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Bidirectional association between arterial and venous thrombosis

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Summary

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent and potentially fatal cardiovascular disease (CVD). VTE and arterial CVD (i.e. myocardial infarction (MI) and ischemic stroke) have been considered as separate diseases. However, recent studies have proposed an association between VTE and arterial CVD. The aim of the thesis was to investigate this association in a general population.

Papers I-III are prospective cohorts with participants from general populations (i.e. the Tromsø Study (papers I-III) and the Diet, Cancer and Health Study (paper II)). Paper IV is a matched cohort with participants attending ≥ 2 carotid ultrasounds in the Tromsø Study.

Incident MI was associated with a transient increase in VTE risk, and a particularly high risk was found for PE during the first 6 months after MI. MI explained 6% of the PE events in the population. Incident VTE was associated with increased risk of future arterial CVD independent of atherosclerotic risk factors in all women and men < 65 years of age, and explained 1% of the arterial thrombotic events in the population. The risk of arterial CVD was particularly high the first year after a PE. Family history of MI (FHMI) was a risk factor for both MI and VTE in a cause-specific and a traditional Cox model. The association between FHMI and VTE applied to unprovoked DVT and was neither explained by atherosclerotic risk factors nor MI as an intermediate event. We found that incident VTE was associated with plaque progression in subjects with carotid plaques, but not with novel carotid plaque formation. The possible association between VTE and carotid plaque progression was not mediated by chronic inflammation secondary to the VTE.

Based on our findings, there appears to be a bidirectional and transient association between VTE and arterial CVD. Family history of MI is a shared risk factor for VTE and MI, and atherosclerosis may partly mediate the association between VTE and future arterial CVD.

Sammendrag

Venøs tromboembolisme (VTE) inkluderer dyp venetrombose (DVT) og lungeemboli (LE) og er en hyppig og potensielt dødelig kardiovaskulær sykdom (KVS). VTE og arteriell KVS (hjerteinfarkt og slag) ble tidligere ansett for å være separate sykdommer. Nyere studier har imidlertid antydet en mulig sammenheng mellom VTE og arteriell KVS. Målet med denne avhandlingen var å undersøke sammenhengen mellom VTE og arteriell KVS i en generell befolkning.

Artikkel I-III er prospektive kohorter med deltakere fra generelle befolkninger (Tromsøundersøkelsen (artikkel I-III) og Diet, Cancer and Health-studien (artikkel II)). Artikkel IV er en kohort av de med ≥2 karotisultralydmålinger i Tromsøundersøkelsen.

Førstegangs hjerteinfarkt var assosiert med en forbigående økt risiko for VTE, og risikoen var spesielt høy for LE de første 6 månedene etter hjerteinfarkt. Hjerteinfarkt forklarte 6% av LE-hendelsene i populasjonen. Førstegangs VTE økte risikoen for fremtidig arteriell KVS uavhengig av aterosklerotiske risikofaktorer blant alle kvinner og menn <65 år, spesielt det første året etter LE, og forklarte 1% av tilfellene med arteriell KVS i populasjonen. Familiehistorie av hjerteinfarkt var en risikofaktor for både hjerteinfarkt og VTE, både i en årsaks-spesifikk og en tradisjonell Cox-modell. Sammenhengen mellom familiehistorie av hjerteinfarkt og VTE gjaldt uprovosert DVT og kunne ikke forklares av aterosklerotiske risikofaktorer eller hjerteinfarkt. Førstegangs VTE var forbundet med økt progresjon, men ikke nydannelse av åreforkalkning på halspulsåren. Den mulige sammenhengen mellom VTE og åreforkalkning var ikke mediert av lavgradig inflammasjon.

Basert på våre funn synes det å være en toveis og forbigående sammenheng mellom VTE og arteriell KVS. Familiehistorie av hjerteinfarkt er en felles risikofaktor for VTE og hjerteinfarkt, og åreforkalkning kan mediere sammenhengen mellom VTE og arteriell KVS.

List of papers

The thesis is based on the following papers:

1. Impact of incident myocardial infarction on the risk of venous thromboembolism: the Tromsø Study.

   Rinde LB, Lind C, Småbrekke B, Njølstad I, Mathiesen EB, Wilsgaard T, Løchen ML, Hald EM, Vik A, Braekkan SK, Hansen JB.

   J Thromb Haemost. 2016 Jun;14(6):1183-91.

2. Impact of incident venous thromboembolism on risk of arterial thrombotic diseases.

   Lind C, Flinterman LE, Enga KF, Severinsen MT, Kristensen SR, Braekkan SK, Mathiesen EB, Njølstad I, Cannegieter SC, Overvad K, Hansen JB.

   Circulation. 2014 Feb 25;129(8):855-63.

3. Family history of myocardial infarction and cause-specific risk of myocardial infarction and venous thromboembolism: the Tromsø Study.

   Lind C, Enga KF, Mathiesen EB, Njølstad I, Brækkan SK, Hansen JB.

   Circ Cardiovasc Genet. 2014 Oct;7(5):684-91.

4. Impact of venous thromboembolism on the formation and progression of carotid atherosclerosis: the Tromsø Study.

   Lind C, Småbrekke B, Rinde LB, Hindberg K, Mathiesen EB, Johnsen SH, Arntzen KA, Njølstad I, Lijfering W, Brækkan SK, Hansen JB.

   Manuscript.

Abbreviations

ACCP: American College of Chest Physicians

AF: Atrial fibrillation

ARIC Study: Atherosclerosis Risk in Communities Study

APC: Activated protein C

BMI: Body mass index

CHS: Cardiovascular Health Study

CI: Confidence interval

CRP: C-reactive protein

CT: Computed tomography

CVD: Cardiovascular disease

DCH Study: Diet, Cancer and Health Study

DOAC: Direct oral anticoagulant

DVT: Deep vein thrombosis

F: Factor

GATE Study: Genetic Attributes and Thrombosis Epidemiology Study

HDL: High-density lipoprotein

HR: Hazard ratio

Hs-CRP: High-sensitivity C-reactive protein

HUNT Study: Helseundersøkelsen Nord-Trøndelag Study

ICD: International Classification of Diseases

IMT: Intima-media thickness

LDL: Low-density lipoprotein

LMWH: Low-molecular-weight heparin

MEGA Study: Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis Study

MI: Myocardial infarction

MRI: Magnetic resonance imaging

PAI-1: Plasminogen activator inhibitor 1

PE: Pulmonary embolism

PREVEND Study: Prevention of Renal and Vascular Endstage Disease Study

RCT: Randomized controlled trial

TF: Tissue factor

TPA: Total plaque area

UNN: University Hospital of North Norway

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

vWF: von Willebrand Factor

WHO: World Health Organization

1. Introduction

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), and has been acknowledged as the 3rd leading cause of cardiovascular death in Western countries, following myocardial infarction (MI) and ischemic stroke.[1] Although the clinical manifestations of VTE are diverse, pain, edema and erythema are prevalent symptoms and signs of DVT, and dyspnea, tachypnea and chest pain are frequent PE symptoms.[2] Previously, initial treatment with parenteral anticoagulants (e.g. low-molecular-weight heparin (LMWH)) and subsequent long-term treatment with vitamin K antagonists (VKAs, e.g. warfarin) was recommended for VTE patients without cancer, and LMWH was recommended as treatment for VTE patients with cancer.[3] Growing evidence supports that direct oral anticoagulants (DOACs), including direct thrombin inhibitors (e.g. dabigatran) and factor (F) Xa inhibitors (e.g. rivaroxaban and apixaban), have similar efficacy on VTE recurrence but reduced risk of bleedings when compared with warfarin for the long-term treatment of VTE.[4-7] In the present American College of Chest Physicians (ACCP) guidelines, DOACs are suggested over VKAs in the long-term treatment of VTE in patients without cancer.[8]

1.1 Epidemiology of venous thromboembolism

VTE is a frequent disease with an overall incidence rate ranging from 1 to 2 per 1000 in general populations.[9-14] The incidence of DVT is higher than the incidence of PE,[9-11] and the VTE incidence has consistently been shown to increase exponentially with advancing age.[9-11, 13, 14] Moreover, the VTE incidence has been found to vary according to ethnicity, with the highest incidence demonstrated in subjects of African-American origin, followed by subjects of Caucasian and then Hispanic and Asian origin.[12, 15] A significant increase in the incidence

of VTE has been reported during the last decades, regardless of improvements in VTE prophylaxis, diagnostics and treatment.[10, 16] Over-diagnosis due to increasing use of noninvasive diagnostic procedures such as computer tomography (CT) is suggested to partly explain this observed increase in VTE incidence. In agreement with this, the incidence but not the mortality of PE was found to increase after the introduction of CT.[17]

VTE has been shown to recur in 6 to 13% of VTE patients the initial year after the incident VTE diagnosis,[11, 13, 18] and in up to 30% within 10 years.[13, 18, 19] The highest risk of recurrence has been found during the initial 6 to 12 months after the incident VTE.[13, 18, 20] A particularly high risk of recurrence has also been reported in VTE patients with PE,[21] an unprovoked event,[22, 23] cancer,[20, 22] or high age.[11] Moreover, a tendency for VTE to recur at the same location as the initial event (i.e. DVT or PE) has been shown.[24] The post-thrombotic syndrome, including chronic pain, heaviness, venous stasis, skin changes and venous ulcers in the lower extremity, is the most common complication of DVT, and occurs in 20 to 50% of DVT patients.[13, 19, 22, 25] Specifically, patients with proximal DVT,[22, 26] high body mass index (BMI) or high age[22] have been found to have particularly high risk of the post-thrombotic syndrome. Pulmonary hypertension is a serious complication of PE resulting in elevated pulmonary artery pressure and persistent dyspnea, and occurs in 1 to 4% of PE patients.[23, 27-29]

VTE is also associated with increased risk of death, and up to 14%[9, 11, 30] and 30%[9, 19, 30] of VTE patients are reported to die the initial month and year after the VTE diagnosis, respectively. The highest risk of death has been demonstrated the initial time-period after the VTE diagnosis.[9, 31] A high risk of death has also been found in VTE patients with PE[9, 13, 15, 24] and cancer.[9, 11, 20, 32] Cancer has been identified as the strongest risk factor for all-cause mortality in VTE patients,[11, 32, 33] and PE was the cause or contributing cause of death in a considerable number of hospitalized patients, most of which died within 2.5 hours following the PE.[34]

1.2 Pathophysiology of venous thromboembolism

Autopsy and radiology studies have shown that venous thrombi originate near the vessel wall in the apex of venous valve pockets.[35, 36] In contrast to arterial thrombi, which are preceded by endothelial damage and are rich in platelets, venous thrombi may form independently from endothelial damage and mainly contain red blood cells and fibrin.[35] According to Virchow's triad, the development of venous thrombi results from hypercoagulable changes of the blood composition, alterations of the vessel wall and blood stasis (Figure 1).[37]

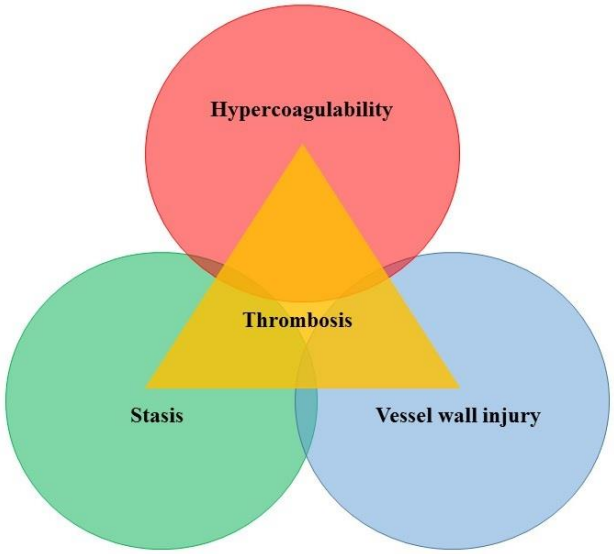

Figure 1. Virchow's triad. Venous thrombus formation results from hypercoagulability, alterations of the vessel wall (e.g. vessel wall injury) and blood stasis.

Stasis frequently occurs in venous valve pockets,[38] and traps the blood in a secondary vortex and triggers hypoxia.[39, 40] Hypoxia in turn modulates the endothelial cells in the venous valve pocket to express adhesion molecules, release chemo attractants and alter the balance of anti- and pro-coagulant proteins.[40-44] This results in binding of circulating leukocytes (e.g. monocytes), platelets and extracellular vesicles (Figure 2).[40, 45, 46] Hypoxia may also activate leukocytes to release extracellular vesicles (Figure 2).[47] Extracellular vesicles are highly pro-coagulant because of presence of tissue factor (TF) and exposure of negatively charged

phospholipids such as phosphatidyl serine on the surface.[48, 49] TF may initiate the coagulation cascade by binding to FVII/VIIa and the TF-FVIIa complex, and phosphatidyl serine facilitates assembly of coagulation factors.[50]

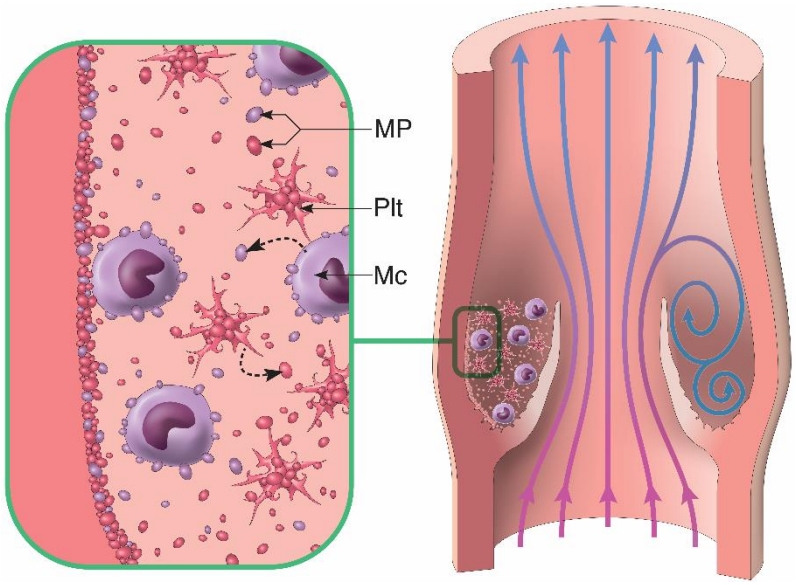

Figure 2. The pathophysiology of venous thromboembolism. The blood is trapped in the venous valve pockets, and subsequent hypoxia promotes a pro-coagulant response in the endothelial cells of the valve pocket and activates blood cells (e.g. platelets (Plt) and monocytes (Mc)). This results in binding of leukocytes, platelets and micro particles (MP, i.e. extracellular vesicles) at the endothelial surface, and release of pro-coagulant extracellular vesicles from the activated blood cells.

Results of emerging studies indicate that venous thrombi originate in deep calf veins,[51, 52] and gradually grow proximally[53] and become symptomatic due to vessel obstruction and impaired venous return.[53, 54] However, thrombi solely in the ilio-femoral veins were found in some DVT patients,[36, 52] indicating that venous thrombi may originate in more proximal veins than calf veins. Thrombi may break free from the lower extremity veins and cause PE if they pass through the right side of the heart, reach the lungs and obstruct a pulmonary artery (Figure 3). In accordance with this, half of the venous thrombi in DVT patients were non-adherent to the vessel wall,[52] and evidence of PE has been demonstrated in nearly 40% of DVT patients without PE symptoms.[55] Moreover, the risk of PE has been

shown to increase with increasing proximity of the DVT to the pelvis.[56-58] Conversely, other studies have shown that only 40 to 60% of PE patients had a concurring leg thrombus,[57, 59, 60] and that PE without DVT was particularly prevalent after trauma[60] and occurred secondary to atrial fibrillation (AF) in 15%.[61] This suggests that PE may arise independently from DVT.

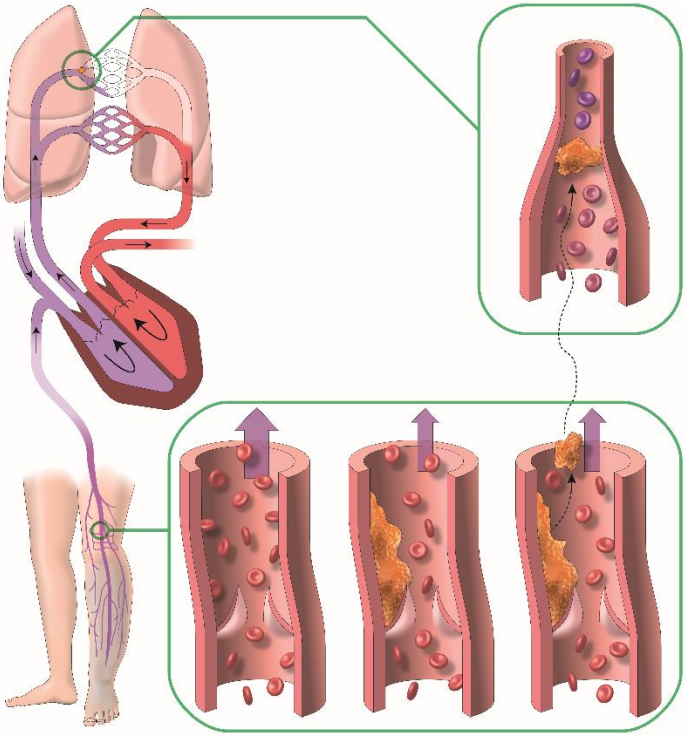

Figure 3. The pathophysiology of deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thrombus formation takes place in valve pockets of deep veins in the lower extremities. Parts of a venous leg thrombus may break free, follow the blood through the right side of the heart and obstruct a pulmonary artery, resulting in PE.

1.3 Risk factors for venous thromboembolism

VTE is a complex disease associated with multiple hereditary and acquired factors (i.e. risk factors). Even if several risk factors for VTE have been identified, 25 to 50% of VTE events in a general population were unprovoked and not attributed to presently known risk factors for VTE.[11, 62] In most VTE patients, a combination of several underlying risk factors has been found.[11, 62] Moreover, the risk of VTE has been shown to change according to age.[9, 11, 13, 14]

Therefore, a dynamic and age-dependent VTE risk model has been proposed.[63] In this model, risk factors interact and venous thrombi form when the combination of risk factors yield a thrombosis potential exceeding the thrombosis threshold of a subject (Figure 4).[63]

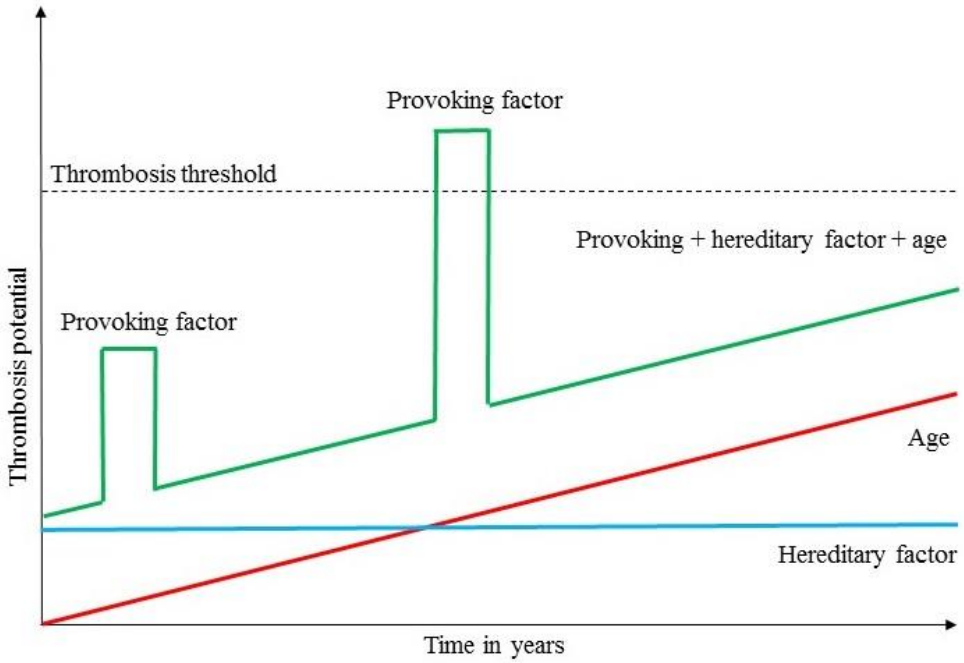

Figure 4. The thrombosis potential model. The blue line represents a hereditary risk factor for VTE (e.g. Factor V Leiden), and the red line represents increasing age. The green line represents the combined effect of the hereditary factor, age and provoking factors (e.g. trauma, surgery or use of oral contraceptives) on the thrombosis potential at different time points. The former combination of risk factors is not sufficient to cause VTE, whereas in the latter situation, the thrombosis potential exceeds the thrombosis threshold.

1.3.1 Hereditary risk factors

Family-based and twin studies have shown that VTE has a strong genetic risk component and an estimated heritability of 50 to 60%.[64-66] The first genetic risk factor discovered for VTE was antithrombin deficiency, which is caused by mutations in the SERPINC1 gene. Antithrombin deficiency is present in approximately 0.02% of the population[67, 68] and has been found to increase the risk of VTE 10-fold.[67] Shortly after the discovery of antithrombin deficiency, non-O blood groups were identified as a genetic risk factor for VTE.[67] Non-O

blood groups are highly prevalent and were present in 70% of VTE patients and 54% of healthy controls in a large meta-analysis.[69] Non-O blood groups have been shown to increase the risk of VTE by 1.5 to 2-fold compared with the O blood group,[67, 70-73] and the risk of VTE associated with non-O blood groups was particularly high for unprovoked events[70] and in subjects with thrombophilia (e.g. FV Leiden or prothrombin 20210A carriers).[70, 72, 74] Non-O blood groups are believed to mediate VTE risk through elevated levels of von Willebrand Factor (vWF) and FVIII,[71] which are demonstrated to have a positive dose-response relationship with VTE occurrence.[75, 76] In agreement with this, genetic loci associated with plasma levels of vWF and FVIII have been identified as risk factors for VTE.[77, 78] However, non-O blood groups remained significantly associated with VTE after taking vWF and FVIII levels into consideration in some studies,[73, 79] which implies that non-O blood groups may mediate VTE risk through other mechanisms than elevated vWF and FVIII levels.

Protein C and S deficiencies have later been identified as risk factors for VTE, and are caused by gene mutations present in 0.03 to 0.2% of the population.[67, 80] Activated protein C (APC) limits clot formation by inactivating FV and FVIII,[67] and low levels or deficiency of protein C have been found to increase the risk of VTE 3 to 7 times.[79, 81, 82] Protein S is a cofactor to APC, and both low and deficient protein S have been demonstrated to increase the risk of VTE.[83-85] FV Leiden is a mutation in the factor V gene resulting in hypercoagulability due to reduced ability of FV to be inactivated by APC.[86, 87] FV Leiden has a frequency of approximately 5% in the European population,[67, 87] and has been found to increase the risk of VTE 3 to 5-fold.[67, 69, 88, 89] The highest risk of VTE associated with FV Leiden has been found for DVT compared with PE.[69, 89, 90] A particularly high risk of VTE has also been shown in homozygous or young FV Leiden carriers.[89] Furthermore, FV Leiden has been demonstrated to have a synergistic effect with oral contraceptives,[89, 90] pregnancy,[91] smoking,[92] obesity[92, 93] and the prothrombin 20210A mutation[89, 90] on the risk of VTE.

The discovery of FV Leiden was followed by the identification of prothrombin 20210A as a potential risk factor for VTE.[67] Prothrombin 20210A is a prothrombin mutation found to significantly increase the plasma prothrombin level.[94] The prothrombin 20210A mutation has a reported prevalence of 2% in the population,[67, 95] and has been shown to increase the risk of VTE 3-fold.[67, 89, 94] Furthermore, prothrombin 20210A has been found to have a stronger effect on VTE risk in women commencing oral contraceptives,[89, 90] pregnant women,[91] heavy smokers[92, 93] and obese.[92] In contrast, other studies have reported that prothrombin 20210A did not significantly increase the risk of VTE after taking factors such as age, sex, BMI, smoking and oral contraceptive use into account,[96] and that prothrombin 20210A was not associated with VTE in the elderly.[97]

During the last two decades, technological advances have made it possible to detect new genetic risk factors for VTE,[67, 88] and 12 genes harboring novel risk alleles for VTE have consistently been identified in genome-wide association studies.[88] Although most of these novel risk alleles have a high frequency in the population, they have been shown to contribute to a small increase in the VTE risk,[88] and are estimated to explain only 5% of the observed heritability of VTE.[88, 98] Consequently, the vast majority of the genetic susceptibility to VTE remains unknown. Hopefully, recent genetic strategies such as next-generation sequencing and whole exome and genome sequencing will reveal yet unknown genetic variants influencing the risk of VTE.[88]

1.3.2 Acquired risk factors

Numerous acquired risk factors for VTE are presently known. Advancing age is an established risk factor for VTE, and the incidence of VTE has consistently been shown to rise exponentially with increasing age.[9, 11, 13, 14] Subjects aged 70 years or older had more than 11

times increased risk of VTE compared with subjects below 50 years of age in the Tromsø Study[14] and more than 3 times higher risk of VTE than those aged 45 to 69 years in the Helseundersøkelsen Nord-Trøndelag (HUNT) Study.[9] The increase in VTE risk associated with increasing age could be explained by accumulation of conventional risk factors for VTE with advancing age (e.g. comorbid conditions or hypercoagulability due to increased plasma pro-coagulants and reduced coagulation inhibitors), age-specific risk factors (e.g. endothelial dysfunction or venous stasis), or a synergistic effect of age with other established risk factors for VTE.[38, 99, 100]

The results regarding the association between sex and VTE are conflicting. Some studies have found similar overall incidence of VTE in men and women,[16, 101] whereas most studies have shown a higher overall risk of VTE in men.[11, 13, 102-104] Moreover, middle-aged and elderly men had higher risk of VTE than women of the same age,[9, 13, 14] whereas women had higher risk of VTE than men during childbearing years in some studies.[9, 13, 105] However, the risk of VTE was 2 times higher in men than women when female reproductive risk factors were taken into account in the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) Study,[106] supporting that male sex also is a risk factor for first VTE.

Body height, pregnancy and endogenous or exogenous hormones may contribute to the observed difference in VTE incidence in men and women. Tall stature has been identified as a risk factor for VTE in men,[104, 107] and the risk of VTE in men increased by 34% per 10 cm increase in height in the Tromsø Study.[107] An association between pregnancy and VTE has consistently been reported, and pregnancy has been found to increase the VTE risk 4 to 5–fold.[91, 108] Specifically, the highest VTE risk associated with pregnancy has been shown during the postpartum period (i.e. the first 3 months after delivery)[91, 108] and in women with thrombophilia.[91] In addition, oral contraceptives are established risk factors for VTE in

women,[94, 109, 110] and have been shown to increase the risk of VTE 2 to 7 times, especially the first months of use.[94, 110] An association between oral contraceptives and VTE may be explained by an acquired APC resistance found in women commencing oral contraceptives.[111] Furthermore, hormone replacement therapy (i.e. with estrogens) in postmenopausal women has been reported to increase the risk of VTE 2 to 3 fold.[112, 113]

Institutionalization (i.e. admittance to a hospital or nursing home) has also been proven an important risk factor for VTE,[11, 15, 62] and accounted for more than 50% of the VTE events in the population.[11, 62] Recent hospitalization has been shown to increase the risk of VTE 6- to 8-fold,[114, 115] and the incidence of in-hospital VTE was more than 100 times higher than the incidence of VTE in community residents in a general population.[116] Accordingly, recognition of hospitalized patients in need of VTE prophylaxis should be emphasized. In order to improve identification of hospitalized patients at high risk of VTE, the Padua Prediction Score for VTE has been proposed.[117] In this prediction model, 11 VTE predictors are included, and those with a cumulative score ≥ 4 (i.e. 3 points each for active cancer, previous VTE, reduced mobility and known thrombophilia, 2 points for recent trauma and/or surgery, and 1 point each for age ≥ 70, heart and/or respiratory failure, acute MI or ischemic stroke, acute infection and/or rheumatologic disorder, obesity and ongoing hormonal treatment) are defined as high risk patients in need of VTE prophylaxis.[117] A high risk of VTE according to the Padua Prediction Score has been demonstrated in 40% of hospitalized medical patients,[117] and medical prophylaxis of VTE has been found to significantly reduce the risk of VTE by 50 to 70%.[118-120] Therefore, VTE prophylaxis is recommended for hospitalized patients at high risk of VTE without the risk of bleeding.[109, 121] Furthermore, VTE treatment has been recognized as a huge economic burden for a hospital, associated with 4 times higher costs compared with VTE prophylaxis.[122] Still, a systematic review revealed that less than 20% of patients receive the appropriate VTE prophylaxis.[123]

The substantial impact of institutionalization on the incidence of VTE may be explained by comorbidities, surgery, trauma or immobilization. Several comorbid conditions and treatments, such as lower-extremity fractures and casts,[11] heart failure,[11, 15, 62] chronic obstructive pulmonary disease,[15] neurological diseases,[13] acute infections,[121] rheumatic and autoimmune diseases,[11, 15] kidney diseases,[11, 15] previous VTE,[56] superficial vein thrombosis,[13] varicose veins,[115] venous compression (e.g. by a mass or hematoma)[11] and cancer,[11, 13, 15] have been recognized as independent risk factor for VTE. Cancer has been acknowledged as a major cause of VTE, and was present in 20-30% of VTE patients.[9, 124, 125] Overall, 4 to 7 times increased risk of VTE has been shown in cancer patients compared with subjects without cancer,[115, 126-129] and VTE has been reported to occur in up to 10% of cancer patients.[129-133] The risk of VTE associated with cancer varies according to cancer site, severity and therapy and with time from the cancer diagnosis. The highest VTE risk has been found in patients with pancreatic, brain, lung, gastro intestinal and metastatic cancer,[126-130, 132, 134] cancer patients receiving chemotherapy,[126, 132] and during the initial months following the cancer diagnosis.[126-128, 130] Cancer has been shown to elevate levels of several pro-coagulant factors, such as TF, FV, FVII and FVIII,[135, 136] and cause activation and aggregation of platelets.[137, 138] This may in part explain the increased risk of VTE associated with cancer. Moreover, venous stasis and vessel wall injury due to tumor growth may contribute to VTE risk in cancer patients.[139]

Recent surgery and trauma have also repeatedly been reported as independent risk factors for VTE,[11, 15, 115] and were associated with 13 to 22-fold increased VTE risk in a general population.[115, 116] A particularly high risk of VTE has been found for invasive neurosurgery, urological, vascular and orthopedic surgeries,[140] and the incidence of VTE has been shown to increase with increasing trauma severity.[141] Furthermore, minor surgical procedures including central venous catheter and pacemaker insertions have also been

identified as risk factors for VTE.[62, 115] Finally, marked immobility has been shown to increase the risk of VTE,[11] and both general immobility[142] and immobilization during traveling[143] have been reported to nearly double the VTE risk.

1.4 Traditional atherosclerotic risk factors and the risk of venous thromboembolism

The association between traditional atherosclerotic risk factors (e.g. hypertension, dyslipidemia, diabetes mellitus and smoking) and VTE has extensively been explored, and the results are partly conflicting. Diabetes mellitus has been identified as a risk factor for VTE in some studies,[102, 144] and increased the risk of VTE 2-fold after adjusting for age and sex in a cohort study.[102] However, the majority of prospective cohort studies have failed to find an independent association between diabetes mellitus or high glucose levels and VTE.[103, 145-147] In a recently published meta-analysis including nearly 250 000 participants from prospective studies, an initially observed association between diabetes mellitus and VTE disappeared after adjusting for BMI.[148] This suggests that that an apparent association between diabetes mellitus and VTE is explained by obesity. Similarly, hypertension was associated with VTE risk in some studies,[103, 149] whereas most prospective cohorts and the aforementioned meta-analysis have shown that there is no association between hypertension and VTE after taking potential explanatory factors such as age, sex and obesity into account.[102, 146-148]

Results regarding the link between dyslipidemia, smoking, alcohol consumption and physical activity and VTE are also conflicting. In some studies, levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglycerides influenced the incidence of VTE.[103, 147, 150] Nevertheless, the majority of prospective cohorts and the recently published meta-analysis have reported that dyslipidemia, including elevated total cholesterol, LDL cholesterol and triglycerides and low HDL cholesterol, was not

independently associated with VTE.[102, 146, 148] Cigarette smoking has been shown to increase the risk of VTE 1.2 to 4.3-fold,[103, 147, 148, 151] and in the Diet, Cancer and Health (DCH) Study, a positive dose-response relationship was found between current cigarette smoking and the risk of VTE.[152] In contrast, other studies have failed to identify cigarette smoking as an independent risk factor for VTE.[102, 149] In the Tromsø Study, an initially observed association between increasing number of pack-years and provoked VTE disappeared after cancer and MI were taken into consideration.[153] This implies that an apparent association between smoking and VTE may be mediated by MI or cancer.

Most studies have shown that alcohol consumption is not a risk factor for VTE.[102, 103, 147] In the Tromsø Study, total alcohol consumption was not associated with increased risk of VTE, but sub-analyses revealed that liquor and wine consumption had an impact on the VTE risk.[154] Moderate physical activity has been found to protect against VTE, whereas strenuous or overall physical activity has been reported to increase the risk of VTE in some prospective cohorts.[147, 155] In contrast, other prospective cohorts have reported that physical activity is not associated with increased risk of VTE.[102, 103] In the Tromsø Study, overall physical activity was not associated with VTE, but strenuous physical activity increased the risk of VTE in the elderly, and moderate exercise was associated with a borderline significant decrease in VTE risk in young and lean subjects.[156]

Obesity is according to the World Health Organization (WHO) defined as BMI $\geq$ 30,[157] and has a reported prevalence of 13%[157] and 25%[158] in the adult population of the World and Norway, respectively. Obesity is the only traditional atherosclerotic risk factor, aside from advancing age, consistently reported as a risk factor for VTE,[144] and BMI $\geq$ 30 has been shown to increase the risk of VTE 1.5 to 3.1-fold.[102, 103, 147, 159-161] In agreement with this, advancing BMI and age were the only shared risk factors for VTE and MI when the influence of atherosclerotic risk factors on the risk of VTE and MI was investigated in the same

population.[101, 162] Moreover, high body weight,[160] total body fat,[160] waist[159-161] and hip circumference,[159-161] and waist-hip[103, 159, 161] and waist-height ratio[161] have also been identified as independent risk factors for VTE. In the Tromsø Study, waist circumference was the anthropometric measure found to identify most obesity-related VTE events.[159, 161]

Obesity is believed to mediate VTE risk through venous stasis, hypercoagulability, release of adipokines, or chronic low-grade inflammation. Venous stasis has been shown to accompany abdominal obesity due to increased intra-abdominal pressure,[163, 164] and increased levels of pro-coagulant factors (e.g. FVIII, vWF and fibrinogen) and decreased fibrinolytic activity has been found in obese.[165] Moreover, adipose tissue secrets adipokines which have been shown to increase the risk of venous disease.[166] Finally, chronic inflammation resulting from obesity[167] may increase the risk of VTE.[149, 168-171] In accordance with this, adjustments for high-sensitivity C-reactive protein (hs-CRP) attenuated the observed association between obesity and VTE in the Tromsø Study.[168]

1.5 Arterial cardiovascular disease and the risk of venous thromboembolism

VTE and arterial cardiovascular diseases (CVD) have traditionally been considered as a separate diseases with distinct pathophysiology and treatment strategies. However, results of emerging studies point to a potential interrelation between arterial and venous thrombosis. Few prospective cohorts have investigated the potential link between arterial thrombotic diseases and future risk of VTE, and the results of existing publications are diverging. An association between coronary heart disease and PE has been described in patients aged 60 years or older.[172] Furthermore, MI was associated with 2 times increased risk of subsequent VTE in a trial of postmenopausal women, whereas no association was found between stroke or transient ischemic attack and future VTE.[114] In contrast, atherothrombosis in cervico-

cranial and peripheral arteries but not in coronary arteries was associated with increased VTE risk in an autopsy study.[173] Moreover, incident coronary heart disease and stroke was associated with a 51% increased risk of future VTE in the Atherosclerosis Risk in Communities (ARIC) Study,[174] whereas a lower risk of VTE was found in those diagnosed with arterial thrombotic events after adjusting for traditional atherosclerotic risk factors in the Cardiovascular Health Study (CHS).[175]

Large Danish population-based registry-studies have demonstrated that hospitalizations for MI or stroke[176] and heart disease[177] were associated with substantially increased risk of VTE in the subsequent 3 months after taking age, sex and information regarding obesity, medication use and comorbidities from the Danish National Patient Registry into consideration. In a more recent study, incident acute MI was associated with 84% increased odds of incident VTE, but the association between MI and VTE disappeared after adjusting for traditional atherosclerotic and VTE risk factors, medication use and comorbidities.[178] The results from these studies should however be interpreted with some caution, as they have limited information on potential confounders, limited validation of both the exposure (arterial CVD) and outcome (i.e. VTE) of interest,[176, 177] or applied a retrospective design.[176-178] Consequently, prospective studies with validated information on exposure, outcome and potential confounders are needed.

1.6 Venous thromboembolism and the risk of arterial cardiovascular disease

Approximately 30% higher number of deaths from MI or ischemic stroke has been found in VTE patients than in the general population,[179] and growing evidence supports an interrelation between VTE and subsequent arterial CVD. An association between unprovoked VTE and future arterial thrombotic events has been described in several studies of VTE patients,[180-185]

and a 3- and 1.6- fold higher risk of arterial thrombosis has been found after adjusting for traditional atherosclerotic risk factors in unprovoked VTE patients compared with subjects without VTE from the general population[182] and provoked VTE patients,[181] respectively. Similarly, a higher frequency of arterial thrombotic events has been shown in patients with unprovoked than provoked PE[180, 184] and controls without PE.[184] However, the risk of arterial CVD in the aforementioned studies was assessed in selected cohorts (e.g. included VTE patients without permanent risk factors for VTE,[180] or did not include those with a short life-expectancy[180, 181] or controls from the general population[180, 181, 184]), or included a low number of study participants.[182]

A large population-based cohort from the Netherlands reported a 42% higher risk of MI, ischemic stroke and cardiovascular death combined after a VTE diagnosis, and showed that the association between VTE and future arterial thrombotic events only applied to unprovoked VTE.[186] However, subjects with previous VTE were not excluded in this study, and the impact of incident VTE on the risk of arterial CVD was not investigated.[186] Incident VTE was a substantial marker of subsequent arterial CVD risk during 20 years of follow-up in a large Danish population-based registry-study including more than 200 000 subjects.[187] In this study, the risk estimates of arterial CVD were similar for provoked and unprovoked VTE.[187] Nevertheless, information about potential confounders such as BMI was not available.[187]

An association between incident VTE and future arterial CVD was further confirmed in the MEGA study, in which VTE was associated with approximately 2 times increased risk of subsequent arterial CVD.[188] VTE patients had nearly 3 times higher risk of MI than controls from the general population without VTE after taking anticoagulant therapy, age, sex, BMI, smoking, chronic diseases and malignancy into account in this study, whereas no independent association was found between incident VTE and future ischemic stroke.[188]

However, information regarding arterial thrombotic diseases was based on discharge diagnoses only and not validated in the MEGA Study.[188] Therefore, further population-based studies with validated information regarding potential confounders and validated exposure and outcome events are needed.

1.7 Family history of myocardial infarction and the risk of venous thromboembolism

A family history of heart disease is an established risk factor with a 2-fold increased risk of MI.[189-191] The risk of MI increases with increasing number of first degree relatives with a history of heart disease[189, 190, 192] and is particularly high for those with relatives diagnosed with MI at a young age.[192, 193] Moreover, family history of MI has been shown to interact with other atherosclerotic risk factors on the risk of MI.[190-192]

A high genetic correlation between arterial and venous thrombotic diseases has been demonstrated,[65] and it has therefore been proposed that family history of MI may also increase the risk of VTE. An association between family history of MI and VTE has been confirmed in the Tromsø Study and the HUNT Study, in which subjects with at least one first degree relative with a history of MI before 60 years of age had approximately 30% increased risk of incident VTE after adjustment for other traditional atherosclerotic risk factors.[14, 149] Similarly, family history of MI was associated with 30% increased odds of VTE, and a particularly high risk of VTE was found in subjects with relatives with MI before the age of 50 years in the Genetic Attributes and Thrombosis Epidemiology (GATE) Study.[194] In contrast, subjects with a parental history of MI had only 3% increased risk of VTE and no association was found between a history of MI in a sibling and VTE risk in a registry-based study.[195] However, the results of this study are limited by lack of a prospective design,

validated VTE events and information regarding traditional atherosclerotic risk factors other than age and sex.[195]

Potentially, the association between family history of MI and VTE is explained by aggregation of common atherosclerotic risk factors or other shared genetic or environmental risk factors for MI and VTE. Furthermore, the observed association between MI and subsequent VTE[176, 177] could imply that the interrelation between family history of MI and VTE is mediated by MI. However, the mechanism for which family history of MI increases risk of VTE has not been assessed in previous studies.

1.8 Venous thromboembolism and the risk of atherosclerosis

Atherosclerosis is a chronic disease of the inner lining of arterial walls resulting in formation of atheromatous plaques.[196] The atheromatous plaques contain lipids, foam cells, leukocytes and smooth muscles cells covered by a fibrous cap that may rupture or obstruct the vessel lumen and cause arterial CVD.[196] Atherosclerosis is frequently measured by ultrasound assessments of carotid plaque presence and intima-media thickness (IMT), and was present in 25% of adults in a general population.[197] Presence of carotid plaques[198, 199] and high IMT[198, 200-205] have been identified as independent risk factors for MI and stroke, and improve the prediction of arterial CVD risk. Moreover, the risks of MI and stroke have been found to increase with 26% and 31%, respectively, per one standard deviation increase in IMT,[202] and to increase with advancing carotid plaque burden.[199] However, a meta-analysis of population-based studies showed that carotid plaques had higher accuracy for predicting arterial CVD than IMT,[206] and in prospective cohorts, carotid plaques, but not carotid IMT, were predictors of coronary heart disease.[198, 207]

Prandoni and coworkers were the first to demonstrate increased odds of plaques and high IMT on carotid ultrasound in unprovoked DVT patients after taking traditional atherosclerotic risk factors into account in a case-control study.[208] Based on these findings, an independent link between unprovoked VTE and subclinical atherosclerosis was proposed. An association between unprovoked VTE and atherosclerosis was confirmed in subsequent case-control studies, in which unprovoked VTE patients had substantially higher frequency of coronary artery calcification on CT angiography[209] and higher IMT and prevalence of plaques on carotid and femoral ultrasound[210] than controls after adjusting for traditional atherosclerotic risk factors. Furthermore, subjects above 50 years of age with unprovoked VTE had 15-fold increased odds of symptomatic and subclinical atherosclerosis, assessed by carotid IMT and plaque presence, in a case-control study.[211] In this study, provoked VTE was also associated with carotid atherosclerosis, but to a lesser extent than unprovoked VTE.[211] In contrast, provoked DVT has previously been shown to not increase the risk of atherosclerosis.[208, 212] An independent association between VTE and atherosclerosis may imply that atherosclerosis mediates the observed link between VTE and future arterial CVD.[187] However, the aforementioned case-control studies were not designed to explore the temporal sequence between VTE and subsequent atherosclerosis.

Prospective studies have failed to demonstrate increased risk of VTE in subjects with subclinical atherosclerosis.[174, 175, 213] No subclinical atherosclerosis measure was associated with increased risk of VTE in the ARIC Study.[174] Moreover, high risk carotid plaques decreased the risk of VTE by 35% in the CHS,[175] and in the Tromsø Study, increasing carotid IMT and total plaque area (TPA) increased the risk of future MI but not VTE in analyses adjusted for traditional atherosclerotic risk factors.[213] Carotid atherosclerosis was only measured at baseline and not updated during follow-up in the aforementioned cohorts.[174, 175, 213] Therefore, regression dilution bias may be present and potentially conceal a weak

association between atherosclerosis and subsequent VTE in these studies. Consequently, further studies with repeated carotid atherosclerosis measurements are warranted. A history of VTE was not significantly associated with preclinical atherosclerosis in a cohort of thrombophilia patients, although a borderline significant association was found between a history of VTE and IMT.[214] However, the association between incident VTE and subsequent carotid atherosclerosis has not been explored in a general population, and the potential impact of atherosclerosis on the observed association between incident VTE and future arterial CVD remains unsettled.

2. Aims of the thesis

The overall aims of this thesis were to investigate the bidirectional association between venous thromboembolism and arterial cardiovascular diseases, and to identify shared risk factors underlying this association.

The specific aims of the thesis were:

A: To investigate the association between myocardial infarction and the future risk of venous thromboembolism in a population-based cohort with validated information on the exposure, the endpoint, and potential confounders (Paper I).

B: To investigate the association between incident venous thromboembolism and future risk of arterial thromboembolic events in a general population (Paper II).

C: To determine the absolute and relative risks of myocardial infarction and venous thromboembolism by family history of myocardial infarction in a population-based cohort study (Paper III).

D: To compare the effect of family history of myocardial infarction on risks of myocardial infarction and venous thromboembolism explicitly by applying a cause-specific model, and explore whether the association between family history of MI and VTE could be explained by atherosclerotic risk factors (Paper III).

E: To investigate whether incident venous thromboembolism was associated with subsequent formation and progression of carotid atherosclerosis, and whether this possible association was mediated by low-grade inflammation in a population-based matched cohort study (Paper IV).

3. Study populations and methods

3.1 The Tromsø Study

The Tromsø Study is a single-center, population-based cohort study with repeated health surveys of inhabitants of Tromsø, Norway. It was initiated in 1974 to investigate potential explanations for the high cardiovascular mortality observed in Northern Norway in the 1970s.[215] Since the initiation, seven surveys have presently been conducted, and a wide range of chronic diseases has been included in the Tromsø Study. The fourth, fifth and sixth surveys of the Tromsø Study (Tromsø 4, 5 and 6, respectively) were conducted in 1994-95, 2001-02 and 2007-08, respectively. Tromsø 4 is the largest survey of the Tromsø Study. To this survey, all inhabitants aged 25 years or older living in Tromsø were invited, and 27 158 (77%) participated. Subjects aged 55-74 years and 5-10% of subjects in other 5-year age groups were offered a more extensive screening, to which 7 965 (78%) participated. Subjects attending the extensive screening in Tromsø 4 who were still alive and had not moved from Tromsø were re-invited to participate in Tromsø 5 and 6. In addition, random samples within different age groups of the Tromsø population were invited to participate in Tromsø 5 and 6, and 8 130 (79%) and 12 984 (66%) participated in these surveys, respectively. An extensive screening similar to the one in Tromsø 4 was conducted in Tromsø 5 and 6.

3.2 The Diet, Cancer and Health Study

The Diet, Cancer and Health Study was conducted in 1993-97 and is a prospective, population-based cohort study aiming to assess the interrelations between diet, lifestyle and cancer.[216] To the DCH Study, all inhabitants living in the urban areas of Copenhagen and Aarhus, Denmark, were identified from a computerized record of the Civil Registration System and invited by mail if they were born in Denmark, between 50 to 65 years of age and

did not have a cancer diagnosis in the Danish Cancer Registry at enrollment. In total, 57 054 (35%) participated.

3.3 Study designs

Paper II in the thesis was based on data from Tromsø 4 and the DCH, paper III was based on data from Tromsø 4 and 5, and papers I and IV were based on data from Tromsø 4-6. In papers I and III, the subjects were followed from the date of enrollment in the Tromsø Study through December 31, 2010. In paper II, the participants were followed from the date of enrollment in Tromsø 4 or the DCH Study and followed through December 31, 2010 and April 30, 2008, respectively. The participants in paper IV were followed from the date of enrollment in the Tromsø Study to the second carotid ultrasound in the extensive screenings in 2001-02 or 2007-08.

3.4 Baseline measurements

In the Tromsø and DCH Studies, baseline information was collected by self-administered questionnaires, blood samples and physical examinations. Questionnaires were used to obtain information on current smoking, physical activity, education level, hypertension, hypercholesterolemia, diabetes mellitus, cancer, MI, stroke, family history of coronary heart disease or MI, and medication use including hormone replacement therapy, oral contraceptives, anti-hypertensives and lipid-lowering drugs. Height and weight were measured with light clothing and without shoes, and BMI calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Obesity was classified according to the WHO definition (i.e. BMI $\geq$30).[157]

In the Tromsø Study, systolic and diastolic blood pressures were measured three times by trained personnel on the upper right arm at one minute intervals with an automatic device (Dinamap Vital Signs Monitor, 1846, Critikon, Tampa, Florida, USA) with the participant in a sitting position after two minutes of rest, and defined as the mean of the last two measurements. Non-fasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after 1 hour in room temperature, and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway (UNN), Tromsø, Norway. Total serum cholesterol was analyzed by use of an enzymatic colorimetric method with 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.

hs-CRP was measured after storage at -70 °C in Tromsø 4 and -20 °C in Tromsø 5 and 6, by a particle-enhanced immunoturbidimetric assay on a Modular P (Tromsø 4 and 6) or Hiatchi 917 (Tromsø 5) autoanalyzer (Roche Hiatchi, Mannheim, Germany), using reagents from Roche Diagnostics (Mannheim, Germany). Samples from Tromsø 4 were analyzed after 12 years of storage, and samples from Tromsø 5 and 6 were analyzed in batches at the time of the surveys. In Tromsø 6, hs-CRP was measured at 2 different time points, and if both measurements were available, the average was recorded. The lower detection limit of the hs-CRP assay was 0.03 mg/L. Blood pressure and blood samples in the DCH Study were collected and analyzed in similar ways.[160] 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.

3.4.1 Family history of myocardial infarction

To identify family history of MI, subjects in the Tromsø Study were asked to report whether their mother, father, sister, brother, child, or none in the family had a history of MI before the age of 60 years. A positive family history was regarded as at least one first degree relative with a history of MI before the age of 60 years.

3.5 Outcome measurements

3.5.1 Venous thromboembolism

In the Tromsø Study, all first-time VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry of UNN.[107] UNN is the only hospital in the Tromsø region, and all hospital care and relevant radiological procedures are offered here. The relevant discharge diagnosis codes were the International Classification of Diseases (ICD)-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994-98 and the ICD-10 codes I26, I80, I81, I82, 167.2, O22.5, O87.1 and O87.3 for the period 1999-2012. The medical record for each potential VTE case was reviewed by trained personnel. A VTE event was only verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with an objective confirmatory radiology procedure (i.e. compression ultrasound, venography, CT, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis made by a physician in the medical record that required treatment (i.e. anticoagulant treatment with LMWH, VKA or similar agents, thrombolytics or vascular surgery). For patients derived from the autopsy registry, a VTE-event was recorded when the autopsy record indicated PE as the cause of death or as a significant condition contributing to death.

In the DCH Study, all incident VTE events during follow-up were identified by linking the cohort with the Danish National Patient Registry and the Danish National Death Registry by use of the unique civil registration number of the study participants.[160] The Danish National Patient Registry contains nationwide data on all non-psychiatric admissions and discharges from emergency departments and outpatient clinics. The relevant discharge diagnosis codes were the ICD-8 codes 450.99, 451.00, 451.08, 451.09 and 451.99, and the ICD-10 codes I26 and I80.2 through I80.9. Trained personnel reviewed the medical records for each potential VTE-case. A VTE diagnosis was only verified and recorded when typical clinical symptoms of VTE were combined with confirmatory diagnostic test results (i.e. ultrasound, venography, CT, perfusion-ventilation scan or echocardiography), or when autopsy verified VTE.

Concurrent DVT and PE were registered as PE, and verified VTE events were classified as unprovoked or provoked based on the presence of provoking factors at the time of diagnosis. In the Tromsø Study, a VTE event was defined as provoked if one or more of the following factors were present: recent surgery or trauma within the previous 8 weeks before the VTE event, acute medical conditions (e.g. acute MI, stroke or major infectious disease), active cancer at the time of the VTE event, marked immobilization (i.e. bed rest for > 3 days, wheelchair use, or long-distance travel exceeding 4 hours within the last 14 days) or any other factor described by a physician in the medical record (e.g. intravascular catheter).[107] A similar classification of the VTE events was performed in the DCH Study.[160] However, in the last update of VTE events in the DCH Study (July 2006 to April 2008), verified VTEs were not further classified.

3.5.2 Myocardial infarction

In the Tromsø Study, all first-time hospital and out-of-hospital events of MI during follow-up were identified by searching medical records, autopsy records and death certificates.[101] 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. The relevant diagnosis codes in the discharge diagnosis registry at UNN and in the National Causes of Death Registry were the ICD-8 codes 410-414, 427, 430-438 and 795-796 for the period 1969-1980, ICD-9 codes 410- 414, 427, 430-438 and 799 for the period 1980-98, and the ICD-10 codes I20-I25, I47.1, I48, I60-I69, R96, R98 and R99 thereafter. Medical records were case validated by an independent endpoint committee. Modified WHO MONICA/MORGAM criteria for MI were used, and these included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable. Linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal MI events that occurred as out-of-hospital deaths, including deaths that occurred outside Tromsø. The death certificates were used to collect relevant information on the MI events from additional sources, such as autopsy reports and records from nursing homes, ambulance services and general practitioners.

In the DCH Study, potential cases of incident MI during follow-up were identified by linkage to the Danish National Patient Registry and the Danish Causes of Death Registry by use of the civil registry number unique to every Danish citizen.[217] The relevant discharge diagnosis codes were ICD-8 codes 410 to 410.99 and 427.27, and ICD-10 codes I21.0 to I21.9 and I46.0 to I46.9. 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.[218] 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.[218]

3.5.3 Ischemic stroke

In the Tromsø Study, all incident hospital and out-of-hospital ischemic stroke events during follow-up were identified by searching medical records, autopsy records and death certificates.[219] 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. The relevant discharge diagnosis codes in the discharge diagnosis registry at UNN and the National Causes of Death Registry were the ICD-8 and -9 codes 430-438 and the ICD-10 codes I60-I69. In addition, manual and/or electronic text searches of hospital records for notes on stroke were performed in all participants with ICD-8 and -9 diagnosis codes 410-414, 427 and 798-799, and ICD-10 diagnosis codes I20-I25, I47.1, I48, R96, R98 and R99 to ensure case completeness. Medical records were retrieved for case validation by an independent endpoint committee. Ischemic stroke was defined according to the WHO definition (i.e. an acute disturbance of focal or global cerebral function with symptoms lasting $\geq$ 24 hours or leading to death of presumed vascular origin),[220] and only validated and recorded when CT or magnetic resonance image (MRI) scans had ruled out brain hemorrhage.

In the DCH Study, potential cases of incident ischemic stroke during follow-up were identified by linkage to the Danish National Patient Registry and the Danish Causes of Death Registry by use of the civil registry number of the study participants.[221] The relevant discharge diagnosis codes were ICD-10 codes I60 to 69.8 and G45. Medical records of each potential ischemic stroke event were reviewed by a physician experienced in stroke medicine

without knowledge of the baseline information of the potential cases. The WHO definition of ischemic stroke was used[220] and an ischemic stroke event was only validated and recorded when symptoms were consistent with stroke, and CT, MRI, spinal fluid examination or autopsy had excluded brain hemorrhage.

3.5.4 Carotid atherosclerosis

High-resolution B-mode and color/pulsed-wave Doppler ultrasonography of the right carotid artery were performed in the extensive screenings in Tromsø 4, 5 and 6 by trained personnel who had completed a two month pre-study training protocol to ensure equal and standardized examination techniques and measurement procedures.[222-224] All sonographers followed identical scanning and reading procedures and used an Acuson XP10 128 ART ultrasound scanner equipped with a 7.5 MHz linear transducer in Tromsø 4 and 5, and a GE Vivid 7 ultrasound scanner with a linear 12 MHz transducer in Tromsø 6. Plaques were registered in the near and far walls of the common carotid artery, the bifurcation and the internal carotid artery (6 locations). A plaque was defined as a local protrusion of the vessel wall into the lumen of ≥ 50% compared with adjacent IMT. For each plaque, a still image was recorded and digitized using the Matrix Meteor II frame-grabber and Matrox Intellicam. Adobe Photoshop 7.0 was subsequently used to measure plaque areas by outlining the perimeter of each plaque with a cursor, and the plaque area was calculated as pixel values. For the resolution used in the present thesis, a plaque area of 167 pixels corresponded to 1 mm^2. In subjects with more than one plaque, TPA was calculated as the sum of all plaque areas. Novel plaque formation was defined as development of new plaques at the second ultrasound in vessels without plaques at the first ultrasound. Plaque progression was defined as an increase in TPA between the first and second ultrasound.

4. Main results

4.1 Paper I: Impact of incident myocardial infarction on the risk of venous thromboembolism: the Tromsø Study

Population-based registry-studies have shown that patients with a history of MI are at increased short-term risk of subsequent VTE.[176, 177] The purpose of this study was to examine the association between incident MI and VTE in a prospective population-based cohort, using Cox regression models with age as the scale time, VTE as outcome, MI as a time-dependent variable and sex, BMI, blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level as covariates. The study participants were 29 506 subjects attending the fourth, fifth and/or sixth surveys of the Tromsø Study in 1994-95, 2001-02 and 2007-08, respectively. Incident MI and VTE events were recorded until December 31, 2010. Non-MI-exposed and MI-exposed failure time was counted from the date of enrollment to the date of VTE, death, migration or the end of the study period, whichever came first. During a median follow-up of 15.7 years, 1 892 participants experienced MI and 699 experienced VTE. MI was associated with a 51% increased risk of VTE (HR 1.51; 95% CI 1.09-2.11), a 83% increased risk of provoked VTE (HR 1.83; 95% CI 1.21-2.79) and a 72% increased risk of PE (HR 1.72; 95% CI 1.07-2.79), but not significantly associated with the risk of DVT or unprovoked events. MI explained 6.2% of the PEs in the population and 78.5% of the PE risk in MI patients. The risk of VTE was high immediately after MI, and the highest risk estimates for PE were observed during the first 6 months following the MI (HR 8.49; 95% CI 4.00-18.77). Thereafter, the VTE risk rapidly declined, and the association between MI and subsequent PE disappeared after 1 year following the MI event. In conclusion, our findings indicate that MI is associated with a transient increased VTE risk, independently of traditional atherosclerotic risk factors, and the risk estimates were particularly high for PE.

4.2 Paper II: Impact of incident venous thromboembolism on risk of arterial thrombotic diseases

A previous registry-based study has found substantially increased long-term risk of hospitalization for arterial CVD in VTE patients.[187] The aims of this study were to investigate the association between VTE and future arterial events, and to determine the population attributable risk of arterial events by VTE in a large prospective cohort recruited from the general population. The study participants were 81 687 subjects attending the Tromsø Study in 1994-95 or the Diet, Cancer and Health Study in 1993-97. Incident VTE, MI and ischemic stroke were registered until December 31, 2010 and April 30 2008 in the Tromsø and DCH Studies, respectively. Non-VTE-exposed and VTE-exposed failure times were calculated from the date of enrollment to the date of MI, ischemic stroke, death, migration or end of the study, whichever came first. There were 1 208 cases of VTE and 90 subsequent arterial events during a median follow-up of 12.2 years. Incident VTE was associated with 35% increased risk of subsequent arterial thrombotic disease (HR 1.35; 95% CI 1.09-1.66). The association between VTE and arterial events only applied to PE, which was associated with 82% increased risk of future arterial CVD (HR 1.82; 95% CI 1.35-2.47). The highest incidence of arterial events was found the first year after a PE event. Only 0.9% of the arterial events were attributed to VTE, and the VTE explained 63.8% of the arterial events among VTE patients. In multivariate hazard models, VTE was associated with arterial thrombotic disease in women <65 years (HR 3.28; 95% CI 1.69-6.35), women ≥ 65 years (HR 1.55; 95% CI 1.11-2.18) and men <65 years of age (HR 2.06; 95% CI 1.32-3.20), whereas no association was found between VTE and future arterial events in men aged >65 years. In conclusion, our findings imply that women and men < 65 years with VTE have higher risk of arterial thrombotic disease than those without VTE. However, only 1% of the arterial thrombotic events in the population were attributed to VTE.

4.3 Paper III: Family history of myocardial infarction and cause-specific risk of myocardial infarction and venous thromboembolism: the Tromsø Study

To investigate whether the previously described association between family history of MI and VTE[14, 149, 194] was mediated by MI, we aimed to determine the risks of MI and VTE by family history of MI using a cause-specific model and to explore whether atherosclerotic risk factors could explain the associations in a population-based cohort. The study included 21 624 subjects recruited from the Tromsø Study in 1994-95 and 2001-02. Incident MI and VTE events were registered until December 31, 2010. In the cause specific Cox model, person-years for each participant were counted from the date of enrollment to the date of MI, VTE, death or migration or until the end of the study period, whichever came first. There were 1 311 MIs and 428 VTEs during a median follow-up of 15.8 years. Family history of MI was associated with a 52% increased risk of MI (HR 1.52; 95% CI 1.35-1.70) and a 26% increased risk of VTE (HR 1.26; 95% CI, 1.02-1.55) in the cause-specific model. Similar results were found using a traditional Cox model. The association between family history of MI and VTE was confined to unprovoked events and DVT. The highest risk associated with family history of MI was found for unprovoked DVT, and family history of MI explained 20.6% of the unprovoked DVTs in the population and 82.6% of the unprovoked DVTs in subjects with family history of MI. The risk of VTE increased with increasing number of affected relatives, and subjects with ≥ 2 relatives with a history of MI had 2.6-fold increased risk of unprovoked DVT (HR 2.65; 95% CI 1.12-6.24). Modifiable atherosclerotic risk factors slightly altered the association between FHMI and MI but had a negligible effect on the association between FHMI and VTE. In conclusion, family history of MI was associated with increased risk of both MI and VTE in a cause-specific model. Apparently, the association between FHMI and VTE applied to unprovoked DVT and was not explained by modifiable atherosclerotic risk factors.

4.4 Paper IV: Impact of incident venous thromboembolism on the formation and progression of carotid atherosclerosis: the Tromsø Study

Atherosclerosis secondary to VTE may be an intermediate in the observed association between VTE and future arterial CVD.[187] We wanted to investigate whether incident VTE was associated with subsequent formation and progression of carotid atherosclerosis in a population-based observational study. Subjects attending ≥ 2 ultrasound examinations of the right carotid artery, with measurements of TPA, in the Tromsø Study in 1994-95, 2002-03 and/or 2007-08 were eligible for the study. We identified 150 subjects diagnosed with incident VTE between the initial and follow-up visit, and randomly selected 600 age- and sex-matched subjects without VTE between the visits. Subjects with VTE and carotid plaque(s) at the first visit had a non-significant 4.1 mm^2 (β 4.12, 95% CI -1.72 to 9.98) larger change in TPA between the first and second visit compared to subjects without VTE after adjustment for change in hs-CRP and traditional atherosclerotic risk factors in the multiple linear regression model. The possible association between VTE and plaque progression in subjects with carotid plaque(s) remained after restricting the analyses to VTE events diagnosed in the first half of the time-interval between the carotid ultrasounds (β 4.02, 95% CI -3.66 to 11.70), supporting that the change in TPA occurred subsequent to the VTE. There was no association between VTE and TPA at second visit among subjects with carotid plaque(s) in any multiple linear regression model, and no association was found between VTE and novel carotid plaque formation in logistic regression models. In conclusion, our findings suggest that VTE is associated with increased carotid plaque progression in those who already have atherosclerosis, but not with novel plaque formation. The possible association between VTE and carotid plaque progression was not mediated by low-grade inflammation assessed by hs-CRP.

5. General discussion

5.1 Methodological considerations

5.1.1 Study design

Observational studies (e.g. cohort and case-control studies) often aim to examine and quantify risk factors for health-related outcomes to identify preventable causes. The results in the present thesis are based on data from population-based cohort studies. In cohort studies, subjects free of a disease of interest are followed over time to investigate the natural history and burden of the disease. Moreover, differences in the disease risk according to an exposure may be assessed. The cohort design has several advantages including relative and absolute risk estimates, the opportunity to examine multiple effects of the same exposure at the same time, and a temporal sequence of the exposure and outcome which may yield implications on causality.[225] In addition, cohort studies may produce generalizable results if a large number of subjects from a general population are included. However, a cohort study may encounter challenges such as loss to follow-up, change in disease risk during follow-up, bias and confounding, inefficiency when examining rare outcomes with long latency periods, and high costs.[225] Furthermore, the cohort design requires a large study population, which may yield problems related to statistical power. Therefore, the low number of VTE events in subgroups of our study populations, may represent a potential limitation of the present thesis. Low statistical power was a particular issue in paper IV, in which we only had a statistical power of 0.29 for the possible association between incident VTE and change in TPA in the multivariable model.

In case-control studies, subjects with and without the outcome of interest are retrospectively compared with regard to an exposure. The case-control has some advantages compared with the cohort design, such as the ability to investigate rare diseases with long latency periods and cost and time efficiency. Nevertheless, risk estimates from case-control

studies are generally considered less valid than those obtained in cohort studies because of difficulties related to selection and matching of the controls, the potential for reverse causality (i.e. when subclinical presence of the disease influences the exposure[226]) and recall bias (i.e. a bias introduced when subjects with the outcome are more likely to recall information regarding the exposure[225]), and the lack of incidence rates and a temporal sequence of the exposure and outcome in a case-control study.

Positive associations identified in cohort studies are theoretical measures suggesting that an exposure may cause the outcome of interest. However, the observed association may be non-causal or due to bias, confounding or chance. In contrast, a positive association in an experimental study design supports true causality according to Bradford Hill's criteria for causality.[227] Moreover, an intervention is needed to investigate the impact of an exposure on an outcome in practice. Consequently, randomized controlled trials (RCTs) are recognized as the gold standard in modern medicine. In RCTs, the participants are randomly assigned to an active or a control group and followed simultaneously to investigate the effect of the intervention on the outcome. Elimination of confounding and bias by randomization and blinding, respectively, is another advantage of RCTs compared with cohort studies.[225] However, RCTs are expensive, may not provide information on the long-term or rare effects of the intervention, and are not always possible to implement due to ethical considerations. Furthermore, RCTs most often include younger and healthier subjects than the general population due to strict inclusion and exclusion criteria. The risk estimates from RCTs may therefore have a lower generalizability than those obtained in population-based cohorts.

Mendelian randomization is a method for assessing causality within an observational study. In this method, the contribution of a modifiable risk factor to disease causation is investigated by examining the association between the disease and a genetic variant influencing the modifiable risk factor.[226, 228] Because alleles are randomly assorted at

conception, confounding by other factors than those related to the genetic variant is eliminated.[226, 228] Furthermore, the fixed genetic makeup at conception excludes the possibility of reverse causation.[226] Mendelian randomization has previously been applied in a prospective cohort study to assess the association between CRP and VTE. In this study, high levels of CRP, but not CRP-associated genotypes, were associated with increased risk of VTE, suggesting that the observed association between CRP levels and VTE was non-causal.[169] Disadvantages of mendelian randomization include small effect sizes and that the method only can be applied to areas where genetic variants relevant to modifiable risk factors are known.[228]

5.1.2 Generalizability

The generalizability of a study refers to the study population's representativeness of its defined reference population (i.e. internal validity), and to what extent the results of the study may apply to other populations (i.e. external validity).[229] The generalizability of a population-based cohort may be limited by selection bias. The inclusion and exclusion criteria for participation, a low response rate, or loss to follow-up (i.e. if subjects lost during the study differ from those remaining regarding the risk of the outcome of interest) may introduce selection bias.[229] Furthermore, a stable disease occurrence during the follow-up (i.e. equal disease risk for those entering and leaving the study at different time points) is an important assumption for risk assessment. Therefore, follow-up time may influence the validity of a cohort study. The median follow-up times in papers I-III were long (12.2-15.8 years). However, there were no differences between the comparison groups regarding follow-up time. Moreover, the hazard ratios were constant over time when evaluating the parallelism between the curves of the log-log survival function and assessing Schonenfeld residuals in the cox

proportional hazard model in these papers. This supports that the assumption for risk assessment was met in the present thesis.

The papers in the thesis are based on data from the Tromsø and DCH Studies. To the fourth and largest survey of the Tromsø Study, all inhabitants aged 25 years or older living in Tromsø were invited, while samples of Tromsø population were invited to the fifth and sixth surveys. To the DCH Study, all inhabitants of the urban areas of Copenhagen and Aarhus between 50 and 65 years were invited if they were born in Denmark and did not have a cancer diagnosis. The attendance rates in Tromsø 4-6 were high, and 66-79% of the eligible population participated. However, the attendance rates were somewhat lower in men than in women and in subjects below 35 and above 80 years of age in the Tromsø Study, which may have reduced generalizability in these subgroups. The generalizability of the DCH Study may be limited by a low participation rate and non-response bias because only 35% of the invited subjects participated in the DCH Study and those who participated had higher socioeconomic status (e.g. higher education, income and occupational status) than the non-participants.[216] Nonetheless, the incidence rate of VTE was only slightly lower in the DCH[160] than in the Tromsø Study.[14] This may be explained by exclusion of subjects aged 65 years or older (i.e. those at highest risk of VTE) in the DCH Study. Although participation rates were high, nonresponse bias may still be present and reduce the generalizability in the Tromsø Study, because subjects with serious illnesses or disabilities tend to refrain from attending health examinations. This may result in healthier study participants than the general population, a low number of outcome events and underestimation of the true association between the exposure and outcome.

The applicability of the results from one population-based cohort study to other populations may also be limited by differences in levels of the exposure, the distribution of potential confounders, or the classification of the exposure or outcome in the populations.[229]

In the present thesis, measurement procedures were standardized, only symptomatic VTE events were included, and established validation criteria for MI and ischemic stroke were applied. Furthermore, our distribution of traditional atherosclerotic risk factors and observed incidences of venous and arterial thrombotic diseases did not differ greatly from those reported in other Western populations.[9, 11, 103, 162, 230-232] This enhances the generalizability of our results to other Western populations.

5.1.3 Confounding and interaction

A confounder is an error in the assessment of the association between an exposure and outcome caused by differences between the comparison groups in other risk factors for the outcome than the exposure itself.[233, 234] In order to confound an association, the confounding factor has to be causally associated with the outcome and associated with the exposure. Furthermore, the confounder has to be differently distributed among the comparison groups and not be an intermediate step in the causal pathway between the exposure and outcome.[233, 234] Confounding may strengthen or weaken a true association. In addition, confounding may lead to report of an effect although no true effect exists, or hide a true effect from the results. Differences between the comparison groups may produce confounding in cohort studies, which are especially vulnerable to unmeasured or unknown confounders.[235] In experimental studies, randomization minimizes the probability of uneven distribution of known and unknown confounders in the comparison groups.[235] Confounding is therefore less likely to occur in an experimental design.

High BMI and advancing age were the only traditional atherosclerotic risk factors associated with both arterial and venous thrombosis when the risks of MI and VTE were investigated in the same population.[101, 162] Moreover, family history of MI is a risk factor for MI consistently shown to also increase the risk of VTE.[14, 149, 194] Consequently, it may be

assumed that of the traditional atherosclerotic risk factors, only obesity, increasing age and family history of MI may confound the observed interrelation between VTE and arterial CVD in the present thesis. Our associations remained statistically significant after adjustments for age and obesity in papers I-II and after additionally adjusting for family history of MI in paper I. This indicates that these risk factors alone cannot fully explain the observed relation between arterial and venous thrombosis. Moreover, inflammation assessed by CRP was a potential confounder of the possible link between VTE and carotid atherosclerosis in paper IV. High CRP has been shown to increase the risk of both VTE[168] and carotid atherosclerosis,[236] and VTE has been demonstrated to result in elevated CRP levels.[237] If, on the other hand, the inflammatory state following VTE in turn caused carotid atherosclerosis, inflammation would be an intermediate step in the causal pathway between VTE and atherosclerosis, and not a confounder. However, there was no association between high CRP and carotid atherosclerosis in the Tromsø Study (Agnethe Eltoft, MD, unpublished data, 2016). In addition, adjustment for hs-CRP did not weaken the possible association between VTE and carotid atherosclerosis in subjects with carotid plaque(s) at the first visit in paper IV. Taken together, this eliminates inflammation as a confounder or mediator of the possible association between VTE and carotid atherosclerosis in the present thesis.

Confounding in cohort studies may be minimized by restriction of the study participants (e.g. inclusion of men only to eliminate confounding by sex), stratification (i.e. division of the study population into subgroups according to the confounding variable) or adjustments in regression models.[233-235, 238] However, restriction and stratification may reduce the statistical power and generalizability. In the present thesis, potential confounders were included in the multivariable regression models in order to control for confounding. In paper III, cause-specific analyses were additionally performed to investigate the effect of family history of MI on the risk of VTE in the complete absence of MI. Furthermore, the risks of MI

and VTE were estimated simultaneously in a population with equal distribution of potential unrecognized confounders in paper III. Matching of the controls to the cases on potential confounders is another strategy to minimize confounding in observational studies.[233] Therefore, the randomly selected subjects without VTE were matched to the VTE patients by age and sex in paper IV.

Although adjustments for potential confounders are made, residual confounding may still be present in cohort studies and in the present thesis. The presence of unknown and unaccounted for confounders or imperfect adjustments for known confounders (e.g. because of imprecise or incomplete assessments) may result in residual confounding.[226] FV Leiden and prothrombin 20210A are risk factors for VTE found to additionally increase the risk of arterial CVD.[239, 240] Consequently, residual confounding by thrombophilia on the observed link between venous and arterial thrombosis may be present in this thesis. In agreement with this, the association between incident VTE and MI diminished after taking genetic thrombophilia (i.e. FV Leiden, prothrombin 20210A and non-O blood groups) into account in the MEGA Study.[188] Furthermore, other yet unknown genetic risk factors for arterial and venous thrombosis may be present and cause residual confounding in the present thesis.

A statistical interaction is present when the effect of the exposure differs between groups of the study population or strata of a second variable (i.e. an effect modifier), and results in different risk estimates in subgroups of the population.[238] A statistical interaction may be positive or negative, and is modelled by stratifying the analyses on the effect modifier or by including an interaction term as a covariate in the analyses. In paper II, statistical interactions between VTE and sex and VTE and age were identified. Therefore, subsequent analyses were stratified on sex and age of 60 years.

5.1.4 Information bias

A bias is a systematic error in a study's design or procedures, including participant selection (i.e. selection bias) and the data collection (i.e. information bias), and may result in incorrect assessments of the association between an exposure and outcome.[241] Misclassification is a type of information bias. Non-differential misclassification of the exposure is present when the misclassification is independent of the outcome and similar across the comparison groups, while differential exposure misclassification is present when the misclassification is dependent of the outcome and differs between the comparison groups.[241] Similarly, misclassification of the outcome is non-differential if it is unrelated to the exposure, and differential if it is dependent of the exposure. A non-differential misclassification most often leads to underestimation of the true association, whereas a differential misclassification may bias the risk estimates in either direction.[241] In prospective cohorts, the exposure is measured prior to the disease occurrence. Consequently, potential exposure misclassification is most likely non-differential in prospective cohorts. In a case-control study, recall bias and differential exposure misclassification may be present because information regarding the exposure is collected after the outcome occurrence.[241]

Most baseline variables from the Tromsø and DCH Studies are based on self-administered questionnaires. Although self-administered questionnaires have several advantages, including cost and time efficiency, they introduce a potential source of misclassification if the study participants provide false information (e.g. misunderstand or refrain from answering questions). This is of particular importance in paper III, in which the exposure was self-reported family history of MI. Among those who reported family history of MI, both over- and under-reporting are possible. However, the potential misclassification of family history of MI was most likely non-differential because information regarding family history of MI was collected prior to the MI and VTE diagnoses. This may have caused

underestimation of the true associations between family history of MI and MI and VTE in our study. Underestimation of the true associations is further supported by a high specificity and a lower sensitivity of self-reported family history of MI previously demonstrated in a validation study.[242] The validity of the information from a self-administered questionnaire may be assessed by investigating the effect of the question of interest on other factors than the outcome. Family history of MI increased the risk of MI in addition to VTE in paper III, as expected from previous publications.[189-191] This supports the validity of the self-reported family history of MI in the assessment of the association between family history of MI and VTE in this thesis.

Blood samples and ultrasound assessment of carotid atherosclerosis were also potential sources of information bias in the present thesis. However, standardized procedures for measurements of blood samples and carotid ultrasound were used in the Tromsø Study to reduce bias. Carotid ultrasound was performed by personnel who had completed a pre-study training protocol to ensure equal and standardized examination techniques and measurements, and all sonographers followed identical procedures and used identical ultrasound scanners. In addition, a previous publications from the Tromsø Study has demonstrated that although carotid plaque thickness measurements were subject to considerable measurement errors, the between- and within-sonographer agreement for carotid plaque occurrence was substantial.[223] Furthermore excellent computer-assisted offline classification for carotid plaques has been found in the Tromsø Study, even if the outlining of plaques was influenced by measurement errors.[243] Hs-CRP was measured from frozen blood samples stored for 12 years in Tromsø 4, which may have introduced bias if the freezing or storage affected the hs-CRP measurements. However, storage of frozen plasma samples over time has previously been shown to not affect the assayed values of biomarkers including CRP.[244]

5.1.5 Modifiable risk factors and time-scale

Modifiable risk factors are a possible limitation of prospective cohort studies, particularly when the exposure is collected at baseline only and the time between the exposure and outcome is long. Modifiable risk factors imply that the risk profile of the study participants may change during follow-up. It may result in regression dilution bias (i.e. underestimation of the true association between the exposure and outcome because information regarding the exposure is collected at baseline only and not updated during follow-up).[241, 245] In agreement with this, results from the Framingham and Whitehall Studies have shown that investigation of the association between the baseline measurement and disease risk underestimated the strength of the real association by 30% during the first decade of follow-up, and that change in risk profile became progressively more important with increasing follow-up time.[245]

In papers I and II, the exposure variables (i.e. MI and VTE, respectively) were included as time-dependent covariates and continuously updated during follow-up, thereby limiting the risk of regression dilution bias. However, most other covariates of interest, such as blood pressure, blood lipids, BMI and smoking, were modifiable and only collected at baseline in paper II. In order to further reduce the potential for regression dilution bias, time-varying analyses in which covariates of interest are updated during follow-up may be performed. In paper I, information regarding the covariates was updated at each survey for subjects who attended more than one survey.

In the Cox proportional hazard model, the variable expected to have the largest effect on the hazard (e.g. time-on study or age) should be used as the time-scale.[246] The hazard of a disease is expected to change more as a function of age than as a function of time-on study because the incidence of most chronic diseases is strongly determined by age, whereas study inclusion rarely affects disease risk.[247] Therefore, age was used as time-scale in papers I and

II. Furthermore, the use of age as time-scale is a more effective method to control for age than the use of time-on study as time-scale and adjusting for age at baseline.[247]

5.1.6 Missing values

Missing values are a common problem in epidemiologic research and may cause bias.[248-250] Missing values may result from subjects not responding to questions in the questionnaire, loss to follow-up, equipment failure or procedural mistakes, or unknown reasons.[248, 251] A few missing values are of minor importance, whereas a large amount of missing values in a variable may threaten the integrity of the study.[248] Although no optimal solution for missing values exists, missing data may be handled by deletion of variables with a substantial amount of missing values, deletion of subjects without a complete dataset (i.e. complete case analysis or listwise deletion), exclusion of subjects with missing values for the variables of interest in the statistical analyses (i.e available case analysis or parwise deletion), or imputation (i.e. calculating an estimate for each missing value and replacing it).[248-251]

Deletions may introduce selection bias if the characteristics of those with missing values differ from the rest of the study population and may result in reduced statistical power.[248, 249, 251] In contrast, imputation ensures the sample size and reduces the risk of selection bias.[249] Imputation is based on the assumption that the missing values are missing at random (i.e. the lack of the observation is unrelated to the unobserved value but is explained by other available observations in the dataset) or missing at completely random (i.e. the lack of the observation is unrelated to the unobserved value and other available observations in the dataset).[248, 250, 251] In the present thesis, missing data were handled by excluding subjects with missing data on the exposure or outcome variable of interest (i.e. complete case analysis), and

by omitting subjects with missing values for covariates in the statistical analyses (i.e. available case analysis).

Missing values were a particular issue in paper III, in which 5 038 subjects (17.6%) had missing values for the exposure variable family history of MI. Most likely, the majority of subjects with missing information on family history of MI refrained from answering the question because they did not have relatives with a history of MI. Consequently, the missing values for family history of MI were most likely not missing at random, and imputation was not performed. A potential bias caused by missing values in a binary variable may be addressed by sensitivity analyses (i.e. examining the effect of replacing the missing values with the extreme scenarios of the variable).[250] When we performed analyses under the assumption that (i) all subjects with missing values did not have a family history of MI, and (ii) that all subjects with missing values had family history of MI, the risk estimates for MI and VTE did not change notably. This supports our use of complete case analysis in paper III.

5.1.7 Registration of incident VTE, MI and ischemic stroke

In the Tromsø Study, all first-time in- and outpatient VTE events during follow-up were retrospectively identified by searching registries at UNN. Because UNN is the only hospital in the Tromsø region, the probability of a complete VTE registry is high. However, some study participants may have been diagnosed with VTE elsewhere and may therefore have been missed. Nevertheless, several of the VTE events diagnosed elsewhere were discovered due to transferal to follow-up at the outpatient clinic at UNN.

Trained personnel reviewed the medical record for each potential VTE case. The VTE events were verified and recorded according to strict criteria as previously described in the thesis to reduce the likelihood of inclusion of asymptomatic events and misclassification.

However, potential outcome misclassification cannot be completely ruled out. The retrospective registration of the VTE events was dependent on accurate and complete information provided in the medical records by the individual medical doctors diagnosing and treating the VTE patients, and there was no standardized instruction for the recording of VTE events in the medical records. Furthermore, assessment of provoking factors relied on information provided for each patient. Nonetheless, the potential misclassification present in the VTE variable is most likely non-differential because the endpoint committee validating the VTE events were blinded to baseline characteristics of the potential VTE patients. Finally, information regarding previous VTE was not available for study participants who were not diagnosed with VTE during follow-up. This may imply that subjects with prevalent VTE are included as healthy subjects and not excluded in the present thesis. However, the proportion of subjects with prevalent VTE is most likely small, and a minor effect on our risk estimates can therefore be expected.

All first-time MI and ischemic stroke events during follow-up were identified retrospectively in the Tromsø Study by searching medical records, autopsy records and death certificates, and by linkage to national and local diagnosis registries and to the National Causes of Death Registry at Statistics Norway. The National Causes of Death Registry covers all subjects registered as inhabitants of Norway at the time of their death, without regard to whether the death took place in Norway or abroad, in order to ensure a complete follow-up status for all-cause mortality. An independent endpoint committee reviewed the medical record for each potential MI and ischemic stroke case, and MI and ischemic stroke events were verified and recorded according to a strict classification protocol to warrant accurate outcome variables as previously described in the thesis. Some MI and ischemic stroke events may have been diagnosed and treated in other hospitals than UNN. However, the number of

MI events observed at other hospitals and the location of the hospitals was available for the retrieved MI cases.

The identification and validation of VTE, MI and ischemic stroke in the DCH study was performed in a similar matter.

5.2 Discussion of main results

5.2.1 Myocardial infarction and the risk of venous thromboembolism

In accordance with previous studies,[174, 176, 177] we found that MI was associated with increased risk of subsequent VTE. The observed association between MI and future VTE applied to PE. In accordance with this, Sørensen et al demonstrated higher risk of PE than DVT after hospitalization for MI when subjects with a history of MI were compared with population-based controls.[176, 177] Similar risk estimates for unprovoked and provoked VTE were found after MI in these Danish registry-based studies.[176, 177] In our study, MI was only associated with subsequent provoked VTE. However, the results of Sørensen and coworkers should be interpreted with caution because the exposure, outcome, potential confounders and provoking factors for VTE were based on information from hospital registries and the Danish National Patient Registry only and not validated.[176, 177] According to our results, the risk of VTE was highest during the initial 6 months following the incident MI event, and then rapidly declined and was no longer significantly increased. Similarly, a particularly high risk of VTE was found the first 3 months after a MI diagnosis in postmenopausal women,[114] and the association between MI and VTE has been reported to diminish[177] or disappear[176] beyond 3 months after MI hospitalization. This indicates that MI patients are at short-term increased risk of VTE.

Our study is the first to investigate the attributable risk and the population attributable risk of incident PE due to incident MI. We found that 6% of the PE events in the population were attributed to MI and that nearly 80% of the PE events among MI patients were explained by the MI. The considerable number of PE events attributable to MI and the transient nature of the VTE risk after MI may suggest a role for anticoagulant therapy in MI patients with high risk of VTE to prevent subsequent PE. Aspirin[252, 253] and statins[254] have previously been shown to reduce the risk of recurrent and incident VTE, respectively. Consequently, concomitant treatment with aspirin and statins following the MI diagnosis may have resulted in underestimation of the true impact of MI on the risk of future VTE.

The underlying mechanisms explaining the observed association between MI and future VTE remain unsettled. Potential mechanisms include common risk factors, indirect factors, and a direct causal interrelation.[255] Adjustment for common risk factors for MI and VTE, such as age, obesity and family history of MI, in addition to other traditional atherosclerotic risk factors had marginal effects on our risk estimates. Furthermore, common risk factors for MI and VTE would mediate a permanent and not a transient increase in the risk of VTE. Consequently, our findings argue against a strong impact of shared risk factors alone on the association between MI and subsequent VTE. However, residual confounding by other shared risk factors may still be present and partially mediate the observed association between MI and future VTE. In addition, synergistic effects of several shared risk factors or a combination of shared risk factors and MI sequela may result in venous thrombus formation in MI patients.

The transient increase in VTE risk after MI we and others have reported[114, 176, 177] points towards causal mechanisms related to the MI itself or indirect factors such as hospitalization, immobilization or other conditions following the MI. Accordingly, decreased left ventricular ejection fraction is a potential complication of MI shown to increase the risk of

future VTE.[256] Moreover, a higher frequency of immobilization and VTE occurrence during hospitalization has been found in VTE patients with symptomatic atherosclerotic disease than in those without.[257] An impact of hospitalization on the association between MI and future VTE is further supported by higher risk estimates for VTE demonstrated when VTE was the second diagnosis in the medical records and lower risk estimates shown when the VTE did not occur during the hospitalization for heart disease by Sørensen et al.[177] This may imply that MI hospitalization rather than the MI itself is a risk factor for VTE, and that MI is indirectly associated with VTE through MI hospitalization. In agreement with this, the strength of the association between MI and VTE found by Barsoum and coworkers was markedly attenuated after adjustment for hospitalization for major surgery or acute medical illnesses.[178] The particularly high PE risk and the transient nature of the VTE risk after MI may also imply that direct causal mechanisms secondary to local disturbances in the cardiopulmonary circulation or the electromechanical activity are responsible for some of the increase in VTE risk observed in MI patients. Accordingly, AF is a potential MI sequelae previously found to be associated with a particularly high risk of PE in the Tromsø Study.[61]

5.2.2 Venous thromboembolism and the risk of myocardial infarction and ischemic stroke

In the present study (paper II), we found that incident VTE was associated with increased risk of future MI and ischemic stroke. Our findings are in accordance with previous publications[180-184, 186-188] and have later been confirmed in a trial of subjects with impaired glucose tolerance and established CVD reporting that VTE patients had more than two times higher risk of death, MI and stroke combined than those without VTE after adjustments including obesity.[258] Moreover, an association between DVT and future arterial events has recently been reported.[259] In contrast, Barsoum and coworkers failed to find an association between incident VTE and MI.[178] However, this study was limited by a lack of power to

detect a significant association between venous and arterial thrombosis of the magnitude we found, and excluded VTE patients who did not survive at least one day after the VTE event.[178] According to our findings, the incidence of arterial CVD was highest the first year after a PE event. Similarly, Sørensen et al reported particularly high risk of arterial thrombotic diseases the first year after a PE, in which PE patients had nearly 3-fold increased risk of MI and stroke.[187] Furthermore, the highest risk of arterial events in VTE patients was found the initial year after the VTE diagnosis in the Prevention of Renal and Vascular Endstage Disease (PREVEND) Study.[186]

Our crude incidence rates of arterial thrombotic diseases after VTE were lower than those previously reported in cohort studies.[180-182, 184] Differences in methodology and particularly selection of the study population may explain these differences in incidence rates. We followed all VTE patients from the initial stage of the disease, including the VTE patients who died shortly after the VTE diagnosis and were no longer at risk of arterial thrombotic diseases. In contrast, other studies only included VTE patients who had completed oral anticoagulant treatment[180] or survived the initial month after the VTE event.[182] Moreover, VTE patients with an indication for long-term anticoagulation have previously been excluded.[182, 184] Anticoagulant therapy has been shown to reduce the risk of MI and cerebrovascular events.[260, 261] Long-term anticoagulant therapy may therefore partly explain the lower incidence rates found in our study. Finally, cancer is a known risk factor for arterial thrombotic diseases,[134] and exclusion of all subjects with a previous cancer diagnosis at baseline from the DCH Study may consequently have contributed to the observed differences in incidence rates of arterial CVD after VTE.

We found that the association between incident VTE and future arterial CVD applied to all women and men below 65 years of age. An interaction between VTE and sex on the risk of arterial thrombosis has not previously been described. However, Sørensen et al reported

slightly higher risk estimates of arterial CVD in women compared with men the initial year after a PE diagnosis.[187] Although our findings should be interpreted with caution because of limited statistical power in subgroup analyses, the sex difference in arterial CVD risk after VTE may suggest a differential pathogenesis of arterial thrombotic disease in men and women. This is further supported by the observed difference in arterial CVD risk according to VTE type in men and women. We demonstrated that PE rather than DVT increased the risk of arterial events in men, whereas PE and DVT provided similar risk estimates of arterial CVD in women. Sørensen and coworkers found lower risk of arterial CVD after DVT compared with PE,[187] whereas similar risk estimates were obtained for arterial thrombotic events following DVT and PE in the MEGA and PREVEND Studies.[186, 188] However, differences in the risk of arterial CVD according to VTE type were not assessed in men and women in these studies. An impact of age on the association between venous and arterial thrombotic diseases has previously been demonstrated. The association between incident unprovoked VTE and MI has been shown to only apply to subjects below 40 years of age,[183] and higher risk of subsequent arterial events has been demonstrated in PE patients aged 40-55 years compared with PE patients above 70 years of age.[187]

Our study is the first to explore the proportion of arterial thrombotic events attributable to incident VTE. Although the population attributable risk of arterial CVD due to VTE was low (1%), a considerable proportion of the arterial events in VTE patients were attributable to incident VTE (64%). Our findings could imply a role for arterial CVD prophylaxis in VTE patients with high risk of arterial events to prevent subsequent arterial CVD. Concomitant anticoagulation and antiplatelet therapy may increase the risk of bleeding, and prediction models to identify the VTE patients at high risk of arterial CVD who may benefit from arterial CVD prophylaxis are therefore needed. However, most of the presently known predictors of subsequent arterial events in VTE patients receiving anticoagulant

treatment (e.g. cancer and anemia) were also predictors of major bleeding.[262] Hopefully, future studies will identify accurate and sensitive predictors of arterial events following VTE and investigate the effects of arterial CVD prophylaxis on the risk of future MI and ischemic stroke in high-risk VTE patients.

Common risk factors such as advancing age and obesity may potentially explain an association between VTE and future arterial CVD.[101, 162] However, adjustment for age and BMI in addition to other traditional atherosclerotic risk factors only slightly attenuated the observed interrelation between venous and arterial thrombosis in our and the MEGA Study,[188] thereby challenging that these common risk factors alone can fully explain the association. Nevertheless, Roach et al showed that the association between incident VTE and MI disappeared after additionally taking FV Leiden, prothrombin 20210A and non-O blood groups and fibrinogen, FVIII and CRP into consideration.[188] Furthermore, an initially observed association between DVT and future arterial events diminished after adjustment for atherosclerotic risk factors and cancer in a recent publication.[259] This supports that common etiologic factors may explain an association between VTE and future arterial CVD. It is also possible that the observed increase in arterial CVD risk in VTE patients is explained by the VTE events themselves or treatment thereof, such as local disturbances in the cardiopulmonary circulation following a PE, paradoxical embolization of a venous thrombus through a patent foramen ovale,[263-265] or vascular calcification caused by VKA therapy.[266]

5.2.3 Family history of myocardial infarction and the risk of myocardial infarction and venous thromboembolism

We found that family history of MI was associated with increased risk of both MI and VTE, thereby confirming the results of previous publications.[14, 149, 189-194] However, our risk

estimates for MI were lower than those previously reported.[189-193] This may be explained by differences in study design and selection of study participants. We recruited subjects from a general population prior to MI occurrence and followed them prospectively for all MI events. In contrast, other studies were retrospective,[189-193] and only included non-fatal MI cases,[189, 191] hospitalized controls[189, 190, 192] or registered relatives of MI patients as controls.[193] In agreement with our finding, a history of MI before 60 years of age in a first degree relative has previously been shown to increase the risk of incident VTE by approximately 30% after adjustment for other traditional atherosclerotic risk factors.[14, 149]

The proportion of incident VTE events attributable to family history of MI was 13% in our study population, compared to 11% in the GATE Study.[194] According to our finding, the proportion of VTE events in the population attributable to family history of MI was comparable with the proportion of VTE events attributable to family history of VTE.[267] This may implicate a role for family history of MI in clinical practice to improve the identification of subjects at high risk of VTE.

In agreement with existing literature,[14, 189, 190, 194] we found that the risk of both MI and VTE increased with increasing number of affected first degree relatives with a history of MI. Moreover, the observed association between family history of MI and VTE applied to unprovoked events, and particularly unprovoked DVT, confirming previous results from the Tromsø and HUNT Study.[14, 149] Taken together, our findings may suggest that shared genetic risk factors for MI and VTE such as factor V Leiden[239, 240] contribute to the observed association between family history of MI and VTE. Factor V Leiden has been identified as a stronger risk factor for DVT than PE.[69, 89, 90, 97] This may explain the particularly high risk of unprovoked DVT found in subjects with a family history of MI.

We confirmed that modifiable atherosclerotic risk factors such age, blood pressure, cholesterol and BMI influenced the association between family history of MI and MI. In addition, family history of MI had a synergistic effect with age, BMI and cholesterol on the risk of MI. In agreement with our findings, dyslipidemia has previously been shown to have a multiplicative effect with family history of MI on the risk of MI.[190-192] Moreover, family history of MI has been reported to have synergistic effects with diabetes mellitus and fibrinogen on the risk of VTE.[194] In contrast, we found no interactions between family history of MI and other traditional atherosclerotic risk factors. Furthermore, modifiable atherosclerotic risk factors had a negligible effect on the observed association between family history of MI and incident VTE. This indicates that the observed association between family history of MI and VTE was not explained by traditional atherosclerotic risk factors. Finally, our risk estimates for VTE by family history of MI were similar in the traditional and the cause-specific Cox model. Consequently, the observed association between family history of MI and VTE was not explained by an indirect relation between MI and VTE previously described in this thesis.

5.2.4 Venous thromboembolism and the risk of carotid atherosclerosis

In the present study (paper IV), a possible association between incident VTE and plaque progression was found in subjects who already had carotid plaque(s). An association between carotid plaques and VTE has previously been described in case-control studies reporting significantly higher prevalence of carotid plaques in unprovoked DVT patients than controls without VTE.[208, 210] However, these studies only included DVT patients and were not designed to explore the temporal sequence between VTE and subsequent atherosclerosis.[208, 210] Our study is the first designed to model the time-sequence between incident VTE and carotid atherosclerosis. Although our findings must be interpreted with caution due to limited

statistical power, the possible association between VTE and carotid plaque progression found among those with established atherosclerosis remained after restricting the analyses to VTE events diagnosed in the first half of the time-interval between the carotid ultrasounds. This supports that the change in TPA in subjects with carotid plaque(s) occurred subsequent to the VTE. However, incident VTE was not associated with subsequent formation of new carotid plaques. To the best of our knowledge, the interrelation between incident VTE and future carotid plaque formation or progression has not previously been investigated in a general population.

Elevated levels of inflammatory markers including CRP have previously been demonstrated in both the acute[268, 269] and chronic[237, 270] phase of VTE, and CRP levels have been shown to remain significantly higher five years after a VTE diagnosis compared with subjects without VTE.[237] Furthermore, CRP has been found to independently increase the risk of arterial CVD,[271-273] and a nearly linear relationship between CRP concentrations and arterial CVD risk has been described.[274] This suggests that chronic low-grade inflammation accompanying VTE may contribute to the increased risk of arterial CVD observed in VTE patients.[187] Inflammation may also be related to atherosclerosis, and high levels of CRP have been found to independently increase the risk of presence[236, 275-280] and progression[236, 278-280] of atherosclerosis. Levels of hs-CRP were independently associated with carotid IMT in a prospective cohort[276] and meta-analysis,[277] and increasing severity of extracranial atherosclerosis with increasing CRP levels has been described.[278] Moreover, CRP levels >2.9 mg/L have been shown to nearly double the odds of carotid atherosclerosis progression compared with CRP levels ≤0.8 mg/L.[279] Taken together, this could imply that the possible association between incident VTE and acceleration of plaque progression we have shown in subjects with carotid plaque(s) was mediated by low-grade inflammation.

However, other studies have failed to find an independent association between CRP and carotid plaques,[281, 282] and demonstrated that although hs-CRP predicted atherosclerosis presence, it was not sensitive to monitor progression of atherosclerosis.[276, 277] Moreover, it has recently been shown that high hs-CRP levels were not associated with progression of carotid atherosclerosis after taking traditional atherosclerotic risk factors into account in the Tromsø Study (Agnethe Eltoft, MD, unpublished data, 2016), and the possible association between VTE and carotid plaque progression we found in subjects with carotid plaque(s) remained unchanged after adjusting for hs-CRP. Finally, we showed that the apparent association between VTE and carotid plaque progression among those who already had atherosclerotic plaques was strengthened when traditional atherosclerotic risk factors, and specifically smoking and BMI, were taken into consideration. Similarly, Jezovnik and coworkers found higher risk estimates for atherosclerotic plaques in DVT patients after adjusting for atherosclerotic risk factors.[210] Taken together, this may imply that the possible association between incident VTE and atherosclerosis progression in those with already established carotid plaque(s) is independent of traditional atherosclerotic risk factors and low-grade inflammation accompanying the VTE.

6. Conclusions

A: We found that incident MI was associated with increased risk of future VTE, and particularly of PE, after adjusting for potential confounders, and that 6% of the VTE events in the population could be attributed to MI. The VTE risk after MI was transient, which suggests that direct or indirect causal mechanisms related to the MI event itself are primarily responsible for the observed association.

B: In our study, we found that all women and men <65 years of age with incident VTE had increased risk of future MI and ischemic stroke after adjusting for potential confounders, such as BMI. However, only 1% of the arterial thrombotic events in the population were attributed to VTE.

C: In our study, incidence rates of MI and VTE according to family history of MI were 7 and 2 per 1000 person-years, respectively, and family history of MI increased the risk of both incident MI and VTE. Apparently, the association between family history of MI and VTE applied to unprovoked DVT, and the risk of unprovoked DVT increased with increasing number of affected first-degree relatives with a history of MI.

D: The associations between family history of MI and incident MI and VTE were similar in the cause-specific and the traditional Cox model, and modifiable atherosclerotic risk factors did not explain the association between family history of MI and VTE.

E: We found that incident VTE was associated with atherosclerosis progression in those with already established carotid plaques, but not with novel plaque formation. The possible association between VTE and carotid plaque progression was not mediated by low-grade inflammation assessed by hs-CRP.

7. Final remarks and future perspectives

Based on the existing literature and the findings in this thesis, there appears to be a bidirectional association between incident VTE and arterial CVD. MI explained 6% of the PEs in our study population and the attributable risk of PE due to MI was high. Development of a VTE risk prediction model to recognize high risk MI patients in need of VTE prophylaxis is therefore pivotal, and future studies are needed to identify predictors of VTE following MI and assess whether implementation of a VTE risk prediction model in MI patients may reduce the incidence of VTE. The transient increased risk of VTE following MI may imply a role for prolonged anticoagulant therapy in high-risk MI patients to prevent subsequent VTE. Moreover, results of RCTs indicate that short-term VKA therapy is more effective than aspirin in reducing the risk of future arterial CVD in MI patients.[260, 261] However, the effect of prolonged anticoagulation and the effect of VKA on future VTE risk was not investigated, and further studies are warranted.

Similar inferences may be drawn from the observed association between VTE and future arterial CVD. However, the number of arterial events attributed to VTE in our study population was low. Implementation of a prediction model to recognize high risk VTE patients in need of arterial CVD prophylaxis is therefore unlikely to influence the incidence of arterial CVD greatly. Finally, aspirin to prevent arterial events in VTE patients is controversial because of the lower potency of aspirin compared with anticoagulant therapy in preventing arterial events found in MI patients.[260, 261] Statin treatment has been shown to decrease the risk of incident VTE.[254] From this it may be hypothesized that statins in VTE patients at high risk of arterial events may reduce the risk of both recurrent VTE and subsequent arterial CVD. However, statins as a supplement to anticoagulant therapy in VTE patients has to the best of our knowledge not previously been explored and further studies are needed.

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