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Risk factors for carotid plaque progression after optimising the risk factor treatment: substudy results of the Atherosclerotic Plaque Characteristics Associated with a Progression Rate of the Plaque and a Risk of Stroke in Patients with the carotid Bifurcation Plaque Study (ANTIQUE)

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ABSTRACT

Background and aim Carotid plaque progression contributes to increasing stroke risk. The study aims to identify factors influencing carotid plaque thickness progression after changing the preventive treatment to the 'treating arteries instead of risk factors' strategy, that is, change in treatment depending on the progression of atherosclerosis.

Methods The study participants who completed sonographic controls over the course of 3 years were enrolled to the analysis. Duplex sonography of cervical arteries was performed in 6-month intervals with measurement of carotid plaque thickness. Plaque thickness measurement error (σ) was set as 3 SD. Only evidently stable and progressive plaques (defined as plaque thickness difference between initial and final measurements of $<\sigma$ and $>2\sigma$, respectively) were included to analysis. Univariate and multivariate logistic regression analysis was performed to identify factors influencing plaque progression.

Results A total of 1391 patients (466 males, age 67.2±9.2 years) were enrolled in the study. Progressive plaque in at least one carotid artery was detected in 255 (18.3%) patients. Older age, male sex, greater plaque thickness, coronary heart disease, vascular surgery/stenting history and smoking were more frequently present in patients with progressive plaque (p<0.05 in all cases). Multivariate logistic regression analysis identified only the plaque thickness (OR 1.850 for left side, 95% CI 1.398 to 2.449; and OR 1.376 for right side, 95% CI 1.070 to 1.770) as an independent factor influencing plaque progression.

Conclusion Carotid plaque thickness corresponding to stenosis severity is the only independent risk factor for plaque thickness progression after optimising the prevention treatment.

Trial registration number NCT02360137.

INTRODUCTION

Large vessel atherosclerosis is the most common cause of ischaemic stroke.[1]

Approximately 18%–25% of all strokes are due to carotid atherosclerotic disease.[2] Carotid bifurcation and proximal part of internal carotid artery (ICA) are the predominant locations for atherosclerotic plaque formation.[3] Identification of carotid artery atherosclerosis is conventionally based on measurements of luminal stenosis and surface irregularities using in vivo imaging techniques, including sonography, CT angiography, MR angiography and digital subtraction angiography.[4] Nevertheless, both histopathological[5 6] and imaging[4 7 8] studies have shown significant differences in the risk of stroke between carotid plaques with the same degree of stenosis. Thus, carotid atherosclerotic plaque diagnosis has shifted from pure stenosis quantification to more detailed plaque characterisation including plaque progression, which allows for more precise patient risk stratification and management.[4 7 8]

Duplex ultrasound is an accurate, noninvasive, low-cost mode of diagnostic imaging. It has become a first-line examination method for carotid diseases.[9] Due to sufficient resolution in B-mode, duplex sonography enables accurate characterisation of plaque features related to stroke risk.[10 11] Moreover, noninvasiveness and low cost make ultrasound an optimal method to assess the progression of the atherosclerotic plaque.[7 12]

Spence *et al* introduced a new paradigm for the treatment of carotid atherosclerosis based on the combination of lifestyle changes with smoking cessation, a Mediterranean diet, daily

exercise, maintaining a fit weight, moderate consumption of alcohol and medical therapy with effective control of blood pressure and diabetes, intensive treatment with lipid-lowering drugs and antiplatelet agents, and treatment adjustment in case of detection of plaque progression instead of risk factor treatment only.[13] However, these changes in treatment strategy called 'treating arteries instead of risk factors' may alter the effect of individual risk factors on plaque progression.

The aim of this study was to identify factors influencing carotid plaque thickness progression in patients after changing the preventive treatment to the 'treating arteries instead of risk factors' strategy.

MATERIALS AND METHODS
Patients
All consecutive patients from the ANTIQUE study (Atherosclerotic Plaque Characteristics Associated with a Progression Rate of the Plaque and a Risk of Stroke in Patients with the Carotid Bifurcation Plaque Study—ClinicalTrials.gov Identifier: NCT02360137) who underwent all clinical and ultrasound examinations over a 36-month period and did not underwent carotid endarterectomy or stenting were included in the analysis. The ANTIQUE study inclusion criteria were as follows: patient age 30–90 years; atherosclerotic plaque localised in the carotid bifurcation or proximal part of the ICA with a thickness of ≥2.0 mm in B-mode transverse plane; sufficient image quality of atherosclerotic plaque in the carotid bifurcation and ICA using ultrasound; self-sufficiency defined as a modified Rankin Scale score of 0–2 points; and signed informed consent was provided. Exclusion criteria were serious disease with a low probability of survival for at least 3 years and other objective obstacles preventing regular 6-month ultrasound scans.

Clinical examination
All patients underwent neurological and physical examinations at 6-month intervals over the course of 36 months. The examinations included blood pressure (one measurement at rest after the sonographic examination), height and weight measurements (including calculation of body mass index), collection of demographic and medical data (age, sex, and medical history), occurrence of diseases (arterial hypertension,[14] diabetes mellitus,[15] hyperlipidaemia,[16] coronary heart disease, atrial fibrillation, history of myocardial infarction or other cardiac diseases, stroke, including stroke type, and surgery or stenting of any vessels, including carotid arteries, coronary or lower limb and other arteries), smoking, daily alcohol consumption dose and medication use.

Treatment
All patients were treated using the 'treating arteries instead of risk factors' strategy.[13] Briefly, all patients were examined for cholesterol blood level, glycaemia and blood pressure at their baseline visit. In case of pathological values, appropriate treatment was used with target LDL-cholesterol values of <2.5 mmol/L (<2.0 mmol/L in diabetics and stroke patients), target fasting glucose of 3.9–7.2 mmol/L, and blood pressure of ≤130/80 mm Hg. All smokers were instructed to stop smoking immediately. Furthermore, all patients were on a Mediterranean diet, performed an ideal amount of daily physical activity, and consumed a suitable daily amount of alcohol. Images of atherosclerotic plaques were shown to all patients at each visit to improve compliance.[17–19] All patients received the brochure with information about atherosclerosis, risk factors, healthy life style, optimal diet, exercise and drug treatment possibilities.
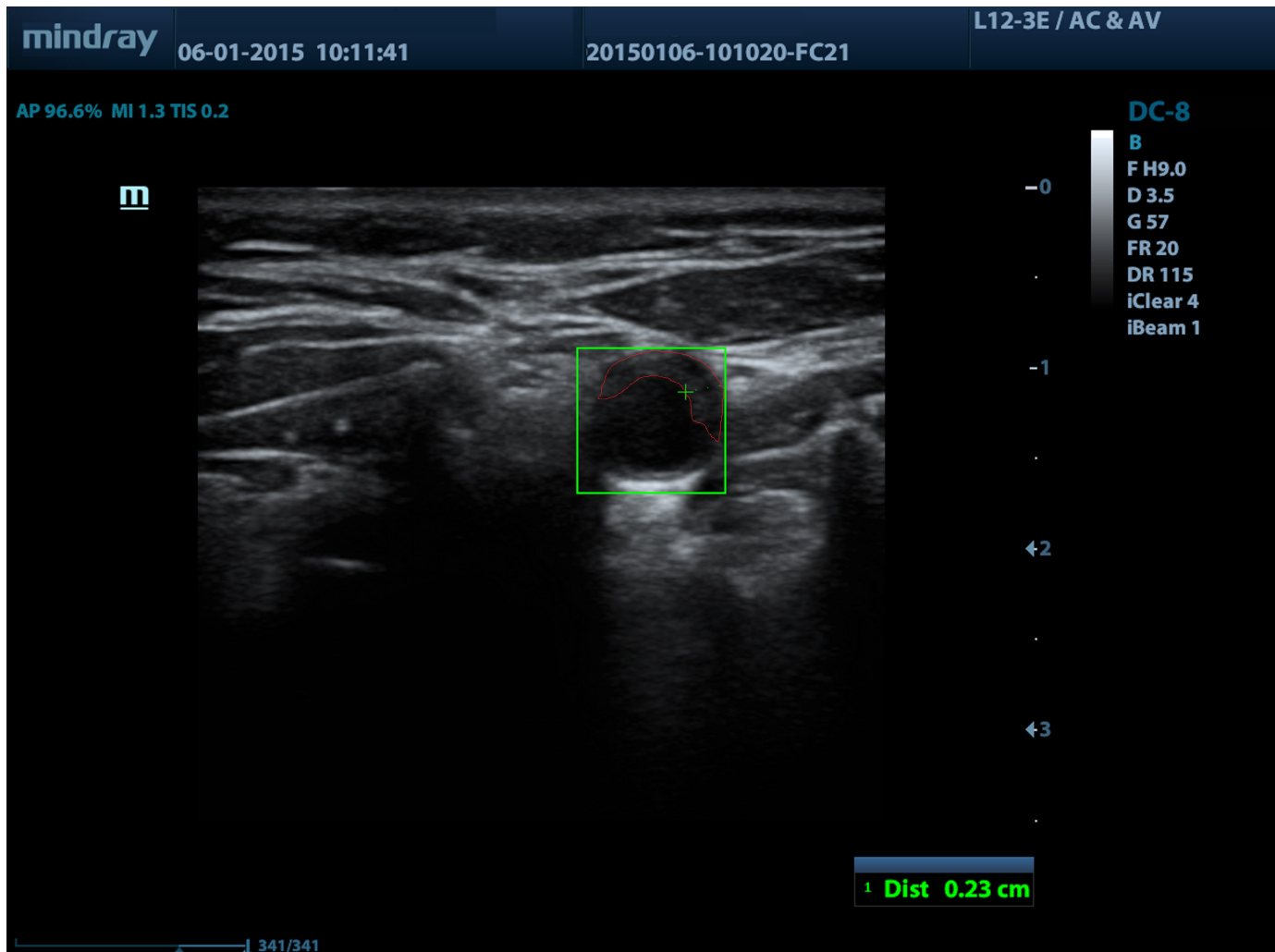
In case of detection of atherosclerotic plaque thickness progression of ≥0.1 mm between the two visits, patients with treated hypercholesterolaemia were advised to double the statin dose. Ezetimibe was added in cases when the maximum statin dose was already reached. Niacin in non-diabetics or fibrate in diabetics were recommended in cases of previous ezetimibe treatment. In patients with blood pressure >130/80 mm Hg, it was recommended to adjust the antihypertensive treatment by adding ACE inhibitor or sartan, if possible. The use of pioglitazone or metformin was recommended in non-diabetic patients with insulin resistance.[13]

Ultrasound examination
Neurosonological examination was performed in all patients at standard conditions during the baseline visit, 2 weeks later, and then in 6-month intervals within 36 months (totally eight measurements). Patients were instructed not to drink alcohol or smoke 48 hours prior to the examination. All patients underwent a routine clinical duplex ultrasound imaging of carotid arteries (common, internal and external carotid arteries) using B-mode, colour-mode and Doppler mode with a Mindray DC8 scanner (Mindray, Shenzhen, China) and linear probe 3–12 MHz (L 12-3E) to assess the carotid plaque characteristics, including plaque thickness and stenosis severity. The scanner settings were standardised to optimise acquisitions: acoustic power (maximum); mechanical index (1.3); frame rate (20 fps); main frequency (9.0 MHz), harmonic frequencies (on); dynamic range (115 dB); iClear (4); iBeam (1); depth and gain were individually adjusted. Then, 10-s cine-loops of longitudinal and transverse sections of all plaques in the carotid bifurcation were acquired.

The following plaque characteristics were evaluated: plaque echogenicity, homogeneity, plaque surface and calcifications. Plaque thickness measurement was performed in the transverse section of carotid artery in the area of maximum plaque thickness. The measurement was performed five times using a wall perpendicular to the artery (figure 1). The maximal measured plaque thickness was used for analysis.

Plaque thickness measurement error (σ) was set as 3 SDs (99.7th percentile) of the difference between the two measurements in 2-week intervals. Only evidently stable and progressive plaques were included to the analysis. A

Figure 1 Measurement of atherosclerotic plaque thickness in the B-mode transverse section of the internal carotid artery.

stable plaque was defined as a plaque with the thickness difference between initial and final measurements of $<\sigma$. Total plaque area and plaque volume differences between the first and final examinations were subsequently measured in plaques evaluated as stable. All plaques with differences in total plaque area or plaque volume of $>10\%$ were excluded from the stable plaque group. A progressive plaque was defined as a plaque with a thickness difference between initial and final measurements of $>2\sigma$. Plaques with the border change (1σ–2σ) were not included to the analysis as well as plaques with change $\leq\sigma$ contralaterally to progressive plaque.

All sonographic examinations were performed by an experienced certified neurosonographer (DŠ). The second sonographic examination 2 weeks after the baseline visit was performed by two certified neurosonographers (DŠ and PK) to evaluate the interobserver and intraobserver variabilities of the plaque thickness measurement.

Statistical analyses

Normal data distribution was tested using Shapiro-Wilk test. Demographic data were expressed as the average and SD or as numbers and percentages. The interclass correlation coefficient was used for the evaluation of the interobserver and intraobserver reliability. Continuous variables were compared using the two-sample t-test. Ordinal categorical data were compared with Fisher exact test for two categorical variables, otherwise the Mann-Whitney U test was used.

Univariate and multivariate logistic regression analyses were used to identify independent risk factors (age, sex, body mass index, blood pressure, carotid plaque thickness, arterial hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease, atrial fibrillation, history of myocardial infarction, stroke, vascular surgery/stenting, smoking and alcohol consumption) for plaque progression defined as an increase of the thickness difference between initial and final measurements of >2 ME. All factors were included in the multivariate analysis (backward stepwise method).

All statistical tests were performed at a significance level of $p\leq0.05$. The statistics software IBM SPSS Statistics V.23 (SPSS) was used for all data processing.

Table 1 Demographic and clinical characteristics of subjects included to the analysis

		Patients included to the analysis	ANTIQUE patients died prior to the final visit	ANTIQUE patients excluded due to other reason
No of subjects; n (%)		1391	119	81
Plaque thicknesson the left side; mean±SD		2.955±1.090	3.625±1.126	3.760±1.327
Plaque thicknesson the right side; mean±SD		2.987±1.470	3.577±1.107	3.634±1.269
Age (years); mean±SD		68.5±10.3	76.1±7.2	70.1±9.7
Male sex; n (%)		466 (33.5)	77 (64.7)	40 (49.4)
Weight (kg); mean±SD		80.5±14.7	82.8±15.9	82.9±14.4
Height (cm); mean±SD		168.1±9.1	168.6±9.6	170.7±10.5
Body mass index; mean±SD		28.4±4.4	29.1±4.9	28.4±4.2
Systolic blood pressure (mm Hg); mean±SD		134.4±12.4	134.9±12.0	132.9±12.4
Diastolic blood pressure (mm Hg); mean±SD		79.8±8.8	80.6±7.5	80.2±8.8
Arterial hypertension; n (%)		1091 (78.4)	95 (79.8)	66 (81.5)
Diabetes mellitus; n (%)		299 (21.5)	27 (22.7)	15 (18.5)
Hyperlipidaemia; n (%)		754 (54.2)	61 (51.3)	40 (49.4)
Coronary heart disease; n (%)		355 (25.5)	30 (25.2)	25 (30.9)
Atrial fibrillation; n (%)		165 (11.9)	13 (10.9)	15 (18.5)
History of myocardial infarction; n (%)		131 (9.4)	10 (8.4)	8 (9.9)
History of stroke; n (%)		279 (20.1)	24 (20.2)	25 (30.9)
History of vascular surgery/stenting; n (%)		218 (15.7)	12 (10.1)	17 (21.0)
Smoking; n (%)		183 (13.2)	11 (9.2)	9 (11.1)
Alcohol consumption (IU/day); n (%)	1	598 (43.0)	53 (44.5)	25 (30.9)
	2	526 (37.8)	32 (26.9)	38 (46.9)
	2	249 (17.9)	31 (26.1)	17 (21.0)
	3 and more	22 (1.6)	3 (2.5)	1 (1.2)

The intraobserver reliability of plaque thickness measurement was ICC=0.996, while the interobserver reliability was ICC=0.973. The measurement error σ=0.2 mm.
ANTIQUE, Atherosclerotic Plaque Characteristics Associated with a Progression Rate of the Plaque and a Risk of Stroke in Patients with the Carotid Bifurcation Plaque Study; ICC, interclass correlation coefficient; IU, international unit; n, number.

RESULTS

A total of 1391 patients (466 males and 925 females; mean age, 67.2±9.2 years) out of 1591 (583 males and 1008 females; mean age, 69.4±10.9 years) patients enrolled in the ANTIQUE study were included in the analysis. Patient demographics are listed in table 1 and online supplemental table S1. Out of 200 patients who did not complete all visits, 119 patients died (77 males and 42 females; mean age, 80.1±7.2 years), nine patients suffered from a new severe stroke and stayed immobile, 66 patients become immobile due to non-vascular disease, and 6 patients were lost to follow-up due to relocation. Demographic data of ANTIQUE study patients included to the study are in the table 1.

Stable plaques in both carotids were detected in 332 patients (125 males and 207 females; mean age, 66.7±9.7 years). Progressive plaque in at least one carotid artery was detected in 255 patients (126 males and 129 females; mean age, 69.5±8.3 years) (table 2). None plaque regressed of >2σ.

Older age (66.7 vs 69.5 years; OR (OR)=1.035 per 1 year), male sex (37.7 vs 49.4%; OR=1.617), greater plaque thickness (2.61 vs 3.12 mm for left side; OR=1.749; and 2.65 vs 3.13 mm for right side; OR=1.540), coronary heart disease (19.6 vs 28.6%; OR=1.648), vascular surgery or stenting medical history (11.1 vs 22.8%; OR=2.359) and smoking at baseline (9.9 vs 17.3%; OR=1.889) were more frequently present in patients with progressive plaque ($p<0.05$ in all cases) (see tables 2 and 3). Univariate logistic regression analyses for carotid plaque progression separately for males and females are in online supplemental table S2. Nevertheless, multivariate logistic regression analysis identified only the plaque thickness (OR 1.541 per 1 mm for left side, 95% CI 1.230 to 1.930; and OR 1.369 per 1 mm for right side, 95% CI 1.062 to 1.772) as the independent factor influencing plaque thickness progression (see table 4).

DISCUSSION

This study results demonstrated that optimising prevention treatment based on the 'treating arteries instead of

Table 2 Demographic and clinical characteristics of subjects with stable and progressive plaques

		Stable plaque	Progressive plaque	P value
No of subjects; n (%)		332	255	NA
Age (years); mean±SD		66.7±9.7	69.5±8.3	0.0002*
Male sex; n (%)		125 (37.7)	126 (49.4)	0.005†
Weight (kg); mean±SD		81.2±14.8	80.6±14.0	0.591*
Height (cm); mean±SD		167.6±9.3	168.6±9.2	0.167*
Body mass index; mean±SD		28.9±4.4	28.3±3.9	0.078*
Systolic blood pressure (mm Hg); mean±SD		133.9±12.2	135.0±12.9	0.283*
Diastolic blood pressure (mm Hg); mean±SD		80.0±9.0	80.0±9.0	0.928*
Plaque thickness on the left side (mm); mean±SD		2.61±0.94	3.12±0.98	<0.0001*
Plaque thickness on the right side (mm); mean±SD		2.65±0.94	3.13±1.16	<0.0001*
Arterial hypertension; n (%)		251 (75.6%)	207 (81.2%)	0.109†
Diabetes mellitus; n (%)		65 (19.6%)	48 (18.8%)	0.834†
Hyperlipidaemia; n (%)		178 (53.6%)	153 (60.0%)	0.131†
Coronary heart disease; n (%)		65 (19.6%)	73 (28.6%)	0.011†
Atrial fibrillation; n (%)		31 (9.3%)	26 (10.2%)	0.779†
History of myocardial infarction; n (%)		25 (7.5%)	28 (11.0%)	0.191†
History of stroke; n (%)		56 (16.9%)	56 (22.0%)	0.138†
History of vascular surgery/stenting; n (%)		37 (11.1%)	58 (22.8%)	0.0002†
Smoking; n (%)		33 (9.9%)	44 (17.3%)	0.013†
Alcohol consumption (IU/day); n (%)	0	132 (39.8%)	98 (38.4%)	0.384‡
	1	140 (42.2%)	100 (39.2%)	
	2	55 (16.6%)	49 (19.2%)	
	≥3	5 (1.5%)	8 (3.1%)	

*Two-sample t-test
†Fisher's exact test
‡Mann-Whitney U-test
IU, international unit; n, number; NA, not applicable.

risk factors' strategy modify the negative effect of selected modifiable risk factors on carotid atherosclerotic plaque thickness progression.

Atherosclerosis is the leading cause of death worldwide, accounting for about half of deaths in developed countries.[20 21] The most important modifiable risk factors are arterial hypertension, diabetes mellitus, hypercholesterolaemia, smoking, alcohol abuse, obesity and lack of exercise.[22] Treatment of these risk factors significantly reduces the risk of atherosclerosis progression, vascular events and death.[23 24] Nevertheless, Spence et al have identified a high Framingham risk score in only 30% of patients who would experience a cerebrovascular event, whereas 70% of the events occurred among patients with extensive carotid plaques (the top quartile of total plaque area).[25] For these reasons, a new strategy for preventing atherosclerosis progression and vascular events called 'treating arteries instead of risk factors' has been developed.[13] When the strategy was implemented in vascular prevention clinics in Argentina, the annual rate of cardiovascular events declined from 5.86% to 2.35% between 2011 and 2015.[24] In addition, this strategy with showing

patients images of their arteries significantly improves compliance with medical advice.[17 19]

Atherosclerotic plaque progression within 3 years, defined in presented study as >0.4 mm plaque thickness progression corresponding to a mean relative progression of >14%, was detected in only 18.3% of patients in this study. Only detected risk factor for plaque progression was the plaque thickness but no cardiovascular risk factor. Each 1 mm of plaque thickness increase the risk of progression within 3 years by 54% for left side plaque and 37% for the right plaque, resp. Spence et al[25] have found carotid plaque progression, defined as total plaque area progression, in 63% of patients within 5 years of standard risk factor treatment. The plaque progression was defined as progression of total plaque area of >5 mm², which corresponds to the mean relative progression of >11%. The change in vascular risk factor treatment to the 'treating arteries instead of risk factors' strategy led to a significant decrease in risk of any cardiovascular event (stroke, myocardial infarction, carotid endarterectomy or death) from 17.6% to 5.6%. Moreover, the annual rate of carotid plaque progression declined by 66% from 69 to

Table 3 Univariate logistic regression analysis for carotid plaque progression

	OR	95% CI	P value
Age (per 1 year)	1.035	1.015 to 1.054	0.0004
Male sex	1.617	1.162 to 2.252	0.004
Weight (per 1 kg)	0.997	0.986 to 1.008	0.591
Height (per 1 cm)	1.013	0.995 to 1.031	0.167
Body mass index (per 1 unit)	0.966	0.928 to 1.005	0.083
Systolic blood pressure (per 1 mm Hg)	1.007	0.994 to 1.020	0.283
Diastolic blood pressure (per 1 mm Hg)	0.999	0.981 to 1.017	0.928
Plaque thickness on the left side (per 1 mm)	1.749	1.454 to 2.103	<0.0001
Plaque thickness on the right side (per 1 mm)	1.540	1.294 to 1.832	<0.0001
Arterial hypertension	1.392	0.931 to 2.080	0.107
Diabetes mellitus	0.953	0.629 to 1.442	0.818
Hyperlipidaemia	1.298	0.932 to 1.806	0.122
Coronary heart disease	1.648	1.123 to 2.418	0.011
Atrial fibrillation	1.102	0.637 to 1.909	0.728
History of myocardial infarction	1.515	0.860 to 2.668	0.150
History of stroke	1.387	0.918 to 2.096	0.120
History of vascular surgery/stenting	2.359	1.504 to 3.701	0.0002
Smoking	1.889	1.164 to 3.067	0.010
Alcohol consumption			0.429
0 vs 1 IU/day	0.962	0.667 to 1.388	0.836
0 vs ≥2 IU/day	1.280	0.818 to 2.001	0.280

IU, international unit.

23 mm^2. As estimated, this would correspond to a 3-year progression in 12.6% of patients, which is consistent with our findings.

Overall mortality in the patient group was 7.48%, which means 2.49% per year. This value is considerably lower (by 34%) compared with 3.34% annual mortality in age-rated general population in the Czech Republic.[20] These results are also in concordance with published studies that state that the 'treating arteries instead of risk factors' strategy leads to a significant decrease in vascular events including vascular death.[13 26]

Reading study results, one may hypothesise that early detection of carotid atherosclerosis with modifiable vascular risk factors treatment based on the 'treating arteries instead of risk factors' strategy is the appropriate approach for prevention of atherosclerosis complications, especially cerebrovascular events and vascular deaths. This treatment strategy with a control of plaque progression at regular intervals might lead to a decreased risk of carotid plaque progression and a significant reduction in vascular complications and death. Nevertheless, randomised trial comparing this new strategy and usual care should be carried out.

This study has several limitations. First, the stability and progression of atherosclerotic plaques were evaluated using maximum plaque thickness. Plaque thickness progression corresponding to the increase of stenosis percentage measured using European Carotid Surgery Trial study methodology[27] was used as the only evaluation parameter. Thus, plaque with progression of plaque volume or total plaque area without progression of plaque thickness was not determined as progressive. In contrast, plaque thickness, total plaque area and plaque volume were used as parameters for stable plaque evaluation. This may lead to exclusion of some plaques with volume progression from the plaque progression group. As the dynamic range of plaque thickness (estimated ~10–30 mm) is much less than that of total plaque area (0–1200 mm^2), the risk factors for progression in the total plaque area or volume might differ from our findings.[28] Second, only patients with clearly stable and progressive plaques were included to the analysis. Third, only one sonographer performed all neurosonology examinations. This might decrease the measurement bias but it will not allow to compare results between sonographers with different skills. Fourth, the laboratory risk factors were not included to our analysis. Spence and Solo found that serum creatinine was a significant factor for the 'resistant atherosclerosis'.[29] Thus, laboratory markers and their relation to the plaque progression should be studied in next studies. Finally, 13% of patients enrolled

Table 4 Independent predictors of carotid plaque progression (multivariate logistic regression method backward stepwise)

	OR	95% CI	P value
Thickness of left carotid plaque (per 1 mm)	1.541	1.230 to 1.930	0.0002
Thickness of right carotid plaque (per 1 mm)	1.369	1.062 to 1.772	0.019
Age (per 1 year)	1.026	0.995 to 1.058	0.100
Smoking	2.028	0.921 to 4.465	0.079

in the ANTIQUE study did not pass all neurosonology visits. Patients who died within 36 months after study enrolment might especially bias the final study results.

CONCLUSIONS

Higher age, male sex, smoking, carotid plaque thickness and history of vascular disease were associated with plaque progression. Multivariate regression analysis identified carotid plaque thickness corresponding to stenosis severity as the only independent risk factor for plaque thickness progression in patients treated using the 'treating arteries instead of risk factors' strategy.

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