The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima–media thickness

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Background It is unclear whether the carotid intima–media thickness can be influenced by antihypertensive treatment and whether some antihypertensive agents, such as calcium antagonists, may have a greater effect on this parameter than others, such as diuretics. The present paper reports the principal results of the ultrasound substudy of the randomized, prospective, controlled, Verapamil in Hypertension and Atherosclerosis Study (VHAS).

Design and methods In 498 hypertensive patients in eight Italian centres, randomized to either verapamil (240 mg once a day) or chlorthalidone (25 mg once a day), a B-mode ultrasound scan was performed according to a standardized procedure at baseline and after 3, 12, 24, 36 and 48 months of treatment. The maximum intima–media thicknesses of the far walls of common, bifurcation and internal carotid arteries were measured bilaterally, and the following indices calculated: the mean thickness at the six measured sites, the mean thickness at the common and bifurcation sites and the single maximum thickness. The primary endpoint for treatment efficacy was the slope of the change over 4 years (rate of change, mm/year), corrected by using the initial mean over the six sites (baseline + 3 months) as a covariate (mm/year per mm). The patients were also classified into three strata according to their baseline single maximum thickness: those with normal carotid arteries (single maximum (1 mm), those with thickened carotid arteries (single maximum >1 and $\leqslant 1.5$ mm and those with carotid plaques (single maximum >1.5 mm).

Results Among the 456 patients with satisfactory baseline ultrasound readings, 33% were classified with normal carotid arteries, 27% with thickened carotid arteries and 40% with plaques. In the intention-to-treat population (377 patients with ultrasound measurements taken on at least three different occasions over a period of at least 2 years), the rate of change in the mean thickness at the six sites measured was rather small (0.015 mm/year), but significantly ($P<0.05$) smaller in patients with plaques (0.003 mm/year) than in patients with thickened or with normal carotids (0.023 and 0.025 mm/year, respectively). When related to initial values, the rate of change in the mean thickness at the six sites had a negative slope (−0.059 mm/year per mm, $P<0.01$). Although rates of change in the carotid intima–media thickness in unstratified patients were not different in those treated with verapamil or with chlorthalidone, when changes in the mean thickness of six sites were related to the initial value, the slope of this relationship was significantly different in the two treatment groups (verapamil −0.082 versus chlorthalidone −0.037 mm/year per mm, $P<0.02$). The blood pressure-lowering effect of the two randomized treatments was similar. Taking fatal and nonfatal, major and minor cardiovascular events together, there were 19 events in the verapamil group and 35 in the chlorthalidone group, with a significantly ($P<0.01$) greater incidence in patients with plaques, and among patients with plaques in those who were randomized to chlorthalidone ($P<0.05$).

Conclusions In accord with evidence from animal models of atherosclerosis, the calcium antagonist verapamil was more effective than the diuretic chlorthalidone in promoting regression of thicker carotid lesions. Changes in the carotid intima–media thickness were small in both groups, and the differences between the changes under the two treatments were consequently small, but the observation that these small differences in carotid wall changes were paralleled by differences in the incidence of cardiovascular events (better intima–media thickness regression with verapamil paralleled by a lower cardiovascular event rate) suggests that even small effects on carotid plaques may have clinical and prognostic relevance. *J Hypertens* 1998, 16:1667–1676

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Introduction

A number of studies using ultrasound scanning of the carotid arteries have consistently reported significant correlations between the carotid intima–media thickness (IMT) and cardiovascular disease risk factors, such as age [1–7], systolic blood pressure [1,2,4–13], male sex [1,3,5–7,14], serum cholesterol [1,4–7,14], triglycerides [1,7], diabetes [15], smoking [4–7] and previous cardiovascular disease [16]. Using quantitative B-mode ultrasound, a few trials [17,18] have started to compare the effects of different antihypertensive drugs on the carotid IMT and plaque progression in hypertensive patients [19]. The first of these trials has been completed and its results reported [20], but technical problems have made these results difficult to interpret [21]. Other trials are under way [7,22,23]. The present paper reports the principal results of the ultrasound substudy of the Verapamil in Hypertension and Atherosclerosis Study (VHAS) [24].

The primary aims of the VHAS ultrasound substudy were (1) to determine the prevalence of carotid intima–media thickenings and plaques in mild to moderate hypertensive patients; (2) to evaluate the changes occurring during prolonged (4 years) blood pressure lowering; and (3) to compare the effects of two randomly assigned antihypertensive drug regimens, using either the calcium antagonist verapamil or the diuretic chlorthalidone, on carotid IMT changes. An additional objective of the study was to monitor cardiovascular events and assess their relationship to baseline carotid alterations and to the randomly assigned drug treatment.

Materials and methods

Study design

VHAS was a prospective, multicenter, randomized, parallel-group, clinical trial comparing the effect of treatment with slow-release verapamil at 240 mg once a day or chlorthalidone at 25 mg once a day. The study design, treatment protocol and procedures have been described previously [24].

The study population comprised men and women aged 40–65 years, with essential hypertension (sitting systolic blood pressure $\geqslant$ 160 mmHg and diastolic blood pressure $\geqslant$ 95 mmHg at the end of a placebo run-in period of 3 weeks). At the end of the 3 weeks' placebo run-in period, eligible patients were randomly assigned either to verapamil at 240 mg or chlorthalidone at 25 mg once a day; captopril was added at 25 mg once a day after 1 month (and increased to 50 mg a day as required after 2 months) in patients whose blood pressure did not reach the goal (defined as sitting diastolic BP $\geqslant$ 90 mmHg, or $<$ 95 mmHg with a reduction of at least 10% from baseline values). After the first 6 months of double-blind treatment, the patients continued the randomized treatment according to an open design. Patients withdrawn from randomized treatment were treated according to their physicians' choice (free therapy) but followed-up according to an intention-to-treat design. Of the 1414 hypertensive patients randomized in VHAS, 498 were included in the ultrasound substudy, and followed up for 4 years (instead of the 2-year period used in the rest of the cohort). These patients were those recruited in eight Italian ultrasound centers (Ancona, n = 41; Bologna, n = 59; Brescia, n = 60; Milan, n = 62; Montescano, n = 77; Naples, n = 48; Padua, n = 83; Perugia, n = 68). In these centers, a carotid B-mode ultrasound scan was performed according to a standardized procedure (see below) in order to determine the ultrasonographic eligibility of the subjects, which included the absence of anatomical abnormalities and of acoustic shadowing that might prevent a correct IMT measurement. In patients meeting these criteria, the ultrasound carotid examination was repeated after 3, 12, 24, 36 and 48 months.

Carotid ultrasound

B-mode imaging of carotid arteries was performed using ultrasound devices equipped with a 7.5–8 Mhz probe. High-quality equipment was used in the various centers, comprising Hewlett–Packard Sonos 1000 (Hewlett–Packard, Andover, Massachusetts, USA), ATL Ultramark 9 (ATL, Bothell, Washington, USA) and Biosound 2000 II s.a. (Biosound Inc., Indianapolis, Indiana, USA).

In each ultrasound center, recordings [0.5 inch (12.7 mm) super video home system (VHS) videotape] of the entire scanning procedure, performed by the same expert sonographer, were analyzed using morphometry software; all measurements were recorded by two different readers, unaware of the subject's identity, clinical condition and

assigned treatment. Averages of the two readings were considered for subsequent calculations. The measurements included the largest end-diastolic (minimum diameter) IMT (taken as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line) of the far walls in the distal segment of the common carotid artery, the carotid bifurcation and the extracranial portion of the internal carotid artery on both sides. The end-diastolic diameters of the right and left common carotid arteries were also measured. Three indices were calculated: the mean maximum IMT (M_{max}), calculated as the mean of the maximum IMTs detected in the far walls of up to six of the carotid segments examined (at least four segments in 81% of the patients); the mean of the maximum IMTs of the common and bifurcation far walls bilaterally (CBM_{max}; at least three segments in 80% of the patients); and the single maximum IMT among common, bifurcation and internal carotid arteries bilaterally (T_{max}; in the internal carotid or bifurcation arteries in 75% of patients). According to protocol, the baseline T_{max} was also used to stratify the patients into three groups, comprising stratum I (patients with a normal wall thickness, defined as $T_{max} \leqslant 1$ mm), stratum II (patients with intima–media thickening, $T_{max} > 1$ and $\leqslant 1.5$ mm) and stratum III (patients with plaques, $T_{max} > 1.5$ mm).

The angular coefficient of the linear regression analysis of measurement of M_{max} at baseline and at 3 months was used to calculate accuracy, which was found to be 99.6% (range 96.7–101.8 in the various ultrasound centers).

Statistical analysis

All statistical analyses were done by an independent statistical center. BMDP statistical software programs (BMDP Software, Los Angeles, California, USA) were used. All data are expressed as means ± SD. All randomized patients were included in the final analysis according to intention-to-treat procedures. Per protocol analyses limited to the patients remaining on randomized treatment throughout the trial were also performed, for descriptive purposes only.

The primary endpoint for treatment efficacy was the slope of the 4-year change in M_{max} (rate of change, mm/year), corrected by using the initial M_{max} as a covariate (mm/year per mm). Both uncorrected and corrected rates were used. In order to minimize the effect of regression to the mean, the average of the baseline and 3-month M_{max} values was used as the initial M_{max}. Rates of changes were calculated only in patients with at least three measurements, obtained over a period of at least 2 years. The rate of change was estimated by weighting in proportion to the number of arterial walls used to compute each M_{max} value and to the number of measurements during the follow-up period. Rates of changes in CBM_{max} and T_{max} were calculated similarly. The M_{max} rate of change, corrected and uncorrected for the initial M_{max}, was also separately calculated in the two groups of patients treated with either verapamil and chlorthalidone, as well as in the three groups of patients divided according to baseline T_{max} (strata I, II and III).

All statistical tests were two-sided with a significance level of $P < 0.05$. Student's t test was used to assess differences in the demographic, clinical and ultrasound baseline characteristics of patients randomly assigned to verapamil or chlorthalidone; analysis of variance was used to assess differences between the three strata of patients with normal carotid walls, thickenings and plaques; factorial analysis of variance and covariance analysis were used to assess differences in M_{max} progression in the two randomized treatments; and the χ^2 test and the log-linear test were used to compare the incidence of cardiovascular events in the various strata and according to treatment. Bonferroni corrections for multiple comparisons were applied as appropriate.

Results

Demographic, clinical and ultrasound characteristics of patients at baseline

A total of 498 patients were randomly assigned to either verapamil (n = 244) or chlorthalidone (n = 254). For 42 of these patients, ultrasound measurements were available only for the carotid near walls, and therefore these patients were excluded from the ultrasound analyses according to protocol. The analyses here reported refer to 456 patients, 224 randomly assigned to verapamil and 232 to chlorthalidone. The population characteristics at baseline are summarized in Table 1. No significant differences in age, sex, smoking habit, body mass index, lipid profile and other metabolic variables were observed between the two treatment groups. No significant differences were found in sitting systolic and diastolic blood pressure and heart rate values.

Figure 1 shows the distribution of the patients into the three strata, defined according to protocol: 33% of all patients had a normal carotid IMT (stratum I), 27% had carotid thickenings (stratum II) and 40% had plaques (stratum III). Figure 1 also shows the distribution into the three strata of patients randomly assigned to treatment with verapamil or chlothalidone. No significant differences were found in any of the three ultrasound measurements (M_{max}, CBM_{max}, T_{max}) between the two treatment groups, although all measurements tended to be very slightly higher in the chlorthalidone group.

Effect of antihypertensive treatment on blood pressure, heart rate and metabolic variables

In the whole population of randomized patients (intention-to-treat analysis), antihypertensive treatment significantly ($P < 0.01$) reduced systolic blood pressure from 167.6 ± 9.8 to 141.3 ± 12 mmHg, diastolic blood pressure

Table 1 **Demographic, clinical and ultrasound characteristics of patients at baseline**

	All patients	Verapamil group	Chlorthalidone group
Age (years)	54.1 ± 7.0	54.2 ± 6.8	53.9 ± 7.2
Sex (%)			
Male	52.2	53.1	51.3
Female	47.8	46.9	48.7
Patients smoking (%)			
Never	62.9	62.5	63.4
Ex-smokers	19.3	21.0	17.7
Yes	17.8	16.5	19.0
Body mass index (kg/m^2)	27.0 ± 4.0	27.2 ± 3.8	26.9 ± 4.2
Systolic blood pressure (mmHg)	167.6 ± 9.8	168.0 ± 10.5	167.2 ± 9.2
Diastolic blood pressure (mmHg)	102.3 ± 5.1	102.2 ± 5.2	102.4 ± 5.1
Heart rate (beats/min)	74.5 ± 9.2	74.3 ± 9.8	74.7 ± 8.6
ECG Sokolow index ⩾3.5 mV	7.9%	9.2%	6.6%
Total cholesterol (mg/dl)	230.4 ± 38.6	229.7 ± 39.4	231.0 ± 37.8
HDL cholesterol (mg/dl)	49.3 ± 13.4	48.8 ± 13.2	50.2 ± 13.7
LDL cholesterol (mg/dl)	152.7 ± 36.8	152.8 ± 36.9	152.7 ± 36.9
Triglycerides (mg/dl)	141.8 ± 66.1	143.4 ± 60.1	140.2 ± 71.5
Glucose (mg/dl)	99.7 ± 16.3	100.7 ± 17.6	98.7 ± 14.8
Potassium (mmol/l)	4.23 ± 0.33	4.21 ± 0.33	4.24 ± 0.34
Creatinine (mg/dl)	0.93 ± 0.18	0.92 ± 0.17	0.94 ± 0.19
M_{max} (mm)	0.877 ± 0.341	0.857 ± 0.328	0.896 ± 0.352
CBM_{max} (mm)	0.914 ± 0.377	0.880 ± 0.355	0.947 ± 0.395
T_{max} (mm)	1.271 ± 0.721	1.213 ± 0.658	1.327 ± 0.744

Values for continuous variables are means ± SD and those for categorical variables are percentages. Data are from 456 patients, 224 randomly assigned to verapamil and 232 to chlorthalidone. HDL, high-density lipoprotein; LDL, low-density lipoprotein; ECG, electrocardiogram; M_{max}, mean maximum intima–media thickness (IMT), calculated as the mean of the maximum IMTs detected in the far walls of up to six carotid segments; CBM_{max}, mean of the maximum IMTs of the common and bifurcation far artery walls; T_{max}, single maximum IMT. No differences between groups were significant (Student's t test).

from 102.3 ± 5.1 to 86.6 ± 6.9 mmHg and the heart rate from 74.5 ± 9.1 to 72.0 ± 8.6 beats/min. At the time of the last visit, systolic blood pressures (verapamil 142.7 ± 13, chlorthalidone 139.9 ± 12 mmHg), diastolic blood pressures (verapamil 86.7 ± 7.3, chlorthalidone 86.5 ± 6.6 mmHg) and heart rates (verapamil 71.3 ± 8.7, chlorthalidone 72.6 ± 8.4 beats/min) were not significantly different in the two groups. Both treatment groups showed an equally small decrease in total cholesterol (about 5 mg/dl) and an equally small increase in high-density lipoprotein cholesterol (about 2 mg/dl); only serum potassium was slightly increased (+0.136 ± 0.510 mmol/l) in the verapamil group and slightly decreased (–0.176 ± 0.473 mmol/l) in the chlorthalidone group ($P < 0.0001$ between groups).

At the last visit, 357 patients were still receiving the randomly assigned treatment (179 taking verapamil, with captopril added in 61; 178 taking chlorthalidone, with captopril added in 66), while 71 patients were on free therapy (36 among those initially randomized to verapamil, 35 among those initially randomized to chlorthalidone). The average duration of blood pressure follow-up was 38.1 ± 13.4 months (verapamil 39.0 ± 12.9, chlorthalidone 37.2 ± 13.8) .

Effect of antihypertensive treatment on carotid IMT

Common carotid diameter

There was a significant reduction in the common carotid end-diastolic diameter from baseline to the third month of treatment (from 7.13 ± 1.05 to 7.07 ± 1.03 mm, $P < 0.01$), probably related to the blood pressure decrease. No further reduction in carotid diameter occurred between the first and fourth year of follow-up, when blood pressure values remained stable.

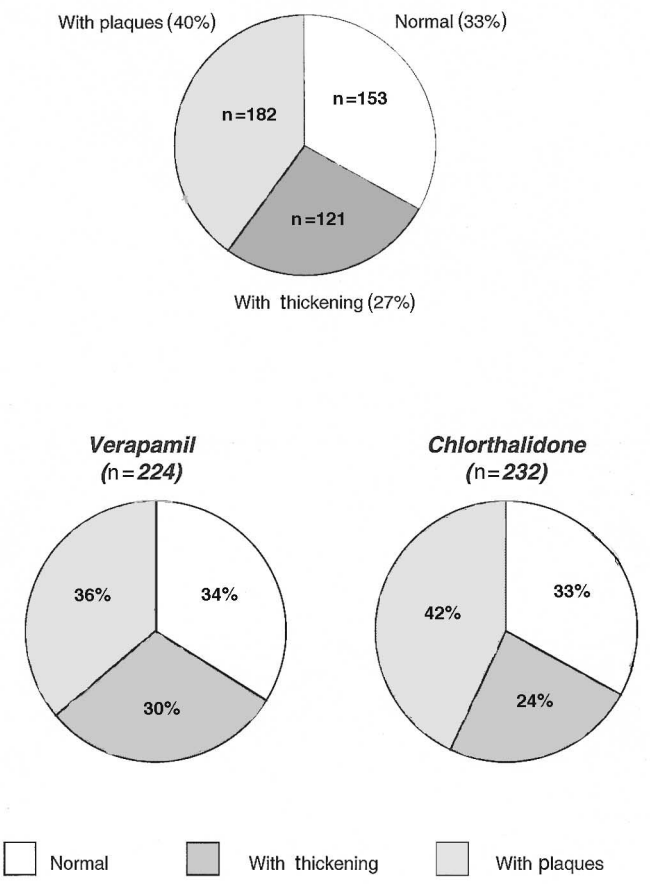
Rate of IMT change

Overall, ultrasound measurements for 377 patients, taken on at least three different occasions over a period of at least 2 years, were available to calculate the rate of IMT change according to protocol criteria. The average follow-up in these patients was 44.2 ± 7.7 months and last visit blood pressure was 140.5 ± 12/86.6 ± 6.7 mmHg.

Rates of IMT change are indicated in Table 2. The changes were rather small on the whole, with M_{max} and CBM_{max} showing small yearly progression rates, and T_{max} showing a small yearly regression rate. When IMT changes were analyzed separately by strata, statistically significant differences between strata were found for all IMT indices, with a lesser progression (M_{max}), or regression rather than progression (CBM_{max} and T_{max}), in patients with plaques (stratum III).

As mentioned under Methods, the primary endpoint of the study was the rate of M_{max} change corrected by the initial IMT. In order to minimize the possibility of regression to the mean, the initial IMT was calculated as the average of M_{max} at baseline and at 3 months, representing an average of up to 12 measurements (up to six measurements on each of the two occasions). Figure 2 shows that the regression of the rate of M_{max} change on initial M_{max}

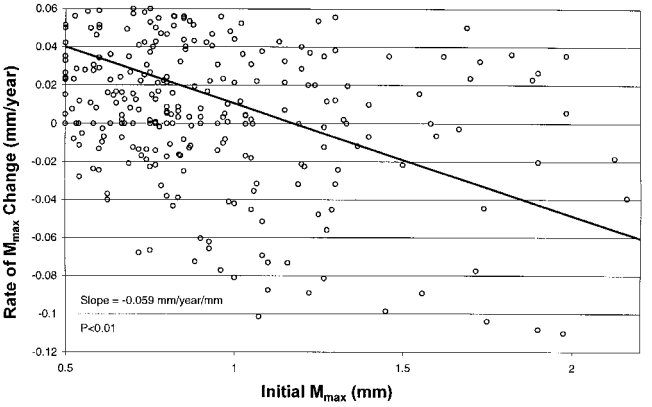
Fig. 1



Distribution of carotid status in patients at baseline. The upper circle refers to all the patients included in the ultrasound study, and the lower two refer to patients randomly assigned to verapamil (left) and chlorthalidone (right).

had a negative slope ($b = -0.059$ mm/year per mm, $P < 0.01$), indicating that during long-term antihypertensive treatment, carotid arteries with an M_{max} greater than about 1.2 mm underwent regression proportional to the initial thickness. Normal or mildly thickened carotid walls appeared to undergo some slight progression. Similar results were obtained when the analysis of IMT changes during the treatment period was repeated according to protocol rather than intention-to-treat criteria, which

Fig. 2



Slope of the regression of the rate of change (mm/year) in the mean maximum intima–media thickness (M_{max}; detected in the far walls of up to six carotid segments) on the initial M_{max} value (mm; mean of baseline + 3 month values) in all patients (n = 377) independently of the treatment to which they were randomized.

excluded 62 patients withdrawn from the randomized treatment and given nonrandomized therapy. A significantly smaller progression rate was found in the patients of stratum III, and the regression rate of M_{max} change on initial M_{max} also had a significant negative slope ($b = -0.048$ mm/year per mm, $P < 0.01$).

Comparison of the effects of verapamil- and chlorthalidone-based treatments on carotid IMT

Of the 377 patients who contributed to the analysis of IMT changes during randomized treatment, 186 were assigned to verapamil and 191 to chlorthalidone. Last-visit systolic/diastolic blood pressures were not significantly different between the two groups: 142.5 ± 12.6/86.9 ± 6.9 (verapamil) and 138.5 ± 11.1/86.2 ± 6.5 mmHg (chlorthalidone).

Common carotid diameter

The small reduction in common carotid end-diastolic diameter described for the whole cohort of patients in the third month of treatment was not significantly different in the two randomized treatment groups (from 7.23 ± 1.08

Table 2 **Rate of change in intima–media thicknesses (IMT, mm/year) during 4 years of antihypertensive treatment**

Ultrasound index	All patients (n = 377)	Stratum I (normal carotid, n = 132)	Stratum II (thickenings, n = 91)	Stratum III (plaques, n = 154)	*P*
M_{max}	0.015 ± 0.069	0.025 ± 0.042	0.023 ± 0.048	0.003 ± 0.092	< 0.05
CBM_{max}	0.012 ± 0.073	0.025 ± 0.040	0.022 ± 0.053	−0.006 ± 0.098	< 0.01
T_{max}	−0.011 ± 0.144	0.015 ± 0.071	−0.002 ± 0.100	−0.041 ± 0.201	< 0.01

Values are means ± SD. M_{max}, mean maximum IMT, calculated as the mean of the maximum IMTs detected in the far walls of up to six carotid segments; CBM_{max}, mean of the maximum IMTs of the common and bifurcation far walls; T_{max}, single maximum IMT. Baseline values (all patients) were: M_{max} 0.905 ± 0.383; CBM_{max} 0.907 ± 0.393; T_{max} 1.249 ± 0.736. *P* values indicate significance of differences between the three strata assessed by analysis of variance.

Table 3 **Rates of change in intima–media thicknesses (IMT, mm/year) during 4 years of follow-up in patients randomly assigned to either verapamil (V) or chlorthalidone (C)**

Ultrasound index	All patients		Stratum I (normal)		Stratum II (thickening)		Stratum III (plaques)	
	V (n = 186)	C (n = 191)	V (n = 62)	C (n = 70)	V (n = 53)	C (n = 38)	V (n = 71)	C (n = 83)
M_{max}	0.015 ± 0.071	0.016 ± 0.067	0.028 ± 0.042	0.022 ± 0.041	0.024 ± 0.055	0.021 ± 0.038	−0.006 ± 0.095	0.011 ± 0.091
CBM_{max}	0.012 ± 0.074	0.012 ± 0.073	0.030 ± 0.042	0.022 ± 0.038	0.024 ± 0.061	0.020 ± 0.041	−0.011 ± 0.097	−0.001 ± 0.100
T_{max}	−0.010 ± 0.141	−0.013 ± 0.148	0.027 ± 0.083	0.004 ± 0.056	−0.002 ± 0.118	−0.001 ± 0.071	−0.050 ± 0.185	−0.033 ± 0.213

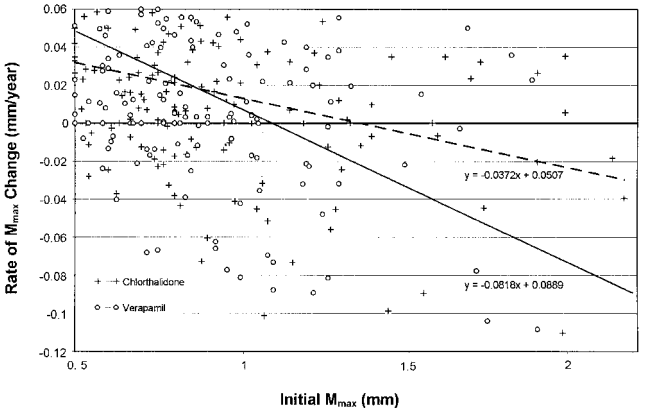
Values are means ± SD. M_{max}, mean maximum IMT, calculated as the mean of the maximum IMTs detected in the far walls of up to six carotid artery segments; CBM_{max}, mean of the maximum IMTs of the common and bifurcation far walls; T_{max}, single maximum IMT. No differences between two treatments were significant (assessed by analysis of variance). Baseline values (all patients) for verapamil were: M_{max} 0.902 ± 0.380, CBM_{max} 0.890 ± 0.393, T_{max} 1.215 ± 0.684; and for chlorthalidone: M_{max} 0.908 ± 0.388, CBM_{max} 0.922 ± 0.412, T_{max} 1.283 ± 0.784

to 7.18 ± 1.06 mm in the verapamil group, and from 7.01 ± 1.08 to 6.97 ± 1.08 mm in the chlorthalidone group).

Rate of IMT change

Table 3 shows a comparison of the rates of IMT change in the two treatment groups according to intention-to-treat criteria. When the two groups were compared independently of strata and also when they were compared separately by strata, progression rates were not significantly different between the randomized treatment groups. Although the rates of IMT change in stratum III (plaques) were regularly smaller or more frequently negative in the verapamil than in the chlorthalidone group, these differences did not achieve statistical significance. However, when the primary endpoint was analyzed by calculating the regression of the rate of M_{max} change on initial M_{max} separately for the verapamil and the chlorthalidone groups (Fig. 3), the two slopes were significantly different from each other (b = –0.082 mm/year per mm for patients randomized to verapamil and b = –0.037 mm/year per mm for patients randomized to chlorthalidone; $P < 0.02$ between groups), indicating that verapamil was able to induce more regression in carotid walls with a greater initial IMT.

Fig. 3



Slope of the regression of the rate of change (mm/year) in the mean maximum intima–media thickness (M_{max}; detected in the far walls of up to six carotid segments) on the initial M_{max} value (mm; mean of baseline + 3 month values), separately for patients (n = 186) randomly assigned to chlorthalidone (crosses, dashed line) and patients (n = 191) randomly assigned to verapamil (circles, continuous line).

The conclusions of the intention-to-treat analysis were confirmed by the per-protocol analysis. Even after excluding the 62 patients treated freely, the rates of IMT changes were more frequently negative in the verapamil (n = 154) than in the chlorthalidone group (n = 161), and the slopes of the regressions of the rates of M_{max} change over initial M_{max} calculated separately for the two treatment groups were significantly different from each other (b = –0.077 mm/year per mm for verapamil and –0.019 mm/year per mm for chlorthalidone; $P < 0.01$ between groups).

Cardiovascular events

Table 4 summarizes all cardiovascular events occurring during the follow-up, analyzed according to intention-to-treat. These were subdivided into fatal and nonfatal events, and the latter classified as major or minor events. There were only six cardiovascular deaths (two in the verapamil and four in the chlorthalidone group). Taking fatal and nonfatal, major and minor cardiovascular events together, there were 19 events (in 19 patients) in the verapamil group and 35 events (in 31 patients) in the chlorthalidone group. When all cardiovascular events, independently of treatment, were analyzed by IMT strata (Table 5, left), a significant ($P < 0.01$) difference in

Table 4 **Deaths and cardiovascular events occurring during the study**

Event	Verapamil (n = 224)	Chlorthalidone (n = 232)
All deaths	2	4
Cardiovascular deaths	2	4
Cardiac	1	4
Cerebrovascular	1	0
Nonfatal cardiovascular events	17	31
Major events	8	8
Myocardial infarction	2	3
Stroke	3	1
CHF	2	2
Revascularization procedures	1	2
Minor events	9	23
Transient ischemic attack	2	8
Angina	4	13
Claudication	3	2
Fatal and nonfatal events	19	35
Patients with any events	19	31

Table 5 Cardiovascular events according to baseline carotid status and treatment

	All patients	Verapamil	Chlorthalidone
Stratum I (normal)	8/153	3/76	5/77
Stratum II (thickenings)	11/121	5/67	6/54
Stratum III (plaques)	31/182**	11/81†	20/101

Values are numbers of patients. **$P < 0.01$, significant differences between strata assessed by χ^2 test; †$P < 0.05$ versus chlorthalidone by log-linear test.

event incidence was observed, in that the patients with plaques had a risk ratio three times greater than the patients with normal carotid wall thickness. When cardiovascular events were analyzed by IMT strata and by randomized treatment, a significant difference was found in event incidence between patients with plaques randomized to verapamil or to chlorthalidone, with a 50% higher risk ratio in the chlorthalidone patients. As expected, the patients with plaques were somewhat older, more frequently male, had a slightly higher baseline systolic (but not diastolic) blood pressure, a slightly higher serum cholesterol (but not lower high-density lipoprotein cholesterol) and a slightly higher glucose level. However, a logistic regression model retained only age, carotid IMT stratum, treatment and sex to account for the probability of cardiovascular events among the patients of our study.

Discussion

Several major conclusions can be drawn from the VHAS ultrasound substudy: (1) The prevalence of carotid wall alterations was high in this sample of otherwise uncomplicated hypertensive patients; (2) under antihypertensive treatment, the rate of change in carotid wall lesions was rather small, and when it was analyzed by strata or, more accurately, related to initial IMT, a tendency towards regression was observed in the more severe lesions; (3) although rates of IMT change in unstratified patients were not significantly different in patients treated with verapamil or chlorthalidone, when IMT changes were related to initial IMT (the primary endpoint), regression of larger lesions was significantly greater in patients randomly assigned to verapamil than in those assigned to chlorthalidone, indicating that verapamil had a significantly greater effect on carotid lesions in hypertensive patients; (4) cardiovascular events appeared to be related to carotid status, with a significantly greater incidence in patients with plaques, and these patients appeared to suffer events less frequently with verapamil than with chlorthalidone treatment. These conclusions are discussed below.

Prevalence of carotid lesions in hypertension

There was a high 67% prevalence of carotid wall alterations, either plaques (40%) or thickenings (27%), in the group of otherwise uncomplicated hypertensive patients studied in the VHAS ultrasound study. On the whole, this high prevalence is consistent with results reported by a large number of previous studies showing that IMT and plaques are strongly correlated with systolic blood pressure [1,2,4–13] or the presence of hypertension [25,26].

IMT changes under antihypertensive treatment

In VHAS patients followed-up during antihypertensive treatment for 4 years, the rate of IMT change was rather small, and when the rate of change was related to initial IMT, a regression of the thicker lesions was observed. The precautions taken in order to avoid our calculations being affected by the statistical phenomenon of regression to the mean have been mentioned. It is unlikely that the negative slope of IMT change over initial IMT is an expression of this phenomenon, as we used up to 12 IMT measurements to obtain the initial value (average of M_{max} at baseline and after 3 months). Furthermore, although strict ultrasound quality control procedures were not included in our protocol, the accuracy and reproducibility were found to be very good; we used only expert sonographers and readers, who were not changed during the study and remained unaware of the treatment to which the patients had been assigned.

From the present study, it is not possible to draw a definitive conclusion that the small size of the IMT changes, and their negative slopes when the IMT rate of change was related to initial IMT, were consequences of antihypertensive treatment. For obvious ethical reasons, VHAS did not include a placebo-treated group. However, the Systolic Hypertension in the Elderly Program (SHEP) Doppler substudy indicated that antihypertensive treatment with chlorthalidone does indeed influence the progression of carotid stenotic lesions to a greater extent than placebo [27]. It is thus likely that the small rate of IMT changes observed in VHAS patients was due, at least in part, to beneficial effects of the antihypertensive treatment.

An important phenomenon demonstrated clearly by our study is that larger carotid wall alterations progress to a lesser extent and regress to a greater extent with antihypertensive treatment. Although this phenomenon has never been explicitly described by previous investigators, our observation is supported by a careful analysis of other studies. The SHEP Doppler substudy [27] concentrated only on stenotic lesions and reported that under antihypertensive treatment with chlorthalidone, 32% of these obviously large lesions showed signs of regression while only 14% showed progression. An accurate examination of data reported by the Multicenter Isradipine/Diuretic Atherosclerosis Study (MIDAS) [20] also indicates that with antihypertensive treatment (isradipine or hydrochlorothiazide), the 3-year IMT progression was greatest in normal segments (0.208 mm), intermediate in borderline segments (0.123 mm) and smallest in diseased segments (0.103 mm). Finally, the recent Carotid Artery Italian Ultrasound Study (CAIUS) has reported that lipid-

lowering treatment with pravastatin affected the thicker carotid bifurcations to a greater extent than the thinner common carotid walls [28]. Thus it appears that carotid artery plaques may be more susceptible to the beneficial action of antihypertensive and lipid-lowering therapies than smaller lesions. This conclusion is only relevant to the range of IMT values in the present VHAS patients, as well as in the MIDAS and CAIUS patients, as all these studies excluded patients with occlusive or calcified lesions.

Comparative efficacy of verapamil and chlorthalidone treatment on the rate of change in IMT

When the two randomized treatments were compared taking the rate of change in IMT as the endpoint, without considering the initial IMT value, no significant difference was found between the two treatments. However, when the patients were subdivided by strata and stratum III was considered, a smaller progression was calculated in verapamil-randomized patients (M_{max} – 0.006 mm/year) than in chlorthalidone-randomized patients (M_{max} 0.011 mm/year), although the smallness of the sample of patients in stratum III did not allow these changes to reach statistical significance. When the full sample of all patients was used without stratification and the initial IMT value was used as a covariate (this being the primary endpoint according to pre-analysis decisions), a significantly steeper regression slope was found in verapamil-randomized (–0.082 mm/year per mm) than in chlorthalidone-randomized patients (–0.037 mm/year per mm). This indicates that verapamil had a significantly greater effect on IMT, proportional to the initial extent of IMT. As outlined in Results (Table 1), IMT was somewhat greater (although not significantly greater) in the chlorthalidone-randomized group, and this may have slightly reduced the difference between the effects of verapamil and chlorthalidone on IMT. Changes in the carotid diameter occurred only during the first year, consisting of small reductions that were equal in the two treatment groups, and therefore cannot have contributed either to the IMT regression observed in the overall sample or to the difference in IMT regression between the two treatment groups. Furthermore, blood pressure was reduced to a similar extent in the two treatment groups, and therefore differences in blood pressure control cannot be held responsible for the different effects on IMT in the two treatment groups. Finally, when analyses were performed per protocol after exclusion of those patients who had been removed from randomized treatment and continued with open-label therapy, the difference in the primary endpoint (slope of regression line of IMT changes over initial values) between patients randomized to verapamil and those randomized to chlorthalidone was still equally significant. Only about one-third of the patients who remained in the randomized treatment groups throughout the study were treated with captopril in addition to the randomized drug, and the proportion of patients taking captopril was substantially the same in the two randomized groups. Therefore, the per protocol analysis confirmed that the greater regression in IMT observed in the verapamil-treated than in the chlorthalidone-treated patients was really due to a different effect of the two drugs on the carotid wall.

The effect of verapamil on atherosclerotic lesions is compatible with experimental reports showing that calcium antagonists [29,30], including verapamil [31–33], are effective in animal models of atherosclerosis. Our observations are also compatible with recent observations in humans, suggesting that verapamil may hinder the development of coronary restenosis after percutaneous transluminal coronary angioplasty [34]. Finally, our conclusion that verapamil was significantly more effective than chlorthalidone when patients with larger IMT values were considered is not inconsistent with MIDAS data [20]. Although a reading drift in MIDAS made it impossible to calculate slopes in IMT changes, Table 2 from the MIDAS paper [30] showed a significantly smaller 3-year progression with the calcium antagonist isradipine than with the diuretic hydrochlorothiazide in diseased segments (–0.035 mm/3 years, $P < 0.02$), whereas differences between the two treatments were smaller and nonsignificant in borderline (–0.022 mm/3 years) and in normal segments (–0.004 mm/3 years).

Cardiovascular events: relation to carotid status and treatment

The size of the patient sample included in the VHAS ultrasound substudy was clearly too small to draw firm conclusions about cardiovascular events. The incidence of cardiovascular events (also including minor events such as angina and claudication) was not particularly elevated in the VHAS ultrasound substudy (27 per 1000 patient-years) nor in the larger VHAS cohort followed for 2 years (28 per 1000 patient-years). However, the incidence of cardiovascular events was significantly higher among patients in stratum III (with plaques), who suffered approximately 40 events per 1000 patient-year. This figure is consistent with that reported for MIDAS patients (35 events per 1000 patient-years). All MIDAS patients had plaques, which were, however, defined as IMT $\geqslant$ 1.3 rather than > 1.5 mm. The relationship between cardiovascular event incidence and carotid status is strengthened by the results of a multiple regression analysis that retained carotid IMT stratum as a significant factor for cardiovascular morbidity. Our conclusion is supported by findings in patients from the Kuopio Ischaemic Heart Disease Risk Factor study [35], showing a threefold increase in the risk of an acute myocardial infarction among those with ultrasound signs of carotid atherosclerosis compared with patients with normal carotid walls. Likewise, a SHEP substudy has reported a 10.9% incidence of cardiovascular events among elderly patients with isolated systolic hypertension without peripheral atherosclerosis, a 29.8% incidence among those with

subclinical atherosclerosis and a 58.3% incidence among those with clinical evidence of carotid or femoral atherosclerosis [36]. The risk ratio of 3 calculated in our hypertensive patients with carotid plaques is therefore identical to the risk ratios calculated by Salonen and Salonen [35] and by the SHEP investigators [36].

At clear variance with results reported by MIDAS [20], in the VHAS ultrasound substudy, the patients randomized to the calcium antagonist suffered a smaller incidence of cardiovascular events than the patients randomized to the diuretic, and the difference was particularly marked in patients with plaques. The difference in the event rate between verapamil and chlorthalidone was particularly related to the incidence of transient ischemic attacks and angina. Although the known anti-anginal action of verapamil may have contributed, the very small difference in the heart rate between the two groups meant that the pressure–rate products at the end of the treatment period were practically identical in the two groups (10 174 for the verapamil and 10 156 for the chlorthalidone group).

The difference between our observations and those reported by MIDAS may be attributed to the different properties of verapamil and isradipine, or to a less satisfactory control of systolic blood pressure with isradipine than with hydrochlorothiazide in MIDAS, or to the size of both the MIDAS and the VHAS samples being insufficient to allow firm conclusions about incidence of cardiovascular events. However, our observations in the VHAS ultrasound substudy are strengthened by the results of the multiple regression analysis that retained treatment as one of the significant factors of cardiovascular morbidity.

Conclusions

In accord with the evidence from animal models of atherosclerosis, the calcium antagonist verapamil had a greater effect than the diuretic chlorthalidone on the regression of thicker carotid lesions. Changes in carotid IMT were small in both groups, however, and the differences between the changes under the two treatments were consequently small. The clinical significance of these small differences is not clear, but in the patients of our study, these small differences in carotid wall changes were paralleled by differences in the incidence of cardiovascular events (better IMT regression with verapamil paralleled by a lower cardiovascular event rate), suggesting that even small effects on carotid plaques may have clinical and prognostic relevance.

The main limitation of our study is the relatively small size of our patient sample, and therefore our conclusions are subject to confirmation by larger studies such as the European Lacidipine Study on Atherosclerosis (ELSA) [7].

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