Repeated Measurements of Carotid Atherosclerosis and Future Risk of Venous Thromboembolism. The Tromsø Study

Birgit Småbrekke[1], Ludvig Balteskard Rinde[1], Erin Mathiesen Hald[1,2], Inger Njølstad[1, 3], Ellisiv B. Mathiesen[1,4,5], Stein Harald Johnsen[4,5], John-Bjarne Hansen[1,2], Sigrid K. Brækkan[1,2], Willem M. Lijfering[6]

[1]K.G. Jebsen – Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[2]Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

[3]Epidemiology of Chronic Diseases Research Group, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[4]Brain and Circulation Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[5]Department of Neurology, University Hospital of North Norway, Tromsø, Norway

[6] Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands

Correspondence to: Birgit Småbrekke, B.Sc. K.G. Jebsen Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT The Arctic University of Norway, N-9037, Norway

E-mail: birgit.smabrekke@uit.no, telephone: +4798693789

Summary

Background: Whether a relationship between atherosclerosis and subsequent venous thromboembolism (VTE) exists is controversial.

Objective: To investigate the association between carotid atherosclerosis and VTE using repeated measurements of intima media thickness (IMT) and total plaque area (TPA) in participants recruited from the general population.

Methods: Participants were recruited from the fourth (1994-1995), fifth (2001-2002) and sixth (2007-2008) surveys of the Tromsø study. In total, 10426 participants attended, for whom measurements of carotid IMT and TPA and potential confounders were updated at each available survey. Time-varying Cox-regression models were used to calculate hazard ratios (HR) of VTE across various levels of IMT and TPA adjusted for age, sex and body mass index.

Results: There were 368 incident VTE events during a median follow-up of 10.8 years. Participants with increasing IMT were on average older and had a less favorable cardiovascular risk profile. There was no association between tertiles of increasing TPA and risk of VTE in the time-varying model, and increasing IMT was not associated with increased risk of VTE (HR 0.96, 95% CI 0.86-1.07). Neither plaque formation nor plaque progression was associated with risk of VTE (HR 1.00, 95% CI 0.98-1.02 and HR 0.96, 95% CI 0.84-1.11, respectively).

Conclusion: Carotid IMT and TPA was not associated with increased risk of VTE in time-varying analyses. Furthermore, there was no association between plaque initiation or plaque progression and subsequent VTE.

Key words: Atherosclerosis – Cohort studies – Repeated measurements – Risk factors – Venous thromboembolism

Essentials

- The relationship between atherosclerosis and venous thromboembolism (VTE) is controversial
- In total, 10426 participants recruited from the general population were included
- Carotid intima media thickness and total plaque area was not associated with VTE
- There was no association between plaque initiation or plaque progression and subsequent VTE

Introduction

Although medical textbooks consider venous thromboembolism (VTE) and arterial cardiovascular disease as different disease entities [1], Virchow's triad (1856) postulates that the pathophysiology of thrombosis, either venous or arterial, is an interplay between 1) stasis of the blood, 2) hypercoagulability, and 3) vessel wall injury [2]. The vascular component of Virchow's triad has been much less studied in the etiology of VTE as compared with arterial cardiovascular disease where vessel wall injury is an established precursor of disease.

Interestingly, recent studies have shown that arterial cardiovascular diseases, such as myocardial infarction and ischemic stroke, are associated with an increased risk of VTE [3-5]. In addition, in a landmark study from 2003, Prandoni *et al.* reported that atherosclerosis, measured by total plaque area [TPA], was twice as prevalent in patients with unprovoked venous thrombosis as in age and sex matched controls [6]. These findings suggested that atherosclerosis could be a shared risk factor for arterial cardiovascular disease and VTE. Although the association between atherosclerosis and arterial cardiovascular disease is well established [7-9], the association between atherosclerosis and VTE remains controversial. For instance, case-control studies are not designed to reveal the direction of the association and does not enable interpretations on causality due to the undetermined temporal sequence between exposure and outcome. Furthermore, the association between atherosclerosis and VTE might be explained by presence of confounding risk factors, such as increasing age and obesity [10].

Previous cohort studies did not show any association between atherosclerosis and subsequent VTE [11-13]. However, these cohorts were based on a single measurement of

TPA and carotid intima media thickness (IMT) obtained at the beginning of a follow-up period that lasted for more than 10 years. Because atherosclerosis may develop over time, a long follow-up with several years between the baseline measurement and the event could introduce regression dilution bias and thereby lead to underestimation of the true association [14, 15]. Therefore, a small effect of atherosclerosis on VTE risk could be masked in traditional cohort studies with single measurements and long-term follow-up. The potential problem of regression dilution could be overcome by utilizing repeated assessments of the atherosclerosis status within the same individuals during follow-up. This will provide a more accurate estimation of the risk status at the time before the outcome occurs.

We therefore aimed to investigate the association between the presence, formation and progression of carotid atherosclerosis and VTE using a large prospective cohort with repeated measurements of IMT and TPA, in participants recruited from the general population.

Methods

Study population

Participants were recruited from the fourth, fifth and sixth surveys of The Tromsø Study, conducted in 1994-95, 2001-02 and 2007-08, respectively. In the fourth study, all inhabitants aged 55-74 years and a random 5-10% sample in the other age groups >24 years, were invited to a second, more extensive examination, including ultrasound scanning of the carotid artery [16]. Subjects who attended the second visit of Tromsø 4, in addition to random samples within different age-groups, were eligible for the second

visit of Tromsø 5 and in Tromsø 6. A detailed description of the Tromsø Study has been published elsewhere [17]. Participants with a previous history of VTE were excluded. In addition, participants attending the ultrasound examination, but with missing information on the measures of carotid atherosclerosis, were excluded. In total, 10426 participants attended an ultrasound examination of the right carotid artery in Tromsø 4, 5 and/or 6 (Figure 1). The study was approved by the regional committee for research ethics in North Norway, and all participants gave their informed, written consent.

Atherosclerotic risk factors and assessment of atherosclerosis

Information on atherosclerotic risk factors was collected by physical examination, blood samples and self-administered questionnaires, and repeated at each survey. Height, weight, blood pressure and non-fasting serum lipids were measured as previously described in detail [18]. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Questionnaires were used to obtain information on use of lipid-lowering drugs, current smoking, diabetes mellitus, physical activity and education.

Ultrasound examination of the right carotid artery was performed for assessment of TPA and IMT. A thorough description of the ultrasonographic examination has been published previously [16, 19-21]. In brief , high-resolution B-mode ultrasonography of the right carotid artery was performed by experienced examiners, with the use of an ultrasound scanner (Acuson Xp10 128 ART equipped with a 7.5 MHz linear-array transducer in Tromsø 4 and 5; and a GE Vivid 7 with a linear 12 MHz transducer in Tromsø 6). The right carotid artery was scanned longitudinally from the level of the

clavicle, through the carotid bulb (bifurcation segment) and the proximal internal carotid segment (ICA) as far downstream as possible. A plaque was defined as a localized protrusion of the vessel wall into the lumen of at least 50% compared to the adjacent IMT. Still images were reported for each plaque and digitized using the Matrox Meteor II frame grabber card and Matrox Intellicam. With the use of Adobe Photoshop 7.0, measurements of plaque area were made by outlining the perimeter of the plaque, and the plaque area was calculated as pixel values. For the resolution used in the present study, a plaque area of 167 pixels corresponded to 1 mm^2. In each subject, a maximum of six plaques were registered in the near and far walls of the distal part of the common carotid artery (CCA), bifurcation, and ICA, respectively. TPA was calculated as the sum of all plaques. IMT was defined as the average of the mean IMT values of the near and far wall of the CCA and far wall of the bifurcation. To minimize variability in IMT during the cardiac cycle, image capturing was standardized by recording images at the top of the R wave in an ECG signal. Plaque initiation was defined as development of new plaques at follow-up in vessels without plaques at the previous examination, and plaque progression as the difference in TPA two measurements. Participants with negative progression were included in the no progression group [16, 22].

Identification and validation of VTE

All incident VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. The University Hospital of North Norway is the only hospital in the region, and all diagnostic radiology and hospital care is provided

exclusively by this hospital. The medical record for each potential case of VTE was reviewed by trained personnel, and a VTE event was considered adjudicated when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (by compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, autopsy), and resulted in a VTE diagnosis that required treatment, as previously described in detail [23]. DVTs were recorded in the upper and lower extremities including inferior vena cava, and at unusual sites (the mesenteric veins, portal veins, and in the venous sinuses). VTE cases from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or a significant condition contributing to death.

Statistical analysis

Statistical analyses were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA). As the distribution of TPA was skewed to the right, TPA was square root transformed to approximate normal distribution for the analyses in which TPA was used as a continuous variable. Cox proportional hazard regression models were used to assess the association between atherosclerosis (i.e. TPA and IMT) and VTE in a time-varying analysis. In these analyses, all participants contributed with one or more observation periods, each lasting from one measurement until the next, or until a censoring event (i.e. migration, death or end of study period) occurred. The follow-up ended on December 31, 2012. Atherosclerosis measurements and other risk factors were updated at every survey, when available, and used as time-varying covariates. Of the 10426 participants included in the study, 5154 participants attended two or three surveys,

which resulted in a total number of 18154 observation periods for the time-varying analyses. For participants attending only one survey, measurements were valid from baseline to the first censoring event. Age was used as time-scale, with the participants' age at study enrolment defined as entry-time and age at the censoring event as exit-time. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated, and all analyses were adjusted for age (as time-scale), sex and BMI. The proportional hazards assumption was confirmed by the Schoenfeld's global test. Statistical interactions between the covariates and the main exposures were tested by including the cross-product terms in the proportional hazard model, and no interactions were found.

We performed two sensitivity analyses. In the first sensitivity analysis we censored participants at the next survey they did not attend. This analysis was performed to ensure that the carry-on of measurements in participants who only attended one survey did not dilute the effect in the original analyses. Statin use may potentially confound the association between atherosclerosis and VTE. Since we did not have sufficient information on statin use among the Tromsø 4 participants, the second sensitivity analysis was restricted to participants who did not use lipid-lowering drugs in Tromsø 5 or Tromsø 6.

Results

During a median follow-up of 10.8 years, 368 participants experienced an incident VTE event. Baseline characteristics of traditional atherosclerotic risk factors and TPA across quartiles of carotid IMT are shown in Table 1. In general, all traditional atherosclerotic risk factors changed for the worse across increasing quartiles of IMT. Participants in the

fourth quartile had higher blood pressure, BMI, triglycerides and total cholesterol, and lower HDL cholesterol, compared with participants in the first quartile. Participants in the highest quartile also comprised a higher proportion of males as well as participants with hypertension and self-reported diabetes, and a lower proportion of physically active and highly educated participants. Each quartile of IMT comprised approximately the same proportion of current smokers.

HRs for VTE by TPA and IMT as continuous and categorical variables are shown in Table 2. There was no association between TPA as a continuous variable and VTE (HR per standard deviation [SD] increase 0.99, 95% CI 0.90-1.11), and no linear trend of increased risk of VTE across increasing tertiles of TPA when no plaque was set as the reference group (*P* for trend=0.9). IMT was not associated with risk of VTE (HR per SD increase 0.96, 95% CI 0.86-1.07) and the *P* for trend across increasing quartiles of IMT was 0.7. Additional adjustment for total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus and diastolic blood pressure had a negligible effect on the risk estimates (HR per SD increase for TPA and IMT were 0.98 [95% CI 0.88-1.09] and 0.96 [0.86-1.07], respectively). Similar results were observed when the participants were censored at the first survey they did not attend (Supplementary table 1) and when the analyses were restricted to participants not using lipid-lowering drugs in Tromsø 5 or 6 (Supplementary table 2).

HR for VTE according to formation and progression of carotid plaques are displayed in Table 3. There was no association between plaque formation and future risk of VTE (HR 1.00, 95% CI 0.98-1.02). Progression of carotid plaque size was not associated with VTE (HR 0.96, 95% CI 0.84-1.11), and there was no linear trend of VTE

risk across tertiles of plaque progression in TPA (*P* for trend=0.5). The multivariable adjusted model showed similar results for both plaque formation and plaque progression.

Discussion

Previous case-control studies have reported an association between carotid plaques and VTE [6, 24], whereas later cohort studies [11-13] have not shown any association between carotid atherosclerosis and future risk of VTE. A potential limitation of cohorts with long follow-up is that changes in atherosclerosis over time could lead to an underestimation of the true association between atherosclerosis and VTE [14, 15]. To investigate whether the apparent discrepant results in case-control and cohort studies could be explained by regression dilution bias, we conducted a study with repeated measurements of carotid atherosclerosis within the same individuals during follow-up. We found that measures of carotid atherosclerosis were not associated with future risk of VTE. Our findings suggest that atherosclerosis as measured with carotid ultrasound is not an intermediate for the association between arterial and venous thrombosis.

Our results are in accordance with previous cohort studies on the association between atherosclerosis and VTE using time-fixed analyses [11-13]. The Atherosclerosis Risk in Communities **(**ARIC) study, which included 13,000 subjects aged 45-64 years with a median follow-up time of 12.5 years, found no association between increased carotid IMT or presence of carotid plaques, and VTE risk [11]. The Cardiovascular Health Study (CHS) study followed 4100 subjects aged 65 and older over 12 years, and measured subclinical atherosclerosis by IMT, presence of carotid plaques, ankle brachial index and ECG abnormalities. In this study, subclinical atherosclerosis was not associated

with increased risk of overall or unprovoked VTE. Unexpectedly, they found an inverse relationship between high-risk carotid plaques and VTE [12]. Furthermore, a previous study from the Tromsø cohort with 15.4 years of follow-up, including more than 6200 participants, found that single measurements of IMT and TPA at baseline were associated with future myocardial infarction, but not VTE [13].

The finding of no association between atherosclerosis and VTE in cohort studies is in contrast to the results from two previous case-control studies [6, 24]. Prandoni *et al* reported a higher frequency of carotid plaques in 153 patients with unprovoked VTE compared to 146 patients with provoked VTE and 150 hospitalized controls. In this study plaques were defined as a protrusion into the vessel lumen of at least 2 mm (6). In a study including 89 cases of unprovoked VTE and 89 controls, Hong *et al* reported an association between coronary artery calcification and VTE (22). Several factors may explain the diverging results from cohorts and case-control studies conducted on this topic. Recruitment of controls that are not fully representative of the source population from which the cases were derived, may result in overestimation of the true effect in case-control studies. This problem is more likely to occur when the size of the control group is small. Moreover, the exposure is measured after the outcome in case-control studies, and therefore the temporal sequence of the events cannot be determined. In conventional cohorts, exposure may change over time and this may lead to underestimation of the true effect. However, with repeated measurements it was possible to update an individual's risk status over time, and consequently get a better estimation of an individual's atherosclerosis status in the period before the VTE diagnosis. Using this

approach, we did not find any association between carotid atherosclerosis measures and VTE risk.

Although some studies have reported associations between atherosclerotic risk factors such as diabetes, hypertension and dyslipidemia, and risk of VTE [25-27], the only atherosclerotic risk factors that have consistently been shown to increase the risk of VTE are age and obesity [18, 28, 29]. A recent meta-analysis of 9 cohorts, including almost 250,000 participants and 5000 VTEs, found no association between traditional, modifiable atherosclerotic risk factors and VTE, using traditional time-fixed Cox regression models adjusted for age, sex and BMI [30]. The only exception was cigarette smoking, which was associated with increased risk of provoked VTE, an association that was possibly mediated through other conditions such as cancer. Furthermore, in a previous report from the Tromsø study, based on repeated measurements of atherosclerotic risk factors, we showed that BMI, but not blood pressure, serum lipid levels, diabetes or smoking, were associated with increased risk of VTE [31].

Major strengths of our study include the prospective design with repeated exposure measurements and long follow-up, the large number of participants recruited from the general population, and the thorough validation and adjudication of VTE. The repeated measurements of atherosclerosis and potential confounders made it possible to update risk status over time, and thereby to reduce the chance of regression dilution bias. The study has some limitations. Unfortunately, we did not have verified baseline information on previous history of VTE among all the study-subjects. We started to identify VTE cases in January 1994, and those who were registered with a recurrent event in the study period (1994-2012), and those who had a VTE shortly before inclusion, were

identified and excluded from the analyses due to previous VTE. Subjects who had a VTE before 1994 and did not experience a recurrence in the study period would not be detected, and consequently, these would be treated as healthy participants during follow-up. As the prevalence of VTE in the general population is relatively low, this would lead to only a small change in the overall number of person-years at risk, and thus would presumably have a negligible influence on the risk estimates. Carotid ultrasonography is operator dependent and prone to measurement errors. However, a previous study found the overall reproducibility of TPA to be good, with small inter-observer mean arithmetic and mean absolute differences [16]. Although the measurement errors in carotid ultrasonography are too big to study progression of atherosclerosis at an individual level, carotid ultrasonography at a population level gives enough power to overcome the measurement variability, and makes it possible to detect even weak associations [16]. Examination of only one carotid artery may potentially introduce misclassification. However, studies comparing ultrasound IMT measurements of the left and right common carotid artery found no significant difference between the sides in the normal population [32, 33]. Furthermore, studies have shown that carotid atherosclerosis correlates well with the general extent of atherosclerotic disease in an individual [34, 35]. Statins has been shown to reduce the risk of VTE in some [36-38], but not all studies [39, 40]. Statin use reduces carotid plaque development and lowers plaque progression [41, 42], and lack of adjustment for statin use could result in underestimation of the association between atherosclerosis and VTE. However, sensitivity analysis restricted to participants who did not use statins showed no association between carotid atherosclerosis and VTE. Aspirin is often prescribed to subjects at risk of cardiovascular disease, but may also prevent venous

thrombosis. However, although aspirin use has been associated with decreased risk of recurrent VTE [43, 44], it has not been associated with reduced risk of incident VTE in population based studies [37, 45].

In conclusion, we found that formation and progression of carotid atherosclerosis, as measured with ultrasound, was not associated with future risk of VTE in time-varying analyses. Our findings suggest that atherosclerosis is not an intermediate for the association between arterial cardiovascular diseases and VTE.

Addendum

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Conceptualization: JBH, SKB, WML

Data curation: IN, EBM, SHJ

Formal analysis: BS, SKB

Funding acquisition: JBH

Methodology: JBH, SKB

Project administration: JBH, SKB, WML

Supervision: JBH, SKB

Visualization: JBH, SB, WML, BS

Writing – original draft: BS

Writing – review and editing: JBH, SB, WML, LBR, EMH, IN, EBM, SHJ

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Table 1. Baseline characteristics of traditional atherosclerotic risk factors across quartiles of carotid intima media thickness (IMT). In total, 10426 participants were included in the study. The Tromsø Study, 1994-2012.

The Tromsø Study	**1st quartile** 0.36-0.73 mm	**2nd quartile** 0.73-0.83 mm	**3rd quartile** 0.83-0.95 mm	**4th quartile** 0.95-2.49 mm
Number of participants, n	2612	2618	2590	2606
VTE events, n	69	92	79	128
Age, years	53.2 ± 10.4	59.1 ± 6.7	61.5 ± 6.6	64.2 ± 6.7
Male sex, %	31.9 (832)	39.5 (1034)	51.1 (1323)	59.2 (1542)
Systolic BP, mmHg	131 ± 19	139 ± 21	144 ± 22	152 ± 23
Diastolic BP, mmHg	78 ± 11	81 ± 12	83 ± 12	85 ± 13
Hypertension, %*	34.0 (887)	50.9 (1331)	62.9 (1626)	75.1 (1956)
BMI, kg/m^2	25.2 ± 3.7	26.4 ± 4.1	26.8 ± 4.0	27.2 ± 4.2
Triglycerides, mmol/L	1.47 ± 0.98	1.61 ± 0.99	1.67 ± 1.01	1.80 ± 1.02
Total cholesterol, mmol/L	6.19 ± 1.23	6.40 ± 1.26	6.43 ± 1.27	6.61 ± 1.35
HDL cholesterol, mmol/L	1.61 ± 0.45	1.59 ± 0.44	1.53 ± 0.42	1.46 ± 0.43
Self-reported diabetes, %	1.6 (42)	2.8 (72)	3.7 (95)	6.0 (155)
Smoking, %	31.6 (823)	26.9 (703)	27.0 (699)	29.2 (761)
Physical activity, % †	32.8 (817)	33.9 (844)	31.6 (776)	25.6 (632)
Education, % ‡	26.1 (653)	23.8 (584)	21.7 (522)	17.4 (426)
Total plaque area, mm^2	0.55 ± 1.29	1.18 ± 1.79	1.98 ± 2.23	3.97 ± 2.68
No plaque, %	82.8 (2163)	65.9 (1725)	50.5 (1307)	21.9 (570)
1st tertile, %	10.7 (280)	18.2 (476)	18.1 (468)	12.7 (330)
2nd tertile, %	4.8 (126)	10.8 (282)	18.8 (488)	25.2 (658)
3rd tertile, %	1.7 (43)	5.1 (135)	12.6 (327)	40.2 (1048)

Values are % (n) or mean ± SD. BP indicates blood pressure; BMI, body mass index; HDL, high-density lipoprotein.

* Hypertension: systolic BP ≥140 or diastolic BP ≥90 or use of antihypertensive medicine

† Hard physical activity 1 hour or more every week

‡Over/equal to 15 years of education (corresponding to 3 years in university or academy)

Table 2. Hazard ratios (HR) with 95% confidence intervals (CI) of venous thromboembolism (VTE) according to total plaque area and intima media thickness using a time-varying Cox regression model. The Tromsø Study 1994-2012.

Risk factors	Events	Person-years	HR (95% CI) †
Total Plaque Area*	368		**0.99 (0.90-1.11)**
No plaque	140	54062	Ref.
1st tertile (1.018-3.506 mm^2)	64	19648	0.93 (0.69-1.29)
2nd tertile (3.506-5.031 mm^2)	78	19141	1.04 (0.79-1.38)
3rd tertile (5.031-15.696 mm^2)	86	18685	1.00 (0.75-1.32)
P for trend			*0.9*
Intima Media Thickness*	368		**0.96 (0.86-1.07)**
1st quartile (0.358-0.743 mm)	58	29229	Ref.
2nd quartile (0.744-0.849 mm)	81	28210	0.95 (0.68-1.34)
3rd quartile (0.849-0.970 mm)	101	27201	1.02 (0.73-1.43)
4th quartile (0.971-2.748 mm)	128	26896	1.07 (0.77-1.50)
P for trend			*0.5*

* Per standard deviation (SD) increase; 1 SD TPA = 2.60 mm^2; 1 SD IMT = 0.19 mm

† Adjusted for age (as time scale), sex and BMI

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by initiation and progression of carotid plaques. The Tromsø Study 1994-2012.

	Model 1 **HR (95% CI) §**	**Model 2** **HR (95% CI) ¶**
Plaque formation*	1.00 (0.98-1.02)	1.00 (0.98-1.02)
Plaque progression†	0.96 (0.84-1.11)	0.96 (0.83-1.11)
No progression‡	Ref.	Ref.
0.010-8.250 mm^2 increase	0.85 (0.42-1.01)	0.68 (0.44-1.05)
8.254-17.8401 mm^2 increase	0.99 (0.68-1.44)	1.00 (0.68-1.46)
17.850-131.734 mm^2 increase	0.85 (0.57-1.25)	0.84 (0.56-1.25)
P for trend	*0.5*	*0.5*

* Initiation of plaque, i.e. increase from 0. Based on TPA measurement

† 1 standard deviation (SD) change in plaque size based on TPA measurement. 1 SD = 13.2 mm^2 increase

‡ Participants with negative change were included in the no progression group.

§ Adjusted for age (as time scale), sex and BMI

¶ Adjusted for age (as time scale), sex, BMI, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus and diastolic blood pressure

Figure 1. Study population. Study population recruited from the second visit at the fourth, fifth and sixth surveys of The Tromsø Study, conducted in 1994-95, 2001-02 and 2007-08, respectively.