Therapeutic Advances in Cardiovascular Disease
(2007) 1(2) 97–106
DOI: 10.1177/1753944707085982

Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study

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Abstract

Objective The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study was a double-blind trial in patients with hypertension at increased cardiovascular risk with carotid wall thickening and a defined atherosclerotic plaque that used non-invasive 2- and 3-dimensional (D) ultrasound (US), to compare the effects of a 2-year treatment based on either olmesartan medoxomil or atenolol on common carotid (CC) intima-media thickness (IMT) and plaque volume (PV).

Methods A total of 165 patients (with systolic/diastolic blood pressure 140–180/ 90–105 mmHg) were randomized to receive either olmesartan (20–40 mg/day) or atenolol (50–100 mg/day). US was performed at baseline and 28, 52 and 104 weeks. The primary efficacy outcome was the change from baseline (Δ) in CC-IMT assessed by 2D US. Secondary outcomes included Δ PV assessed by 3D US and blood pressure (BP).

Results Olmesartan and atenolol produced comparable significant reductions in CC-IMT; mean Δ IMT (SEM) was −0.090 (0.015) mm for olmesartan and −0.082 (0.014) mm for atenolol. Mean Δ PV was −4.4 (2.3) µl and 0.1 (1.5) µl in the olmesartan and atenolol treated subjects, respectively, without significant between-treatment differences. In the subgroup of patients with baseline PV ≥ median (33.7 µl), significant between-treatment differences existed in Δ PV ($p = 0.023$), because PV regressed significantly with olmesartan (Δ PV: −11.5 (4.4) µl) but not with atenolol (Δ PV: 0.6 (2.5) µl). In these patients BP reductions were comparable.

Conclusions Carotid IMT and BP decreased similarly with olmesartan and atenolol, but only olmesartan reduced the volume of larger atherosclerotic plaques.

***Keywords*:** carotid arteries, atherosclerosis, hypertension, olmesartan, atenolol

Introduction

Angiotensin-receptor blockers (ARBs) have been shown in experimental animal models to exert an antiatherosclerotic action that is independent of their blood pressure (BP) lowering effect [Strawn *et al.* 2000; Miyazaki *et al.* 2002; Takai *et al.* 2005]. The effects of ARBs on atherosclerotic plaque in human hypertension are unknown. Previous 2-dimensional (2D) ultrasound (US) investigations of carotid intima-media thickness (IMT), as a marker of generalized atherosclerosis [Lorenz *et al.* 2007],

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reported reductions in IMT with ARBs in hypertensive patients that were either comparable [Ludwig *et al.* 2002; Ariff *et al.* 2006] or superior [Olsen *et al.* 2005] to those observed with beta-adrenoreceptor blockade. The atherogenic nature of intima-media thickening is uncertain, since 2D US does not measure medial and intimal thickness separately [Persson *et al.* 1994], and therefore, cannot distinguish between media remodelling due to tensile (hypertensive) stress or intimal thickening reflecting early atherosclerosis [Zanchetti *et al.* 2002]. Plaque volume assessed by 3D US [Fenster, *et al.* 2001] may represent a more reliable measure of atherosclerosis than IMT [Mintz *et al.* 2001], and non-invasive 3D US imaging of the carotid arteries has emerged as a precise and reproducible method for measuring plaque volume and determining its change during treatment [Landry *et al.* 2004; Ludwig *et al.* 1998]. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study is the first trial to take advantage of carotid 2D and 3D US to compare the effects of a 2-year treatment based on either an ARB (olmesartan medoxomil) or a beta-blocker (atenolol) on changes in IMT and is a pilot study to assess atherosclerotic plaque volume changes in hypertensive patients.

Methods

Study population

Participants were recruited at 31 clinical centres throughout Austria, the Czech Republic, Germany, Italy, and Poland. Local independent ethical committee approval was obtained by all participating centres and patients gave written informed consent before entering the study. The study was performed in accordance with the principles of the Declaration of Helsinki, and the regulatory requirements of the International Conference on Harmonisation guidelines on Good Clinical Practice, and was registered at ClinicalTrials.gov (NCT00185185). The study began in November 2001 and ended in February 2006.

Eligible patients were male and female Caucasians, aged 35–75 years, with seated systolic blood pressure (SBP) of 140 to 180 mmHg and seated diastolic blood pressure (DBP) of 90 to 105 mmHg, an increased common carotid artery (CC) IMT of between 0.8 and 1.6 mm, at least one plaque in the CC or the carotid bulb (plaque volume: 4 to 500 µl), and ≥ 1 of the following predefined risk factors: smoking, diabetes mellitus, dyslipidemia (high-density lipoprotein (HDL)-cholesterol < 0.9 or low-density lipoprotein (LDL)-cholesterol > 2.6 or triglycerides > 1.7 mmol/l), left ventricular hypertrophy and history of cardiovascular disease, or complications of cardiovascular disease.

Exclusion criteria were as follows: secondary or malignant hypertension, significant valvular disease, stroke, myocardial infarction within the previous 6 months, 2nd or 3rd degree atrioventricular block and atrial fibrillation. Patients who had started treatment with a lipid-lowering agent, and/or an angiotensin-converting-enzyme inhibitor (ACEI), or an ARB within 6 months prior to the start of the study as well as patients who received a lipid-lowering agent for more than six months but with a modification of the dosage within this period, were also excluded. The protocol was approved by the appropriate institutional review board or Ethics Committee at each centre involved. All patients gave written informed consent.

Study treatment

Patients on antihypertensive treatment underwent an initial 2-week tapering-off period. All patients entered a 2-week placebo run-in phase, followed by randomization to double-blind treatment with either olmesartan (20 mg; Sankyo Co., Ltd., Tokyo, Japan) or atenolol (50 mg; Merckle, Ulm, Germany). Patients with uncontrolled BP (DBP > 90 mmHg and/or SBP $>$ 140 mmHg) at these dose levels after 4 weeks of treatment were titrated to olmesartan 40 mg or atenolol 100 mg once daily. Hydrochlorothiazide (Isis Pharma, Zwickau, Germany) at a dose of 12.5 mg with up-titration to 25 mg after another 4 and 8 weeks, respectively, was added if BP remained uncontrolled. A computer-generated randomisation list was prepared centrally by PRA International, Mannheim, Germany, using appropriate blocks and guaranteeing that in study centres patients were assigned to one of the treatment groups. The study medication was provided in externally indistinguishable capsules. Hydrochlorothiazide tablets were administered unblinded. Medication release was performed by Sankyo Pharma GmbH, Pfaffenhofen, Germany; data management and quality control assessments were carried out by PRG1 Ltd., Darmstadt, Germany.

Assessments

At screening, patients underwent a complete physical examination, ultrasound measurements

of IMT and PV were made and assessments of BP, and routine laboratory parameters were carried out. After randomization, patients made 10 further visits to the study centres. Visits to ultrasound centres for measurements of IMT and PV were scheduled at screening, weeks 28, 52 and 104.

For BP, three conventional (sphygmomanometry) measurements of seated SBP and DBP were made between 6:00 and 11:00 a.m. at each visit, approximately 24 hours after the previous dose of trial medication, and the mean of the measurements was used for analysis.

Ultrasound measurements

Ultrasound measurements of IMT and PV were carried out by certified sonographers (Appendix) at 14 ultrasound referral centres using a high-resolution Voluson 530 D MT, 2D-/3D CFM-Ultrasound System (Kretz-Technik AG, Zipf, Austria) equipped with a mechanical 10 MHz sector motor-driven probe that provided an axial resolution of 0.1 mm. An integrated 6.9 MHz Doppler system was used to determine the grade of possible stenoses. All sonographic measurements were performed by manual planimetry, and the results were stored on s-VHS videotape and magneto-optical discs (MODs) which were sent to the European Ultrasound Teaching and Reading Centre (Feldafing, Germany). Blinded ultrasound readings and quality assessment evaluations were carried out using a specifically designed 2D and 3D Post Processing Image Analysis System (PPAS) with an option for re-performing measurements on the MODs.

Intima-media thickness (IMT)

The ultrasound examination and image analysis procedures used to measure IMT have been described previously [Ludwig *et al.* 2002]. In brief, IMT was measured on the far wall of the common carotid artery along a 1 ± 0.3 cm long section proximal to the carotid bulb. From the 2D US acquired longitudinal image 3 single measurements were carried out at the side (left or right common carotid) with the greater IMT, the mean of these measurements used for further calculation and statistical analysis. The lumen diameter (LD) of the CC was measured at end-diastole in the same segment used for IMT measurements. The PPAS was used to locate the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall, which defined LD. The cross-sectional area of IMT (CSA-IMT) was calculated according to standard method [Linhart *et al.* 1996]. If the IMT of the leading side (side with the greater IMT) was ≥ 0.8 and ≤ 1.6 mm at screening then the patient was included (dependent upon fulfilment of remaining entry criteria).

Plaque volume (PV)

For assessment of PV by 3D US, the volume of one plaque without shadowing from mineralization in the common carotid artery or bulb was determined. If more than one plaque was detected, the largest one with clear proximal and distal limits was investigated, and used for all subsequent measurements during the study. To measure PV, a longitudinal scan of the common carotid artery and bulb was carried out followed by volume acquisition. The volume acquisition results were stored on the MOD and sent to the Reading Centre. The data was presented in 3 orthogonal planes, longitudinal, transverse and horizontal. Plaque volume calculations were carried out from the transverse plane starting at the edge of the plaque and moving along the longitudinal axis toward the opposite edge of the plaque. Cross-sectional area of the plaque was delineated from 8-12 transverse sections of the image between the edges of the plaque using the 3D CFM Ultrasound System. The mean of 3 measurements of the volume of each plaque was used for analysis. The methodology for PV measurement and its validation has been described previously [Ludwig *et al.* 1998; Ludwig, 1997; Ludwig *et al.* 2007].

Reliability of IMT and PV measurements

Intra- and inter-reader variability within the reading process was investigated in a blinded technical quality control sub-study that was carried out at the same time, and involved the same centres and methodology. Following a defined scheme, the scans of 45 patients with one plaque in the common carotid artery or bulb were recorded on videotapes and MODs, blinded with respect to all information (i.e., patient number, date of IMT and PV measurement, treatment allocation), and sent to the Reading Centre for data quality assessment. Three readers at the Reading Centre performed two independent re-readings. The intra-class correlation coefficient (ICC), as determined by ANCOVA [Shrout & Fleiss, 1979], was used to assess reliability [Shoukri, 2004]. The ICC among the three readers (inter-variability) was 0.978 for IMT and

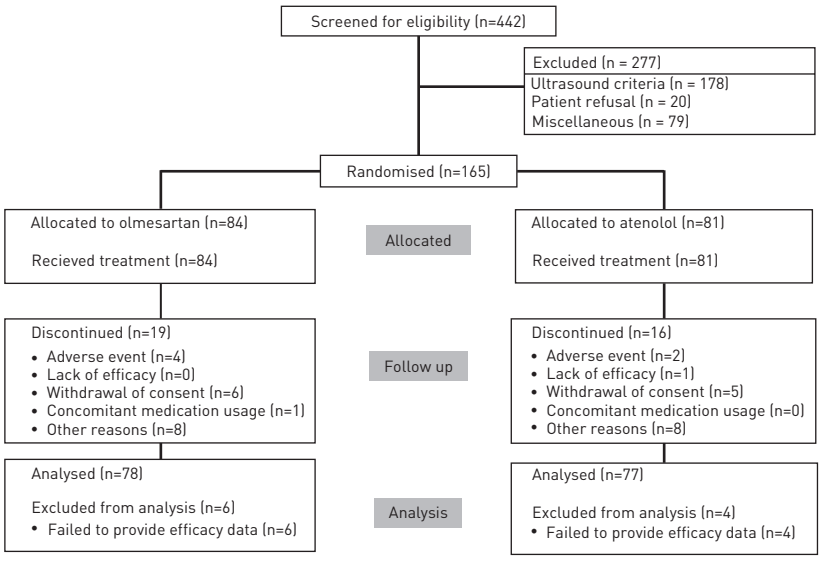


Figure 1. Disposition of patients. The reasons for patient exclusion are given in the frame boxes.

0.964 for PV. The intra-reader variability (intra-variability) calculated separately for each of the readers, resulted in ICC values for IMT of 0.994, 0.979 and 0.981, and for PV of 0.985, 0.967, and 0.969 for the first, second and third reader, respectively.

Study outcomes

The primary efficacy outcome was the change in CC-IMT of the leading carotid side (i.e., side with the greater IMT) from baseline after 104 weeks. Changes at 28 and 52 week were secondary efficacy variables. Additional secondary efficacy parameters were changes in PV, overall mean IMT (i.e. mean of IMT measurements from both carotids), SBP and DBP from baseline at 28, 52, and 104 weeks.

Statistical analyses

The change in IMT of the leading carotid side after 104 weeks of treatment was defined as the primary efficacy variable. Sample size estimation was based on a 2-sided significance test applying the t-test model with $\alpha = 0.05$, $\beta = 0.20$, an estimated standard deviation (SD) of 0.1 mm [Ludwig *et al.* 2002] and a limit of clinically relevant treatment difference of $\Delta = 0.05$ mm. The resulting number of patients required was calculated as 64 for each treatment group. Taking into account an estimated 25% of patients not being available for evaluation for efficacy, it was planned to randomize a total of 170 patients. Primary efficacy analysis was planned for the intention-to-treat (ITT) data set using the last-observation-carried-forward (LOCF) approach for imputing missing data (at the 1- and 2-year follow-up). Statistical evaluation of the primary efficacy variable was carried out by means of analysis of covariance (ANCOVA) with treatment group and ultrasonographic centre as effects and baseline IMT as covariate. The treatment-by-baseline interaction was examined by including this term in the statistical model of an additional analysis. Quantitative secondary efficacy variables such as changes in PV and in BP were analyzed by means of the same ANCOVA models that were applied for the primary efficacy variable. Within-group changes of efficacy criteria were tested for significance by means of the one-sample t-test. Additional analyses of changes in IMT and PV stratified by baseline values $<$ or $\geq$ median were performed on an exploratory basis in a post-hoc subgroup analysis. The median was chosen as the cut-off point because this approach leads to approximately the same numbers of patients in the investigated subgroups. Possible associations between variables of interest were assessed by the Bravais-Pearson correlation coefficient.

Results

Patients

Of 442 patients screened, 174 were enrolled in the study (Figure 1). 9 patients withdrew prior to randomization and the safety population comprised 165 patients (olmesartan = 84, atenolol = 81). A further 10 patients were withdrawn after receiving at least one dose of study medication but without providing efficacy data, so the ITT-population comprised 155 patients (olmesartan = 78, atenolol = 77). In the atenolol group, one patient was excluded from the IMT- and PV-analyses due to technical problems with ultrasound measurements, so for the analyses of IMT and PV the atenolol group comprised 76 patients. Both treatment groups were similar in terms of baseline characteristics (Table 1), except that the atenolol group contained a slightly greater proportion of males, smokers, and patients with a history of cardiovascular disease. Adjustment of the results for these factors had no effect on outcomes. The proportion of patients that were on stable statin therapy before entering the study and remained on it during follow-up did not differ between the two treatment groups.

Table 1. Baseline Data by Treatment Allocation in the Intent-to-Treat Population.

Characteristic	Atenolol $n = 77$	Olmesartan $n = 78$
Age, years	62.1 (6.6)	62.3 (7.4)
Sex, % male	72.7	50.0
BMI, kg/m^2	27.3 (2.9)	27.5 (3.7)
Serum total cholesterol, mmol/l	5.45 (1.0)	5.35 (0.86)
Serum HDL cholesterol, mmol/l	1.38 (0.30)	1.50 (0.35)
Serum LDL cholesterol, mmol/l	3.20 (0.87)	3.22 (0.67)
Serum triglycerides, mmol/l	1.85 (1.11)	1.62 (0.77)
Serum uric acid, µmol/l	353 (81)	359 (74)
Systolic BP, mmHg	157.1 (7.6)	157.6 (7.7)
Diastolic BP, mmHg	96.3 (3.7)	95.9 (3.9)
Duration of hypertension, years	9.4 (8.4)	8.1 (6.6)
History of cardiovascular disease, %	13.7	9.0
Current smoking, %	37.7	30.8
Type 2 diabetes, %	3.8	3.8
Antihypertensive pre-treatment, %	64.9	61.5
Lipid lowering treatment		
Statins, %	29.9	29.5
Fibrates, %	6.5	6.4
IMT, mm	0.968 (0.16)	0.984 (0.18)
LD, mm	7.27 (1.3)	7.38 (1.2)
CSA-IMT, mm^2	25.2 (6.9)	26.0 (6.4)
PV, µL	50.5 (40.6)	49.7 (46.6)

Data are mean (SD). BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; IMT, intima-media thickness; LD, lumen diameter; CSA, cross-sectional area; PV, plaque volume.

The percentage of patients on monotherapy differed slightly between the two groups. 33.8% of the atenolol and 46.2% of the olmesartan treated subjects were maintained at the low dose, and at study end, a greater proportion of patients on atenolol (39.0%) than on olmesartan (30.8%) received the high dose of study drug in combination with HCTZ.

Changes in blood pressure and laboratory parameters

Both treatment groups achieved marked reductions in SBP and DBP at 104 weeks (atenolol −21.5/−13.8 mmHg and olmesartan −24.6/−15.2 mmHg). The between-treatment differences were in favour of olmesartan for SBP and DBP but were not statistically significant ($p = 0.075$ and $p = 0.120$ for SBP and DBP, respectively). The decreases in SBP and DBP with both atenolol and olmesartan were evident at 28 and 52 weeks of treatment (28 week: atenolol −20.6/−13.3 mmHg and olmesartan −25.7/−14.3 mmHg; 52 week: atenolol −21.6/−14.2 mmHg and olmesartan −25.6/−14.9 mmHg), and the between-treatment differences in favour of olmesartan were significant for SBP, but not for DBP, at 28 and 52 week follow-up ($p = 0.004$ and $p = 0.025$, respectively). There were no significant changes in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides in either treatment group. Uric acid increased to a greater extent with atenolol (18 µmol/L, $p = 0.012$) than with olmesartan (8.2 µmol/L, $p = 0.35$) without a significant between-treatment difference.

IMT changes

CC-IMT of the leading side at 104 weeks had significantly ($p < 0.0001$) decreased from baseline in both the atenolol-treated and olmesartan-treated patients, and the changes did not differ between the two treatments (Table 2). The decreases in IMT with both atenolol and olmesartan were significant ($p < 0.0001$) at 28 and 52 week follow-up. Lumen diameter (LD) was reduced slightly, but not significantly more with atenolol than olmesartan with no significant between-treatment difference (Table 2). CSA-IMT, calculated from IMT and LD, declined comparably ($p < 0.0001$ for each) in both treatment groups. Changes in IMT were dependent on baseline values ($r = -0.290$; $p = 0.011$

Table 2. Changes (Δ) from Baseline in Carotid IMT, PV, LD and CSA-IMT.

	Atenolol ($n = 76$)			Olmesartan ($n = 78$)			Difference* ($n = 154$)	
	Mean	SEM	*P*	Mean	SEM	*P*	95% CI	*P*
Δ IMT, mm								
28 week follow-up	−0.053	0.012	<0.0001	−0.057	0.012	<0.0001	−0.037; 0.033	0.9243
52 week follow-up	−0.070	0.016	<0.0001	−0.064	0.013	<0.0001	−0.032; 0.050	0.664
104 week follow-up	−0.082	0.014	<0.0001	−0.090	0.015	<0.0001	−0.045; 0.035	0.817
Δ PV, µl								
28 week follow-up	−0.4	1.2	0.736	−3.4	1.9	0.081	−6.9; 1.7	0.226
52 week follow-up	0.5	1.6	0.742	−3.8	2.2	0.091	−9.5; 1.0	0.114
104 week follow-up	0.1	1.5	0.972	−4.4	2.3	0.059	−9.0; 1.0	0.120
Δ LD, mm								
104 week follow-up	−0.22	0.14	0.126	−0.18	0.11	0.113	−0.25; 0.40	0.646
Δ CSA-IMT, mm^2								
104 week follow-up	−2.81	0.59	<0.0001	−3.18	0.63	<0.0001	−1.76; 1.42	0.832

*Differences are olmesartan minus atenolol; Confidence Intervals (CI) and P values for difference between treatments were calculated by means of analysis of covariance adjusted for ultrasound centre and baseline value.

Table 3. Changes from Baseline in IMT and PV in Subgroups of Patients† after 104 weeks follow-up.

	Atenolol ($n = 76$)				Olmesartan ($n = 78$)				Difference* ($n = 154$)		
	n	Mean	SEM	*P*	*n*	Mean	SEM	*P*	*n*	95% CI	*P*
Baseline IMT, mm											
< Median	38	−0.055	0.016	0.001	35	−0.046	0.017	0.011	73	−0.045; 0.058	0.803
≥ Median	38	−0.109	0.022	<0.0001	43	−0.126	0.023	<0.0001	81	−0.094; 0.035	0.368
Baseline PV, µl											
< Median	35	−0.6	1.2	0.622	42	1.7	1.5	0.259	77	−0.3; 7.0	0.075
≥ Median	41	0.6	2.5	0.817	36	−11.5	4.4	0.014	77	−21.1; −1.6	0.023

†Patients of the ITT population with baseline IMT and PV < median and ≥ median; post-hoc analysis.
*Differences are olmesartan minus atenolol; Confidence Intervals (CI) and *P* values for difference between treatments were calculated by means of analysis of covariance adjusted for ultrasound centre and baseline value.

and $r = -0.189$; $p = 0.087$ for the atenolol and olmesartan group, respectively). Table 3 shows that in subjects with baseline IMT ≥ median (0.93 mm) both treatments reduced IMT to a greater extent than in those with baseline IMT < median. Overall mean IMT at 104 weeks also decreased significantly ($p < 0.0001$) with both atenolol (Δ mean IMT: -0.047 ± 0.009 mm) and olmesartan (Δ mean IMT: -0.054 ± 0.013 mm). Treatment effects in both groups were evident from 28 weeks onwards, and between-treatment differences were not significant.

PV changes

PV declined with a trend towards significance ($p = 0.059$) in the olmesartan-treated patients. No similar trend was seen in the atenolol-treated patients, and between-treatment differences were not significant (Table 2). However, the treatment-by-baseline interaction term was significant ($p < 0.001$) when included in the statistical model. Changes in PV from baseline correlated significantly with baseline PV in the olmesartan group ($r = -0.593$; $p < 0.0001$) but not in the atenolol group ($r = -0.127$; $p = 0.274$, Figure 2).

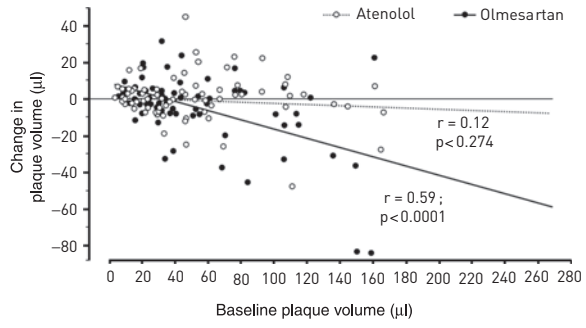
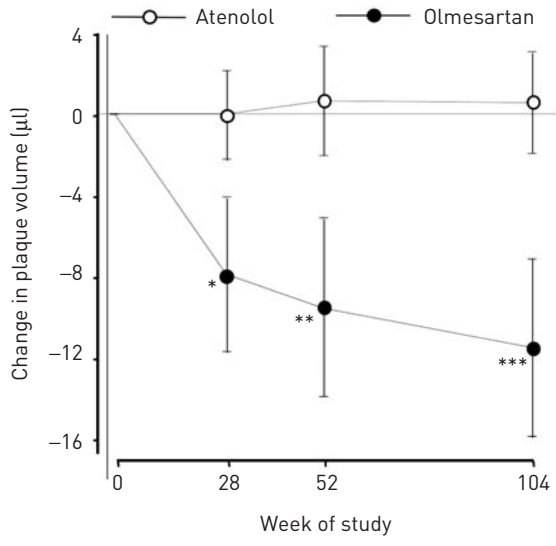


Figure 2. Relationship between baseline plaque volume (PV) and changes in plaque volume from baseline for the olmesartan and atenolol groups.



*p=0.044 vs. baseline, 0.083 vs. atenolol
**p=0.036 vs. baseline, 0.032 vs. atenolol
***p=0.014 vs. baseline, 0.023 vs. atenolol

Figure 3. Mean changes in plaque volume at 28-, 52- and 104-week of follow-up in atenolol ($n = 41$) and olmesartan ($n = 36$) treated patients with baseline plaque volume $\geq$ median (33.7 µl). Horizontal bars indicate SEM.

Exploratory (post-hoc) analyses

To further investigate the correlation between baseline plaque volume and the reduction in PV (Figure 2) a post-hoc analysis was performed which showed that in the subgroup of patients with baseline PV $\geq$ median (33.7 µl) changes in PV differed significantly ($p = 0.023$) between treatments because PV decreased with olmesartan (ΔPV: -11.5 µl; $p = 0.014$) but not with atenolol (ΔPV: $+0.6$ µl) (Table 3). Significant decreases in PV with olmesartan were seen at 28 weeks, and PV continued to decline over the entire observation period with significant ($p < 0.05$) between-treatment differences from 52-week onwards (Figure 3). In the subgroups of patients with PV $\geq$ median, similar reductions in SBP and DBP were seen in both treatment groups at all time points (28 week: atenolol $-23.5/-13.2$ and olmesartan $-23.3/-13.7$ mmHg; 52 week: atenolol $-25.2/-15.2$ and olmesartan $-24.0/-15.2$ mmHg; 104 week: atenolol $-23.6/-14.0$ and olmesartan $-22.9/-15.5$ mmHg).

Discussion

The MORE-study was a double-blind, comparative trial designed to assess the effects on carotid IMT and atherosclerosis of blockade of the AT_1-receptor with olmesartan medoxomil and blockade of the beta-adrenergic receptor with atenolol in patients with hypertension and defined CV risk. The principal results show that treatment with either olmesartan or atenolol produced significant decreases in carotid IMT without significantly altering PV. However, a post-hoc analysis showed that in the non-prespecified subgroup of patients with carotid plaques that were $\geq$ median volume at baseline, PV significantly decreased with olmesartan but not with atenolol.

For the primary efficacy measure, change in IMT from baseline at 104 weeks, a significant decrease was seen with both treatments. There was no difference between the two groups. CSA-IMT, an estimate of wall mass, also decreased significantly in both groups and no significant between-treatment differences were observed. The changes in IMT and CSA-IMT were associated with equal reductions in SBP and DBP in each group. Our findings confirm previous evidence that lowering of blood pressure is associated with a reduction in IMT and mass of larger arteries [Boutouyrie *et al.* 2000; Wang *et al.* 2006]. The results are also in agreement with two recent studies in hypertensive patients which reported regression effects of angiotensin-receptor blockade with losartan or candesartan on IMT that were comparable [Ludwig *et al.* 2002; Ariff *et al.* 2006] to those observed with beta-receptor blockade. In another study, losartan resulted in greater reduction in IMT than atenolol [Olsen *et al.* 2005]. In the current study, IMT decreased more in subjects with larger baseline IMT than with smaller IMT, a finding which corresponds to data of the VHAS-study which reported greater regression effects of antihypertensive treatment on more advanced than on less

advanced carotid wall lesions as assessed by IMT [Zanchetti *et al.* 1998].

Carotid IMT ultrasound does not measure medial and intimal thickness separately, and therefore, cannot distinguish between medial remodelling as a result of an adapted response to tensile (hypertensive) stress, or of intimal thickening primarily indicating an early manifestation of atherosclerosis [Zanchetti *et al.* 2002]. IMT changes in the MORE study, however, are likely to reflect changes in medial remodelling rather than atherosclerosis, because IMT was measured in the distal common carotid artery at sites free of atherosclerotic plaque, and medial remodelling is specifically related to hypertension [Chobanian, 1989]. Thus, our results suggest that angiotensin-receptor blockade and beta-receptor blockade might be similarly effective in reducing vascular wall hypertrophy.

The MORE trial extended its investigation to atherosclerotic plaques, and assessed the effects of treatment on changes in plaque volume. Plaque measurements using 3-D US provide direct assessment of localized atherosclerosis and changes in PV are thought to be the most rigorous measure of atherosclerotic disease progression and regression [Mintz *et al.* 2001; Landry *et al.* 2004]. In this study, we found a small mean reduction in carotid PV in patients treated with olmesartan that marginally failed to reach significance. Further post-hoc analyses of the results showed a strong and statistically significant correlation between changes in PV and baseline PV in the olmesartan arm and revealed an interaction between Δ PV and baseline PV such that larger plaques showed a greater response to olmesartan. Thus, in plaques with a volume equal to or above the baseline median, a significant between-treatment difference in PV-reduction in favour of olmesartan was found. Although, there are limitations in terms of sample size and the sub-analyses based on baseline PV were not pre-specified there was a strong and statistical significant decrease in volume of larger plaques in the olmesartan-treated patients during the entire observation period from 28 weeks onwards whereas no significant change in PV was observed in the atenolol-treated subjects.

From a technical and methodological perspective, our findings are reliable, given that PV was measured with the same 3D US equipment at all study sites by specifically trained and certified sonographers. Consistency of data analysis was ensured by recording ultrasound examinations on video tape and MOD at each study site and subsequently analyzing the recordings in a standardized manner at a central reading laboratory using specialized software. Intra- and inter-reader reliability was high (see methods), indicating that the method used is suitable for tracking progression or regression of PV.

The results of the PV analysis of the subgroup of patients with plaques larger than the median baseline PV raise the question of why olmesartan should exert a preferential regressive effect on larger plaques. A possible explanation is that there are limitations in the method to monitor precisely the volume of very small plaques. In fact, analysis of the effect of plaque volume on observer variability in 3-D US measurements has found that PV measurement variability increases with smaller and decreases with larger plaque size [Landry *et al.* 2004].

The pathophysiological mechanisms underlying the treatment effects of angiotensin-receptor blockade on plaque volume are not clear at this time. Blood pressure may play a role in determining the reduction in PV, because mean SBP had decreased significantly more at 28 and 52 weeks with olmesartan as compared with atenolol. The reductions in PV observed with olmesartan are apparently independent of BP lowering, as in the subgroup of patients with PV larger than the median, decreases in SBP and DBP at all time points were similar in the two treatment groups. However, the possible role of differences in central blood pressure [Williams *et al.* 2006] cannot be excluded. Differences in the concomitant use of statins are unlikely to account for the different treatment effects on PV, because the proportion of patients on stable statin therapy was the same in the two treatment groups. Also, changes in total cholesterol, LDL-, HDL-cholesterol and triglycerides as well as serum concentrations of these lipids at study end did not differ significantly in either treatment group. Other mechanisms, however, are more likely to be important. Experimental evidence suggests that activation of the angiotensin II type 1 (AT_1) receptor is decisively involved in the initiation and progression of atherosclerosis [Nickenig and Harrison, 2002]. Studies in ApoE and angiotensin II type 1A receptor double-knockout mice indicate that deletion of the AT_1-receptor or AT_1-blockade with irbesartan

resulted in significant inhibition of atherosclerosis in the aorta and endothelial dysfunction [Wassmann *et al.* 2004]. Studies in monkeys have confirmed and extended these findings: losartan and olmesartan have been shown to slow lipid accumulation within the aorta of animals fed a high-cholesterol diet [Strawn *et al.* 2000; Miyazaki *et al.* 2002]. Furthermore, olmesartan was found to exert a regressive effect on aortic lipid accumulation in monkeys with diet-induced hypercholesterolemia [Takai *et al.* 2005].

In the present study, in contrast to olmesartan, atenolol did not affect plaque volume. Atenolol was chosen as comparator because it is one of the most widely used beta-blockers clinically and has been used as reference drug in several randomized controlled ultrasound studies investigating antihypertensive treatment effects on IMT [Ludwig *et al.* 2002; Ariff *et al.* 2006; Olsen *et al.* 2005; Zanchetti *et al.* 2002].

A recent meta-analysis has questioned the principal efficacy of atenolol and its use as a reference drug in outcome trials in hypertension [Carlberg *et al.* 2004]. Atenolol is a very hydrophilic compound with low permeability into lipid-containing tissues [Parker *et al.* 1990; Carlberg *et al.* 2004] compared with olmesartan, which is a very lipophilic drug. Antiatherosclerotic effects are more attributed to lipophilic drugs. These principle pharmacological differences between the two comparator drugs used in this trial might additionally explain the observed effects on PV reduction. The design of the present study did not include, for obvious ethical reasons, a placebo control group.

Our findings as to PV-changes were limited by the fact that the study was a pilot trial with respect to plaque volume that was not powered for this major secondary endpoint, and the post-hoc sub-analyses based on baseline PV were not pre-specified. Therefore, further studies with larger sample size are needed to confirm the results by selecting patients with larger plaques to delineate more fully the importance of angiotensin receptor blockade in mediating the antiatherosclerotic effects that were observed in the current investigation.

In conclusion, in patients with hypertension and carotid atherosclerosis, the MORE study has found comparable reductions in carotid IMT with olmesartan and atenolol, and a preferential decrease in the volume of larger plaques with olmesartan. These changes occurred despite similar reductions in BP, suggesting an antiatherosclerotic action of olmesartan that is independent of its blood pressure-lowering effect.

Appendix

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Acknowledgements

We thank all of the participating MORE study investigators for their dedicated work.

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