Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism

The Tromsø Study


Objective—Recent studies have suggested that arterial and venous thrombosis share common risk factors. Although carotid atherosclerosis is associated with arterial cardiovascular events, its role in venous thromboembolic disease is unclear. We wanted to investigate and compare the effect of carotid atherosclerosis on the risk of myocardial infarction (MI) and venous thromboembolism (VTE) in a general population, taking into account competing risks.

Approach and Results—Mean intima-media thickness and total plaque area in the right carotid artery were measured with ultrasound in 6257 people aged 25 to 84 years who participated in a population-based health study, the Tromsø Study, from 1994 to 1995. Incident MI and VTE events were registered from date of enrollment to end of follow-up on December 31, 2010. Cox proportional hazards regression models using age as time scale were used to estimate cause-specific hazard ratios with 95% confidence intervals for MI and VTE by increasing levels of intima-media thickness and total plaque area. There were 894 incident MI cases and 256 VTE events during a median of 15.4 years of follow-up. The risk of MI increased significantly across quartiles of mean intima-media thickness (P for trend <0.001) and with increasing total plaque area (P for trend <0.001), but neither intima-media thickness (P for trend=0.94) nor total plaque area (P for trend=0.45) was associated with VTE risk in multivariable-adjusted analysis.

Conclusions—In this study, carotid atherosclerosis was strongly associated with future MI but not with VTE. Our findings suggest that carotid atherosclerosis does not represent a link between arterial and venous thrombosis. (Arterioscler Thromb Vasc Biol. 2014;34:226-230.)

Key Words: atherosclerosis ■ carotid stenosis ■ epidemiology ■ myocardial infarction ■ venous thromboembolism

Recent studies have demonstrated an association between arterial cardiovascular disease and venous thromboembolism (VTE), but the mechanisms underlying these observations are not fully clarified. The 2 conditions share common risk factors, such as age, obesity, and family history of myocardial infarction (MI), but the effect of traditional atherosclerotic risk factors, such as hypertension, dyslipidemia, smoking, and diabetes mellitus, on the risk of VTE remains controversial.

On the arterial side, ultrasonographic measurements of intima-media thickness (IMT) and the presence of plaques in the carotid arteries are widely used as surrogate markers of cardiovascular disease. The presence of carotid atherosclerosis, as measured by IMT and total plaque area (TPA), is strongly associated with future arterial cardiovascular events. Prandoni et al also found a higher prevalence of carotid atherosclerosis in patients with unprovoked VTE than in age-matched and sex-matched hospitalized controls. Because atherosclerosis is associated with activation of platelets, blood coagulation, and increased fibrin turnover, it is plausible that such a procoagulant state may trigger VTE. However, later prospective studies failed to confirm an association between carotid atherosclerosis and future risk of VTE.

A competing risk approach to calculate cause-specific hazards for 2 possibly interrelated diseases has several advantages. Calculating failure time to the first event eliminates the opportunity that one event alters the risk of another and that apparent common risk factors are confounders by acting as a proxy for cause. Furthermore, confirmation of the already established relationship between carotid atherosclerosis and

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risk of MI also ensures appropriate measurement and classification of the exposure variable (carotid atherosclerosis measures). To date, no other study has examined the effect of carotid atherosclerosis on VTE risk while accounting for the competing risk of MI. In the present cohort study, we sought to assess the effect of carotid atherosclerosis, as measured by IMT and TPA, on the risk of future MI and VTE in a general population using a competing risk model.

Materials and Methods
Materials and Methods are available in the online-only Supplement.

Results
The mean baseline age was 59.9 years (range, 25–84 years; standard deviation [SD], 10.3 years), and 52.2% (n=3264) were women. During a median follow-up of 15.4 years, there were 894 incident MIs and 256 incident VTEs. Thirty-nine participants experienced development of both MI and VTE, of which 28 had MI and 11 had VTE as their first event, respectively. The overall crude incidence rates were 11.4 (95% confidence interval [CI], 10.7–12.2) per 1000 person-years for MI and 3.3 (95% CI, 2.9–3.7) per 1000 person-years for VTE.

Table 1 shows the baseline distribution of atherosclerotic risk factors in participants who did not develop any event during follow-up and in those who developed MI and VTE, respectively. People who experienced either an MI or a VTE event were older and had a higher body mass index and higher total cholesterol than those who did not experience an event during follow-up. Participants with MI were more frequently men, had diabetes mellitus, were smokers, and had higher triglycerides and lower high-density lipoprotein cholesterol. Hypertension was most prevalent among participants with MI, followed by participants with VTE.

Plaques were present in 2985 participants (47.9%) at baseline. Table 2 shows crude incidence rates and cause-specific hazard ratios (HR) with 95% CI for MI and VTE by plaque status (no plaque and tertiles of TPA). Using age as a time scale, increasing TPA was associated with MI risk (P for trend <0.001) in both crude analysis and after adjustment for sex, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking, diabetes mellitus, and hypertension (P for trend <0.001). In multivariable analysis, participants in the upper tertile of TPA had a 1.70-fold increase in MI risk compared with participants without plaques at baseline (95% CI, 1.42–2.03; Table 2). In contrast, TPA was not associated with VTE in either crude-adjusted or multivariable-adjusted analysis (Table 2). Excluding participants with high TPA measurements (values ≥2 SD above the upper tertile mean) did not alter the risk estimates (results not shown).

Comparable findings were observed for mean IMT (Table 3). IMT was significantly associated with MI in both crude-adjusted and multivariable-adjusted analyses (P for trend <0.001), with an HR of 1.88 (95% CI, 1.45–2.459) for participants in the upper quartile versus the lower quartile of mean IMT. In contrast, IMT was not associated with VTE risk in either crude-adjusted or multivariable-adjusted analysis (P for trend=0.82 and 0.57, respectively). When examining IMT as a continuous variable, results were similar. Increasing IMT remained associated with MI after multivariable adjustment (HR per 1-SD increase in IMT 1.17 [95% CI, 1.10–1.25]) but not with VTE (HR per 1-SD increase in IMT 0.94 [95% CI, 0.81–1.09]; Table 3). Comparable results were found for plaque-free mean common carotid artery far wall IMT, which was associated with MI after multivariable adjustment (HR per 1-SD increase in IMT 1.17 [95% CI, 1.10–1.25]) but not with VTE (HR per 1-SD increase in IMT 1.02 [95% CI, 0.99–1.05]; data not shown in Table).

Examining the assumption of proportional hazards using Schoenfeld residuals revealed that IMT violated the assumption of proportional hazards, suggesting that the effect of IMT

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
</tr>
<tr>
<td>HR</td>
</tr>
<tr>
<td>IMT</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>TPA</td>
</tr>
<tr>
<td>VTE</td>
</tr>
</tbody>
</table>

Table 1. Baseline Distribution of Traditional Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No Event (n=5107)</th>
<th>MI (n=894)</th>
<th>VTE (n=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.9±10.6</td>
<td>64.3±7.4</td>
<td>63.6±7.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>46</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8±3.9</td>
<td>26.7±4.3</td>
<td>26.8±3.7</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.6±1.30</td>
<td>6.9±1.27</td>
<td>6.8±1.24</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.5±0.87</td>
<td>1.75±1.12</td>
<td>1.51±0.78</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.5±0.45</td>
<td>1.44±0.42</td>
<td>1.53±0.41</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>133±21</td>
<td>148±22</td>
<td>144.5±21</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>79.5±12</td>
<td>83.7±12</td>
<td>82.2±12</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>45.3</td>
<td>67.0</td>
<td>55.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>4.6</td>
<td>11.5</td>
<td>8.2</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>32.4</td>
<td>38.7</td>
<td>28.7</td>
</tr>
</tbody>
</table>

Numbers are mean±SD or percentage. The Tromsø Study, 1994 to 2010. BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; MI, myocardial infarction; and VTE, venous thromboembolism.
is time-dependent (ie, dependent on age). To assess this association, we examined the risk of MI in people younger than and older than 60 years of age. In agreement with previous reports, increased IMT conferred a higher relative risk of MI in younger (<60 years) than in older (≥60 years) participants (multivariable HR, 1.35 [95% CI, 1.05–1.72] and HR, 1.15 [95% CI, 1.08–1.24] per 1-SD increase in IMT, respectively).

For venous thrombosis, the multivariable HRs per 1-SD increase in IMT were not significant for either of the 2 groups (HR for people aged <60 years, 0.90 [95% CI, 0.48–1.24] and HR for people aged ≥60 years, 0.93 [95% CI, 0.80–1.09]).

### Discussion

In this study, carotid atherosclerosis, as measured by carotid IMT and TPA, was clearly associated with risk of future MI but not with VTE. The risk estimates for MI increased over levels

<table>
<thead>
<tr>
<th>Mean IMT (mm±SD)</th>
<th>Events</th>
<th>Crude IR (95% CI)</th>
<th>Model 1* HR (95% CI)</th>
<th>Model 2† HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.65±0.06</td>
<td>83</td>
<td>3.9 (3.2–4.8)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Q2</td>
<td>0.78±0.03</td>
<td>179</td>
<td>8.8 (7.6–10.2)</td>
<td>1.62 (1.24–2.11)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.89±0.04</td>
<td>263</td>
<td>14.1 (12.5–15.9)</td>
<td>2.31 (1.79–2.98)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.11±0.15</td>
<td>362</td>
<td>20.6 (18.5–22.8)</td>
<td>3.04 (2.37–3.90)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR per 1-SD‡ increase in IMT</td>
<td>1.57 (1.49–1.65)</td>
<td>1.17 (1.10–1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.65±0.06</td>
<td>40</td>
<td>1.9 (1.4–2.6)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Q2</td>
<td>0.78±0.03</td>
<td>75</td>
<td>3.7 (2.9–4.6)</td>
<td>1.28 (0.87–1.89)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.89±0.04</td>
<td>65</td>
<td>3.5 (2.7–4.4)</td>
<td>1.03 (0.68–1.54)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.11±0.15</td>
<td>74</td>
<td>4.2 (3.3–5.3)</td>
<td>1.08 (0.72–1.61)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.82</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR per 1-SD increase in IMT</td>
<td>1.26 (1.12–1.41)</td>
<td>0.94 (0.81–1.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of IMT and TPA in both crude and multivariable-adjusted analyses, whereas no such trend was observed for VTE.

Calculating cause-specific hazards to account for competing risks has several advantages when examining risk factors for interrelated diseases. By eliminating the possibility of one outcome influencing the risk of another, the direct effect of the risk factors in question on each outcome is assessed. Comparison within the same population also ensures that the degree of possible confounding is similar for the 2 outcomes. In our study, the risk estimates for MI by carotid atherosclerosis were similar to that of other cohorts, suggesting that the nonassociative nature of carotid atherosclerosis and VTE is not explained by unrecognized confounding or inappropriate measurement and classification of the exposure variable (carotid atherosclerosis measures).

For both TPA and IMT, our MI risk estimates are in agreement with those of previous reports. In a large meta-analysis including 37,197 participants, Lorenz et al found an overall age-adjusted and sex-adjusted HR for MI of 1.26 (95% CI, 1.21–1.30) per 1-SD difference in common carotid artery IMT. Similar findings were recently published from the PROG-IMT collaborative project, in which the mean IMT of 2 separate carotid scans was associated with future MI after multivariable adjustment (HR, 1.22; 95% CI, 1.14–1.30). For a combined cardiovascular end point (MI, stroke, aortic aneurism, angina pectoris, or revascularization procedures), the presence of carotid plaques had a predictive odds ratio of 2.09 (95% CI, 1.05–4.16).16

Our null findings for VTE are in concurrence with those of 2 large population-based prospective studies (the Atherosclerosis Risk in Communities and the Cardiovascular Health Study) in which subclinical atherosclerosis was evaluated as a VTE risk factor in participants younger than and older than 65 years, respectively. In the former study, neither increased IMT nor the presence of carotid plaque was associated with VTE risk in 13,081 participants after a mean follow-up of 12.5 years. In the latter study, IMT and plaque measurements were supplemented with registration of major ECG abnormalities and ankle brachial index registration as manifestations of subclinical atherosclerosis in an older cohort of 4108 people. During follow-up, none of these atherosclerosis measures was associated with increased risk of total or unprovoked VTE. Surprisingly, both high-risk carotid plaques and the highest internal carotid artery IMT quartile were inversely associated with VTE risk.12,13

Prandoni et al reported a higher prevalence of carotid plaques among patients with previous unprovoked deep vein thrombosis compared with patients with provoked deep vein thrombosis and hospitalized controls. In their study, participants tended to be older, and plaques were defined differently compared with our study. Hong et al found the presence of coronary artery calcium, a marker of systemic atherosclerosis, to be significantly associated with VTE. However, the case–control design of these latter 2 studies makes the temporal sequence of events difficult to establish. Furthermore, both studies used other hospitalized patient controls, which reduces generalizability and introduces possible selection bias. The discriminatory effect of TPA and IMT measurements on MI and VTE found in our study indicates that atherosclerosis is not an important risk factor in the pathogenesis of VTE.

Several studies have demonstrated an association between VTE and overt cardiovascular disease. In a meta-analysis by Becattini et al, patients with unprovoked VTE had a 1.5-fold increased risk of cardiovascular disease compared with control groups. However, prospective studies report varying results on atherosclerotic risk factors and VTE, with a majority of null findings. To date, 2 large cohort studies have used a competing risk approach to assess the effect of traditional cardiovascular risk factors on arterial and venous thrombosis. In both the Tromsø Study and the Physicians’ Health Study, hypertension, dyslipidemia, diabetes mellitus, smoking, and physical activity (inverse) were significantly associated with risk of MI but not with VTE. Because established cardiovascular risk factors (apart from obesity) fail to show a consistent association with VTE, it is plausible that the link between venous and arterial thrombosis is explained by mechanisms of thrombus formation and hypercoagulability rather than atherosclerosis. Spencer et al found a 3-fold increase in risk of MI in patients with VTE compared with controls, but only in participants aged <40 years, who were generally lacking atherosclerotic risk factors.

Major strengths of this study include the large number of participants recruited from a general population, the high attendance rate, the prospective design, and the measurements of potential confounders. The municipality of Tromsø is served by a single hospital, and the supplemental use of the National Causes of Death registry and the National population registry allowed for a rigorous case validation for both end points. Some limitations also merit consideration. TPA and IMT were measured only in the right carotid artery, whereas measurements on both sides might have been more representative of the individual’s atherosclerotic status. Also, both the carotid measurements and potential confounders were assessed at baseline only, and these factors could have changed over time and thereby resulted in underestimations of the true effects in our study. Thus, we cannot rule out the possibility that changes in carotid atherosclerosis over time may be associated with VTE. Even so, this same limitation is present for MI. In general, comparing the effect of carotid atherosclerosis on risk of MI and VTE within the same population reduces the risk of nondifferential misclassification bias because it is likely that the degree of random misclassification of exposure was similar with regard to both outcomes. In conclusion, our study showed that carotid atherosclerosis is a strong risk factor for MI but not for VTE.

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Disclosures
None.

References


**Significance**

Venous thrombosis is a common and potentially fatal disease. Because ≤50% of events occur without known predisposing conditions, identifying novel risk factors is important. Although several previous studies have suggested that venous and arterial thrombosis share risk factors, our study is the first to use a competing risk method to evaluate the effect of carotid atherosclerosis, a known risk factor for arterial thrombotic disease, on venous thromboembolism and myocardial infarction within the same population. In a competing risk model, one eliminates the possibility of one outcome (venous thrombosis) influencing the risk of another (myocardial infarction); thus, the direct effect of the risk factor in question (carotid atherosclerosis) is assessed.
Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism: The Tromsø Study
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Materials and methods

**Study population**
The study participants were recruited from the fourth survey of the Tromsø Study, a single-centre, prospective, population-based health study of the inhabitants of Tromsø, Norway, carried out in 1994-95. All inhabitants aged 55-74 years and 5-10% samples in other 5-year age groups (25-54 and 75-85 years) were offered an ultrasonographic examination of the right carotid artery, and 88% (n=6727) of the invited participants attended. Participants not consenting to medical research (n=40), participants with limited measurements (n=3), those with prior VTE (21) or prior MI (n=393) or participants not officially registered as inhabitants of the municipality of Tromsø at baseline (n=13) were excluded. In total, 6257 participants were followed from the date of enrolment to the end of the study period, 31st December 2010. The median follow-up time was 15.4 years (range 0.01-16.3 years). Informed written consent was obtained from all participants, and the study was approved by the Regional Committee for Medical and Health Research Ethics.

**Carotid ultrasound examination**
Details about the ultrasound methods and reproducibility have been published previously. Briefly, high-resolution B-mode ultrasonography of the right carotid artery was performed by experienced examiners, with the use of an Acuson Xp10 128 ART ultrasound scanner equipped with a 7.5 MHz linear-array transducer. The far wall (FW) and near wall of the right common carotid artery (CCA), the bifurcation (bulb) and the internal carotid artery (ICA) (6 locations) were scanned for the presence of plaques. A plaque was defined as a localized thickening of the vessel wall of more than 50% compared with the adjacent intima-media thickness (IMT). Still images were recorded for each plaque and digitized using the Matrox Meteor II frame grabber card and Matrox Intellicam version 2.07. With the use of the Adobe Photoshop image-processing program (version 7.0.1), measurement of plaque area were made by outlining the perimeter of the plaque with the Lasso tool, 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 mm². Total plaque area was calculated as the sum of all plaque areas. Automated measurement of IMT was performed in the FW of the CCA (CCA-FW-IMT), near wall of the CCA, and the FW of the bulb. Measurements of IMT were performed in 10-mm segments, and mean IMT from the 3 preselected images was calculated for each location. If present in the predefined location of interest, plaques were included in the IMT measurements. The average of the mean IMT measured in all 3 locations (mean IMT) was used in the analyses.

**Baseline measurements**
Baseline information was collected by physical examination, non-fasting blood samples and self-administered questionnaires. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846; Critikon Inc., Tampa, FL, USA) by trained personnel. Participants rested for 2 min in a sitting position and then three readings were taken on the upper right arm at 2-min intervals. The average of the two last readings was used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. Non-fasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after one hour respite at
room temperature and analyzed at the Department of Clinical Biochemistry, University Hospital of North Norway. Serum total cholesterol was analyzed by an enzymatic colorimetric method using a commercially available kit (CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Determination of glycosylated hemoglobin (HbA1c) in EDTA whole blood was based on an immunoturbidimetric assay (UNI-MATES, F. Hoffmann-La Roche AG, Basel, Switzerland). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Information on diabetes, current smoking and previous cardiovascular disease (stroke, angina pectoris or MI) was obtained from a self-administered questionnaire. The self-reported diabetes data were supplemented with data on confirmed diabetes from the diabetes registry of the Tromsø Study, and persons with HbA1c levels ≥ 6.5% at baseline were also defined as diabetic.

**Outcome assessment of venous thromboembolism**

All first lifetime VTE events during follow-up were identified by searching the discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway, as previously described. A potential VTE episode was recorded as a confirmed case if each and all of the following criteria were met: (1) objectively confirmed by diagnostic procedures including compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan (high or moderate probability for pulmonary embolism), pulmonary angiography, or autopsy; (2) the medical record indicated that a physician had made a diagnosis of deep vein thrombosis or pulmonary embolism; (3) signs and symptoms consistent with deep vein thrombosis or pulmonary embolism were present; and (4) treatment with anticoagulants (heparin, warfarin), thrombolytic therapy, or vascular surgery was required. For patients derived from the autopsy registry, a VTE-event was recorded when the autopsy record indicated VTE as cause of death or as a significant condition contributing to death. All medical records were reviewed by trained personnel.

**Outcome assessment of myocardial infarction**

The Norwegian national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of possible incident myocardial infarction were identified by linkage to the hospital discharge diagnosis registry at the University Hospital of North Norway with a broad search for the International Classification of Diseases (ICD), 9th Revision codes 410 to 414, and 430 to 438 in the period 1994 to 98 and thereafter for the ICD, 10th Revision codes I20-I25, and I60-I69. The hospital medical records were retrieved for case validation. We performed manual and/or electronic text searches in paper versions (used until 2001) and digital versions of hospital records for notes on myocardial infarction in all participants with one or more of these diagnoses. Linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal incident cases of myocardial infarction that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø, as well as information on all-cause mortality. Information from the death certificates was used to collect relevant information of the event from additional sources such as autopsy reports and records from nursing homes, ambulance services, and general practitioners. Validation of hospitalized and out-of hospital MI events was performed by an independent endpoint committee and based on data from hospital and out-of
hospital records, autopsy records, and death certificates. Slightly modified World Health Organization MONICA/MORGAM criteria for myocardial infarction were used and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and (when applicable) autopsy reports.\(^5\)

**Statistical Analyses**

Statistical analysis was carried out using SPSS version 17.0 (SPSS, Chicago, IL, USA) and STATA version 12.0 (Stata corporation, College Station, TX, USA). The significance level was 0.05. Attained age was used as time-scale, with participants' age at study enrolment defined as entry-time, and exit-time defined as age at the censoring event (MI, VTE, death, migration or study end). All participants had at most 1 of the 2 outcomes on the date of first occurrence. The data were prepared by duplication of the dataset, giving each subject a separate observation for each outcome as described by Lunn and McNeil.\(^6\) The distribution of TPA was skewed to the right, and the square root of this variable was used in analyses where TPA was used as a continuous variable to approximate normal distribution. Cox proportional hazard regression models, stratified by event type, were used to assess the association between IMT and TPA and outcomes in both crude and multivariable adjusted analyses. The multivariable cause-specific HRs were adjusted for potential confounders including sex, BMI, smoking, diabetes, hypertension, cholesterol levels and HDL cholesterol levels. Potential two-way interactions were tested by including cross-product terms for risk factors with sex in the regression models. A test of the proportional hazard assumption using Schoenfeld residuals revealed that IMT violated the assumption of proportional hazards. HRs in different age groups (younger vs. older participants) were therefore calculated. Power analyses were performed using PASS 11 (NCSS, LLC. Kaysville, Utah, USA). Post-hoc power analysis showed that a HR of 1.19 for VTE per 1 SD change in IMT/TPA could be detected with a power of 0.8 and a significance level of 0.05.