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Predictors of carotid plaque progression over a 4-year follow-up in the Reykjavik REFINE-study

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ABSTRACT

Background and aims: Carotid plaque is an arterial marker suggested as a surrogate end point for cardiovascular disease. The aim of this study was to examine the association of risk factors at visit 1 with plaque formation and progression of total plaque area (TPA) during follow-up.
Methods: We examined 1894 participants (50–69 years of age) in the population-based REFINE (Risk Evaluation For INfarct Estimates)-Reykjavik study.
Results: Among those with no plaque at baseline, plaque formation was associated with low density lipoprotein, sex, waist, former smoker and physical activity. Furthermore, both the Icelandic Heart Association (IHA) coronary heart disease (CHD) risk score and the atherosclerotic cardiovascular disease (ASCVD) risk score were highly associated with plaque formation in these individuals ($p < 0.001$) and a better cardiovascular health score was protective. In those with plaque present at baseline, metabolic syndrome was associated with increased risk, while older age and statin use were associated with reduced risk of new plaque formation. Statin use was the only factor associated with the relative TPA progression, where participants not on treatment had 5.7% (p=0.029) greater rate of progression compared with statin users.
Conclusions: A number of conventional risk factors at visit 1 were individually associated with plaque formation, also when combined into CHD and ASCVD risk scores, but not with the relative progression in TPA. Medical intervention with statins can reduce the relative progression rate of TPA in the general population with low grade of atherosclerosis, supporting statin use to slow progression of atherosclerosis.

1. Introduction

Atherosclerosis is the major cause of CVD. It is an asymptomatic chronic disease that develops silently for decades before clinical events occur [1]. The pathogenesis is complex and involves interactions between modifiable and non-modifiable risk factors [1]. Non-invasive imaging has been suggested as a method to estimate subclinical atherosclerosis to improve cardiovascular risk assessment [2] and to monitor response to treatment [3]. B-mode ultrasound is an imaging method widely used to detect and measure early stages of atherosclerosis in the carotid arteries. This method provides measures on both carotid plaques and carotid intima-media thickness (cIMT), which are structural markers independently associated with cardiovascular risk factors [4,5] and cardiovascular disease [6].

There are only few studies using B-mode ultrasound imaging of carotid arteries in general populations to study the progression of carotid plaques as number of new plaque formed [7] or as increase in total plaque area (TPA) [5]. The aim of this study was to prospectively examine new plaque formation and the relative progression of TPA over four years in a general population, and characterize the association with cardiovascular risk factors at visit 1. The relative common carotid intima-media thickness (CCA-IMT) progression was also evaluated.

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2. Materials and methods

Individuals in the present study are participants in the REFINE (Risk Evaluation For INfarct Estimates)-Reykjavik study of the Icelandic Heart Association, which is an ongoing longitudinal population based study. In the REFINE-Reykjavik study, a random sample of 9480 men and women, born between 1935 and 1985, and living in the Reykjavik area in November 2005, was drawn from the Icelandic National Registry [8]. Of those, 6941 individuals attended (73%). The first phase of the REFINE study was carried out between December 2005 and March 2011, and the second phase between May 2010 and May 2013. All participants gave written informed consent and the study was approved by the National Bioethics Committee (05-112-S1) and the Data Protection Authority.

This study was limited to participants 50–69 years of age, with baseline and follow-up data on risk factors and carotid ultrasound (n = 1894). Physical examination included standardized measurements of waist circumference, height and weight, and body mass index (BMI) was calculated. Blood pressure was measured with computer-controlled device that automatically inflated the cuff to a user preset maximum pressure and then precisely controlled deflation at 2 mmHg/s. Study subjects were in a supine position for at least 15 min before blood pressure measurement [9]. Blood samples were drawn after overnight fasting to measure blood parameters, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG), glucose and high-sensitivity C-reactive protein (CRP). Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula if triglyceride level was <4.5 mmol/L [10]. Non-HDL was calculated subtracting HDL from TC. Questionnaires were used to record smoking status, family history of myocardial infarct (MI), educational level and physical activity (exercised regularly, yes/no).

For information on medication use, participants brought their medication to the visit. Hypertension was defined as the use of antihypertensive medications, self-report, or measurements of systolic blood pressure (SBP)≥140 mm Hg or diastolic blood pressure (DBP)≥90 mm Hg. Diabetes mellitus type 2 (DM2) was defined as self-report, medication use or fasting serum glucose concentration ≥7.0 mmol/L [11]. History of coronary heart disease (CHD) was defined as previous MI, coronary artery bypass graft or percutaneous transluminal coronary angioplasty and/or stent obtained from hospital records [12]. Metabolic syndrome was defined as the presence of at least three of the following criteria; 1) waist circumference >102 cm in men and >88 cm in women, 2) triglycerides ≥1.7 mmol/L, 3) HDL <1.0 mmol/L in men and HDL <1.3 mmol/L in women, 4) blood pressure ≥130/≥85 mmHg or antihypertensive medication use; 5) fasting glucose ≥6.1 mmol/L [13].

The Icelandic Heart Association's risk calculator (IHA-CHD risk score) estimates the probability of getting coronary heart disease in the next 10 years [14]. Value ≥ 10% is the cut-off for defining patients at high risk, who could benefit from statin treatment. The ACC/AHA Pooled Cohort Equations Risk Calculator (ASCVD risk score) is designed to predict 10-year risk of atherosclerotic cardiovascular disease, defined as nonfatal MI, fatal CHD, fatal or nonfatal stroke [15]. Value ≥ 7.5% is the cut-off for statin treatment.

A cardiovascular (CV) health score was also calculated. The American Heart Association (AHA) has defined “ideal cardiovascular health” by simultaneous presence of 7 ideal health metrics [16]. In the current study we had information on all but one (diet). Total cholesterol, glucose, blood pressure, BMI, physical activity and smoking status were stratified according to the AHA definition into ideal, intermediate or poor metrics, coded as 2, 1 and 0 respectively. A CV health score was calculated by summing the score for each metric resulting in variable with a range from 0 to 12.

2.1. Carotid ultrasound

Detailed protocols for imaging and reading have been published [17]. In brief, images of the right and left common carotid artery (CCA), bifurcation, and internal carotid artery (ICA) were acquired with an Acuson Sequoia C256 with a two-dimensional 8 MHz linear array transducer. Images of the intima-media thickness were acquired from a predefined 10 mm segment (extending from 10 mm to 20 mm proximal to the tip of the flow divider) at defined interrogation angles using the Meijers Arc. Standard images were obtained from 4 angles at each side. The mean IMT of the near and far walls was determined from a single image at each interrogation angle for both the right and left CCA. The mean of all these IMT values comprised the CCA-IMT outcome parameter.

The presence of plaque was assessed in the near and far walls of the bifurcation and ICA on both the left and right side. A plaque was defined as an isolated thickening at least two times the adjacent normal cIMT by visual assessment [18]. Our definition of plaque as described previously is the same used in clinical trials, and not only represents significant atherosclerotic plaque in the carotids but includes some areas that are more intermediate atherosclerosis stages. This has been pointed out in the Mannheim Carotid Intima-Media Thickness and Plaque Consesus, where intermediate stages between increasing carotid IMT and significant atherosclerotic plaque formation cannot be reliably differentiated by either B-mode ultrasound or histological examination [19].

The presence/absence of plaque was assessed during ultrasound examination and the most severe lesion per segment was evaluated qualitatively as: 1) no plaque, complete absence of plaque but cIMT thickening may be observed, 2) minimal plaque, small isolated thickening approximately two times the adjacent normal cIMT, 3) moderate plaque, clear and reasonable easy to visualize plaque, with or without calcifications and may cause some diameter reduction and 4) severe plaque, significant plaque formation very easy to image with or without calcifications, causing clear diameter reduction. Individuals with severe plaque were few (n = 19) and were therefore combined with the group of individuals with moderate plaque and termed significant plaque.

The Artery Measurement System (AMSII) software (v2.02) was used to quantitatively assess plaque area. Plaque boundaries were traced with a cursor on the computer screen, and for each outlined plaque, the program automatically computed the area (mm [2]). A longitudinal view of each plaque, where boundaries were clear and the plaque appeared largest, was selected for tracing. Total plaque area (TPA) was calculated by summing areas of all individual plaques.

Plaque progression was defined both as a categorical and continuous variable. New plaque formation was examined separately in those with no plaque and in those with plaque at visit 1. The relative TPA progression was evaluated in those with plaque at visit 1.

2.2. Ultrasound quality control

Details on ultrasound quality control procedures and on the inter- and intraobserver reproducibility of CCA-IMT and plaque measurements were published previously [19]. Mean intraobserver variability in TPA measurements for two observers (intraclass correlation and percent coefficient of variation (CoV) respectively) based on the rereading of the same 10 subjects was 0.98 and 9.82% for observer 1 and 0.96 and 16.03% for observer 2. Inter-observer variability for the same 10 subjects was 0.91 (correlation) and 18.20% (CoV). In the reproducibility estimate for the ultrasound acquisition, where 20 subjects were scanned and measured twice by one observer, the correlation was 0.95 and CoV

of 12.40%.

2.3. Statistical analyses

Risk factors and atherosclerotic measures were reported as means and standard deviation (SD) or median with interquartile range (IQR). Categorical variables were reported in frequencies and percentages (%). Variables with skewed distribution were log transformed to achieve normal distribution, including TG and CRP.

Modified Poisson regression approach was used to estimate the relative risk of new plaque formation. Age, sex and time adjusted analyses were performed for each risk factor at visit 1. TPA and CCA-IMT were log-transformed to estimate the relative progression over time. The effects of risk factors at visit 1 on the relative progression in TPA and CCA-IMT were estimated using a mixed effects regression model for repeated measures, where we included a random effect for subject. The risk factors being evaluated as fixed effects were: sex, age, time (between visits) and the interaction between risk factor and time. The significance of the interaction term was used to estimate if the risk factor was an effect modifier for the progression rate in TPA and CCA-IMT. Sex- and age-specific analyses are included in Supplemental material.

All tests were two-sided and p values < 0.05 regarded statistically significant. All statistical analyses were carried out with SAS software version 9.3.

3. Results

A total of 1894 subjects where included in the study. Table 1 presents the clinical characteristics at visit 1. The sample consisted of 49% men, the average age was 58.8 (SD 5.0) years, 6.3% had known CHD, 5.8% had DM2, and 19.5% were current smokers, 14.8% used statins and 37.7% used antihypertensive medications. Plaques were detected in 1432 (75.6%) participants, and of those, 311 had significant plaque. The average CCA-IMT was 0.82 (SD 0.12) mm. The average time between visits was 4.2 (SD 0.4) years.

Table 1
Characteristics of participants at visit 1.

	Total sample (n = 1894)
Sex, men (%)	931 (49.2)
Age, years	58.8 (5.0)
TC, mmol/L	5.5 (1.0)
HDL, mmol/L	1.5 (0.4)
LDL, mmol/L[a]	3.4 (0.9)
TG, mmol/L (IQR)	1.1 (0.8–1.5)
Non-HDL, mmol/L	3.9 (1.0)
Glucose, mmol/L	5.6 (0.9)
CRP, mg/l (IQR)	1.6 (0.8–3.1)
BMI, kg/m^2	27.9 (4.6)
SBP, mmHg	126.5 (17.1)
Hypertension (%)	947 (50.0)
DM2 (%)	109 (5.8)
Smoking status (%)	
Never	695 (36.7)
Former	830 (43.8)
Current	369 (19.5)
CHD (%)[b]	119 (6.3)
Family history of MI (%)[c]	844 (45.7)
Physically active (%)[d]	823 (43.5)
Metabolic syndrome (%)	465 (24.6)
Medication use (%)	
Statins	281 (14.8)
Antihypertensive	714 (37.7)
Glucose lowering	56 (3.0)
Risk scores	
IHA CHD risk score [e]	0.07 (0.07)
IHA CHD risk score ≥10 (%)	480 (26.1)
ASCVD risk score	0.08 (0.07)
ASCVD risk score ≥7.5 (%)	790 (41.7)
CV health score	7.29 (2.09)
Carotid ultrasound	
Maximal plaque category	
No	462 (24.4)
Minimal	1121 (59.2)
Significant	311 (16.4)
Plaque number	2.2 (1.8)
TPA, mm^2	43.9 (33.9)
CCA-IMT, mm	0.82 (0.12)

TC, total cholesterol; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein; BMI, body mass index; SBP, systolic blood pressure; DM2, type 2 diabetes mellitus; CHD, coronary heart disease; MI, myocardial infarct; IHA, Icelandic Heart Association; ASCVD, atherosclerotic cardiovascular disease; CV health score, cardiovascular health score; TPA, total plaque area; CCA-IMT, common carotid artery-intima media thickness.
[a] LDL could not be calculated for 12 participants.
[b] Missing information on 67 subjects.
[c] Missing information on 48 subjects.
[d] Missing information on 3 subjects.
[e] Missing information on 51 subjects.

3.1. New plaque formation

3.1.1. Participants with no plaque

Table 2 shows the association between risk factors at visit 1 and plaque formation. Among participants with no plaque (n = 462) at visit 1, 137 developed at least one plaque between visits. The risk of plaque formation was associated with sex, TC, LDL, TG, non-HDL, waist and former smoker. The association with CRP was borderline statistically significant (p=0.050). Physical activity was associated with lower risk of plaque formation. Every 5% increase in 10 year IHA-CHD risk score was associated with 31% (95% CI 19–44%) greater risk of plaque formation, and the corresponding value for ASCVD was 18% (95% CI 10–27%). Every one unit increase in CV health score was associated with reduced risk of plaque formation by 8% (95% CI 2–14%). In multivariable analyses, LDL (RR 1.27, 95% CI 1.09–1.49) was the only risk factor associated with plaque formation when adjusting for age, sex, glucose, CRP, waist, SBP, smoking status, family history of MI, physical activity, statin and antihypertensive medication use (Supplemental Table 2).

3.1.2. Participants with plaque

Of those with plaque present at visit 1 (n = 1432), 374 participants had developed at least one new plaque at visit 2. The average plaque number was 2.9 (SD 1.5) and 3.2 (SD 1.5) at visit 1 and 2, respectively. The risk of plaque formation was greater in those with metabolic syndrome, but reduced in older participants and in those using statins (Table 2). The association with CV health score was borderline statistically significant (p=0.058), where for every one unit increase in CV health score, the risk of plaque formation was reduced by 4% (95% CI 0–8%). In multivariable analyses, statin use (RR 0.74, 95% CI 0.55–1.00) and older age (RR 0.89, 95% CI 0.81–0.97) were associated with plaque formation when adjusting for sex, LDL, SBP, smoking status, family history of MI, statin and antihypertensive medication use (Supplemental Table 3).

3.1.3. Total sample

In a combined analysis of all participants, risk of plaque formation was associated with sex, TC, LDL, TG, non-HDL, SBP, PP, smoking and metabolic syndrome. Physical activity and statin use were associated with lower risk of plaque formation. Every 5% increase in the 10-year IHA-CHD risk score was associated with 6% (95% CI 1–12%) greater risk of plaque formation. Every one-unit increase in CV health score reduced the risk of plaque formation by 5% (95% CI 2–8%). No risk factor was associated with plaque formation in a multivariable analysis (Supplemental Table 4).

Table 2
Predictors of new plaque formation. Age, sex and time adjusted associations.

	No plaque at visit 1 (137/462)[a]	Plaque at visit 1 (374/1432)[a]	Total sample[b] (511/1894)[a]
	RR (95% CI)	RR (95% CI)	RR (95% (CI)
Sex, men[c]	**1.37 (1.04–1.81)***	1.14 (0.96–1.36)	**1.19 (1.03–1.38)***
Age, 5 years[d]	1.14 (0.99–1.31)	**0.89 (0.82–0.98)***	0.95 (0.88–1.03)
TC, mmol/L	**1.17 (1.01–1.36)***	1.05 (0.97–1.15)	**1.09 (1.01–1.17)***
HDL, SD = 0.4 mmol/L	0.88 (0.75–1.03)	0.98 (0.89–1.07)	0.95 (0.88–1.02)
LDL, mmol/L	**1.22 (1.05–1.43)***	1.06 (0.97–1.16)	**1.10 (1.02–1.19)***
Log TG, mmol/L (IQR)	**1.48 (1.13–1.92)****	1.08 (0.91–1.29)	**1.18 (1.02–1.37)***
Non-HDL, mmol/L	**1.23 (1.07–1.40)****	1.06 (0.98–1.15)	**1.11 (1.03–1.19)****
Glucose, mmol/L	1.13 (0.99–1.28)	0.99 (0.90–1.09)	1.02 (0.94–1.10)
Log CRP, mg/l	1.14 (1.00–1.31)	1.02 (0.93–1.11)	1.05 (0.97–1.13)
BMI, 5 kg/m^2	1.09 (0.94–1.26)	1.03 (0.94–1.13)	1.05 (0.97–1.13)
Waist, 10 cm	**1.12 (1.00–1.25)***	1.00 (0.93–1.07)	1.03 (0.97–1.09)
SBP, 10 mmHg	1.06 (0.98–1.14)	1.04 (0.99–1.09)	**1.05 (1.00–1.09)***
DBP, 5 mmHg	1.00 (0.93–1.08)	1.00 (0.96–1.05)	1.01 (0.97–1.05)
PP, 5 mmHg	1.04 (0.99–1.10)	1.03 (0.99–1.06)	**1.03 (1.00–1.06)***
Hypertension	1.02 (0.77–1.37)	0.97 (0.81–1.16)	0.98 (0.85–1.15)
DM2	1.13 (0.59–2.20)	0.89 (0.61–1.30)	0.93 (0.67–1.30)
Smoking status			
Former	**1.38 (1.02–1.87)***	1.13 (0.92–1.39)	1.18 (0.99–1.40)
Current	1.28 (0.81–2.00)	1.23 (0.97–1.55)	**1.25 (1.01–1.53)***
CHD	1.08 (0.36–3.23)	0.74 (0.50–1.10)	0.73 (0.50–1.07)
Family history of MI	1.29 (0.97–1.72)	0.87 (0.72–1.03)	0.96 (0.83–1.12)
Physically active	**0.75 (0.56–1.00)***	0.87 (0.73–1.04)	**0.83 (0.72–0.97)***
Metabolic syndrome	1.34 (0.97–1.84)	**1.22 (1.01–1.46)***	**1.25 (1.06–1.47)****
Medication use			
Statins[e]	1.12 (0.70–1.78)	**0.72 (0.55–0.95)***	**0.77 (0.61–0.98)***
Antihypertensive	1.00 (0.73–1.36)	0.95 (0.79–1.14)	0.95 (0.81–1.12)
Education			
Elementary	1.01 (0.68–1.50)	0.95 (0.75–1.21)	0.96 (0.78–1.18)
High school	1.01 (0.72–1.41)	0.88 (0.71–1.08)	0.91 (0.76–1.08)
Junior college	0.91 (0.54–1.52)	0.94 (0.67–1.32)	0.93 (0.70–1.24)
Risk scores[f]			
IHA-CHD, per 5%	**1.31 (1.19–1.44)*****	1.01 (0.95–1.08)	**1.06 (1.01–1.12)***
ASCVD, per 5%	**1.18 (1.10–1.27)*****	1.01 (0.95–1.07)	1.05 (1.00–1.10)
CV health score, 1 unit	**0.92 (0.86–0.98)***	0.96 (0.92–1.00)	**0.95 (0.92–0.98)****
CCA-IMT, SD = 0.12 mm	1.12 (0.94–1.33)	0.96 (0.87–1.05)	0.98 (0.91–1.07)

*$p < 0.05$; **$p < 0.01$ and ***$p < 0.001$.
[a] Number of participants with new plaque/total number in analysis.
[b] The analysis for total sample is also adjusted for plaque status at visit 1.
[c] Association adjusted for age.
[d] Association adjusted for sex.
[e] Number of statin users in: (i) participants with no plaque at visit 1, plaque formation n = 13 (9.5%), and no plaque formation n = 23 (7.1%); (ii) participants with plaque at visit 1, new plaque formation n = 48 (12.8%) and no new plaque formation n = 197 (18.6%).
[f] Unadjusted association.

3.2. TPA progression

In participants with plaque at visit 1, mean TPA was 43.9 (SD 33.9) mm^2 and 54.4 (SD 39.9) mm^2 ($p < 0.001$), at visit 1 and 2,respectively. After four years, the mean absolute change was 10.4 mm^2 (median 7.1 mm^2) and the relative change was 38.8% (median 20.2%). Statin use at visit 1 was the only factor associated with the TPA progression (Supplemental Table 5), where those not on treatment tended to have a greater progression rate. The estimated TPA progression rate was 17.3% in statin users, and compared with those not on treatment, the difference in progression rate was 5.7% (SE 2.6%, p=0.029). This result remained significant after adjusting for LDL, CRP, SBP, BMI, DM2, smoking status, CHD, family history of MI and antihypertensive medication use at visit 1 (data not shown).

We performed an additional analysis examining the effects of treatment and risk factor control at visit 1 on TPA progression rate (Fig. 1 and Supplemental Table 6). Participants were stratified into four groups on the basis of statin treatment and LDL level at visit 1 (Fig. 1A). Compared with participants on statins with LDL ≥3.0 mmol/L, the TPA progression rate was 12.2% (SE 5.6%, p=0.03) lower in those on statins with LDL<3.0 mmol/L. Participants not on statins had lower TPA progression rate than those on statins, with LDL ≥3.0 mmol/L, but the difference was not statistically significant. The trends were similar but not statistically significant for non-HDL (Fig. 1B).

In a similar analysis for antihypertensive treatment and blood pressure (BP), TPA progression rate was 6.8% (SE 3.3%) lower in those on treatment with BP < 140/<90 (p=0.04) compared with those on treatment with BP = 140 and/or 90 (Fig. 1C). Participants not on treatment had similar progression rate as those on treatment with BP = 140 and/or 90.

3.3. CCA-IMT progression

Mean CCA-IMT was 0.82 (SD 0.12) mm and 0.85 (SD 0.12) mm at visit 1 and 2, respectively. The mean absolute change was 0.03 mm and the relative change 3.9%. CCA-IMT progression rate was 1.6% (SE 0.5%, p=0.004) greater in those not on statins compared with those on statins, 1.3% (SE 0.4%, $p < 0.001$) greater in those not on antihypertensive treatment compared with those on treatment, and 1.1% (SE 0.4%, p=0.004) greater in those free of hypertension compared with hypertensive participants (Supplemental Table 7).

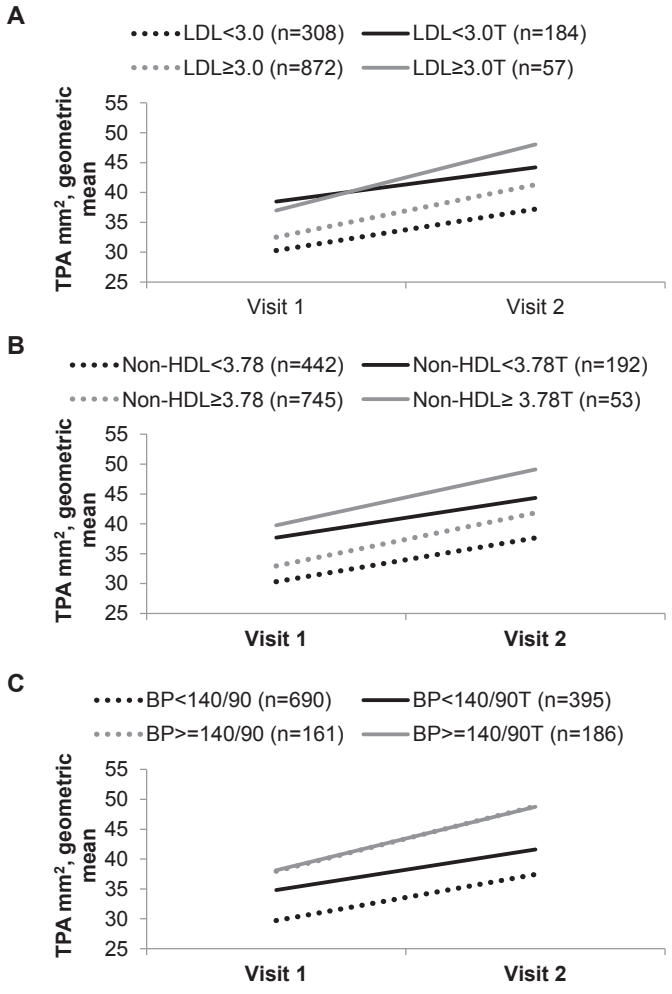

Fig. 1. Participants were stratified into four groups on the basis of medical treatment and risk factor level at visit 1, to examine the effects of risk factor control on TPA progression rate.
Solid lines represent treatment (T), and dotted lines no treatment. Grey lines represent risk factor values above the cut-off point and black lines the value below. (A) Statin treatment and LDL level < or ≥3.0 mmol/L. (B) Statin treatment and non-HDL level < or ≥3.78 mmol/L. (C) Antihypertensive treatment and blood pressure (BP) level where SBP<140 and DBP<90, or one or both values are ≥140/90 mmHg.

4. Discussion

Different risk factors were associated with plaque formation in participants with no plaque at visit 1 and in those with plaque at visit 1. LDL was the primary factor associated with plaque formation in participants free of plaque at visit 1, but other associated factors included sex, triglycerides, waist, former smoker and physical activity. In those with plaque at visit 1, new plaque formation was positively associated with metabolic syndrome but inversely associated with age and statin treatment. The effect of statin treatment was reflected in lower relative total plaque area progression rate in those with plaque at visit 1, but no other risk factor was associated with this outcome. Similarly, the relative common carotid intima-media thickness progression rate was associated with medication use, where the progression rate was lower in those using statins or antihypertensive medications.

Infiltration and retention of LDL in the arterial wall is considered to be the initial event in the development of atherosclerotic lesions [20]. The current findings show a strong relation between LDL level and the formation of plaque in participants free of plaque at visit 1, suggesting that LDL is a key factor in the pathogenesis of atherosclerosis. Men sex, waist, former smoker, CRP and physical activity were also associated with carotid plaque formation; however, these associations lost statistical significance in a multivariable analysis. Our results correspond partially to those of previous studies where plaque formation was associated with older age, men sex, total cholesterol, smoking, systolic blood pressure, family history of atherosclerosis and CRP [21,22].

Our observation that risk scores are predictive of new plaque formation in people with no plaque at first visit suggests that application of those risk scores to the general practitioner's clinic may be of value to determine who should be given more attention to modify or treat individual risk factors. Although treating with statins should clearly be considered.

Treatment with statins is the most effective medical therapy for lowering LDL levels and it has been shown to reduce the risk of cardiovascular events in a number of different populations [23]. Post-trial follow-up of participants enrolled in a primary prevention trial showed a continued reduction in cardiovascular events in those assigned to statin treatment compared with placebo, 15 years after the termination of the trial [24]. There is also some evidence that people with moderate risk of CHD, but one abnormal risk factor, could benefit from such intervention as part of primary prevention [25]. However, the mechanisms by which statin treatment may reduce cardiovascular event rates have not been fully elucidated, but reduction in plaque burden, change in composition towards a more stable plaque, and statins pleiotropic effects, such as reduction in inflammation, are suggested to play important roles [3,26–28]. In the current study, statin treatment at visit 1 reduced the risk of new plaque formation in those with plaque at visit 1 and, as a result of that, the relative TPA progression rate was lower in statin users. Furthermore, the relative CCA-IMT progression rate was lower in statin users. These results are concordant with those reported in the Tromsø study, where TPA and cIMT progression over 13 years was lower in long-term and any-time statin users than in non statin users [29].

The results of therapies in the general population tend to be less effective than in clinical trials [3]. In the current study, 76% of statin users achieved LDL<3.0 mmol/L and 68% of antihypertensive medication users had blood pressure below 140/90 mmHg. In an additional analysis, we examined the combined effects of treatment and risk factor control. In the analysis for statin treatment and LDL level, the relative TPA progression rate was lowest in those on statin treatment who achieved an LDL level<3.0 mmol/L, but greatest in those on statin treatment with LDL level≥3.0 mmol/L. This effect was also reflected in a subgroup analysis (Supplemental Table 5), where men with DM2 had lower relative progression rate than those free of DM2, but men with DM2 had substantially lower LDL level than those free of DM2 (2.7 *vs.* 3.4 mmol/L for all, and 2.0 *vs.* 2.5 mmol/L in statin users). Imaging studies on CHD patients show that to attenuate the progression of atherosclerosis, the LDL level has to be reduced below 2.6 mmol/L [3,28,30], but other risk factors of atherosclerosis, including blood pressure, may also have to be targeted [3,30].

Apart from medical treatment of dyslipidaemia and hypertension, none of the examined risk factors or risk scores were associated with the relative progression of TPA or CCA-IMT. However, previous population studies have demonstrated an association between risk factors at baseline and the absolute change in TPA [5] and CCA-IMT [31].

The strengths of this study are the community-based design, equal representation of both sexes and prospective data collection using standardized methodology. A limitation of this study is that changes in risk factors and medical treatments between visits might dilute the association between risk factors at visit 1 and the

relative progression rate in TPA and CCA-IMT. A short interval between visits may also be a limitation.

4.1. Conclusions

The associations between risk factors and carotid plaque formation differed by plaque status at visit 1. More factors were associated with plaque formation in participants with no plaque at visit 1, and none of the risk factor was associated with plaque formation in both groups, although the primary associated factors are related (LDL in those with no plaque and statin treatment in those with plaque). The traditional risk factors were not associated with the relative TPA progression. Medical intervention with statins can reduce the relative progression rate of TPA in the general population with low grade of atherosclerosis, supporting statin use to slow progression of atherosclerosis.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

RS, VG and TA drafted the manuscript. RS and TA performed the statistical analysis. VG, TA, BT, GE, SS and GB designed the study and collected the data. All authors reviewed and revised the manuscript, and approved the final version.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2017.12.005.

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