment groups.
The major baseline characteristics of the two study groups are provided in *tables 1* and *2*.

Table 1
Description of the DAPHNE population at baseline

	DOXAZOSIN GROUP (n=41)	HCTZ GROUP (n=39)
Demographics		
Age (years)	58.7 ± 6.7	59.4 ± 7.7
LVH on ECG	4 (10%)	5 (13%)
Risk factors		
Current smoking (%)	44	49
Duration of hypertension (years)	5.3 (range 2-12)	6.0 (range 3-8)
Systolic blood pressure (mmHg)	163 ± 16	164 ± 18
Diastolic blood pressure (mmHg)	100 ± 5	101 ± 5
Body mass index (kg/m²)	26.1 ± 2.7	26.6 ± 3.2
Prior history		
Intermittent claudication	33 (81%)	29 (74%)
Peripheral vascular surgery	16 (39%)	19 (49%)
Myocardial infarction	8 (20%)	7 (18%)
Coronary bypass	6 (15%)	2 (5%)
Cerebrovascular disease	3 (7%)	5 (13%)

Data are presented as mean ± SD or as median (25-75%) percentiles.

Table 2
Description of the intima-media thickness at baseline

	DOXAZOSIN GROUP (n=41)	HCTZ GROUP (n=39)
Combined carotid and femoral arteries		
Average of 20 mean far and near walls	1.09 ± 0.13	1.11 ± 0.19
Average of 20 max. far and near walls	1.42 ± 0.19	1.45 ± 0.27
Average of 10 mean far walls	1.11 ± 0.15	1.14 ± 0.21
Average of 10 max. far walls	1.45 ± 0.21	1.47 ± 0.30
Average of 10 mean near walls	1.06 ± 0.16	1.09 ± 0.19
Average of 10 max. near walls	1.39 ± 0.25	1.43 ± 0.29
Carotid arteries		
Average of 12 mean far and near walls	1.05 ± 0.17	1.08 ± 0.19
Average of 12 max. far and near walls	1.39 ± 0.24	1.43 ± 0.30
Femoral arteries		
Average of 8 mean far and near walls	1.14 ± 0.17	1.17 ± 0.21
Average of 8 max. far and near walls	1.46 ± 0.23	1.49 ± 0.29

Data are presented in mm (mean ± SD).

Drug effects on blood pressure and adverse events

Systolic and diastolic blood pressure decreased significantly from baseline in the two treatment groups. In the doxazosin group, the SBP decreased from 163 ± 16 mmHg at baseline to 155 ± 24 mmHg (p<0.001) after three years of follow-up. The DBP decreased from 100 ± 5 mmHg to 87 ± 8 mmHg (p=0.002). In the HCTZ group the SBP decreased from 164 ± 18 mmHg to 148 ± 19 mmHg (p=0.002). The DBP decreased from 101 ± 5 mmHg to 87 ± 7 mmHg (p<0.001). On the follow-up visits the SBP in the doxazosin group was 6 mmHg higher than in the HCTZ group, adjusted for baseline SBP (p<0.01). No difference in treatment effect on DBP was seen between the groups (p=0.62). In both groups eight patients withdraw because of adverse events. The number of patients with major vascular events did not differ significantly between the two treatment groups. In both treatment groups, five patients had peripheral vascular surgery because of progressive peripheral artery disease. In the doxazosin group four patients suffered from a myocardial infarction, while in the HCTZ group two patients had a cerebrovascular event. The number of serious and non-serious events was not significantly different between the treatment groups (p=0.12). One patient discontinued the trial because of poor compliance. Four patients in the doxazosin group and three patients in the HCTZ group were discontinued because of inadequate blood pressure lowering. A total of 29 patients in the doxazosin group and 27 in the HCTZ group completed the study. The baseline SBP in the HCTZ-treated group was slightly higher in the 'non-completers' as compared with the 'completers' at 172 and 160 mmHg, respectively (p=0.04). Comparison of baseline DBP, mean IMT, max IMT, cholesterol, TG, HDLc, VLDLc, VLDLtg, IDLc and LDLc between the group that did and the group that did not complete the study showed no differences.

Drug effects on blood lipids

Within six months of treatment a significant decrease in TG levels occurred in the doxazosin group; this effect remained over three years of treatment (*figure 1*). At the end of the trial, TG levels were decreased by an average of 13.7% (p<0.01) as compared with baseline levels. In the HCTZ group, the TG was slightly increased, but this did not reach the level of significance. The difference in effect on TG levels between the two groups over three years was significant (p<0.005)(*figure 1*). Changes in the total TG concentration over three years paralleled the changes in VLDLtg concentration as shown in *table 3*. In the doxazosin group the total HDLc concentration increased by 25.7% (p<0.001). A substantial 30.1% decrease in the concentration

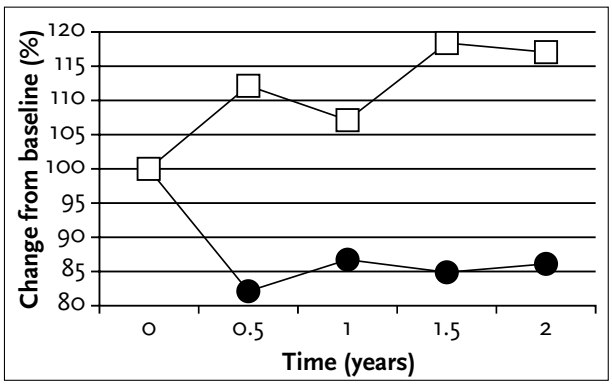

Figure 1

Effects of doxazosin (closed circles) and hydrochlorothiazide (open blocks), on fasting triglycerides concentration during three years of treatment

Table 3

Lipids and lipoproteins at baseline and their change after three years of follow-up

	BASELINE	DOXAZOSIN TREATMENT	CHANGE*	BASELINE	HCTZ TREATMENT	CHANGE*	DIFFERENCE IN EFFECT (CI)†	P VALUE
Lipids								
Cholesterol	6.15 ± 0.76	5.95 ± 0.81	-0.11 ± 0.78	5.83 ± 0.94	5.72 ± 0.89	-0.08 ± 0.72	(-0.41; 0.14)	0.33
TG	2.03 (1.51-2.50)	1.60 (1.14-2.29)	-0.46 ± 0.95‡	1.96 (1.44-2.66)	1.99 (1.25-2.55)	+0.15 ± 0.8	(70%; 92%)	0.002
HDLc	1.08 ± 0.26	1.33 ± 0.26	+0.22 ± 0.24‡	1.14 ± 0.28	1.24 ± 0.25	+0.10 ± 0.30	(-0.06; 0.14)	0.42
Lipoproteins (ultracentrifugation)								
VLDLtg	1.26 (0.90-1.96)	0.90 (0.5-1.6)	-0.41 ± 0.92‡	1.27 (0.82-1.81)	1.38 (0.69-1.81)	+0.23 ± 0.74	(59%; 87%)	0.001
VLDLc	0.53 (0.34-0.77)	0.38 (0.23-0.70)	-0.18 ± 0.35‡	0.49 (0.29-0.72)	0.49 (0.23-0.78)	+0.07 ± 0.33	(57%; 101%)	0.06
IDLc	0.16 (0.07-0.27)	0.13 (0.07-0.18)	-0.05 ± 0.12‡	0.09 (0.05-0.20)	0.09 (0.06-0.17)	-0.02 ± 0.08	(73%; 121%)	0.63
LDLc	4.03 ± 0.83	3.72 ± 0.83	-0.26 ± 0.70	3.72 ± 0.93	3.54 ± 0.82	-0.18 ± 0.90	(-0.34; 0.19)	0.56
HDLc	0.95 ± 0.26	0.98 ± 0.25	+0.03 ± 0.20‡	0.93 ± 0.23	0.95 ± 0.29	+0.0 ± 0.27	(-0.10; 0.07)	0.67

** Due to dropouts, the change is not exactly equal to the difference between the mean after treatment and the mean at baseline, † the 95% confidence intervals, the result from the repeated measurements analysis, being the difference doxazosin – HCTZ (absolute number) or ratio doxazosin/HCTZ*100% (%), ‡ statistically significant difference from baseline value tested by paired Student's t-test. Data are presented as mean SD or as median (25-75% percentiles).*

of IDLc was observed in the doxazosin group (p<0.05), while IDLc was not affected in the HCTZ group. Neither of the two treatment groups showed changes in the total cholesterol or the LDLc concentration over three years of treatment (*table 3*). In both groups a decrease in Apo B concentration was observed in 17.5% and 11.3%, respectively (both p<0.001, data not shown).

Drug effects on arterial wall thickness

Hypertension treatment with either doxazosin or HCTZ resulted in a significant reduction of the IMT of the combined arterial walls of the carotid and femoral arteries over three years (*table 4*). Separate analyses of the combined far wall IMTs and the combined near wall IMTs showed similar results (*table 4*). There was no difference in treatment effect on carotid and femoral IMT (p=0.66 for mean IMT, p=0.83 for maximal IMT). After three years of treatment a significant decrease of the maximal carotid artery IMT was observed in the doxazosin group (p<0.05) and in the HCTZ-treated group (p<0.005), respectively. A significant difference in treatment effect between the two drugs on the femoral or carotid arteries was not observed (*table 4*). On studying the treatment effect without taking the basal IMT into consideration, the same conclusion was reached (data not shown).

DISCUSSION

Hypertension treatment with either doxazosin or HCTZ in hypercholesterolaemic patients with peripheral vascular disease resulted in a comparable effect on the arterial IMT. In the doxazosin-treated group favourable changes in plasma triglycerides, HDLc and IDLc levels were seen within six months of treatment and present throughout the study. In the HCTZ-treated group no such favourable changes in fasting lipids were observed. This did not result in a greater treatment effect on the arterial IMT: in both treatment groups the maximal and the mean thickness of the combined carotid and femoral arterial walls showed a comparable regression over three years. Under the restriction that IMT is only a surrogate for atherosclerosis, this study suggests that in a highly selected population of males with hypertension, hypercholesterolaemia and peripheral atherosclerosis, lowering of blood pressure with either doxazosin or HCTZ is equally effective with regard to progression of atherosclerosis.

It cannot be excluded that the favourable effects of doxazosin on lipids contributed to atherosclerosis regression. However, this effect could not be observed by B-mode ultrasound IMT measurements in the relatively small DAPHNE population. We have no indications for methodological or technical factors that could explain the lowering of IMT. We studied whether our data are influenced by a so-called 'regression to the mean' effect. In order to do so we analysed the groups with a low and a high basal IMT, i.e. below and above median (1.114 mm). In both these two groups IMT decreased significantly, 0.045 mm (p=0.03), CI (0.0038-0.0871) and 0.173 mm (p=0.0001), CI (0.1284-0.2173), respectively. This indicates that treatment effect also occurs in subjects with relatively small IMT values.

It cannot be excluded that beneficial changes of plasma lipids on IMT by doxazosin are balanced by the greater reduction of systolic blood pressure by HCTZ. The Systolic

Table 4

Quantitative change of mean and maximal combined or isolated carotid and femoral artery intima-media thickness after three years of follow-up

	IMT CHANGE FROM BASELINE		DIFFERENCE IN 3 YEARS		
	DOXAZOSIN	HCTZ	CHANGE	(CI)	P VALUE
Combined arteries					
Average of 20 mean far and near walls	-0.08 ± 0.13**	-0.12 ± 0.14**	0.013	(-0.044; 0.069)	0.66
Average of 20 max. far and near walls	-0.18 ± 0.14**	-0.21 ± 0.21**	-0.009	(-0.09; 0.073)	0.83
Average of 10 mean far walls	-0.07 ± 0.18*	-0.09 ± 0.19*	-0.011	(-0.093; 0.071)	0.79
Average of 10 max. far walls	-0.16 ± 0.21**	-0.14 ± 0.27*	-0.044	(-0.149; 0.062)	0.41
Average of 10 mean near walls	-0.09 ± 0.14**	-0.15 ± 0.13**	0.034	(-0.021; 0.090)	0.23
Average of 10 max. near walls	-0.20 ± 0.18**	-0.27 ± 0.20**	0.025	(-0.049; 0.010)	0.50
Carotid arteries					
Average of 12 mean far and near walls	-0.05 ± 0.14	-0.08 ± 0.12**	0.007	(-0.054; 0.068)	0.82
Average of 12 max. far and near walls	-0.15 ± 0.16**	-0.18 ± 0.20**	-0.008	(-0.090; 0.075)	0.85
Femoral arteries					
Average of 8 mean far and near walls	-0.13 ± 0.20**	-0.16 ± 0.2**	0.018	(-0.064; 0.099)	0.67
Average of 8 max. far and near walls	-0.23 ± 0.24**	-0.24 ± 0.29**	0.013	(-0.090; 0.116)	0.80

*Data in mm (mean ± SD). * Significantly different from baseline p<0.05, ** p<0.005.*

Hypertension in the Elderly Programme (SHEP) reported a reduction in morbidity from vascular disease in patients treated for systolic hypertension by chlorthalidone.[27] In the SHEP trial, SBP was 13 mmHg lower with active treatment than with placebo. Therefore we can not exclude that the difference in SBP treatment effect in the DAPHNE study of 6 mmHg in favour of HCTZ affected the IMT. To analyse the effect of change in SBP on IMT, we created two groups of patients, one with patients whose decrease in SBP was greater than the average, and a second group with patients whose SBP decreased less than average. Comparison of the three-year treatment effect on changes in IMT between these two groups did not show a statistical difference (p=0.08).

A previous trial, known as the Multicentre Isradipine Diuretic Atherosclerosis Study (MIDAS) with 883 hypertensive patients, compared the effect of isradipine and HCTZ on the progression of early atherosclerosis in carotid arteries over three years.[28] In contrast to the results of the DAPHNE trial, the progression of IMT was not changed by hypertension treatment. There are several important differences between these two trials: in the MIDAS trial fixed doses of medication were used,[28] while in the DAPHNE study the dose was adjusted up to a threshold of diastolic blood pressure. The latter mode of treatment may have a greater effect on blood pressure and consequently on vascular wall thickness. Another difference between the trials is that the DAPHNE population was selected by the presence of peripheral artery disease. Recently the Verapamil in Hypertension and Atherosclerosis Study (VHAS),[29] with four years of follow-up, showed that a difference in treatment effect was only observed in the thicker carotid IMTs. Therefore, the selection of patients with thick IMTs in the DAPHNE study may have added to the observed favourable changes in IMT.

At the start of this millennium, the doxazosin-treatment arm was discontinued in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), a very large study with 40,000 patients.[30] This decision was based on a significantly higher percentage of patients on doxazosin developing congestive heart failure and on the view that doxazosin was unlikely to be better than the diuretic chlorthalidone in preventing coronary heart disease. In DAPHNE none of the patients were known to have congestive heart failure or developed congestive heart failure. Doxazosin and the diuretic HCTZ appeared to be equally effective in the reduction of the IMT.

EFFECTS ON LIPIDS

This study confirms other studies showing that TG and HDLc are the lipid fractions most affected by doxazosin.[10,11,31] We did not observe the previously described adverse changes of plasma lipid levels in the HCTZ group, which have been attributed to an adverse effect of HCTZ on insulin resistance.[32,33] Several epidemiological and clinical studies have demonstrated a relation between plasma TG levels and risk of cardiovascular disease, with an enhancement of this risk in the presence of a combined elevation of TG and LDLc.[34-36] Additionally it has been shown that a reduction of fasting TG levels could induce a decrease in atherosclerotic disease.[37,38] Triglyceride-rich lipoprotein species may either have direct atherogenic effects or indirect effects via changes in other lipoproteins associated with atherosclerosis, such as IDLc.[39,40] The IDLc levels were shown to be strongly and independently predictive of progression of carotid artery intima-media thickness and coronary disease risk.[39] It has also been shown that a high concentration of IDLc plays an important role in the development and severity of peripheral vascular disease.[41] Favourable changes in lipid levels only occurred in the doxazosin-treated group: TG and IDLc levels decreased and HDLc increased. However, this did not result in a difference in IMT between doxazosin and HCTZ within three years of study. Most studies into the effects of doxazosin consistently report a slight 2 to 3% decrease in calculated LDL cholesterol levels, especially in hypercholesterolaemic patients.[33] In DAPHNE, the measured LDLc concentration was decreased to the same extent (-5%) as has been found previously. However, this change did not reach the level of significance. Lipid intervention trials with HMG-CoA reductase inhibitors, which predominantly lower LDLc levels, showed prevention of atherosclerotic disease as measured by ultrasound of the carotid and femoral arteries,[15,21,42-44] coronary angiography[45,46] and morbidity of vascular events.[47-51] Therefore, the absence of a significant effect by doxazosin or HCTZ on LDLc may add to the absence of a difference in IMT in DAPHNE.

The DAPHNE study was performed in a highly selected population of male patients with signs or symptoms of peripheral atherosclerosis, in combination with hypertension and hypercholesterolaemia, and of whom approximately 50% admitted smoking cigarettes during the study. For this special group of patients we conclude that hypertension treatment with the diuretic HCTZ and the α_1-blocker doxazosin have comparable effects on peripheral vascular parameters as assessed by B-mode ultrasound, despite large favourable differences in lipid variables by doxazosin which may be balanced by a greater reduction of systolic blood pressure by HCTZ.

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