Impact of incident venous thromboembolism on risk of arterial thrombotic diseases

First author: Lind

Short title: Venous thromboembolism and risk of arterial events

Caroline Lind, BSc[1]; Linda E. Flinterman, PhD[2], Kristin F. Enga, MD, PhD[1,3], Marianne T. Severinsen, MD, PhD[4], Søren R. Kristensen, MD, PhD[5], Sigrid K. Brækkan, PhD[1,3], Ellisiv B. Mathiesen, MD, PhD[6,7], Inger Njølstad, MD, PhD[8], Suzanne C. Cannegieter, MD, PhD[9], Kim Overvad, MD, PhD[2,10], John-Bjarne Hansen, MD, PhD[1,3].

[1]Hematological Research Group, Department of Clinical Medicine, University of Tromsø, Norway, [2]Section for Epidemiology, Department of Public Health, Aarhus University, Denmark, [3]Division of Internal Medicine, University Hospital of North Norway, Norway, [4]Department of Haematology, Aalborg University Hospital, Denmark, [5]Department of Clinical Biochemistry, Cardiovascular Research Center, Aalborg University Hospital, Denmark, [6]Brain and Circulation Research Group, Department of Clinical Medicine, University of Tromsø, Norway, [7]Department of Neurology and Clinical Neurophysiology, University Hospital of North Norway, Norway, [8]Department of Community Medicine, University of Tromsø, Norway, [9]Department of Clinical Epidemiology, Leiden University Medical Center, Netherlands, [10]Department of Cardiology, Aalborg University Hospital, Denmark.

Correspondence: Caroline Lind, Hematological Research Group, Department of Clinical Medicine, University of Tromsø, N-9037 Tromsø, Norway. Fax: +47 77646838. Telephone: +47 77620707. E-mail: caroline.lind@uit.no

Total word count: 6 974. Journal Subject Codes: 172, 173

Abstract

Background: Growing evidence support an association between venous thromboembolism (VTE) and arterial thrombotic diseases (i.e. myocardial infarction (MI) and ischemic stroke). We aimed to study the association between VTE and future arterial events, and to determine the population attributable risk (PAR%) of arterial events by VTE in a large prospective cohort recruited from the general population.

Methods and Results: In 1994-1995 and 1993-1997, 81 687 subjects were included in the Tromsø Study and in the Diet, Cancer and Health Study and followed to the date of incident venous and arterial events (MI or ischemic stroke), death or migration, or to the end of the study period (2010 and 2008, respectively). There were 1 208 cases of VTE and 90 subsequent arterial events during a median follow-up of 12.2 years. An association between VTE and future arterial events was found in all women and men <65 years, but not in men >65 years. Women <65 years with VTE had 3.3-fold higher risk of arterial disease (adjusted HR 3.28, 95%CI 1.69-6.35) compared to women of the same age without VTE. The corresponding HR in men <65 years was 2.06 (95%CI: 1.32-3.20). Only 0.9% of the arterial events were attributed to VTE, and the VTE explained 63.8% of the risk of arterial events among VTE patients.

Conclusions: Our findings imply that women and young men with VTE have higher risk of arterial thrombotic disease than those without VTE. However, only 1% of the arterial thrombotic events in the population are attributed to VTE.

Key Words- venous thrombosis, myocardial infarction, ischemic stroke, cohort study

Introduction

Arterial thrombotic diseases (i.e. myocardial infarction (MI) and ischemic stroke) and venous thromboembolism (i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE)) have traditionally been considered as separate diseases with distinct etiology and treatment strategies. However, later studies have suggested a potential link between arterial and venous thrombosis. A higher frequency of carotid plaques has been found in patients with unprovoked VTE compared to patients with provoked VTE and hospitalized controls.[1] Moreover, a study of consecutive autopsies reported an association between atherothrombosis and VTE,[2] and the highest prevalence of previous hospitalization for MI and stroke was found among VTE patients in a case-control study of more than 60 000 VTE patients and population controls.[3]

Growing evidence support an association between VTE and future arterial thrombotic events. In studies of patients with VTE, subjects with unprovoked events had higher risk of arterial thrombotic disease than patients with provoked events.[4-7] However, the risk was assessed in selected cohorts (e.g. patients with a previous history of PE),[4-6] or included a low number of study participants.[7] A large population-based registry study, with more than 200 000 subjects, reported that patients with VTE had substantially higher long-term incidence of subsequent arterial thrombotic diseases.[8] However, information about potential confounders, such as body mass index (BMI), was not available in this study.[8] In addition, the attributable risk and the population attributable risk of arterial thrombotic disease due to VTE were not reported. Such data are essential, as a considerable proportion of arterial events attributable to VTE could imply a role for long-term treatment to prevent subsequent arterial events in VTE patients.

The aim of this study was to investigate the association between incident VTE and future risk of arterial thromboembolic events in a general population, and adjust for potential

confounders such as BMI. We conducted individual-level analyses of two prospective population-based cohorts and assessed the absolute and relative risks of first-time arterial thrombotic disease, including acute MI and ischemic stroke, after a first episode of VTE.

Methods

Study population

Subjects were recruited from the fourth survey of the Tromsø Study (conducted in 1994-95), and from the Diet, Cancer and Health (DCH) Study (conducted in 1993-97). The Tromsø Study and the DCH Study are population-based studies, with repeated health surveys of inhabitants in Tromsø, Norway, and Copenhagen and Aarhus, Denmark, respectively. The study populations have been described in detail elsewhere.[9, 10] In the fourth survey of the Tromsø Study, all inhabitants aged 25 years or older were invited and 27 158 (77% of the eligible population) participated. In the DCH Study, all inhabitants living in the urban areas of Copenhagen and Aarhus were invited to participate if they were born in Denmark, between 50 to 65 years of age and did not have a diagnosis of cancer in the Danish Cancer Registry at enrollment, and 57 054 subjects participated.

The study was approved by the regional committees for research ethics in Tromsø, Aarhus and Copenhagen, respectively, and all subjects gave their informed written consent. Subjects who did not consent to medical research (n= 243) and subjects not officially registered as inhabitants of the municipalities at baseline (n= 44) were excluded from the study. Furthermore, subjects were excluded if they had a pre-baseline history of VTE (n= 495), ischemic stroke (n= 163) or MI (n= 1 573). Thus, a total of 81 693 subjects were included, and followed from the dates of enrollment in Denmark (1993-97) and Norway

(1994-95) through the end of the study periods in 2008 and 2010, respectively. The overall median follow-up time was 12.2 years.

Atherosclerotic risk factors

Baseline information was collected by physical examinations and self-administered questionnaires. Height and weight were measured, BMI calculated and blood pressure was recorded, as described elsewhere.[11, 12] Detailed information on diabetes mellitus, hypertension, hypercholesterolemia, smoking, physical activity, education level and medication use including hormone replacement therapy, oral contraceptives, antihypertensives and lipid lowering drugs, was collected from self-administered questionnaires. Non-fasting blood samples were collected and total cholesterol measured as previously described.[11, 12] Obesity was classified based on BMI according to the World Health Organization (WHO) definition.[13] Hypertension was classified as mean systolic blood pressure ≥ 140 mmHg, mean diastolic blood pressure ≥ 90 mmHg, self-reported use of blood pressure lowering drugs, or self-reported hypertension. Hypercholesterolemia was classified as total serum cholesterol ≥ 6.5 mmol/l, self-reported use of lipid lowering drugs, or self-reported hypercholesterolemia.

Registry of VTE

Only objectively verified symptomatic VTE events were included in the study and the VTE events were similarly validated and recorded in the Tromsø and the DCH Study. All first-time events of VTE during follow-up in the Tromsø Study were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure

registry of the University Hospital of North Norway from date of enrollment (1994-95) to December 31, 2010, as previously described.[14] A VTE event derived from the hospital discharge diagnosis registry or the radiology procedure registry, was verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmatory tests (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment. VTE cases from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or as a significant condition contributing to death.

In the DCH Study, all incident VTE events were identified by linking the cohort with the Danish National Patient Registry and the Danish National Death Registry by use of the civil registration number of the study participants from date of enrollment (1993-97) to April 30, 2008, as described elsewhere.[12] A VTE diagnosis was verified when typical clinical symptoms of VTE were combined with confirmatory diagnostic test results (ultrasound, venography, echocardiography, ventilation-perfusion lung scan, or computed tomography scan), or when autopsy verified VTE.

In both studies, trained personnel reviewed the medical records for each potential VTE-case. Concurrent DVT and PE were registered as PE. Verified events were classified as unprovoked or provoked based on the presence of provoking factors at the time of diagnosis, as previously described in detail.[12, 14] In the last update of VTE events in the DCH Study (July 2006 to April 2008), verified VTEs were not further classified. Therefore, 136 VTE patients had missing information on localization (DVT/PE) and 146 had missing on classification (unprovoked/provoked).

Registry of arterial thrombotic events

In the Tromsø Study, all first-time events of myocardial infarction and ischemic stroke were identified by searching the hospital and out-of hospital medical records, the autopsy registry and the death certificates, as previously described.[11, 15] The national unique 11-digit identification number allowed linkage to national and local diagnosis registries and to the National Causes of Death Registry at Statistics Norway. Medical records were case validated by an independent endpoint committee. Slightly modified WHO MONICA/MORGAM criteria for myocardial infarction were used and these included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable. Ischemic stroke was defined according to the WHO definition when CT or MRI scans had ruled out brain hemorrhage. In the DCH Study, potential cases of incident myocardial infarction and ischemic stroke were identified by linkage to the Danish National Patient Registry and the Danish Causes of Death Registry, as described elsewhere.[16, 17] From baseline through 2003, potential MI cases were validated by direct review of medical records in accordance with the guidelines of the American Heart Association and the European Society of Cardiology for use in epidemiology. From January 2004 until end of follow up in April 2008, and for participants whose medical records were not available for review in the period 1993-2003, all participants with a diagnosis of MI were accepted as cases without further validation. These diagnoses had a positive predictive value above 90% in the Danish National Patient Registry. For ischemic stroke, the WHO definition[18] was used and all cases were verified by CT, MRI, spinal fluid examination or autopsy.

Statistical analyses

Subjects who developed VTE during the study period contributed with non-exposed person-time from the baseline inclusion date to the date of a diagnosis of VTE, and then with exposed person-time from the date of VTE and onwards. For each participant, non-exposed and exposed person-years were counted from the date of enrollment to the date of an incident diagnosis of arterial thrombotic disease (i.e. MI and ischemic stroke), the date the participant died or moved from the municipalities, or until the end of the study period (December 31, 2010 Tromsø, and April 30, 2008 DCH), whichever came first. Subjects who died or moved from the municipalities during follow-up were censored at the date of migration or death. Subjects with VTE and an arterial event on the same day (n=6) were excluded from all analyses, since the temporal sequence of exposure and outcome could not be determined.

Statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX). Baseline differences between groups were tested by one-way ANOVA for continuous variables, and by chi-square for categorical variables. Crude incidence rates (IR) of arterial thrombotic disease were calculated and expressed as number of events per 1000 person-years at risk. Cox proportional hazard regression models were used to estimate crude and multivariable adjusted hazard ratios (HR) with 95% confidence intervals (CI) for arterial thrombotic disease, MI and ischemic stroke. Age was used as time-scale, with participants' age at study enrollment defined as entry-time, and exit-time defined as age at the censoring event (arterial thrombotic disease, death, migration or study end). The exposure variable (VTE) was included as a time-dependent covariate, i.e. no participants were registered with VTE at baseline, but the variable was updated for those who developed VTE during follow-up. The multivariable HRs were adjusted for age, BMI, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, and education level. In addition, subgroup analyses of PE and DVT as exposure variables for arterial thrombotic disease were performed using the same time-varying approach. Statistical interactions between VTE and age or sex

were tested by including cross-product terms in the proportional hazard model. Further analyses were stratified by sex and age (≥65 years). The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function.

In order to show the change in risk of arterial events over time, crude incidence rates of arterial thrombotic disease, MI and ischemic stroke were plotted against time (1, 3, 5, 7 and 10 years) after an episode of VTE, DVT or PE, respectively, using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA).

Attributable risk (AR%), the proportion of events among the exposed subjects that can be explained by the exposure, was calculated from incidence rates of arterial thrombotic disease in the VTE (I_e) and non-VTE (I_0) population ($100\% * (I_e - I_0) / I_e$). Population attributable risk fraction (PAR%), the proportion of events in the study population attributable to the exposure, was calculated using the incidence rates of arterial thrombotic disease in the general population (I_p) and in the non-VTE (I_0) population ($100\% * (I_p - I_0) / I_p$).

Results

In our population, 1 208 subjects with a first-time VTE event were identified, of which 90 developed a subsequent incident arterial thrombotic event (i.e. MI and ischemic stroke). Baseline characteristics of study participants are shown in Table 1. Compared to those who developed arterial events only, those who developed an incident arterial thrombotic disease after a VTE event had higher mean age and BMI values, comprised higher proportions of subjects with diabetes, hypertension and hypercholesterolemia, and had a lower proportion of men and subjects who regularly performed exercise.

Characteristics of the VTE events are shown in Table 2. Among the 1 208 VTE events, 648 (53.6%) were DVT and 424 (35.1%) were PE events. Moreover, 513 (42.5%) events were classified as provoked and 548 (45.4%) as unprovoked. The use of estrogens was associated with 208 (17.2% of the total and 35.1% of the female) VTE events, and 146 (12.1%) of the VTE subjects had other medical conditions present at the time of VTE (Table 2).

Incidence rates and hazard ratios for arterial thrombotic diseases by VTE and subtypes of VTE are shown in Table 3. In total, there were 6 344 incident arterial thrombotic events (3 666 MIs and 2 678 ischemic strokes) during a median of 12.2 years of follow-up. In subjects without VTE, 6 254 arterial events were identified during a total of 967 604 person-years of follow-up (IR 6.5 per 1000 person-years), while there were 90 arterial events during 5 039 person-years of follow-up in subjects exposed to VTE (IR 17.9 per 1000 person-years). Overall, VTE was associated with a 35% (adjusted HR 1.35; 95% CI 1.09-1.66) increased risk of arterial thrombotic disease. Investigating the risk of MI and ischemic stroke separately yielded HRs of 1.31 (95% CI 1.00-1.72) and 1.33 (95% CI 0.96-1.84), respectively (Table 3). The attributable risk of arterial thrombotic disease among VTE patients was 63.8%, and 0.9% of the arterial events in the population were attributable to VTE. In subgroup analyses, PE, but not DVT, was associated with increased risk of arterial thrombotic disease (adjusted HR 1.82; 95% CI 1.35-2.47), MI (adjusted HR 2.02; 95% CI 1.38-2.95), and ischemic stroke (adjusted HR 1.53; 95% CI 0.92-2.55) (Table 3). The incidence rate of arterial events in VTE subjects differed according to VTE type, and changed with time after the VTE episode (Figure 1). The highest crude incidence rate of arterial thrombotic disease (Figure 1a), MI (Figure 1b) and ischemic stroke (Figure 1c) was found the first year after a PE event.

A significant statistical interaction was found between VTE and sex, and between VTE and age. When analyses were stratified by sex and the age of 65 years, the association

between VTE and subsequent arterial thrombotic disease applied to all women and to men below 65 years of age (Table 4). Women below 65 years of age with VTE had a 3.3-fold higher risk of arterial thrombotic disease (adjusted HR 3.28; 95% CI 1.69-6.35), 3.6-fold higher risk of MI (adjusted HR 3.62; 95% CI 1.49-8.80) and 3.2-fold higher risk of ischemic stroke (adjusted HR 3.16; 95% CI 1.18-8.47) compared with women in the same age-group without VTE. Women aged 65 years or older had the highest incidence rates of arterial thrombotic disease (IR 24.1 per 1000 person-years) after a VTE event, and the absolute risk increase was also highest (14 additional events per 1000 persons per year). The relative risk estimates for arterial thrombotic diseases were 40-60% higher in women of this age group with VTE compared with no VTE (adjusted HR for arterial disease: 1.55; 95% CI 1.11-2.18, MI: 1.41; 0.89-2.24 and stroke: 1.66; 1.01-2.74). Men below 65 years of age with a VTE had 2.1-fold higher relative risk of arterial thrombotic disease (adjusted HR 2.06; 95% CI 1.32-3.20), 2.1-fold higher risk of MI (adjusted HR 2.11; 95% CI 1.22-3.65) and 2.0-fold higher risk of ischemic stroke (adjusted HR 1.95; 95% CI 0.93-4.12) compared with those without VTE, whereas no association was found between VTE and arterial events in men aged 65 years or older (Table 4). Adjusting for the use of estrogens in women did not change the risk estimates (data not shown). In subgroup analyses, pulmonary embolism was associated with increased risk of arterial thrombotic disease in all women and men below 65 years (Table 4). A higher risk of myocardial infarction was found in both men and women below 65 years with PE compared with those without VTE (adjusted HRs 4.80; 95% CI 2.39-9.62 and 4.06; 95% CI 1.00-16.40, respectively). Women below 65 years with DVT had higher risk of arterial thrombotic disease (adjusted HR 3.32; 95% CI 1.48-7.44), MI (adjusted HR 3.35; 95% CI 1.07-10.46), and ischemic stroke (adjusted HR 3.66; 95% CI 1.17-11.42) compared with women in the same age-group without VTE, whereas no association was found in men below 65 with DVT. Moreover, no association was found between PE or DVT and arterial

events in men aged 65 years or older. The lowest proportion of DVT and PE events were found in women below 65 years of age (Table 4).

Discussion

In the present study, incident venous thromboembolism was associated with increased risk of future myocardial infarction and ischemic stroke. Specifically, women of all ages and men below 65 years of age suffering from a VTE event had higher risk of major arterial thrombotic diseases compared with those without VTE. In women, PE and DVT provided similar risk estimates of arterial events, whereas PE rather than DVT appeared to predict arterial thrombotic diseases in men. The incidence rate of arterial events was highest the first year after a PE episode. The population attributable risk of arterial thrombotic disease by incident VTE was only 0.9%, and the VTE event explained 64% of the risk for arterial events in VTE patients.

The mechanism behind the observed association between VTE and arterial thrombotic diseases is not fully understood. Potentially, atherosclerosis may initiate both venous and arterial thrombosis by a similar pro-thrombotic trigger, such as inflammation.[19, 20] Prospective studies of general populations have, however, failed to confirm an association between atherosclerosis and VTE.[21, 22] Moreover, growing evidence support the concept that traditional atherosclerotic risk factors including diabetes, hypertension and dyslipidemia are not associated with venous thrombosis.[11, 23-26] Obesity and advancing age are shared risk factors for arterial and venous thrombosis. However, adjustments for age and BMI in addition to traditional atherosclerotic risk factors only modestly affected the risk estimates, indicating that these two common factors could not fully explain the observed association between VTE and risk of future MI. Modifiable risk factors such as smoking, diabetes, hypertension and hypercholesterolemia may change over time, and residual confounding by these factors cannot be ruled out. Moreover, unknown confounders may still be present, and could potentially explain the association. In a recently published study, common etiologic factors including genetic thrombophilia and procoagulant markers explained the increased risk of

arterial cardiovascular disease after VTE.[27] A family history of MI has been shown to be associated with both arterial thrombotic disease[28, 29] and VTE,[30, 31] suggesting a common genetic component for both diseases. Concordantly, some inherited thrombophilias have also been associated with arterial thrombosis.[32, 33] Furthermore, several risk factors for VTE, including high levels of coagulation factors VIII, IX and XI, plasminogen activator inhibitor-1 and von Willebrand factor, have been reported as risk factors for arterial cardiovascular disease.[34, 35]

It is also possible that the observed association is not explained by common risk factors, but restricted to the events themselves or treatment thereof. In our study, PE was a stronger predictor than DVT for future MI. Thus, it can be hypothesized that local disturbances in the cardiopulmonary circulation caused by PE may predispose for clotting in the coronary arteries. In addition, a paradoxical embolism from a venous source through a patent foramen ovale may lead to ischemic stroke and MI.[36, 37] Vascular calcification is associated with increased cardiovascular risk. In animal models, treatment with vitamin K antagonists led to arterial calcification,[38] and long-term use of vitamin K antagonists was associated with extracoronary vascular calcification in humans, even after adjustments for other risk factors.[39] Thus, hypothetically, long-term treatment of VTE with vitamin K antagonists could lead to arterial thrombotic disease through arterial calcification.

VTE was not associated with higher risk of arterial events in elderly men. Although these findings should be interpreted with caution due to limited statistical power in subgroup analyses, it may shed light over differential pathogenesis of arterial thrombotic disease in men and women. In general, women have lower risk of arterial events and are older at time of diagnosis than men with similar risk profiles.[40] The risk factors associated with arterial events in females are found to cluster after menopause.[41] Furthermore, women are likely to be exposed to risk factors for VTE earlier in life because of oral contraceptive use or pregnancy.

A hypercoagulable state is found to play an important part in development of arterial events in younger subjects.[42] Thus, if arterial and venous thrombosis are caused by common risk factors other than atherosclerosis, a VTE may be more likely to occur before an arterial event in women and young men, whereas elderly men may be more prone to develop arterial events, irrespective of other risk factors, due to their high atherosclerotic burden.[40]

The highest incidence rate of arterial thrombotic disease, MI and ischemic stroke was found the first year after a PE event. As the median duration of anticoagulant therapy after a PE was 12 months, many of the arterial thrombotic events occurred during anticoagulant treatment. Oral anticoagulant treatment efficiently reduces the risk of MI and cerebrovascular events.[43, 44] Thus, it is likely to assume that the observed risk estimates are underestimations of the true risk of arterial events after a VTE in our study. This may also explain why our crude incidence rates of arterial thrombotic diseases after a VTE event were lower than those reported in previous cohort studies[4-7] in which only VTE subjects who had completed oral anticoagulant treatment,[4] survived the first month after the VTE event,[7] or had no indication for long-term anticoagulant therapy[5, 7] were included. Moreover, the fact that we followed all VTE patients from the initial stage of the disease (including the 207 (17.1%) subjects who died within a year after the VTE episode and no longer were at risk of developing arterial thrombotic disease), and that all subjects with a history of cancer before enrolment (who are also at increased risk of arterial thrombotic events[45]), were excluded from the DCH Study may additionally explain the lower incidence rate.

Our findings may have some clinical implications. Even though only 1% of the arterial thrombotic events in the total population could be attributed to incident venous thromboembolism, 64% of the arterial thrombotic events among the VTE patients were due to the incident VTE. Recent randomized controlled trials reported that acetylsalicylic acid (ASA) reduced the risk of recurrent VTE and major vascular events in patients with

unprovoked VTE without increasing the risk of bleeding.[46, 47] ASA reduced the risk of major vascular events by 34% and recurrent VTE by 28%.[47] Extrapolated to our population, this may suggest prevention of 3 out of the 9 per 1000 major arterial events attributable to VTE in our population, and 50 out of the 180 per 1000 recurrent VTE events found in the randomized controlled trial.

The main strengths of our study include the prospective design, large number of participants recruited from a general population, wide age distribution, long-term follow-up, and validated events of VTE and arterial thrombotic disease. However, the study has some limitations. Non-response bias is a possible limitation of cohort studies as those who participate in cohort studies tend to be healthier than the general population. The risk estimates may therefore be lower than expected. Furthermore, due to a low number of both exposure and outcome events in our cohort, we may have lacked the statistical power to assess the potential impact of VTE on risk of arterial thrombotic disease in some subgroup-analyses.

In conclusion, our cohort study implies that all women and men below 65 years of age with incident VTE have increased risk of future arterial thrombotic disease, including myocardial infarction and ischemic stroke. However, only 1% of the arterial thrombotic events in the population can be attributed to VTE.

Acknowledgements

None.

Funding sources

The Research Council of Norway. The University of Tromsø, Norway. The Northern Norway Regional Health Authority.

Disclosures

None.

References

1. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, Prins MH,Girolami A. An association between atherosclerosis and venous thrombosis. *N Engl J Med*. 2003;348:1435-41

2. Eliasson A, Bergqvist D, Bjorck M, Acosta S, Sternby NH, Ogren M. Incidence and risk of venous thromboembolism in patients with verified arterial thrombosis: A population study based on 23,796 consecutive autopsies. *J Thromb Haemost*. 2006;4:1897-1902

3. Sorensen HT, Horvath-Puho E, Sogaard KK, Christensen S, Johnsen SP, Thomsen RW, Prandoni P, Baron JA. Arterial cardiovascular events, statins, low-dose aspirin and subsequent risk of venous thromboembolism: A population-based case-control study. *J Thromb Haemost*. 2009;7:521-8

4. Becattini C, Agnelli G, Prandoni P, Silingardi M, Salvi R, Taliani MR, Poggio R, Imberti D, Ageno W, Pogliani E, Porro F, Casazza F. A prospective study on cardiovascular events after acute pulmonary embolism. *Eur Heart J*. 2005;26:77-83

5. Klok FA, Mos IC, Broek L, Tamsma JT, Rosendaal FR, de Roos A, Huisman MV. Risk of arterial cardiovascular events in patients after pulmonary embolism. *Blood*. 2009;114:1484-8

6. Prandoni P, Ghirarduzzi A, Prins MH, Pengo V, Davidson BL, Sorensen H, Pesavento R, Iotti M, Casiglia E, Iliceto S, Pagnan A, Lensing AW. Venous thromboembolism and the risk of subsequent symptomatic atherosclerosis. *J Thromb Haemost*. 2006;4:1891-6

7. Bova C, Marchiori A, Noto A, Rossi V, Daniele F, Santoro C, Ricchio R, De Lorenzo R, Umbaca R, Prandoni P. Incidence of arterial cardiovascular events in patients with idiopathic venous thromboembolism. A retrospective cohort study. *Thromb Haemost*. 2006;96:132-6

8. Sorensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: A 20-year cohort study. *Lancet*. 2007;370:1773-9

9. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. *Int J Epidemiol*. 2012;41:961-7

10. Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: A population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health*. 2007;35:432-41

11. Braekkan SK, Hald EM, Mathiesen EB, Njolstad I, Wilsgaard T, Rosendaal FR, Hansen JB. Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso Study. *Arterioscler Thromb Vasc Biol*. 2012;32:487-91

12. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjonneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: A danish follow-up study. *Circulation*. 2009;120:1850-7

13. The Norwegian Institute of Public Health. Overweight and obesity in Norway: fact sheet. Accessed November 26, 2012. Available from: http://www.fhi.no/eway/default.aspx?pid=238&trg=MainLeft_5976&MainArea_5811=5976:0:15,5012:1:0:0:::0:0&MainLeft_5976=5825:74991::1:5977:12:::0:0:

14. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: the Tromso Study. *Am J Epidemiol*. 2010;171:1109-15

15. Mathiesen EB, Johnsen SH, Wilsgaard T, Bonaa KH, Lochen ML, Njolstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: A 10-year follow-up of 6584 men and women: the Tromso Study. *Stroke*. 2011;42:972-8

16. Stegger JG, Schmidt EB, Obel T, Berentzen TL, Tjonneland A, Sorensen TI, Overvad K. Body composition and body fat distribution in relation to later risk of acute myocardial infarction: a Danish follow-up study. *Int J Obes*. 2011;35:1433-41

17. Johnsen SP, Overvad K, Sorensen HT, Tjonneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol*. 2002;55:602-7

18. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases iii. *Stroke*. 1990;21:637-76

19. Hansson GK. Inflammatory mechanisms in atherosclerosis. *J Thromb Haemost*. 2009;7 Suppl 1:328-31

20. Roumen-Klappe EM, den Heijer M, van Uum SH, van der Ven-Jongekrijg J, van der Graaf F, Wollersheim H. Inflammatory response in the acute phase of deep vein thrombosis. *J Vasc Surg*. 2002;35:701-6

21. Reich LM, Folsom AR, Key NS, Boland LL, Heckbert SR, Rosamond WD, Cushman M. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. *J Thromb Haemost*. 2006;4:1909-13

22. van der Hagen PB, Folsom AR, Jenny NS, Heckbert SR, O'Meara ES, Reich LM, Rosendaal FR, Cushman M. Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study. *J Thromb Haemost*. 2006;4:1903-8

23. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*. 2005;162:975-82

24. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: Results from the Copenhagen City Heart Study. *Circulation*. 2010;121:1896-1903

25. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: The longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162:1182-9

26. Wattanakit K, Lutsey PL, Bell EJ, Gornik H, Cushman M, Heckbert SR, Rosamond WD, Folsom AR. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thromb Haemost*. 2012;108:508-15

27. Roach RE, Lijfering WM, Flinterman LE, Rosendaal FR, Cannegieter SC. Increased risk of CVD after VT is determined by common etiologic factors. *Blood*. 2013;121:4948-54

28. Roncaglioni MC, Santoro L, D'Avanzo B, Negri E, Nobili A, Ledda A, Pietropaolo F, Franzosi MG, La Vecchia C, Feruglio GA, et al. Role of family history in patients with myocardial infarction. An italian case-control study. GISSI-EFRIM Investigators. *Circulation*. 1992;85:2065-72

29. Nielsen M, Andersson C, Gerds TA, Andersen PK, Jensen TB, Kober L, Gislason G, Torp-Pedersen C. Familial clustering of myocardial infarction in first-degree relatives: A nationwide study. *Eur Heart J*. 2013;34:1198-1203

30. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso Study. *J Thromb Haemost*. 2008;6:1851-7

31. Quist-Paulsen P, Naess IA, Cannegieter SC, Romundstad PR, Christiansen SC, Rosendaal FR, Hammerstrom J. Arterial cardiovascular risk factors and venous thrombosis: Results from a population-based, prospective study (the HUNT 2). *Haematologica*. 2010;95:119-25

32. Ye Z, Liu EH, Higgins JP, Keavney BD, Lowe GD, Collins R, Danesh J. Seven haemostatic gene polymorphisms in coronary disease: Meta-analysis of 66,155 cases and 91,307 controls. *Lancet*. 2006;367:651-8

33. Mahmoodi BK, Brouwer JL, Veeger NJ, van der Meer J. Hereditary deficiency of protein C or protein S confers increased risk of arterial thromboembolic events at a young age: Results from a large family cohort study. *Circulation*. 2008;118:1659-67

34. Doggen CJ, Rosendaal FR, Meijers JC. Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: Opposite and synergistic effects of factors XI and XII. *Blood*. 2006;108:4045-51

35. Thogersen AM, Jansson JH, Boman K, Nilsson TK, Weinehall L, Huhtasaari F, Hallmans G. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: Evidence for the fibrinolytic system as an independent primary risk factor. *Circulation*. 1998;98:2241-7

36. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: A meta-analysis of case-control studies. *Neurology*. 2000;55:1172-9

37. Grogono J, Fitzsimmons SJ, Shah BN, Rakhit DJ, Gray HH. Simultaneous myocardial infarction and ischaemic stroke secondary to paradoxical emboli through a patent foramen ovale. *Clin Med*. 2012;12:391-2

38. Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. *Arterioscler Thromb Vasc Biol*. 1998;18:1400-7

39. Rennenberg RJ, van Varik BJ, Schurgers LJ, Hamulyak K, Ten Cate H, Leiner T, Vermeer C, de Leeuw PW, Kroon AA. Chronic coumarin treatment is associated with increased extracoronary arterial calcification in humans. *Blood*. 2010;115:5121-3

40. Lam CS, Little WC. Sex and cardiovascular risk: Are women advantaged or men disadvantaged? *Circulation*. 2012;126:913-15

41. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: Evolving knowledge. *J Am Coll Cardiol*. 2009;54:1561-75

42. Choudhury L, Marsh JD. Myocardial infarction in young patients. *Am J Med*. 1999;107:254-61

43. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1990;323:147-52

44. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. *Lancet*. 1994;343:499-503

45. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, Soff G, Parameswaran R, Hassoun H. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: A large retrospective analysis. *J Clin Oncol*. 2011;29:3466-73

46. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, Grandone E, Prandoni P, Investigators W. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366:1959-67

47. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J, Investigators A. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367:1979-87

Figure legend:

Figure 1.

Changes in crude incidence rate per 1000 person-years of arterial thrombotic disease (a), myocardial infarction (b) and ischemic stroke (c) with time after an episode of venous thromboembolism (VTE), deep vein thrombosis (DVT) or pulmonary embolism (PE).

Table 1. Baseline characteristics of participants without venous thromboembolism (VTE) or arterial thrombotic disease (ATD), with VTE only, ATD only, and ATD after VTE during follow-up (n= 81 687). P values denote statistical differences between the four groups.

	No event (n = 74 225)	**VTE only (n = 1 118)**	**ATD only (n= 6 254)**	**VTE & ATD (n = 90)**	**P**
% (n)/ mean ± SD					
Age (years)	53 ± 10	57 ± 10	60 ± 9	62 ± 10	< 0.001
Sex (male)	45.5 (33 764)	50.9 (569)	63.1 (3 949)	51.1 (46)	< 0.001
BMI (kg/ m²)	25.6 ± 4.0	26.8 ± 4.4	26.8 ± 4.2	28.5 ± 4.6	< 0.001
Self-reported diabetes	1.6 (1 187)	2.4 (27)	5.1 (318)	5.6 (5)	< 0.001
Hypertension*	19.8 (14 708)	29.3 (328)	44.6 (2 792)	55.6 (50)	< 0.001
Hypercholesterolemia†	14.0 (10 378)	24.1 (269)	31.1 (1 942)	33.3 (30)	< 0.001
Smoking‡	35.3 (26 174)	37.1 (414)	46.6 (2 912)	41.1 (37)	< 0.001
Physical activity§	58.8 (43 420)	51.2 (572)	46.0 (2 877)	37.8 (34)	< 0.001
Education‖	24.7 (18 344)	19.1 (213)	15.7 (980)	11.1 (10)	< 0.001

* Mean systolic/diastolic blood pressure ≥ 140/≥ 90 mmHg, use of blood pressure lowering drugs or self-reported hypertension.

† Total cholesterol ≥ 6.5 mmol/L, use of lipid lowering drugs or self-reported hypercholesterolemia.

‡ Self-reported daily smoking, yes/no.

§ ≥1 hour of moderate or high physical activity per week, yes/no.

‖ >10 years of education.

Table 2. Characteristics of venous thromboembolism (VTE) events (n=1 208).

	% (n)
Clinical characteristics*	
Deep vein thrombosis	53.6 (648)
Pulmonary embolism	35.1 (424)
Unprovoked VTE	42.5 (513)
Provoked VTE	45.4 (548)
Clinical risk factors	
Estrogen use†	17.2 (208)
Other medical conditions‡	12.1 (146)

* Information on localization (deep vein thrombosis or pulmonary embolism) available in n= 1 072. Information on classification (unprovoked or provoked) available in n= 1 061.

† Current or previous use of hormone replacement therapy or oral contraceptives.

‡ Myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, inflammatory bowel disease, chronic infections or myeloproliferative disorders.

Table 3. Incidence rates (IR) and hazard ratios (HR) with 95% confidence interval (CI) for arterial thrombotic disease (ATD), myocardial infarction (MI) and ischemic stroke after venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE).

	Person-years	**ATD-events**	**Crude IR(95% CI) ***	**HR (95% CI) †**	**HR (95% CI) †‡**
Total ATD					
No VTE	967 604	6 254	6.5 (6.3-6.6)	Ref.	Ref.
VTE	5 039	90	17.9 (14.5-22.0)	1.42 (1.15-1.75)	1.35 (1.09-1.66)
DVT	3 277	49	14.9 (11.3-19.8)	1.13 (0.85-1.50)	1.07 (0.81-1.42)
PE	1 870	42	22.5 (16.6-30.4)	1.89 (1.40-2.57)	1.82 (1.35-2.47)
MI					
No VTE	948 179	3 613	3.8 (3.7-3.9)	Ref.	Ref.
VTE	4 887	53	10.8 (8.3-14.2)	1.40 (1.07-1.84)	1.31 (1.00-1.72)
DVT	3 182	26	8.2 (5.6-12.0)	0.98 (0.66-1.44)	0.92 (0.63-1.36)
PE	1 813	27	14.9 (10.2-21.7)	2.16 (1.48-3.16)	2.02 (1.38-2.95)
Ischemic stroke					
No VTE	941 549	2 641	2.8 (2.7-2.9)	Ref.	Ref.
VTE	4 874	37	7.6 (5.5-10.5)	1.37 (0.99-1.90)	1.33 (0.96-1.84)
DVT	3 189	23	7.2 (4.8-10.8)	1.26 (0.83-1.90)	1.21 (0.80-1.83)
PE	1 793	15	8.4 (5.0-13.9)	1.55 (0.93-2.57)	1.53 (0.92-2.55)

* Per 1000 person-years.

† Age (as time scale) and sex-adjusted HR

‡ Adjusted for age, sex, BMI, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, education level.

Table 4. Age and sex-stratified incidence rates (IR) and hazard ratios (HR) with 95% confidence interval (CI) for arterial thrombotic disease (ATD), myocardial infarction (MI) and ischemic stroke after venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE).

	Person-years	**ATD-events**	**IR(95% CI) ***	**HR (95% CI) †**	**Multivariable HR(95% CI) †‡**
Total ATD					
Women < 65					
No VTE	359 227	744	2.1 (1.9-2.2)	Ref.	Ref.
VTE	892	9	10.1 (5.2-19.4)	4.08 (2.11-7.88)	3.28 (1.69-6.35)
DVT	546	6	11.0 (4.9-24.5)	4.45 (1.99-9.94)	3.32 (1.48-7.44)
PE	350	3	8.57 (2.8-26.6)	3.42 (1.10-10.62)	3.10 (0.99-9.66)
Women ≥ 65					
No VTE	165 106	1 561	9.5 (9.0-9.9)	Ref.	Ref.
VTE	1 450	35	24.1 (17.3-33.6)	1.63 (1.16-2.28)	1.55 (1.11-2.18)
DVT	843	19	22.5 (14.4-35.3)	1.44 (0.92-2.27)	1.40 (0.89-2.21)
PE	655	16	24.4 (15.0-39.9)	1.76 (1.07-2.88)	1.64 (1.00-2.69)
Men < 65					
No VTE	319 284	1 835	5.7 (5.5-6.0)	Ref.	Ref.
VTE	1 255	20	15.9 (10.3-24.7)	2.24 (1.44-3.48)	2.06 (1.32-3.20)
DVT	908	10	11.0 (5.9-20.5)	1.55 (0.83-2.89)	1.40 (0.75-2.61)
PE	354	10	28.2 (15.2-52.5)	3.87 (2.08-7.20)	3.74 (2.01-6.97)
Men ≥ 65					
No VTE	123 986	2 114	17.0 (16.3-17.8)	Ref.	Ref.
VTE	1 442	26	18.0 (12.3-26.5)	0.85 (0.57-1.25)	0.83 (0.56-1.22)
DVT	979	14	14.3 (8.5-24.1)	0.64 (0.38-1.08)	0.61 (0.32-1.04)
PE	511	13	25.5 (14.8-43.8)	1.31 (0.76-2.26)	1.36 (0.79-2.34)
MI					
Women < 65					
No VTE	355 271	337	0.9 (0.8-1.1)	Ref.	Ref.
VTE	864	5	5.8 (2.4-13.9)	5.21 (2.15-12.62)	3.62 (1.49-8.80)
DVT	524	3	5.7 (1.8-17.8)	5.16 (1.66-16.10)	3.35 (1.07-10.46)
PE	345	2	5.8 (1.4-23.2)	5.16 (1.28-20.74)	4.06 (1.00-16.40)
Women ≥ 65					
No VTE	160 591	828	5.2 (4.8-5.5)	Ref.	Ref.
VTE	1 401	19	13.6 (8.6-21.3)	1.54 (0.98-2.44)	1.41 (0.89-2.24)

DVT	814	11	13.5 (7.5-24.4)	1.46 (0.80-2.66)	1.37 (0.76-2.51)
PE	636	8	12.6 (6.3-25.2)	1.54 (0.77-3.10)	1.36 (0.68-2.74)
Men < 65					
No VTE	312 631	1 187	3.8 (3.6-4.2)	Ref.	Ref.
VTE	2 147	13	10.6 (6.2-18.3)	2.32 (1.34-4.01)	2.11 (1.22-3.65)
DVT	879	5	5.7 (2.4-13.7)	1.24 (0.51-2.98)	1.10 (0.46-2.65)
PE	349	8	22.9 (11.5-45.8)	4.89 (2.44-9.81)	4.80 (2.39-9.62)
Men ≥ 65					
No VTE	1 221	1 261	10.5 (10.0-11.1)	Ref.	Ref.
VTE	1 401	16	11.4 (7.0-18.6)	0.84 (0.51-1.38)	0.81 (0.50-1.34)
DVT	965	7	7.2 (3.5-15.2)	0.50 (0.24-1.04)	0.47 (0.22-1.00)
PE	484	9	18.6 (9.7-35.8)	1.59 (0.82-3.06)	1.65 (0.85-3.18)
Ischemic stroke					
Women < 65					
No VTE	355 440	407	1.1 (1.0-1.3)	Ref.	Ref.
VTE	864	4	4.6 (1.7-12.3)	3.34 (1.25-8.95)	3.16 (1.18-8.47)
DVT	529	3	5.7 (1.8-17.6)	4.12 (1.32-12.83)	3.66 (1.17-11.42)
PE	338	1	2.9 (0.4-22.0)	2.08 (0.29-14.79)	2.14 (0.30-15.30)
Women ≥ 65					
No VTE	159 963	733	4.6 (4.3-4.9)	Ref.	Ref.
VTE	1 404	16	11.4 (7.0-18.6)	1.67 (1.02-2.75)	1.66 (1.01-2.74)
DVT	812	8	9.9 (4.9-19.7)	1.40 (0.70-2.81)	1.42 (0.70-2.86)
PE	641	8	12.5 (6.2-25.0)	1.89 (0.94-3.80)	1.81 (0.90-3.65)
Men < 65					
No VTE	308 473	648	2.1 (1.9-2.3)	Ref.	Ref.
VTE	1 199	7	5.8 (2.8-12.2)	2.13 (1.01-4.50)	1.95 (0.93-4.12)
DVT	883	5	5.7 (2.4-13.6)	2.09 (0.87-5.03)	1.88 (0.80-4.54)
PE	324	2	6.2 (1.5-24.6)	2.16 (0.54-8.65)	2.08 (0.52-8.34)
Men ≥ 65					
No VTE	117 674	853	7.2 (6.8-7.7)	Ref.	Ref.
VTE	1 407	10	7.1 (3.8-13.2)	0.79 (0.42-1.47)	0.77 (0.41-1.44)
DVT	965	7	7.2 (3.5-15.2)	0.77 (0.37-1.62)	0.74 (0.35-1.56)
PE	490	4	8.2 (3.1-21.8)	0.98 (0.37-2.63)	1.02 (0.38-2.72)

* Per 1000 person-years.

† Age (as time scale).

‡ Adjusted for age, BMI, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, education level.