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Venous thromboembolism: incidence, recurrence and mortality

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Lists of papers

I Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population.

Arshad N, Isaksen T, Hansen JB, Brækkan SK.

European Journal of Epidemiology; March 2017; 32(4): 299-305.

II Recurrence and mortality after first venous thromboembolism in a large population-based cohort.

Arshad N, Bjøri E, Hindberg K, Isaksen T, Hansen JB, Brækkan SK.

Journal of Thrombosis and Haemostasis; February 2017; 15(2): 295-303.

III Hospital-related first venous thromboembolism and risk of recurrence.

Bjøri E, Arshad N, Johnsen HS, Hansen JB, Brækkan SK.

Journal of Thrombosis and Haemostasis; December 2016; 14(12): 2368-75

IV Myocardial infarction is a risk factor for venous thromboembolism (VTE) recurrence in women with a first VTE.

Arshad N, Lijfering WM, Cannegieter SC, Hansen JB, Rosendaal F, Brækkan SK.

Manuscript

Summary

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), is associated with substantial morbidity and mortality. To plan and evaluate prevention and treatment strategies for VTE, understanding into the epidemiology and current magnitude of VTE is needed. The aims of this thesis were (i) to assess time-trends in the incidence of VTE in the period 1996-2012, (ii) to assess the incidence of recurrence and mortality after a first VTE, and to investigate association between (iii) hospital-related, and (iv) myocardial infarction (MI)-related first VTE and risk of VTE recurrence.

All four papers in this thesis utilize the Tromsø Study, a large population-based cohort with repeated health surveys (1-7). In paper I, we followed 26 855 participants from the inclusion in Tromsø 4 (1994-95) throughout 2012, and assessed the biennial incidence rates of VTE. In Papers II-IV, patients with a first VTE in the period 1994-2012 derived from Tromsø 4 (Paper II) or Tromsø 1-6 (Papers III and IV) were followed from their first VTE until the date of recurrence, death or emigration, or the end of the study period, whichever came first. Paper IV additionally included data from the Multiple Environmental and Genetic Assessment of Risk Factors for venous thrombosis (MEGA) follow up study.

We found that the overall age-adjusted incidence of VTE increased by 27% from 1996 to 2012. The observed incremental trend was largely due to an increase in the rate of PE. Furthermore, we found that the rates of recurrence and mortality remained high, particularly during the first year after the VTE event. Among patients with hospital-related VTE, the reason for hospitalisation appeared to have a great influence on recurrence risk. In traditional analysis, patients with cancer-related VTE appeared to have the highest risk of recurrence. However, when competing risk of death was taken into account, the risk estimates dropped substantially. Patients with a first VTE related to hospitalisation for medical illness had similar recurrence risk as patients with a non-hospital-related first VTE. Finally, we found that a history of MI was associated with increased risk of VTE recurrence, particularly in women.

Abbreviations

a	Activated
ACCP	American College of Chest Physicians
APC	Activated protein C
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
CTPA	Computed tomographic pulmonary angiography
CTPH	Chronic thromboembolic pulmonary hypertension
CVD	Cardiovascular disease
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ECG	Electrocardiogram
F	Factor
FVL	Factor V Leiden
GWAS	Genome-wide association studies
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICD-CM	International Classification of Diseases-Clinical Modification
IR	Incidence rate
KM	Kaplan-Meier
LMWH	Low molecular weight heparin
LRT	Log-rank test
Mc	Monocytes
MEGA	Multiple Environmental and Genetic Assessment Study
MI	Myocardial infarction
MONICA	Monitoring of trends and determinants in cardiovascular disease
MORGAM	MONICA risk, genetic archiving and monograph project
MP	Microparticles
MRI	Magnetic resonance imagining
MV	Microvesicles
OR	Odds ratio
PAI-1	Plasminogen activator inbibitor-1

PE	Pulmonary embolism
Plt	Platelets
PTS	Postthrombotic syndrome
PY	Person years
RR	Relative risk
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
TF	Tissue factor
VKA	Vitamin K antagonist
VQ scan	Perfusion-ventilation scan
VTE	Venous thromboembolism
vWF	von Willebrand factor
WHO	World Health Organization

1. Introduction

1.1 Venous thromboembolism

Thrombosis occurs when a blood clot (i.e. thrombus) is formed inside a blood vessel. Thrombosis may occur in arteries or in veins. A thrombosis in arteries predominantly results in myocardial infarction (MI) if cardiac supply is involved, ischemic stroke in case of cerebral involvement, and rarely ischemia in other locations if peripheral arteries are involved. A thrombosis in a deep vein that interferes with normal venous blood flow back towards the heart is referred to as deep vein thrombosis (DVT). DVT commonly occurs in the large veins of the leg, thigh or pelvis, but it can also occur in other parts of the body, such as the upper extremities, inferior vena cava, portal- and mesenteric veins, or cerebral sinus veins. Classical signs and symptoms of DVT are swelling, tenderness, warmth and discolouration of the affected extremity. An embolus is a thrombus that dislodges from its original site and travels via the bloodstream through the right side of the heart and into the lungs. The embolus becomes lodged where the vessel narrows, and subsequently blocks the blood flow in a pulmonary artery. This condition is referred to as pulmonary embolism (PE). PE is a serious and life-threatening complication of DVT. Clinically, PE is characterized by dyspnoea, tachypnoea, pleuritic-chest pain, haemoptysis, and in severe cases, circulatory collapse and death. Venous thromboembolism (VTE), a collective term for DVT and PE, is a public health concern with substantial economic burden (1).

Anticoagulant drugs are the main therapy for patients with VTE. For many years, standard treatment of VTE patients without cancer constituted an initial phase of low-molecular-weight heparin (LMWH) and a vitamin K antagonist (VKA) such as warfarin, followed by VKA in monotherapy for long-term treatment (3-12 months). LMWH is the recommended treatment for VTE patients with cancer. Recent evidence indicates that direct oral anticoagulants (DOACs) including direct thrombin inhibitors (e.g. dabigatran) and factor (F) Xa inhibitors (e.g. rivaroxaban, edoxaban and apixaban) have similar efficacy on VTE recurrence and an additional advantage of less bleeding risk when compared with warfarin for the long-term treatment of VTE (2). Recently published guidelines from the American

College of Chest Physicians (ACCP) recommend DOACs over warfarin in acute and long-term treatment of VTE in patients without cancer (3).

The first case of DVT was reported seven centuries ago (4), however, understanding into the aetiology and pathogenesis of VTE began in the mid-1800s. A German physician, Rudolph Virchow proposed in 1856 a triad of physiological alterations that increase the risk of VTE. He postulated three major contributors to the pathophysiology of thrombosis: stasis of blood (alterations in the blood flow), a state of hypercoagulability (changes of blood composition), and venous injury (changes of the vessel wall) (figure 1). This classification remains valid and continues to serve as the foundation of our understanding of the pathophysiological mechanism of VTE (5, 6).

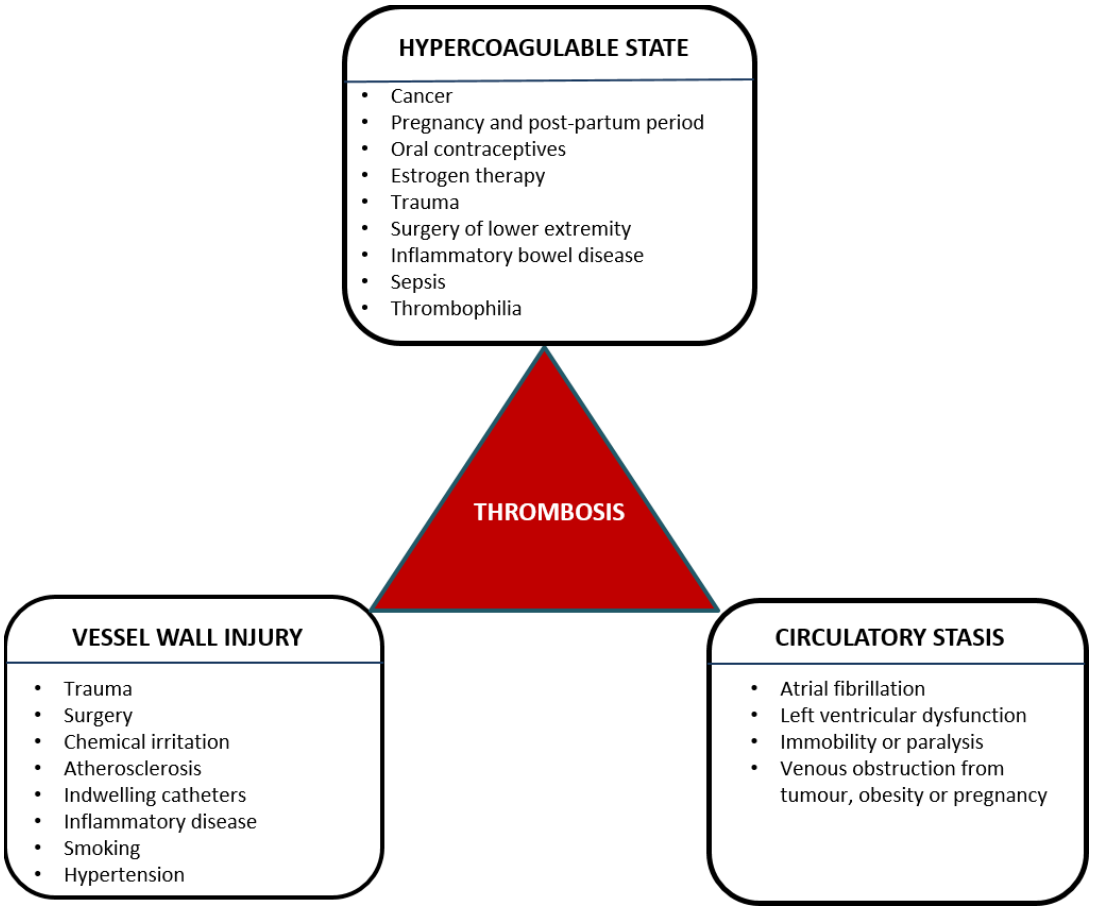

Figure 1. Virchow's Triad

1.2 Pathogenesis of venous thromboembolism

Autopsy and radiological studies have shown that venous thrombi originate near the vessel wall in the apex of the venous valve pocket, and that venous thrombi mainly contain red blood cells and fibrin (7). The venous valve pocket of the calf vein is prone to hypoxia (8) and a common location for the initiation of venous thrombi (figure 2).

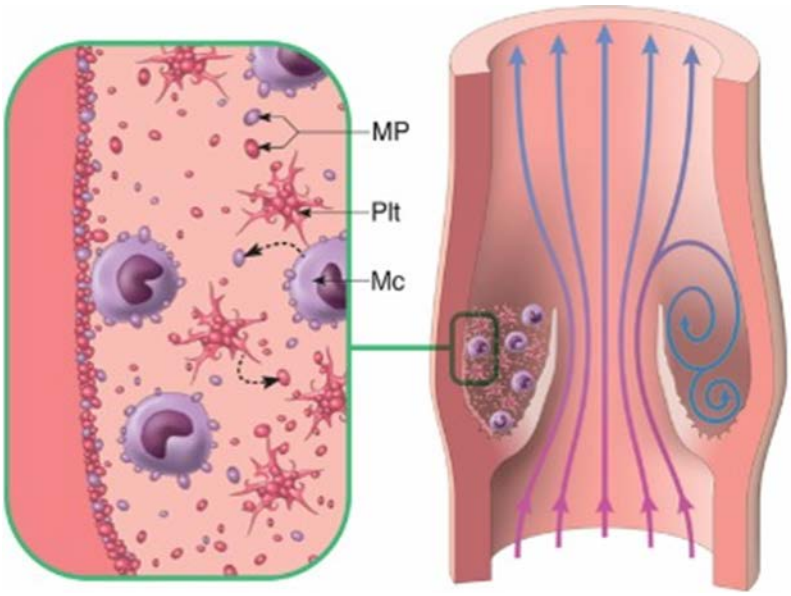

Figure 2. The pathology of DVT in the venous valves: The venous valvular sinus is a predilection site for thrombus formation. The vortical flow pattern at the venous valvular sinus leads to a steep decline in oxygen tension. The resultant hypoxia activates the venous endothelium, leading to the recruitment and binding of monocytes (Mc), platelets (Plt), and tissue factor (TF)-positive microparticles (MP). Consequently, TF from activated Mc and MP may activate the coagulation cascade and initiate thrombosis formation.

Hypoxia is suggested to be associated with prothrombotic and proinflammatory processes within the endothelial cells (7, 8) and it has been hypothesized that hypoxia caused by blood *stasis* leads to the activation of endothelial cells. A healthy and undamaged endothelium is a metabolically active interface between blood and the underlying tissues. It prevents adherence of cells and proteins required for clotting, hence preventing thrombosis (9). The endothelium is activated by hypoxia and/ or inflammatory mediators. Activation of the endothelium results in expression of P-selectin and E-selectin, which in turn facilitate adhesion of leukocytes (monocytes), platelets and TF^{+} microvesicles

(MVs) on the surface of the endothelium (10) with subsequent activation of the coagulation cascade. The activation of the coagulation cascade overwhelms the protective anticoagulant pathways and triggers thrombus formation (7). Together, activated (a) factor VIIa and TF, trigger the extrinsic coagulation pathway via activation of FIX and FX through FVIII. Activated FX and FV convert prothrombin (FII) to thrombin (FIIa). Thrombin further converts fibrinogen (FI) to fibrin (FIa) and activates FXIII which ultimately leads to stabilized fibrin (7). In addition, *injury to the endothelium* results in expression of TF, exposure of the sub-endothelial vascular collagen to platelets and clotting factors, and adhesion of white blood cells to the endothelial surface (11).

1.3 Epidemiology of incident venous thromboembolism

1.3.1 Venous thromboembolism in the general population

VTE is the third most common cardiovascular disease after MI and stroke, (12) and is a major cause of morbidity and mortality worldwide. VTE is a common condition with an overall incidence of 1 to 2 per 1000 persons each year in Western countries (13, 14). The annual number of symptomatic VTE in Europe is more than one million (15). Additionally, approximately 0.3 million deaths occur annually due to sudden PE or following undiagnosed VTE (15), which is more than twofold the combined deaths due to acquired immune deficiency syndrome (AIDS), breast and prostate cancer, and transport accidents (15).

DVT accounts for approximately two-thirds of all VTE events, whereas PE makes up nearly one-third, although the two conditions often exist simultaneously (16, 17). Out of those presenting with symptomatic DVT, 50-80 % have silent PE (18), whereas, among individuals with symptomatic PE, 50% have asymptomatic DVT (19) .

VTE has serious short and long-term complications. Short-term thrombosis sequelae include extension of the thrombus, early recurrence, and mortality. VTE is also associated with long-term

complications such as postthrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTPH), late recurrence, and death (20, 21). Recurrent thrombosis is relatively common, particularly in patients with unprovoked VTE (22). Approximately 30% of patients develop recurrence within the next 10 years following a first VTE diagnosis (23). Anticoagulant-related major bleeding occurs in about 5-10% in the first year following an initial VTE diagnosis (24). For nearly one-fourth of PE patients, the initial clinical presentation is sudden death (20). Moreover, PE is estimated to be the leading preventable cause of death in hospitalized patients (25). PTS is the most common complication of DVT, affecting between 20-50% of patients with lower limb DVT (21, 22). Symptoms of PTS include pain, heaviness, cramps and persistent swelling of the affected extremity (21). Risk factors for development of PTS include female sex, obesity, proximal DVT, recurrent DVT and varicose veins (26). Prognosis mainly depends on the affected anatomic segment and time till restoration of vessel strength (21). PTS impairs patient mobility, quality of life and increases the risk of disability pension (21). Chronic obstruction of major pulmonary arteries results in CTPH that causes additional workload on the right side of the heart due to abnormally high blood pressure in the arteries. CTPH occurs in 0.5-1.5% of all PE cases and in 1.5-4.0% of patients with unprovoked PE. The majority of the CTPH cases were identified within the first 2 years after the initial PE diagnosis (27).

1.3.2 Time-trends in incidence rates of venous thromboembolism

The reported incidence of an initial episode of VTE varies substantially in previous literature as it ranged between 62 and 143 per 100,000 individuals per year (13, 24, 28-32). The incidence of first-time PE ranged between 19 and 80 per 100,000 per year, and incidence of first-time DVT ranged between 35 and 95 per 100,000 per year (13, 24, 28-32). These variations may be due to population characteristics such as age distribution, ethnicity, available data sources, case definition and validation procedures, study design, and dependence on hospital inpatient databases (13, 14, 16, 33, 34). Moreover, some other studies did not separate incident events from recurrent events or did not

include autopsy-identified events (35). Modification in risk factors, prevention strategies, increased awareness of VTE risk, and the use of thromboprophylaxis in high-risk situations can influence the rates of VTE in the community (36). For instance, the prevalence of VTE risk factors such as old age, obesity and cancer are increasing at the population level in Western countries (15, 34, 35). The widespread use of LMWH for VTE prophylaxis (24) as well as the introduction and utilization of more sensitive and objective diagnostic tools, such as multidetector row computed tomographic pulmonary angiography (CTPA) and magnetic resonance imagining (MRI) for detection of PE, may have influenced the rates during the last 20 years (37-39).

Scientific literature describing the incidence of VTE vary considerably, and the majority of the population-based studies were carried out several decades ago (14, 20, 24, 25). Few studies have investigated recent time trends in the incidence of VTE. Two studies reported an 80% increase in the rates of VTE in the period 1985-2009 (39) and 1993-2006 (38) with a considerable increase from 1999 to 2009, primarily due to an increase in PE (13, 38-40).

To summarise, few studies have focused on the trend in VTE-incidence during the last decades. Increased awareness of VTE and a better understanding of VTE epidemiology may assist better public health outcomes through further research into VTE risk factors and targeted prevention.

1.3.3 Classification of venous thromboembolism

VTE events can be broadly categorized as being provoked (secondary/ environmental) or unprovoked (idiopathic/ non-environmental), depending on the presence of risk factors at the time of VTE diagnosis. This classification has implications for the risk of VTE recurrence and length of treatment (41). VTE events are categorized as provoked if they occur in the presence of either transient (e.g. hospitalization, acute medical illness, recent surgery, trauma, and long-haul travel) or persistent (e.g. active cancer, paralysis) provoking factors. Risk factors are further classified into major and minor. Provoked VTE events occur in the presence of major transient risk factors (e.g. major trauma, surgery

with general anaesthesia for more than 30 minutes, or acute illness with admission to hospital for at least 3 days) in the 3 months before an event. Minor transient risk factors include surgery with general anaesthesia for less than 30 minutes, acute illness with admission to hospital for less than 3 days, oestrogen therapy, and pregnancy in 2 months before a VTE diagnosis. When VTE occurs in patients with a minor transient risk factor, or occurs many months after a major risk factor, it can be controversial whether the risk factor is prognostically significant enough to justify categorization of the VTE as provoked. VTE events are considered unprovoked if they occur in the absence of a provoked factor, transient or persistent (41).

1.3.4 Risk factors for venous thromboembolism

In epidemiology, a risk factor is a characteristic (or exposure) that affects the incidence of disease and has a causal role in the development of disease (42, 43). Stasis, hypercoagulability, and alteration of the vessel wall (endothelial activation or injury) are the major factors responsible for thrombus formation and propagation according to Virchow's triad (44). Almost all risk factors for VTE fall into one or more categories of this triad. VTE is a complex and a multicausal disease associated with several risk factors, which must be present for an event to occur (45).

The complex interplay between risk factors for VTE may be explained by the thrombosis potential model (45) (figure 3). This model is based on the assumption that each risk factor enhances the risk, called an individual's thrombosis potential, and when the combined effect of these risk factors exceeds the thrombosis threshold, the result is a VTE event.

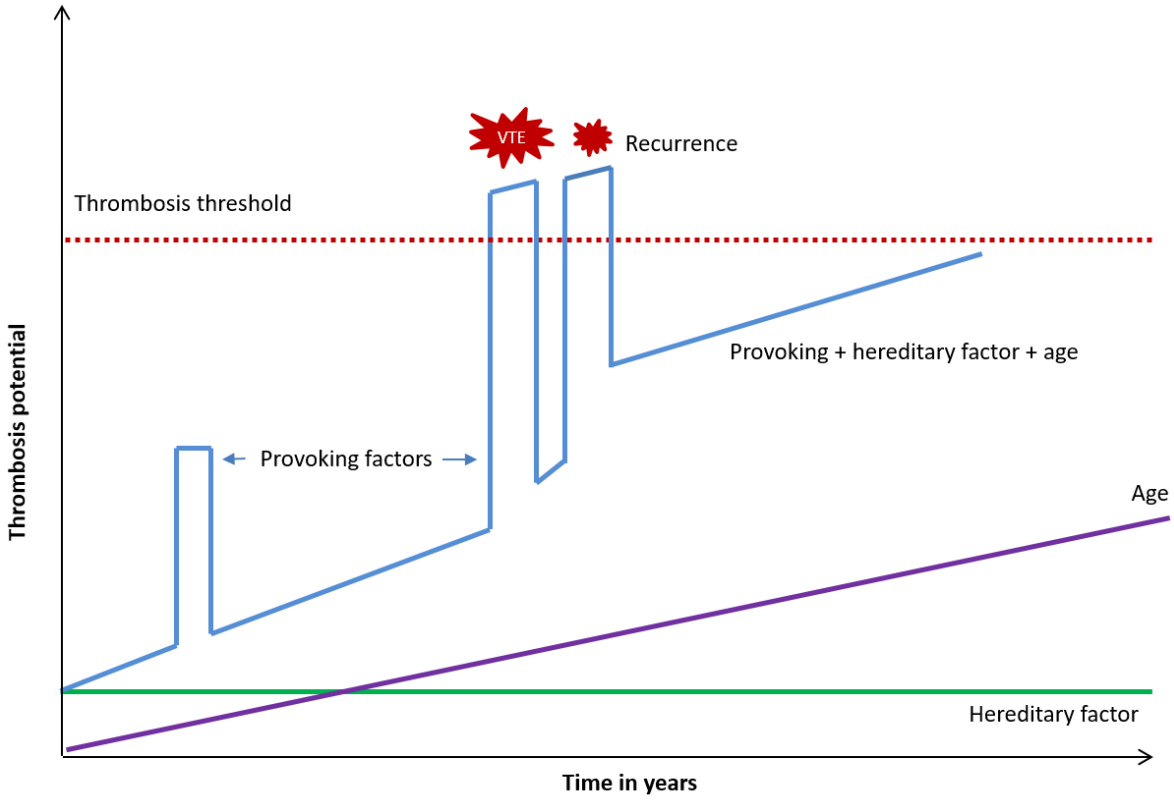

Figure 3. The Thrombosis potential model. The green line represents a heredity factor for VTE (e.g. Factor V Leiden), and the purple line represents the effect of a risk factor that increases over time (e.g. age). The blue line demonstrates the joint effects of the heredity factor, age and provoking factors (e.g. trauma, surgery or use of oral contraceptives) on the thrombosis potential at different time points. Provoking factors in early years of life may not be sufficient to reach the thrombosis threshold. However, a provoking factor later in life may contribute to exceed the thrombosis threshold (red line) and result in a VTE. If the thrombosis potential keeps on increasing following an incident VTE event, a provoking factor may exceed the thrombosis threshold again and result in a recurrent VTE.

Classical **environmental exposures (acquired risk factors)** for VTE include advancing age, major surgery, trauma, hospitalization, obesity, prolonged immobilization, cancer, oral contraceptives, hormone replacement therapy, pregnancy, puerperium, acute medical conditions, and antiphospholipid antibodies (34, 46, 47).

Advancing age is one of the strongest risk factors for VTE, and a number of studies support an association between increasing age and higher incidence of VTE (13, 16, 30, 48, 49). The incidence of VTE increases exponentially (14, 28) from 5 per 100 000 per year in individuals <15 years, to approximately 500 per 100 000 per year among individuals over 80 years (16). The risk increases

rapidly after the age of 45 years (13). Studies have reported that age increases the risk of VTE nearly 2-fold per decade (48) and the risk of VTE is 10 to 15-fold higher in individuals over 75 years as compared to those aged 45-54 years (50, 51). The reason for the increased risk of thrombosis with age is not fully investigated. However, it is suggested that it might be related to decreased mobility, degenerative vascular changes (46), more co-morbidities and increased plasma levels of haemostatic factors (fibrinogen, FVIII, FVII, d-dimer and homocysteine) or a combination of these (33, 52, 53). Although VTE occurs more frequently in older individuals (35), it can affect individuals of any age and sex (13). With increasing age in both males and females, PE accounts for an increasing proportion of the VTEs (13). The association between **sex** and risk of first time VTE has been assessed in many large cohort studies. Some studies reported higher risk of VTE in men than in women (13, 48), whereas others have shown a higher incidence of VTE in women than in men (24, 28, 54, 55). Moreover, in some other studies, the incidence of first VTE was approximately equal between the sexes (16). The variation in results of these studies could be explained by differences in the selection of the study population since the risk of VTE varies with age. Women have slightly higher risk of VTE during childbearing age (16-44 years) compared with men of similar age,(13, 28, 56) whereas men have an overall higher risk of VTE after the age of 45 years (28, 29, 56). The Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study reported that the risk of a first VTE is 2-fold higher in men than in women once female reproductive risk factors (oral contraception use, post-menopausal hormone therapy, or pregnancy) for VTE are taken into consideration (57), suggesting that the risk of incident VTE is higher in men than in women. The pathophysiology behind these observations has not yet been disentangled.

Recent major **surgery** is considered a strong risk factor for VTE (58). Surgical procedures associated with a high risk include neurosurgery, major orthopaedic surgery of the lower extremity, cancer surgeries of the thorax, abdomen or pelvis, and renal transplantation (59). Major surgery is associated with a 4 to 22-fold increased risk of VTE (58, 60). Several factors, such as advancing age, presence of comorbid conditions, endothelial damage and subsequent immobility after surgery, as

well as type and duration of surgery have been recognized as risk factors for VTE post operatively (61). Growing evidence also suggests increased TF expression and levels of procoagulant factors VII and fibrinogen on day 3 after major orthopaedic surgery of the lower extremity (62, 63). Additionally, minor surgical procedures, including central venous catheter and pacemaker insertion, have also been highlighted as risk factors for VTE (58, 64).

Hospitalization is another risk factor for VTE. The average age- and sex-adjusted incidence of in-hospital VTE was 960 (95 % confidence interval [CI] 795-1125) per 10 000 person-years (PY) and 7.1 (95% CI 6-7) per 10 000 PY among community residents (65). A population-based study reported that 61% (95% CI 57-66%) of all confirmed cases of VTE could be attributed to institutionalization (current hospital or nursing home confinement) within the preceding 3 months (64). In a case control study, recent hospitalization with and without surgery was associated with a 22-fold and 8-fold increased risk of VTE respectively (58). Without prophylaxis, the estimated incidence of hospital-associated VTE in adult medical or general surgical patients ranges from 10% to 40% (66). Many of these events are not clinically evident, however, still could lead to life-threatening complications like PE. A study reported that approximately 10% of all deaths in hospitalized medical patients are linked to PE (67). **Acute medical conditions**, for instance, MI, stroke, infections, congestive heart failure and respiratory diseases are known to increase the risk of thrombus formation (3, 68, 69). Hospitalization for acute medical illness is associated with an 8-fold increased risk of VTE (70).

Cancer is recognized as one of the most important risk factors for VTE. Almost 20% of all incident VTE events are associated with cancer (64, 71), and the overall risk of VTE is estimated to be 4 to 7-fold higher in patients with cancer (58) compared with cancer-free individuals (23). The risk of VTE among cancer patients varies according to cancer type, stage and treatment options. The risk of VTE is high among cases with metastatic stage cancers particularly cancer of the brain, pancreas and stomach, whereas, prostate and breast cancer have generally been associated with a low VTE risk (72, 73). In a population-based study, after adjusting for age, race, and cancer stage, VTE was associated

with a significant reduction in survival in cancer patients during the first year (range of hazard ratios [HR], 1.6-4.2; p <0.01) (72). Hospitalized patients with cancer had twice the incidence of DVT and PE as hospitalized patients without cancer (74). Risk of VTE is highly dependent on cancer-related (cancer type, stage, tumor grade, histological type, and time since cancer diagnosis), patient-related (advancing age, obesity, immobility, comorbid conditions, and inherited thrombophilias), and treatment-related (surgery, chemotherapy, radiotherapy, central venous catheters, erythropoiesis-stimulating agents, and blood transfusions) risk factors (75). Several pathogenic mechanisms may promote thrombus formation in cancer patients including tumour induced platelet activation, enhanced expression of TF, reduced clearance of coagulation factors and decreased anticoagulant synthesis (63, 76). Moreover, it is likely that the tumour itself increases the risk of thrombosis by causing a procoagulant state through release of humoral factors (46).

Patients with **multiple trauma** are also at high risk of developing VTE (77). In the absence of anticoagulant prophylaxis, thrombosis (symptomatic or asymptomatic) occurs in 50 % to 60 % patients with head trauma, spinal injury, pelvic, femoral, and tibial fractures (78). The magnitude of injury according to injury severity score, impact of operative interventions, presence of pelvic injury and spinal cord injuries are factors that places the individual patient at a higher risk of developing VTE (77).

The rising prevalence of **obesity**, especially in the Western countries, is a growing public health concern. According to 2017 estimates from the World Health Organization (WHO), worldwide obesity rates have nearly tripled since 1975 (79). Growing evidence suggests that obesity (body mass index [BMI] over 30 kg/m^2) is a risk factor for VTE (80). All measurements of obesity including BMI, body weight, waist circumference, hip circumference, and total body fat mass are associated with an increased risk of VTE (81-83). Elevated levels of FVIII, FIX, and plasminogen activator inhibitor-1 (PAI-1) in obese individuals could likely contribute to the increased risk of VTE (7). Moreover, excess abdominal body fat may result in compromised venous return with subsequent venous stasis (80).

Venous stasis is an important risk factor for VTE and **immobilization** of the extremities, for instance due to paralysis, bed rest, plaster casts, and long-haul flights, increases the risk of thrombus formation (84, 85). In one study, immobilization (confinement to bed or armchair) was found to be associated with a 6-fold (95 % CI 2.3-13.7) increased risk of DVT (86). Moreover, in another study, asymptomatic DVT was found in 60% of paralysed limbs of stroke patients compared with 7% in the non-paralysed limbs (85). Prolonged immobility combined with other risk factors increases the probability of VTE (47). Without much difference for the various modes of travel, **long haul flights** (≥ 4 hours) was associated with a 3-fold increased risk of thrombosis. The risk was mainly due to immobilization and reported to be higher for individuals with factor V Leiden (FVL), obesity and users of oral contraceptives (87).

An association between **pregnancy** and VTE is well established and PE is reported to be the leading cause of maternal death in the developed world (88). Pregnant women have a 4 to 5-fold increased risk of VTE compared with non-pregnant women (89, 90). The steep incline in VTE risk during pregnancy may be explained by a large increase in levels of procoagulant factors (for instance, VII, VIII, X, fibrinogen, von Willebrand factor (vWF), and PAI-1 during normal pregnancy which returns to baseline levels after 8 weeks postpartum (91). Additionally, increased venous capacitance and reduced venous return in pregnant women along with mechanical obstruction by the uterus may contribute to pregnancy-related thrombosis (88). In the postpartum or **puerperium** period (6-weeks after delivery), the risk of VTE is 20 to 80-fold higher, probably due to endothelial damage to the pelvic vessels that occurs during labour (88, 89).

Use of **oral contraceptives** is also an established risk factor for VTE in women and has been shown to increase the risk of VTE from 2 up to 7-fold especially during the first year of use depending on the dose of Ethinylestradiol and the type of progestogen (92). The third generation progestogens (desogestrel and gestodene) are associated with the highest risk of VTE (92). Increased levels of procoagulant factors (such as, VII, VIII, IX, X, XII, XIII, II, I), reduced concentration of the natural

anticoagulants (protein S and antithrombin), and an increased resistance to the anticoagulant action of activated protein C (APC) has been observed with oestrogen usage (93-95). Moreover, postmenopausal women taking **hormone replacement therapy** (with oestrogens) have a 2 to 3-fold increased risk of developing VTE (96).

Individuals with **antiphospholipid antibodies**, both with and without underlying systemic lupus erythematosus (SLE) have an increased risk of VTE. Ginsberg *et al.* reported a strong association between lupus anticoagulant and VTE, with an odds ratio (OR) of 9.4 (97).

In addition to acquired risk factors, a variety of **inherited traits** contribute to the overall risk of VTE in an individual. Family and twin studies have revealed that genetic factors account for 50-60% of the VTE risk (98, 99), and a family history of VTE is associated with a 2 to 3-fold higher risk of VTE (100). Inherited thrombophilias increase the risk of VTE predominantly by two mechanisms. The *loss-of-function* of anticoagulant proteins (including deficiency of antithrombin, protein C, or protein S) or *gain-of-function* of procoagulant factors (such as factor V Leiden [FVL], prothrombin G20210A and non-O blood group) (101, 102).

Antithrombin is a glycoprotein produced by the liver and is a strong natural inhibitor of the coagulation cascade. Over 250 genetic mutations may result in **Antithrombin deficiency** (102). Antithrombin deficiency is a rare condition found in 1-2% of the VTE patients, and is associated with a 10 to 50-fold increased risk of VTE (103). Protein C, encoded by the PROC gene, is a vitamin K-dependent plasma glycoprotein that is synthesized in the liver and released into the bloodstream. **Deficiency of protein C** is a congenital or an acquired condition and leads to increased risk of thrombosis (104). Heterozygous protein C deficiency is present in 2-5% of VTE cases and <0.5% of the general population, and associated with a 10-fold increased risk of VTE (105). Protein S, encoded by the PROS1 gene, is a vitamin K-dependent single glycoprotein that is synthesized in the liver. Protein S functions as a cofactor to facilitate the action of activated protein C for the inactivation of activated factor V (FVa) and factor VIIIa. **Deficiency of protein S** is found in <0.5% of the general population and

in 2-12% of selected groups of thrombophilic patients (106), and family studies have suggested that the VTE risk is similar to that in patients with Protein C deficiency (104).

FVL, prothrombin G20210A and non-O blood group are less thrombogenic, however, they are more common than the deficiencies of antithrombin, protein C, or protein S (104). Factor V (FV) is a single-chain glycoprotein encoded by the F5 gene. It is synthesized in the liver and circulates in the plasma as an inactive precursor. APC inactivates the activated form of FV. A polymorphism of FV (**FVL mutation)** is associated with APC resistance. As a result, FV protein retains its procoagulant role in the plasma (104). The overall prevalence of FVL mutation is about 5% among Caucasians in its heterozygous form (107). The FVL mutation yields a 2 to 3-fold increased risk of VTE (108). Prothrombin, encoded by the F2 gene, is a single-chain glycoprotein and one of the vitamin-K dependent factors synthesized in the liver. **Prothrombin gene G20210A mutation** causes the body to produce excess amount of prothrombin (109). The prevalence of this gene mutation is around 2% in the general population and carriers of this polymorphism have 3 to 4-fold increased risk of VTE (110). The occurrence of FVL and prothrombin G20210A varies with ethnicity and are more prevalent among white Europeans and Americans than among individuals of African or Asian descent (104). The ABO gene encodes proteins related to the blood group system that determines the blood group. The ABO phenotype correlates with plasma levels of FVIII and vWF (104). The **non-O blood group** phenotype confers a 1.5-fold increased risk of VTE (108) and to some extent, this association is due to increased levels of vWF and FVIII in individuals with non-O blood group (111). However, some studies have shown that non-O blood group remains significantly associated with VTE even after adjustment for FVIII or vWF levels (112), inferring a contribution of an unidentified pathway linking non-O blood group to the risk of VTE.

Despite significant contribution of genetic factors influencing VTE risk, a review reported that common polymorphisms are expected to explain approximately 5-20% of VTE heritability (108). Genome-wide association studies (GWAS), performed during the last decades, have identified 12 novel

single nucleotide polymorphism (SNPs), which are associated with VTE and are frequent in the population. The OR associated with these risk alleles range from 1.15 to 1.50. These SNPs have a moderate influence on the risk of VTE and are therefore not likely to entirely explain the hereditary predisposition for VTE (108). Much remains to be done to disentangle the genetic variation of VTE. Therefore, it is expected that forthcoming whole-genome sequencing studies will identify novel genetic risk factors for VTE.

1.4 Recurrence of venous thromboembolism

1.4.1 Epidemiology of recurrent venous thromboembolism in the general population

VTE is a chronic disease that frequently recurs (20, 39, 113). The risk of VTE recurrence after an incident VTE is highest during the initial 6 to 12 months, and then it declines with time (114) . The cumulative incidence of first overall VTE recurrence is reported to be 0.6-5% at 30 days, 7-10% at 6 months, 11-18% after one year, 22.8% at five years, and 25-40% at 10 years (22, 23, 35, 48, 115-123). The variations in the reported cumulative incidence rates can potentially be explained by differences in study design, clinical setting, case definition, age restriction, and the time period in which the studies were conducted. In recent years, advances in diagnostics and management, out of hospital diagnosis, and treatment of VTE may have influenced the rates of adverse outcomes after VTE. For instance, the average length of hospital stay after a VTE has been reduced, and a large proportion of VTE cases are treated as outpatients (24, 39). Additionally, knowledge about VTE risk and the use of thromboprophylaxis in high-risk situations may also have affected the recurrence rates. Finally, the extensive use of high-resolution multidetector CTPA to diagnose PE, and the concomitant increased detection rate of subsegmental PE, may have influenced the overall outcome rates after a first VTE (38, 124).

Overall, few studies have assessed and compared the cumulative incidence of recurrence in the presence of competing risk by death in subcategories of patients with an incident VTE (125, 126). Additionally, other studies were conducted decades ago (22, 23), recruited patients after completion of anticoagulant treatment (3-12 months after the first event), and the study population was either outpatients or hospitalized patients (22, 121, 127). We therefore aimed to estimate the cumulative incidence of recurrence after a first VTE. With the purpose to assess the burden of VTE, we used cases derived from a general population cohort including both the hospital and community setting during 1994-2012.

1.4.2 Risk factors for recurrent venous thromboembolism

The aetiology of the first VTE event is the primary driver of the risk of recurrence after discontinuing anticoagulants (128). If VTE occurs in the presence of provoking factors, the risk of recurrence is generally low and does not require prolonged treatment (> 3 months) with anticoagulants (3, 41, 129). For instance, in patients with VTE provoked by a major transient risk factor, the initial treatment can be limited to 3 months, as the annual risk of recurrence is only 1% after stopping anticoagulation (3). Patients with VTE provoked by a major persistent risk factor has a higher risk of VTE recurrence after discontinuing treatment than patients with VTE provoked by transient factors or unprovoked VTE (23, 41, 130). Patients with unprovoked VTE have an intermediate to high risk of recurrence after discontinuing treatment (41, 129). Population-based studies have reported that 50-60% of the VTE events can be classified as provoked (28, 29, 123).

Recurrences often occur at the same site as the initial event (DVT or PE). For instance, patients presenting with PE are three times more likely to suffer recurrence as PE than patients presenting with proximal DVT (131). Moreover, patients with DVT, in general, experience more recurrence than patients with PE. Studies have shown that patients with a first symptomatic DVT have a 1.5 to 2-fold higher risk of recurrence than patients with a first PE (115, 121, 132) .

Predictors of VTE recurrence include increasing age and BMI, male sex, neurologic disease with paresis, active cancer, inferior vena cava filter placement, and neurosurgery (23, 127, 133-135). Recurrent VTE occurs at a higher rate in men than in women, up to 10% per year versus 2-5% per year respectively (127, 136, 137). A meta-analysis reported that men have a 50% higher risk than women of recurrent VTE after stopping anticoagulant treatment (136). This meta-analysis included 11 cohort studies, five of these studies found an increased risk of recurrence in men [relative risk (RR) range= 1.7-6.3], five studies found a weak or no association, whereas one study found a lower risk in men (RR= 0.5). Previous studies have shown that recurrence risk is highest (>2-fold) when the first event was unprovoked (115, 138). In patients with a first unprovoked VTE, Baglin *et al.* reported a 2.5-fold higher risk of recurrent VTE in men compared with women at 2 years (134). Interestingly, men with a provoked first event still had a higher recurrence risk than women with an unprovoked first event (139).

1.4.3 Hospital related venous thromboembolism and recurrence

Hospitalization in itself is an interim exposure and may therefore be considered as a transient risk factor, presumed to be associated with a low risk of recurrence (23, 129). However, studies have reported that short-term hospitalization with (23) or without neurologic disease is associated with an increased risk of recurrence (125). There is not much data available on the risk of recurrence after incident hospital-related VTE, particularly hospitalization for conditions other than cancer or surgery. Therefore, it is necessary to investigate the risk of recurrence and mortality among patients with an incident VTE associated with previous hospitalization and to compare the impact of transient and persistent hospital-related factors such as surgery, cancer or other medical conditions (e.g. MI) on the risk of recurrence in models with and without death as a competing event.

The most common statistical method employed to evaluate the recurrence risk of VTE has been the Kaplan-Meier (KM) approach, through which death is viewed as a censoring event (140-142).

The mortality rate is expected to be higher among patients with cancer and other comorbidities. The KM method, when used to estimate the cumulative incidence of recurrence of VTE, overestimates the cumulative incidence of recurrence due to failure to account for death as a competing risk. In our study, the cumulative incidence of recurrence may be influenced by the competing risk of death. Thus, application of the competing risk model, as suggested by Fine and Gray (143), may yield a more appropriate statistical estimate of the cumulative incidence of recurrence in patients with a hospital related first VTE.

1.4.4 Myocardial infarction related venous thromboembolism and recurrence

Arterial cardiovascular diseases (MI and ischemic stroke) are generally considered to be distinct from venous thromboembolic disease due to different pathophysiology, clinical presentation and treatment (144). In the past decade, however, this concept has been challenged (145, 146) when Prandoni *et al.* (145) found an association between subclinical atherosclerosis and VTE. Later, this finding has been refuted by others (147).

Several epidemiological studies have shown that patients with incident VTE have an increased risk of subsequent arterial cardiovascular disease (CVD) (148-150). A large population-based Danish cohort study reported a 2-fold increased risk of subsequent arterial CVD in patients with VTE as compared with population controls (148). Growing evidence also supports an interrelation between CVD and subsequent VTE. Two large Danish population-based registry-studies have demonstrated that hospitalization for MI or stroke (151), or heart disease (152), was associated with an increased risk of VTE in the following 3 months after taking age, sex, obesity, medication use and comorbidities into consideration. Similarly, Rinde *et al*. showed that patients with MI had an increased risk of VTE, particularly during the first six months after the MI (68). Likewise, a meta-analysis showed that 4% of patients with MI experienced symptomatic PE within approximately 2 weeks after hospitalization (153). The potential mechanism behind the observed association between MI and the future risk of

VTE could include shared risk factors (obesity, smoking, and family history of MI), indirect factors (hospitalizations accompanied by episodes of immobilization following MI) or a direct causal relationship (sudden tissue damage associated prothrombotic response, disturbed cardiopulmonary circulation after MI, and heart failure related venous stasis). The transient increase in risk of VTE after MI reported in the population-based studies, suggests that MI is a transient risk factor for incident VTE (68, 152). This points towards transient mechanisms related to the MI itself (direct relationship), or indirect factors.

If the relationship between MI and risk of VTE is purely transient, one would expect the recurrence risk of VTE to be low. It is, however, uncertain whether VTE patients with a history of MI are at increased risk of VTE recurrence. One study reported that presence of chronic cardiovascular disease in patients with symptomatic VTE was associated with a 2-fold increased risk of recurrent VTE during the initial 3 months of anticoagulant therapy (154). This points towards a persistent risk of VTE in patients with medical conditions such as MI. The risk of VTE recurrence in patients with a history of MI has not been extensively studied. We therefore aimed to investigate the association between history of MI and the risk of VTE recurrence in a cohort of patients with validated information on incident VTE and potential confounders.

1.5 Mortality after venous thromboembolism

1.5.1 Epidemiology of mortality after venous thromboembolism in the general population

VTE is associated with substantial morbidity and mortality and is considered to be the leading preventable cause of in-hospital death (155). Extrapolated data from 6 European countries estimated that 370 012 VTE related deaths occurred in Europe in 2004, clearly indicating that VTE represents a major public health burden. Nearly three quarters of all VTE-related deaths were from hospital-

acquired VTE (15). PE contributes to 5-10% of deaths in hospitalized patients (155). Moreover, 25% of all PE cases are thought to present as sudden death (156).

A large study of 67 354 definite and 35 123 probable VTEs reported 30-day and 1-year case fatality rates of 10.6% and 23.0%, respectively (157). Rates of survival after a first VTE vary widely in previous studies, ranging from 77% to 97% at 1 week and from 61% to 75% at 8 years (22, 48, 115, 122, 156). The short-term survival ranges from 95% to 97% (35, 48) in DVT patients, and from 77% to 94% in PE patients (35, 48, 119, 158), whereas long-term survival ranges from 61% to 75% for both DVT and PE (22, 35, 48, 118, 119). A study reported an overall 8-years cumulative incidence of mortality of 12% (159), whereas another study stated cumulative mortality rate of 52.5% at 8 years (156). The variation in the reported rates may partly be due to differences in study design (clinical trials (160, 161), cohorts or registry databases (162) with limited case validation), clinical setting (hospital (163, 164) or out-patient setting (22, 122)), short follow up time (maximum 10 years (22, 35, 159, 165, 166)), the time period during which the study was conducted, age restriction (age <70 years (159) or 65-89 years (35)), and failure to examine mortality for DVT and PE separately (28, 159, 165). Advances in diagnostics, management and treatment of VTE may have influenced the rates of adverse outcomes after VTE. The length of hospital stay has been reduced since the introduction of LMWH for the treatment of VTE (24, 39, 167-169). Increased awareness of VTE risk and the use of thromboprophylaxis in high-risk situations may also have impacted on mortality rates.

Recent data regarding VTE mortality is limited and previous estimates vary considerably. From a public health perspective, it is important to determine the mortality rates of VTE during the last decades since this information is useful to assess the burden of VTE and its impact on survival.

1.5.2 Predictors of survival after venous thromboembolism

Patients diagnosed with VTE often have malignancy, heart disease or other comorbidities that are associated with increased risk of mortality (33, 170). In the absence of recurrent embolism, death usually results from these coexistent conditions rather than from fatal PE (156).

Predictors of reduced short-term survival include advancing age, male sex, low BMI, confinement to a hospital or nursing home at the onset of VTE, and a history of congestive heart failure (158), chronic lung disease (158), neurological disease, or cancer (156, 158, 170). A cohort study of patients in Olmsted County found that in multivariable adjusted analysis, among patients without cancer, the odds of death within 7 days after VTE for men were 44% higher than for women. A Norwegian study reported that the survival for patients with unprovoked VTE without cancer was higher than for patients with cancer-associated VTE (28). Confinement to a hospital or nursing home at the time of VTE onset was associated with poor survival across all ages (156).

Predictors of reduced long-term survival include increasing age, event type, current or former smoking, confinement to a hospital or nursing home at the onset of VTE, and history of congestive heart failure, chronic lung and renal disease, neurological disease, or malignancy (156). Heit *et al.* reported that long-term survival remained significantly reduced for patients with PE compared with DVT even after adjustment for comorbid conditions (156). Mortality data from the French Epidemiology Center on medical causes of death from 2000 to 2010 indicated that cancer, obesity, osteopathies, and surgical complications were more likely to be the underlying cause of death when PE was listed on the death certificate (171).

2. Aims of the study

The aims of the study were:

I. To describe the 16 years' time trend (1996–2012) in the incident rates of VTE in a large population-based cohort, and to describe the prevalence of clinical risk factors and provoking factors of VTE at the time of VTE diagnosis.

II. To estimate the cumulative incidence of recurrence and mortality after a first VTE by using cases derived from a general population cohort including both the hospital and outpatient setting, during the period 1994–2012.

III. To investigate the risk of recurrence and mortality among patients with a first hospital-related VTE, and to compare the impact of transient and persistent hospital-related factors such as surgery, cancer or other medical conditions on the risk of recurrence in models with and without death as a competing event.

IV. To investigate whether a history of MI was associated with risk of VTE recurrence in a cohort of patients with incident VTE.

3. Methods

3.1 Study populations

3.1.1 The Tromsø Study

Paper I, II and III included in this thesis are based on Tromsø Study, whereas Paper IV also includes the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) follow up study.

The Tromsø Study is a single center, population based cohort with repeated health surveys of the inhabitants of the municipality of Tromsø, Norway. The Tromsø Study is conducted by the Department of Community Medicine at the University of Tromsø. It was originally initiated in 1974 as the Tromsø Heart Study with a purpose to investigate and prevent arterial CVD, since cardiovascular mortality was high in North Norway during that time. The focus of the Tromsø Study has expanded over time, and at present, the Tromsø Study has become a large epidemiological study including a broad spectrum of diseases. So far, seven surveys have been conducted. The first survey was carried out in 1974, followed by surveys in 1979 to 1980, 1986-1987, 1994-1995, 2000-2001, 2007-2008, and most recently the seventh survey in 2015-2016. In all Tromsø surveys, baseline information was collected through self-administered questionnaires, non-fasting blood samples and physical examination performed by the trained personnel.

Tromsø 1 was conducted in 1974 and men aged 20 to 49 were invited and 6 595 participated. The participation rate was 83%. *Tromsø 2* invited men and women between 20 and 54 years and 16 621 individuals participated (participation rate 74%). *Tromsø 3* was conducted from 1986 to 1987 and 21 826 individuals between 12 and 67 years participated, and the participation rate was 75%. *Tromsø 4* was conducted from 1994 to 1995, and a total of 27 158 individuals aged 25 to 97 years participated. *Tromsø 4* is the largest survey of the Tromsø Study with a participation rate of 77%. *Tromsø 5* was conducted from 2001 to 2002 and included 8 130 individuals (participation rate 79%) aged 30 to 89 years. *Tromsø 6* was conducted from 2007 to 2008 and included 12 984 individuals aged 30 to 87 years.

The participation rate was 66%. *Tromsø 7* was conducted from 2015 to 2016 and included 21 083 individuals aged 44 to 104 years (participation rate 65%).

The VTE registry was started in 1994. In Paper I, participants from the fourth survey of the Tromsø Study were followed up from January 1, 1994 until December 31, 2012. In Paper II, participants from the fourth survey of the Tromsø Study who developed a first lifetime VTE were followed from the date of their VTE diagnosis until December 31, 2012 for VTE recurrence and all-cause mortality. In Paper III and IV, patients with a first VTE in the period 1994-2012, derived from the first six surveys of the Tromsø Study, were followed from the date of their first lifetime VTE diagnosis until the date of recurrence, date of death or emigration, or the end of the study period (Dec 31, 2012).

3.2 Outcome measures

3.2.1 Identification and validation of incident VTE events

In the Tromsø Study, VTE events were recorded from January 1, 1994 up till December 31, 2012 (Paper I-IV). Three registries at the University Hospital of North Norway were used to identify VTE events during the follow-up: the hospital discharge diagnosis registry, the autopsy registry, and the radiological procedure registry. The University Hospital of North Norway is the only hospital in the region, and therefore, all outpatient and admitted patient medical care, relevant diagnostic radiology procedures and appropriate treatment of VTE in the Tromsø municipality is provided entirely by this hospital. Relevant International Classification of Diseases (ICD) 9th codes used in the search for cases were 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9 for the period 1994–1998, and the corresponding ICD-10 codes were I26, I67.6, I80, I81, I82, O22.3, O22.5, O87.1, and O87.3 for the period 1999–2012. Trained personnel, who were unaware of patients' baseline variables, reviewed the medical journal for each potential VTE case. For subjects derived from the hospital discharge registry and the radiology procedure registry, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled; (1) signs and symptoms consistent with DVT or PE were present

(2) objective confirmation by diagnostic procedures (e.g. compression ultrasound of the whole leg, venography, CTPA, perfusion-ventilation scan [VQ-scan], or autopsy), (3) the patient's medical records indicated a diagnosis of DVT or PE made by a physician, and (4) the patient received treatment for VTE (anticoagulant medication, thrombolysis, or vascular surgery) unless contraindications were specified. For subjects derived from the autopsy registry, a VTE event was recorded as an outcome when the autopsy record (death certificate) indicated VTE as cause of death or as a significant condition contributing to death.

Verified VTE events were classified as DVT or a PE, and if DVT and PE occurred concurrently, the event was recorded as a PE. The events were further classified as cancer-related, unprovoked or provoked based on the presence of cancer or other provoking factors at the time of VTE diagnosis. The presence of cancer was defined as overt cancer at the time of VTE diagnosis (or, in some cases, if cancer was diagnosed on the same day as the VTE). VTEs occurring in patients with active cancer were classified as cancer-related regardless of other risk factors. A VTE occurring without any provoking factor was defined as unprovoked. In patients without cancer, a VTE event was defined as provoked if one or more of the following factors were present: recent hospitalization, surgery or trauma, (within eight weeks before the event), acute medical condition (acute MI, acute ischemic stroke, acute infections), immobilization (bed rest [3 days or confinement to wheelchair within the last 8 weeks, or long distance travel ≥4 hours within the last 14 days), or other factor specifically described as provoking by a physician in the medical record (e.g. intravascular catheter).

3.2.2 Identification and validation of recurrent VTE events

In the Tromsø Study, all VTE recurrences and deaths among the study participants were recorded during 1994 to 2012. Recurrent VTEs were identified and validated with the same approaches and criteria as used for first VTE described above. Information on deaths was collected from the Norwegian Population Registry by use of the unique national person identification number.

3.3 Myocardial infarction as exposure

In Paper IV, we used MI as an exposure variable. In the Tromsø Study, all first-time events of MI were identified by searching the hospital and out of hospital medical records, the autopsy registry, and death certificates, as described previously (51). 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. This linkage allowed identification of fatal MI events that occurred as out-of-hospital deaths, including deaths that occurred outside Tromsø. The death certificate was used to gather relevant information on the MI events from additional sources, like autopsy reports, reports from nursing homes, ambulance services and general practitioners. Cases of incident MI were identified by linkage to the Discharge Diagnosis Registry at the University Hospital of North Norway with search for ICD 9 codes 410-414 during the years 1994 to 1998 and afterwards ICD 10 codes 120-125. The hospital medical records were case validated by an independent end-point committee. Slightly modified World Health Organization MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease)/MORGAM (MONICA Risk, Genetics, Archiving and Monograph Project) criteria for MI were used; these included clinical symptoms and signs, findings in electrocardiograms (ECG), values of cardiac biomarkers, and autopsy reports when applicable. In our study, a history of MI was defined as an MI that occurred before the first VTE.

3.4 Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) follow-up study

The aim of the MEGA follow-up study was to assess the incidence of recurrent VTE events and to identify novel risk factors and predictors of recurrence. The patients in the MEGA follow-up study were recruited from the population-based case-control MEGA study, the details of which have been described elsewhere (71, 172). Briefly, the *MEGA study* included 4 956 patients, aged 18 to 70 years, with a first objectively confirmed DVT of the leg, PE or both from 6 anticoagulation clinics in The

Netherlands, in the period between March 1, 1999 and August 31, 2004, (participation rate 86%). VTE events were classified as isolated DVT or an isolated PE, and if DVT and PE occurred concurrently, the event was recorded as both. Patients with an upper extremity venous thrombosis were excluded. Each potential VTE case was reviewed and validated by trained personnel by assessment of each patient's medical record. Of the participants in the MEGA case-control study, only cases were further followed for recurrence (*MEGA follow-up study*). For this, 225 did not consent to participate. Thus, 4 731 patients were eligible for the MEGA follow-up study, and these patients were followed from their first VTE. Between 2007 and 2009, the vital status of all MEGA follow-up patients were obtained from the Dutch Population Register. Causes of death were obtained from the National Registry of Death Certificates at the Central Bureau of Statistics and encoded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Between June 2008 and July 2009, questionnaires concerning recurrent VTE were sent by mail to all survivors and consenting individuals, and supplemented by telephone interviews. Additional information on recurrences was acquired from the regional anticoagulation clinics and from hospitals. The end of follow-up was defined as the date of recurrence, date of death or migration, or the date of returning the follow-up questionnaire (the last questionnaire was returned on April 8, 2010). If patients did not respond to the questionnaire, they were censored from the last date the study investigators knew them to be recurrence-free (i.e., last visit to the anticoagulation clinic).

In the MEGA follow-up study, potential cases of incident MI were identified by linkage to the Dutch Hospital Data Registry. For each hospital admission, information on the date of admission and discharge, diagnoses and surgical procedures was available. The diagnosis codes for MI were ICD-9-CM codes 410.0-410.9 and ICD-10-CM code I21. The percentage of correctly coded MI has been reported to be nearly 100% (173). In MEGA follow-up, a history of MI was defined as an MI that occurred before the first VTE.

4. Main results

4.1 Paper I

Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population

Alterations of risk factor levels, prevention strategies, diagnostic tools and treatment modalities over time may alter the rate of venous thromboembolism (VTE) in a community. Changes in the incidence of VTE during the last two decades have not been extensively studied. Therefore, we studied time trends in the incidence rates of DVT and PE in a large population-based cohort. A total of 26 855 participants, aged 25-97 years, were enrolled in the Tromsø study between 1994 and 1995. The participants were followed-up to December 31st 2012. All symptomatic, objectively confirmed, incident VTEs were identified using multiple sources (hospital discharge diagnosis registry, radiology procedure registry and autopsy registry) and validated by review of medical records. Age-adjusted biennial incidence rates per 100 000 PY with 95% confidence intervals (CI) were calculated using Poisson regression. Between January 1, 1996 and December 31, 2012, 693 VTEs occurred during 368 150 PY of follow up. The incidence rate of VTE increased from 158 (95% CI 116–199) in 1996/1997 to 201 (95% CI 160–243) per 100 000 PY in 2010/2011. There was a marked increase in the rates of PE (with/without concurrent DVT) ranging from 45 (95% CI 23–67) in 1996/1997 to 113 (95% CI 82–144) in 2010/2011, whereas the rates of isolated DVT decreased (112, 95% CI 77–146 in 1996/1997 and 88, 95% CI 61–115 in 2010/2011). Despite advances in prophylaxis, the incidence rate of VTE has increased slightly during the last 15 years, mainly due to an increase in PE. Although the introduction of better diagnostic tools to some extent may explain the increase in PE rates, our findings suggest that there is still a need for improvement in risk factor management and prevention strategies of first time VTE.

4.2 Paper II

Recurrence and mortality after first venous thromboembolism in a large population-based cohort

The recurrence and mortality rates after a first episode of VTE vary considerably in previous reports, and most of the studies were conducted several decades ago. Advances in the management and treatment of VTE during the last 15 years may have influenced the rates of clinical outcomes. Therefore, we aimed to estimate the rates of recurrence and mortality after a first VTE in patients recruited from a large population-based cohort. We used the Tromsø 4 Study which included 710 patients with a first, symptomatic, objectively confirmed VTE followed between 1994 and 2012. Recurrent episodes of VTE were identified from multiple sources (hospital discharge diagnosis registry, radiology procedure registry and autopsy registry) and carefully validated by review of patients' medical records. Information of deaths was obtained from the National Population Registry of Norway. Incidence rates and cumulative incidence rates with 95% CIs of VTE recurrence and mortality were calculated. The mean age of the patients was 68 years (range 28 to 102 years), and 166 (23.4%) had cancer at the time of first VTE. There were 114 VTE recurrences and 333 deaths during a median study period of 7.7 years (range 0.04 to 18.2 years). The risk of recurrence was highest during the first year. The overall 1-year recurrence rate was 7.8 (95% CI 5.8–10.6) per 100 PY, whereas the recurrence rate in the remaining follow-up period (1 to 18 years) was 3.0 (95% CI 2.4–3.8) per 100 PY. The risk of dying was highest in the first year following the VTE. The overall 1-year all-cause mortality rate was 29.9 (95% CI 25.7–34.8) per 100 PY, and in those without cancer the corresponding rate was 23.6 (95% CI 17.8–31.3) per 100 PY. Despite advances in VTE management, the rates of adverse events remained fairly high, particularly in the first year following a first VTE.

4.3 Paper III

Hospital-related first venous thromboembolism and risk of recurrence

Hospitalization is a well-established risk factor for first VTE, and previous studies suggest that hospitalization is one of the most important factors influencing the risk of VTE. However, the risk of recurrence, particularly in patients hospitalized for conditions other than cancer or surgery, has scarcely been investigated. The cumulative incidence of recurrence in hospital-related VTE may be influenced by the competing risk of death and may result in an over-estimation of the recurrence risk. Competing risk for death analysis should be taken into consideration when the rate of death differs greatly between two study groups. Therefore, we aimed to investigate the risk of recurrence and mortality among patients with a first hospital-related VTE in models with and without death as a competing event. Information on hospital-related risk factors was collected in 822 patients with a first-lifetime VTE derived from the Tromsø study 1 to 6 surveys occurring in the period from 1994 to 2012. Recurrent VTEs and deaths were recorded in the follow-up period (1994 to 2012). During a median of 2.79 years of follow-up, 132 patients experienced a recurrent VTE. Stratification on hospital-related factors revealed considerable differences in recurrence risk. The 5-year cumulative incidence of recurrence was 27.4%, 11.0% and 20.1% in patients with incident VTEs related to cancer, surgery or other medical illness, respectively, and 18.4% in patients with a non-hospital-related first VTE. The mortality rates were high for all subgroups of hospital-related VTE, except for surgery-related events. Consequently, the cumulative incidence of recurrence dropped in the competing risk analyses, showing a 5-year cumulative incidence of 14.4%, 11.7% and 9.7% in patients with a first VTE related to hospitalization for other medical illness, cancer or surgery, respectively. Our findings suggest that patients with incident VTEs related to hospitalization for medical illness other than cancer or surgery have a high recurrence-risk, even in the presence of competing risk of death.

4.4 Paper IV

Myocardial infarction is a risk factor for venous thromboembolism recurrence in women with a first VTE.

Previous reports suggest that MI is a transient risk factor for VTE. Whether patients with a history of MI and VTE have an increased risk of VTE recurrence, remains unsettled. Therefore, we aimed to assess whether a history of MI was associated with risk of VTE recurrence in a cohort of patients with incident VTE. A total of 5494 VTE patients were recruited from the Tromsø Study and the MEGA follow-up study, and followed from the date of their first VTE until the date of recurrence, death, or emigration, or the end of the study period (Tromsø: Dec 31, 2012; MEGA: date of filling in the short questionnaire. The last questionnaire was returned on April 8, 2010). Cox regression models were used to calculate hazard ratios (HR) with 95% CI for VTE recurrence according to the history of MI adjusted for age, body mass index, cancer, and surgery. As a statistical interaction was found between history of MI and sex, and therefore, the analyses were further stratified by sex. During a median follow up of 11.2 years, 792 patients experienced a recurrent VTE. In women, a history of MI was associated with 2.4-fold increased risk of VTE recurrence (HR 2.44; 95% CI 1.27-4.69). No association between a history of MI and VTE recurrence was observed in men (HR 1.17; 95% CI 0.70-1.94). In women with a history of MI, the 5-year cumulative incidence of recurrence was similar to that in men both with and without a history of MI. Our findings suggest that MI is a persistent rather than a transient risk factor for VTE particularly in women.

5. General discussion

5.1 Methodological consideration

5.1.1 Study design

The first three papers in this thesis utilized data from the Tromsø Study, which is a large prospective population-based cohort. In paper IV, we additionally merged VTE patients from the first six surveys of the Tromsø Study with the MEGA follow-up study, yielding a cohort of VTE patients. The term "cohort" comes via the French word "cohorte" from the Latin word "cohors" in the 15th century. A cohort was originally a standard military unit in the ancient Roman army, and 10 cohorts made up a Roman legion. Each cohort, comprising of 300 to 600 warriers, could be traceable during each battle. In the mid-20th century, its meaning was extended, to any group of individuals with something in common. In epidemiology, *cohort* means a group of people who share a common characteristic or experience within a defined period. In a *cohort study design*, a well-defined population is selected and the participants' exposure status is recorded at study entry. Subsequent to this, the outcome of interest is investigated and compared in non-exposed and exposed individuals. In Papers I-IV, study participants were followed from the date of inclusion in the study until they were censored. *Censoring* is a process for dealing with follow up time when the event of interest (outcome) does not happen during the overall follow up period. Typically, this is due to death or migration or other reasons for loss to follow up, or may be because part of the sample survive the complete follow up time without experiencing the outcome (174). In our study, participants were censored by death, the end of the study period or, migration. In Paper I and II the source population was participants from Tromsø 4, whereas in Paper III and IV the source population comprised of individuals participating in one or more of the Tromsø 1-6 surveys who were still alive and inhabitants of the municipality of Tromsø by January 1, 1994, since the VTE registry was started in 1994. Individuals with a known history of VTE at baseline were excluded from the analysis.

A cohort study is useful in estimating the absolute and relative risks of a disease. In Paper I, incident VTE events and in Paper II, III and IV, recurrent VTE events during the study period were registered and absolute risk estimates in terms of incidence rates and relative risk estimates in terms of hazard ratios were obtained, respectively.

A cohort study has many advantages compared to other observational studies, such as case-control studies and cross-sectional surveys. Cohort studies have a *temporal sequence* of exposure and outcome, which is one of the Bradford Hill criteria for establishing causality (175), and the outcome does not influence the exposure status since exposure(s) of interest is determined before the occurrence of outcome. The retrospective nature of case-control studies makes this design susceptible to temporal bias (reverse causality), as it cannot be established certainly whether the associated variable is a response to rather than a cause of the disease. Another advantage of cohort studies lies in large number of participants which may allow for generalizability of study results to other populations. Furthermore, cohort studies are non-experimental in nature, and therefore ethically safe. However, a cohort design is not the most efficient approach when the incidence of disease is low as it is both time consuming and requires a large number of individuals to be followed up for long periods before a sufficient number of cases occurs to generate statistically meaningful results. Case-control studies are therefore more appropriate for investigating rare diseases as case-control studies are both cost and resource effective.

5.1.2 Bias

Errors, particularly bias, is a principal interest in epidemiological studies and are the prime basis for incorrect results of epidemiologic investigations. Sources of error in measurements are classified as either systematic or random (176). *Systematic errors* depend on any flaw that systematically leads to an over- or under-estimation of association between the exposure and the outcome, and this type of error is independent of sample size (176). For example, if the device we use to measure blood pressure

(sphygmomanometer), systematically over or underestimates the true blood pressure of the individual being evaluated. Rothman defines *random error* as "nothing more than variability in the data that cannot be readily explained" (176). It's the error that remains after systematic error is eliminated. Random errors can be minimized by increasing the sample size. For example, if we measure serum creatinine level three times in the same individual using the same instrument and the same laboratory reagents, we are likely to obtain slightly different values due to clinical fluctuations in the serum creatinine level. Bias may threaten the internal and external validity of a study. The list of biases is a long one, however, Rothman classify bias into three broad categories: selection bias, information bias, and confounding (176).

Selection bias (or Berksonian bias) arises when a systematic error occurs in the enrollment of individuals in a study, and results in a biased association between the exposure and the outcome. Selection bias is more likely to occur in case-control studies than in cohort studies, because, in cohort studies, both exposed and unexposed individuals are selected to the study before the occurrence of the outcome. In contrast, both the exposure and outcome have occurred by the time the patient is recruited into a case-control study. In case-control studies, selection bias may occur when individuals selected as controls are not representative of the population that produced the cases. For example, in a hospital-based case-control study looking at the association between alcohol consumption and the development of liver cirrhosis, the association could potentially be underestimated if controls are taken from a trauma ward. This is because consumption of alcohol in large quantity may result in injury and consequently, an admission to the trauma ward. Self-selection is an issue that can threaten the external validity (generalizability) of a study. *Self-section bias* occurs when individuals select themselves into a group. For example, in the six Tromsø surveys, all, or parts, of the population living in the municipality of Tromsø were invited to participate. Although the attendance rates were high (177), invited individuals who did not attend the Tromsø Study tended to be younger (< 35 years), or older (> 80 years), were more often men and more likely to be single (177). A participation required physical attendance at the study site, and therefore, selection bias due to lower attendance rate in the

severely ill or disabled is likely to have occurred. VTE tend to occur more often in the elderly population, and under-representation of this part of the population may reduce the external validity of the results for this group. It is worth mentioning, however, that selection bias between health survey attendees and non-attendees is probably most theoretical. Since the attendance rate in Tromsø surveys was high, it is unlikely that this bias has a significant impact on our results. In Paper I, absolute risks (i.e. IRs) are predominately reported and we may perhaps expect a minor underestimation of our IRs for VTE in the elderly. However, in Papers II-IV, relative risks (i.e. HRs) are mainly reported, and thus, our results would not be largely affected. In general, non-respondents in population-based surveys tend to have low socioeconomic status and higher mortality than attendees (178). However, it is not likely that the low participation rates and higher proportion of non-attendees with a low socioeconomic status has a large impact on the validity of the study results in this cohort, as the social class differences in Scandinavia are negligible compared to the rest of the world.

In epidemiological studies, ***information bias*** refers to bias arising from measurement error. This systematic error is also denoted as observational bias or *misclassification*. The term misclassification refers to an error in the classification of an exposure or the disease. For instance, misclassification occurs when an exposed individual is classified as unexposed or vice versa, or when a diseased individual is classified as non-diseased or vice versa. An example of misclassification is when normotensive individuals are categorized as hypertensive and vice versa due to the use of an inaccurate instrumentation (e.g. one size blood pressure cuff to take measurements on both lean and obese adults). Misclassification of individuals can be differential or non-differential (179). *Differential misclassification bias* refers to errors on one axis (exposure or disease) that are related to the other axis (exposure or disease). It can lead to either over- or under-estimation of the true association. R*ecall bias* is a classic example of a differential exposure misclassification. Recall bias may occur when the recalled exposure differs between the cases and controls. For instance, patients (cases) are much more prone to remember relevant exposures than healthy controls. *Non-differential misclassification bias* refers to errors on one axis that are unrelated to the other axis and such errors tend to be equally

distributed among cases and non-cases. This means that exposure is equally misclassified in cases and controls. For example, self-reported questionnaires is a possible source of misclassification, as items in the questionnaires may be misunderstood or the participants may over- or under-report their exposure level. For binary variables, non-differential misclassification tends to bias the association towards the null value (180). Cohort studies are more prone to non-differential misclassification, because exposure in a cohort study is usually measured before the onset of outcome (disease) of interest.

In epidemiological and clinical studies, misclassification of both exposure and outcome is likely to occur. In all four papers in this thesis, the exposure and outcome variables were mainly extracted from the patients´ medical records by trained professionals or from validated registries (i.e. VTE and MI variables). Paper IV used information from the Tromsø Study and the MEGA follow-up study. In the Tromsø Study, the VTE and MI registries are separate, complete, and validated registries. In the Tromsø study, incident VTE events among study individuals were registered retrospectively at the end of follow-up by searching the hospital discharge diagnosis registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway. This is the only hospital in the region to provide inpatient care and diagnostic procedures to the inhabitants of the municipality of Tromsø, and this increases confidence in thoroughness and completeness of the VTE Registry. We did a thorough search through all these registries to detect all cases treated at this hospital. However, some VTE cases could potentially have been missed due to diagnosis and treatment outside the region. With the purpose to make disease manifestation as certain as possible, the outcomes (incident VTEs in Paper I and VTE recurrences in Paper II, III and IV) were validated. We assured that the possibility of false positive VTE events was limited by following the strict validation criteria described in the methods section. For instance, by using these criteria, an asymptomatic venous thrombus that was identified by chance using computed tomography (CT) scan and remained untreated with anticoagulants would not be considered a clinical event.

Retrospective registration is dependent on valid and complete information, and incomplete information from patients' record could lead to inaccuracy. Therefore, regardless of using criteria for the validation of the outcome event, misclassification of VTE cases cannot be completely ruled out. Since the personnel who registered VTE events were blinded to the baseline information, any misclassification of VTE was most likely non-differential (called non-differential outcome misclassification). Thus, the misclassification was likely to be similar between the study individuals irrespective of whether they experienced the outcome. There were no standard instructions for reporting presence of clinical risk factors and provoking factors in the medical record and classification of an event as unprovoked or provoked relied on information provided by the individual physician who examined the VTE patient. In case information on the presence of a provoking factor (for example history of surgery during the last three months) was missing, a provoked VTE would be misclassified as unprovoked VTE. This could be a minor concern in Paper II and III where risk of recurrences were estimated according to the classification of the index VTE.

Additionally, we did not have verified baseline information on previous history of VTE among the study individuals. Thus, some of the individuals who were treated as healthy during follow-up could be prevalent VTE cases who, ideally, should be excluded from the study population. For instance, in Paper I, the prevalent VTE cases may have contributed with person-years at risk while calculating the VTE incidence rates. However, as this concerns only a small fraction of the individuals, the effect on the incidence rates is most likely negligible.

In the MEGA follow-up study, the VTE registration was validated as described in the method section. However, MI information was taken from the Dutch Hospital Data Registry because no separate MI registry exists. The percentage of correctly coded MI in the Dutch Hospital Data Registry has been found to be almost 100% (173). Participants of the MEGA follow-up study were linked to this registry through date of birth, sex and postal code. There could be some missing data regarding MI cases in the Dutch Hospital Data Registry and that may potentially be a source of misclassification.

Nevertheless, this potential misclassification of MI would most likely be non-differential since information regarding MI and incident VTE were collected prior to the outcome (VTE recurrence). Such misclassification may have caused underestimation of the true association between MI-related VTE and VTE recurrence in our study.

5.1.3 Generalizability

The validity of a study is usually separated into two components: internal and external validity. *Internal validity* refers to whether the inferences drawn are true to the members of the source population, whereas *external validity* is the degree to which the inferences drawn from a study can be applicable to a broader population beyond the study population (176). All types of studies in epidemiology raise concerns about extrapolation of study findings, which means "*generalizability*" from the study sample to the target population or to other populations or to the entire world.

High external validity means that the results of our study (Paper I to IV) can not only be generalized to the population of Tromsø but to the Norwegian and Scandinavian populations, and even to other Western populations. The VTE incidence found in our population (Paper I, II) is comparable to the incidence reported in other Western populations (28) (123). The Tromsø Study is a large population-based survey, reflecting the general population of the Tromsø municipality aged 25 years and above. The attendance rate range from 66% in Tromsø 6 to up to 83% in Tromsø 1 (177). The MEGA follow-up study also has a high attendance rate, as 79% of the invited population attended (181).

In the Tromsø Study, some groups of people are better represented than others. For example, in the Tromsø 4 survey, the participation rate was low for the youngest (< 35 years) and oldest (> 80 years) population (58.5% and 46.3% respectively), and men had a lower participation rate than women (69.6% versus 74.9% respectively) (177). This threatens the generalizability towards these subgroups. As selection biases are one of the significant threats to external validity, the age-specific participation

rates and their effects on generalizability are mentioned in detail in the selection bias section. In the MEGA study, generalizability to elderly population (i.e. >70 years) could be an issue because patients were included in the study if they experienced their first event of VTE before they were 70 years old (182). Moreover, the majority of individuals in the Tromsø cohort and MEGA study were of Caucasian origin. Due to the limited ethnic diversity, the findings of our studies may not be representative of other ethnic groups.

As previously discussed, respondents in health surveys are generally considered to be more health conscious compared to the general population. Also, individuals who are ill or institutionalised are unlikely to attend health examinations. This bias between respondents and non-respondents may have affected our results; though only marginally, leading to an underestimation of the true incidence rates (IRs), as in Paper I, where absolute risks (e.g. IRs) are predominately reported.

5.1.4 Missing data

Missing observations is a common phenomenon in large cohorts. Missing observations could be due to multiple reasons, such as inadequate responses by the study participants to the questionnaires, participants being lost to follow-up, not all the selected individuals responding to a postal questionnaire survey, failure of the study equipment, or laboratory samples being lost or in a technically dissatisfactory condition (183). Missing data may affect the analysis. There are many ways of handling missing observations in the analysis. One approach is to omit variables with much missing information. An alternative is to omit study participants with incomplete data. Yet another option is to use imputation techniques (estimation) to replace missing values. Imputation refers to the replacement of a missing variable by an estimated value of that variable as derived from the available observed data.

Missing data may introduce bias; though it largely depends on the reasons why data is missing. Missing data are generally classified as (i) missing completely at random, (ii) missing at random, and

(iii) missing not at random. *Missing completely at random* means no systematic differences between the missing values and the observed values. For example, blood pressure measurements may be missing due to the breakdown of the sphygmomanometer. *Missing at random* includes any systematic difference between the missing values and the observed values that can be explained by differences in the observed data. For example, if only males have missing values in a depression survey, the probability of missing data on depression will be related to sex. *Missing not at random* means that systematic differences remain between missing values and observed values even after the observed data are taken into account (184). A prerequisite for imputation is that the missing data is "missing at random". If data is missing completely at random, analyses of only those with complete data will give valid inferences. Deletions may introduce bias if the number of excluded individuals is high and if the characteristics of those with missing values differ significantly from the ones included. Deletion may results in reduced statistical power.

5.1.5 Statistical interaction

The term *statistical interaction* applies to a situation in which the magnitude of the effect of an exposure differs depending on the level of a third variable. This variable is called "effect modifier" and this phenomenon is also known as *effect modification* (180). Not like confounding, where the true association may be weakened or strengthened, interaction can result in variation in the risk estimates across strata of this third variable (180). The presence of statistical interaction is generally assessed in the regression analysis by entering a cross product term into the regression model. When an interaction is present, one common way of dealing with it is by stratifying the data on the effect modifying variable.

In Paper IV, we assessed whether a history of MI was associated with risk of VTE recurrence in a cohort of patients with incident VTE. Epidemiological studies have shown that males have a higher VTE recurrence than females (127, 134). In addition, the incidence of MI is higher in males than in

females (185). We found a statistical interaction between MI-related VTE and sex i.e. the magnitude of the effect of exposure (MI before first lifetime VTE) on the outcome (VTE recurrence) varied according to the presence of a third variable (sex). Therefore, subsequent analyses were stratified on sex and the risk was increased in females but not in males. Stratification can sometimes be troublesome because increasing number of strata can limit the statistical power, since many of the strata may contain few people. This can lead to unreliable risk estimates. Lack of statistical power was a concern in Paper IV therefore, it was not possible to do further stratification.

5.1.6 Confounding

In epidemiology, a *confounding* factor (a third variable) is associated with the exposure and the outcome but is not an intermediate variable in the causal pathway between exposure and outcome (180). A variable laying on the causal pathway between exposure and outcome is called a "*mediator*". Confounding if present, may weaken, strengthen or possibly change the direction of the association between the exposure and the outcome (180). Unlike experimental studies where the use of randomization reduces the likelihood of confounders, cohort studies have a potential issue of confounding. It is therefore necessary to adjust associations for possible confounders.

In cohort studies, i) stratification, ii) multivariate analysis (modeling) and iii) standardisation (direct and indirect) are the analytical methods that are used to control for confounding effects (180). ***Stratification***, includes dividing the study population into strata, or subgroups, based on the confounder and analyse the risk in these strata (180). ***Multivariable analysis*** is a statistical technique used to carry out *adjustment* where potential confounding variables are included as covariates in the regression model (180). In Paper II, III and IV, the Cox regression models were adjusted for sex and age at the time of incident VTE. In Paper II and III, while investigating the risk of VTE recurrence in patients with incident VTE, one concern was whether duration of anticoagulant treatment differed among comparison groups. Therefore, in addition to age and sex, we adjusted the Cox model for the planned

duration of anticoagulant treatment in Paper II. Likewise, in Paper III adjustment for planned duration for anticoagulant treatment was done when comparing hospital-related VTE and non-hospital-related VTE. In both conditions, the risk estimates (HR) were unchanged. Therefore, duration of anticoagulation was not a confounding variable in these groups of patients. While investigating all-cause mortality in Paper II, we found a higher mortality rate in females than in males. This was due to a higher age of females at the index date, as the risk estimates changed after adjustment for age at incident VTE event. Therefore, age at the time of incident VTE event was a confounder for the association between sex and VTE-related mortality.

Direct standardisation is used to control for confounding effects of age and sex in Paper I. Rothman defines ***standardisation*** as "a method of combining category-specific rates into a single summary value by taking a weighted average". The weights used in averaging come from a standard population (176). In epidemiological studies, two methods of standardisation are commonly used. In the *direct standardisation* method, a common age-structured population is used as a standard, whereas in the *indirect standardisation* method a common set of age-specific rates is applied to the populations whose rates are to be standardized. In Paper I, we described 16-years' time trends in incidence rates of VTE in a large cohort. We calculated overall crude incidence rates of VTE and expressed as number of events per 100 000 PY. We have used both direct and indirect standardisation in our study. For the purpose of comparison, we used the direct standardisation method and calculated the overall incidence rate of VTE standardised towards the "World Health Organization (WHO) standard population 2000-2025" (186). Age standardized rates account for the differences in the age structure of the populations being compared (180). Since Tromsø 4 is a closed cohort, the age distribution of the individuals would change over time. To be able to compare the rates over time, we therefore calculated age-adjusted biennial incidence rates of VTE, DVT and PE for the periods 1996/97, 1998/99, 2000/01, 2002/03, 2004/05, 2006/07, 2008/09 and 2010/11 using Poisson regression. With the purpose to investigate whether the change in the incidence of PE and DVT could be attributed to

certain age group, we compared the age-specific incidence rates in the first half period (i.e. 1996-2003) with the second half period (i.e. 2004-2012).

In Paper II and III, we used age as a time-scale. Typically in cohort studies, the time-scale used in the Cox regression model is time-on-study, and age is added as a covariate to the model for the purpose of adjustment. In the time-on-study scale, individuals start follow-up at the calendar time (date) they are included into a study and are followed-up until the date they are censored (experience the outcome, drop out or end of follow-up). When age is used as a time-scale, follow-up begins at the age a person is at study inclusion, and his/her age at censoring (occurrence of outcome or end of follow-up) is the exit-time. The risk of VTE is more dependent on age than the time the person has been in the study. Accordingly, using age as the time-scale, the risk of VTE in study individuals is compared in people of the same age, instead of in people with the same duration of follow-up (187). Therefore, it is more reasonable to use age as a time scale than time-on study as time scale. Age as the time scale approach is considered appropriate in longitudinal studies with a large sample size, since many people are represented in each age group.

Even after using various methods to control for confounding in our analyses, the possibility of *residual confounding* cannot be ruled out. "Residual confounding is a term for confounding that remains even after many confounding variables have been controlled" (179). Residual confounding can occur if data regarding confounders is not collected, if there are differences in risk within a confounder category, or if confounder misclassification is present (179).

5.1.7 Competing risk of death

The concept of censoring is a characteristic feature of survival analysis. In prospective studies, if an individual is lost to follow-up (for instance due to migration) that individual is treated as censored because whether that person experienced outcome of interest or not, remains unknown. Death is often handled as a censoring event in prospective studies, and death from any cause may prevent the

outcome from occurring. An assumption of censored survival time is that censoring should be *non-informative*. This means that at any given point in time, individuals who remain in the study have the same future risk of developing the outcome as those who are no longer under follow-up. In Paper II, patients with cancer-related VTE had higher mortality rates than those without cancer (provoked and unprovoked) and therefore, censoring occurred differently in these exposure categories. Similarly, the mortality rate was expected to be higher among patients with co-morbid conditions (in Paper III).

Competing risk regression is the most commonly used statistical technique when occurrence of one event is likely to alter the chance of another event (143). Cancer (in Paper II) and other comorbidities (in Paper III) are associated with increased mortality and hence death may have interfered with the outcome of interest (VTE recurrence). In routinely used traditional time-to-event analysis methods such as the Kaplan-Meier estimator (1-KM), the log-rank test (LRT) or the Cox proportional hazards model, when a death occurs, the probability of a subsequent VTE drops to zero. To address this issue, Fine and Gray introduced a statistical model which can account for competing events, like death (143). The competing risk of death methods do not censor patients on the date of death. Therefore, the probability of experiencing the outcome of interest is presented irrespective of competing mortality. This theoretically leads to unbiased and perhaps more meaningful results (141).

Ay *et al*. compared competing risk of death analysis with traditional time-to-event approaches (1-KM, LRT and Cox regression) on the risk of VTE in a cohort of cancer patients (140). They concluded that traditional methods (1-KM and Cox regression) provided biased estimates of VTE risk, inferring that risk of VTE was over-estimated when compared with competing risk regression (140, 188). The authors suggested that competing risk of death analysis should be considered in populations at high risk of death, randomized trials with interventions that have a differential effect on death rates, non-randomized trials with diverse death rates between groups, and in risk score developmental studies (prognostic studies) that may potentially have an impact on medical decision making (140). Conversely, traditional analysis methods are suitable for studies dealing with etiological questions.

Competing risk of death analysis was performed in Paper II and III. The risk of VTE recurrence was compared in cancer-related, provoked and unprovoked VTE (Paper II), and in hospital-related and non-hospital-related VTE (Paper III). As expected, the risk estimates were over-estimated using Cox regression when compared with competing risk regression in Papers II and III. In Paper II, when evaluating the risk of VTE recurrence in patients with cancer-related VTE compared to patients with provoked and unprovoked VTE, there was a difference in the risk estimates between the traditional method (1-KM) and the competing risk of death regression approach. The 5-year cumulative incidence rates for cancer-related VTE using 1-KM and competing risk regression were 26.4% and 11.4% respectively. This difference in the risk estimates between the traditional method and competing risk of death regression approach is driven by the differences in mortality among cancer and non-cancer patients. Accordingly, the cumulative incidence of VTE recurrence did not differ greatly between 1-KM method and competing risk regression in provoked VTE (16.7% versus 14.4%) and unprovoked VTE (17.9% versus 16.1%). This is as expected as the mortality rates did not differ much in unprovoked and provoked VTE.

5.2 Discussion of main results

5.2.1 Venous thromboembolism: incidence, recurrence, and mortality

In Paper I, we described trends in the incidence of VTE in a large population-based cohort from 1996 to 2012. Within a well-defined geographical area (i.e. the Tromsø municipality) we observed a 27% increase in the overall age-adjusted incidence of VTE throughout the study period, from 158 to 201 per 100 000 PY in the period 1996/97- 2010/11. The observed incremental trend was largely due to an increase in the rate of PE throughout the study period. The age-adjusted IRs of PE increased by 151% from 45 to 113 per 100 000 PY, while the rates of DVT decreased by 21% from 112 to 88 per 100 000 PY during the study period. Our results indicate that despite advances in thromboprophylaxis, the annual incidence rates of VTE have increased during the last couple of decades. Hence, VTE remains a growing public health challenge.

Studies from other countries have reported similar results (39, 113). In agreement with our findings, the Worcester VTE Study, which included 3887 incident VTE cases, reported an increase in the age- and-sex-adjusted incidence rates of VTE by nearly 40% from 95 to 133 per 100 000 PY in the period 1999-2009. The rate of PE increased by 116% from 30 to 65 per 100 000 PY, whereas the rates of isolated DVT remained almost constant in the same period (39). Additionally, a study based on Medicare and commercial insurance databases reported that the U.S. prevalence of VTE increased by 33% from 317 to 422 per 100 000 PY in the period 2002-2006 (113). Contrary to our findings, Delluc *et al*. reported that the standardised overall annual incidence of VTE was reduced by 28% between 1998 and 2013, and this reduction was mainly driven by reduction in the incidence of DVT of 47%, whereas the standardized annual incidence of isolated PE significantly increased by 29% within the same period of time (37).

How might the observed increase in VTE incidence in our study be explained? The reason for the increase in the IRs of VTE during the study period is likely to be multifactorial. Predominately, the use of one or more noninvasive diagnostic methods for the detection of VTE increased approximately

three times during the study period. The proportion of patients with PE who underwent a high-resolution multi-detector CTPA diagnostic test increased from approximately 23.1% in 1998/1999 to 76.0% in 2010/2011. Thus, the increasing age-adjusted incidence of PE corresponds well with the increased use of CTPA at our hospital from year 2000 and onwards, showing that we are detecting more PEs than before the introduction of newer technology. In a randomized controlled trial that compared CT scan with VQ scan for the management of patients with suspected PE, CT scan strategy resulted in a significant 30% increase in the number of PE diagnoses as compared with VQ scanning (189). In accordance with our findings, Wiener *et al*. (38) conducted a time trend analysis using the Nationwide In-patient Sample with Multiple Cause-of-Death databases, and demonstrated that the introduction of multi-detector CTPA was associated with an increasing frequency of PE in the U.S. In an Australian study, Segard *et al*. (190) found an increase in PE-related imaging from 2002-2010, which was exclusively driven by increased referrals for CTPA, resulting in more PE diagnoses, while the total number of deaths from PE in the population remained unchanged.

A challenging question is whether minor (subsegmental) PEs are of clinical significance? Indeed, the comparatively consistent mortality rate from PE during the last decades, combined with improved case fatality rates point towards overdiagnosis of PE (38, 190, 191). A systematic review and meta-analysis confirmed that many of the additional emboli identified by CTPA were subsegmental emboli that did not lead to adverse outcomes even if left untreated (124). Similar findings were observed in New York State's (NYS) Statewide Planning and Research Cooperative System (SPARCE) database (169). The SPARCE study suggested that the diagnosis of PE in NYS approximately doubled during 1994-2004, while deaths and hospital admissions in patients with PE remained relatively stable. If we take a closer look at our data, the age-adjusted IRs of PE increased by 84.4% during 1996-2005, but were almost constant during 2006-2011. This may indicate that with a wide use of multi-detector CTPA we had reached the maximum detection rate of PE after 2005.

The apparent decline in DVT incidence during our study was most probably explained by the way PE was recorded (i.e. PE with or without coexisting clinical DVT). Detection of more PEs in patients with coexisting symptomatic DVT would consequently result in more events coded as PE rather than DVT. When the second half of the study period (2004-2012) was compared to the first half (1996-2003), the rates of PE appeared to be predominantly increased among those >70 years. The potential explanation could be a lower threshold to perform diagnostic procedures for the detection of PE in the elderly after the introduction of CTPA.

In addition to changes in the diagnostic assessment of VTE, an increase in the IR of VTE observed in our cohort could be related to changes in population characteristics over time. In general, the prevalence of major VTE risk factors such as ageing, obesity and cancer are increasing in Western populations (192). Despite more focus on the use of thromboprophylaxis during the last decades, the incidence of provoked VTE in our study did not decrease over time. This implies that there is still room for improvement in VTE prevention strategies.

In contrast to our findings, Delluc *et al.* (37) reported a decrease in the incidence of VTE in 2013 compared to 1998. It is worth mentioning that this study included both incident and prevalent VTE cases while calculating IRs. Additionally, the study was revolved around two cross-sectional measurements of all symptomatic VTE cases in 1998 and 2013. The IRs could be vulnerable to random fluctuations, and two separate measurements does not necessarily reflect a time-trend. The authors stated that the decrease in the VTE rates observed in their study could be related to a more widespread implementation of thromboprophylaxis in hospitalised patients.

After a first event, VTE has a strong tendency to recur (193). Advances in diagnostic procedures and medical management of VTE during the last decade may have influenced the outcome rates after a first VTE. In Paper II, incidence rates and cumulative incidence (also called cumulative proportion, risk) of recurrence and all-cause mortality after a first event of VTE were assessed. Our study extracted data during 1994-2012 from both hospital and community settings and the follow-up period started

immediately from the date of first VTE. Our cohort had a median follow-up of 2.7 years (range 1 day to 18.1 years) for recurrence and 3.4 years (range 1 day to 18 years) for mortality. This allowed us to describe the clinical epidemiology of VTE and subsequent outcome (recurrence and mortality) in detail.

The overall incidence rate of recurrent VTE per 100 PY was 3.9 but varied substantially over time with a peak at 9.2 in the first 6 months, falling to 6.3 at 6 months-1 year, and 2.3 at 5-10 years. The cumulative incidences were 4.3% at 6 months, 7.3% at 1 year, 18.8% at 5 years, and 28.3% at 10 years. Our recurrence rates were lower than those described in studies using a cohort derived from the United Kingdom Clinical Practice Research Datalink, which assessed the rates of recurrent VTE in patients with (114) and without cancer (194) during 2001-2012. Cohen *et al*. (114) reported an overall incidence rate of recurrent VTE per 100 PY of 9.6; 22.1 in first 6 months, and 7.9 at 6 months- 1 year. In the same study, the cumulative frequencies of recurrence at 6 months and 1 year were 7.4% and 9.2% respectively. The Worcester VTE study (166), conducted during 1999-2003, reported a 1-year cumulative incidence of recurrence of 10.7%, but did not assess long-term follow up. Heit *et al*. (23) investigated recurrence among 1719 patients with a first VTE in the period 1960-1999, and reported an overall cumulative incidence of recurrence of 10.1% at 6 months, 12.9% at 1 year, 22.0% at 5 years, and 30.4% at 10 years. Compared to the previous studies, our rates were lower in the initial year after the VTE, whereas the long-term rates were similar. At our hospital, all distal DVTs are treated with oral anticoagulants, and patients are often treated for 6-12 months. Nearly 65% of the VTE patients in our study were treated with anticoagulants for more than 3 months. Thus, extended duration of treatment in our hospital may to some extent explain the moderately lower 1-year recurrence risk compared to the other studies. The consistent long-term recurrence risk supported a catch-up, or rebound, effect after the initial treatment period.

In our study, the recurrence rates in all subgroups were highest during the first 6 months after the VTE despite the use of anticoagulant therapy during this period. This indicates the importance of recruiting patients at the time of event, especially for descriptive epidemiological purposes, because

studies may lose a significant number of cases that occur in the initial phase if follow-up is started after the withdrawal of anticoagulants (127).

In accordance with previous studies (125, 126), we found highest cumulative risk of recurrence among cancer patients. The mortality rate in patients with cancer-related VTE is high (114). Accordingly, when competing risk of death was taken into account, the cumulative risk of VTE recurrence in our study (Cox regression versus competing risk of death) was markedly lower (16.3% vs. 4.9% in the first year and 26.4% vs. 11.4% at 5 years). Moreover, the cumulative incidence of recurrence was lower in cancer-related VTE that in non-cancer related VTE when competing risk was taken into account. In contrast to our findings, Heit *et al*. (125) reported a higher 5-year cumulative incidence of recurrence in cancer-related VTE when compared with non-cancer-related VTE (34% versus 17%) even after taking competing risk into account. The difference in the results may partly be explained by differences in mortality rates between the studies, especially among cancer patients, the definition of active cancer, and the length of follow up. In unprovoked VTE cases, we found that the recurrence risk in the first 10 years of observation remained high even after competing risk of death regression (30.3% versus 21.7%) as compared to cancer-related (26.3% versus 15.6%) and provoked VTE cases (25.8% versus 19.6%).

In our study, recurrence throughout the 10 years period was influenced by whether the index event was a DVT or PE. The recurrence risk was higher in patients who initially presented with DVT than in those who presented with PE (HR 1.45, 95% CI 0.96-2.18). In a Canadian study of 646 patients with a first symptomatic unprovoked VTE (132), patients with DVT as their index event had a 2-fold [RR 2.1 (95% CI 1.2-3.7)] higher risk of VTE recurrence than patients with PE as their index event. Similarly, Prandoni *et al*. (115) found that patients presenting with primary DVT were 1.4-fold (HR 1.44 95% CI 1.03-2.03) more likely to develop recurrence than patients with PE. A potential explanation for this phenomenon could be the higher fibrinolytic activity in the lungs (195), i.e. that the clot resolution in the lung may be more efficient than in the venous valve. Moreover, impaired coagulation inhibition

could be another reason of DVT recurrence in patients with DVT at first place. Development of post-thrombotic syndrome also predisposes recurrences in DVT (22). Additionally, the introduction of multi-detector CTPA to diagnose PE may have led to increased detection of subsegmental PEs, which have a better prognosis regarding recurrence (38, 196).

The mode of presentation of the first VTE event (DVT or PE) predicts the type of recurrence (131). In accordance with previous studies (131, 193, 197-199), patients with a first PE had a 2.4-fold higher risk of experiencing second PE rather than a DVT in our study. Additionally, our findings showed that those with a first unprovoked VTE were more likely to have a second unprovoked VTE. This finding is in line with a cohort of patients with a first unprovoked VTE (200), where 90% of the recurrences were unprovoked. In our study, those with a first provoked VTE were at equal likelihood of experiencing provoked or unprovoked VTE as their second event. This could potentially be explained by residual vein thrombosis (201, 202) or other pathophysiologic alterations in the veins due to the first VTE that may enhance the risk of recurrence even in the absence of provoking factors.

Risk of recurrent VTE is strongly predicted by the sex of the patient (193). Like other studies (127, 136, 198, 203), our study showed that the overall recurrence risk was higher in men than in women. Most previous studies reported a 2- to 4-fold increased recurrence risk among men (127, 203). The 10-years cumulative risk of recurrence in our study was 35.4% in men and 22.0% in women. However, the relative risk of recurrence was only 30% higher in men than in women, and the difference was not statistically significant. In our study population, the VTE cases were limited to patients of ≥ 25 years, and our data did not contain very young women with a first VTE related to oral contraceptives or pregnancy. In general, young women with hormone-related VTE have a lower risk of recurrence (193, 204), and consequently, the risk difference between men and women will be higher in such VTE population that contains these women. Furthermore, in our study, the cumulative incidence curves for VTE recurrence in men and women started to deviate three years after the initial event. This may to

some extent explain the higher relative risk differences in men versus women observed in studies with a later start of follow-up (after withdrawal of anticoagulants).

In a Norwegian study, Næss *et al.* (28) included 740 incident VTE cases during 1995-2001. The 1-year case-fatality rate was 21.6% in all VTE cases and 63.4% in VTE cases with cancer. In our study, the 1-year mortality rate after VTE remained high and was remarkably similar to that reported by Næss *et al.* (28). We found a lower survival among patients with provoked VTE than those with unprovoked VTE during the study period. This was probably explained by concurrent comorbid conditions and advancing age among patients with provoked VTE. We observed better survival rates among men in our crude analyses. This was, however, explained by the age differences among men and women at the time of first VTE.

Papers I and II confirm that the disease burden of VTE remains substantial. With high long-term morbidity, functional disability, and high rates of recurrence and mortality, VTE (205) remains a major health concern (15, 39, 206). Despite advances in thromboprophylaxis in the recent years, the annual event rate of VTE has increased over time (20, 39, 113). While this increase may partially be explained by improved sensitivity of diagnostic methods, it may also imply that current prevention and treatment strategies are not sufficient. Given the considerable economic burden of VTE (192, 207), imposed by the management of acute events and costs associated with long-term complications, further research is therefore needed to identify novel risk factors in the population in order to improve risk stratification, prevention, and management of VTE. Moreover, public health initiatives are greatly needed to increase awareness of symptoms and risk factors of VTE in the population. Treatment with anticoagulants is effective in preventing VTE recurrence (208) and a minimum of 3 months of anticoagulant treatment is recommended in all patients with VTE (3). Our study showed that the risk of adverse events remained high and continued for at least 10 years and even longer after the incident event. With a purpose to reduce the global burden of VTE, and hence improve patients' survival, future studies should focus on the development of risk prediction models with a purpose to stratify

individuals who are at high risk of developing a VTE with a favourable balance of risks and benefits of anticoagulation treatment.

5.2.2 Hospital-related and myocardial infarction-related first venous thromboembolism and risk of recurrence

In Paper III, we investigated the risk of recurrence and mortality among patients with first hospital-related VTE in models with and without death as a competing event. Studies have reported that the risk of recurrent VTE is generally low for transient risk factors (23, 129, 209) because the effect of the risk factor is reversible. Therefore, the momentary nature of hospitalisation could imply a low recurrence risk, and if this notion holds true, then there should be a low risk of recurrence among those with a first hospital-related VTE. However, in our study, hospitalisation (within 8 weeks preceding an incident VTE as well as patients admitted at the time of event) was not associated with a lower risk of recurrence. A hospital-related VTE per se was not associated with an increased risk of recurrent thrombosis in the age and sex adjusted model (HR 0.99). However, the reason for hospitalisation preceding the first event appeared to have a great influence on the risk of recurrence.

In the traditional Cox regression model, we found that the cumulative risk of VTE recurrence at 5 years was highest in patients with incident VTEs related to cancer (27.4%) followed by patients who were hospitalised for other medical illness within 8-weeks before first VTE (20.1%), and those with non-hospital-related VTE (18.4%). The lowest risk of recurrence was observed in patients who developed a first VTE after surgery (11.0%). Previous studies have also shown that patients with surgery-related first VTE have a low risk of recurrence (23, 121, 129, 130, 138, 154, 193, 209) whereas cancer, which is a persistent and often an irreversible risk factor, is associated with a high risk of recurrence (23, 121, 130, 154).

In our study, a hospital-related first VTE was associated with a 3-fold higher risk of death compared with non-hospital-related VTE. Moreover, compared with non-hospital-related VTE, the risk of death was 7.4-fold and 2.2-fold among patients with a first VTE related to hospitalisation for cancer or other medical illness, respectively. In accordance, previous studies (156, 198, 210-212) have shown that acute medical conditions such as cardiac, neurological, pulmonary, hepatic, and renal diseases are associated with 2-fold to 4-fold increased risk of death in patients with VTE. We found that patients who developed VTE within 8-weeks after surgery had a 13% lower risk of mortality compared with non-hospital-related VTE, which is in agreement with results of previous studies (22, 156, 159, 213). When competing risk of death was taken into account, we found that the 5-year recurrence risk was markedly lowered for cancer (11.7%), and those hospitalised for other medical illness had the highest cumulative incidence (14.4%). This indicated a considerable role of hospital-related mortality in estimating recurrence risk among these patients.

The high risk of recurrence after a first VTE related to hospitalisation for medical illness points towards a persistent nature of the VTE risk in these subjects. Various chronic conditions, such as chronic heart and lung disease, and inflammatory or autoimmune disorders, are associated with coagulation and fibrinolytic abnormalities (214), endothelial dysfunction (214), platelet activation (215), and inflammation (214, 215), which may contribute to a prothrombotic state. Additionally, disease-specific mechanisms, such as hypoxia in patients with chronic obstructive pulmonary disease (COPD) (215), and right ventricular failure with subsequent venous stasis in patients with congestive heart failure (216) may contribute to VTE risk and lead to re-hospitalisation. This notion is supported by Heit *et al*. (125) who reported an almost 6-fold increased risk of VTE recurrence during hospital stay among patients hospitalised for medical illness.

Improved stratification for risk of recurrence after a first VTE is important because it has implications on the duration of anticoagulant treatment (125). This is a complex decision because it requires assessment of an individual patient's risk of developing unprovoked recurrent VTE and

anticoagulant-related major bleeding (125, 208, 217). For patients with a VTE provoked by a non-surgical transient risk factor, current guidelines recommend 3 months anticoagulant treatment over long-term therapy (3). Though hospital admission for a medical condition, besides cancer or surgery, is a transient condition, a high VTE recurrence risk among these patients suggests a persistent underlying VTE risk, which may justify similar treatment recommendations as for those with unprovoked VTE.

In Paper IV, we reported that a history of MI was associated with an increased risk of VTE recurrence in patients with a first VTE. In a sex stratified analyses, history of MI was a risk factor for VTE recurrence in women but not in men. The 5-year cumulative incidence of recurrence in men with and without prior MI was similar. Our findings suggest that a history of MI is a persistent risk factor for VTE recurrence among women.

The association between prior MI and VTE recurrence, and possible mechanisms behind this association in a cohort of patients with incident VTE has not been extensively studied. Although several population-based studies (68, 147, 151, 152, 218), and an individual-level data meta-analysis (219) have shown a link between cardiovascular events and risk of incident VTE, there are no reports describing history of MI and risk of VTE recurrence among patients with first VTE.

In general, our study found that patients with a history of MI had a 45% increased risk of VTE recurrence. Analysis of a randomized controlled trial database involving 1021 patients with VTE (750 with DVT and 271 with PE) who were followed up for 3 months after the start of anticoagulation therapy demonstrated that presence of chronic cardiovascular disease in patients with symptomatic VTE was associated with a 2-fold increased risk of recurrent VTE during the initial 3 months of anticoagulant therapy (154). This study did not report sex-stratified results. As shown in Paper III, patients with a first VTE related to hospitalisation due to medical illness (without cancer or surgery) had a high risk of VTE recurrence even after competing risk of death was taken into account (220).

In our study, the risk of VTE recurrence in women with a history of MI was 2.5 times higher than in those with no history of MI, whereas a weak association was observed in men. A hypercoagulable state is found to play a vital role in the development of arterial events in younger subjects (221, 222). Our findings of a high recurrence risk in female VTE patients with a history of MI, suggests that a hypercoagulable state may play an important role also in the pathogenesis of MI in these patients. Another potential mechanism may be an inflammation. Investigators of The Tromsø Study reported that high levels of C-reactive protein (CRP) were associated with VTE risk particularly in women, and that chronic low-grade inflammation may be a potential common pathway for MI and VTE in obese women (223). Due to their stronger innate inflammatory response, women are at higher risk of developing autoimmune diseases than men (224). Women with autoimmune diseases such as SLE and rheumatoid arthritis have increased risk of cardiovascular events (225, 226), and these autoimmune disorders may predispose for both MI and VTE (214).

Studies have shown that risk of VTE recurrence is higher in men compared with women (127, 134, 136) and men have higher baseline risk for MI (185, 227). In our study, the crude IRs of recurrent VTE according to MI exposure were almost similar among men and women (5.1 and 6.5 per 100 PY, respectively). However, the baseline risk of recurrence in those without MI was higher in men (IR=4.1) than women (IR=1.9). The absolute incidence rate difference per 100 PY was 4.6 in women and 1.0 in men. The higher baseline risk of recurrence among men without a history of MI shows that men are at higher risk of recurrence also due to other risk factors. Thus, history of MI may be a persistent risk factor for VTE recurrence among women with first VTE, whereas it could not be used to distinguish between men at high and low risk of recurrence. Due to the limited statistical power in subgroup analyses, our study findings should be interpreted with caution.

6. Conclusions

I. The rate of VTE has not decreased during the last decades. Our findings indicate that VTE remains a major public health challenge. Future research should focus on improving risk stratification and prevention of VTE in order to reduce the burden of VTE in the society.

II. Despite advances in VTE management during the last decades, the rates of adverse events remained high especially in the first year following a VTE. VTE recurs frequently, and this trend continues for at least 10 years and possibly longer after the incident event. In order to reduce the disease burden associated with VTE, future studies should focus on development of risk prediction models with high precision in order to identify high-risk individuals with a favourable benefit-to-harm ratio for anticoagulant treatment.

III. The risk of recurrence after a hospital-associated first VTE appeared to be dependent on the reason for hospitalization. However, except for surgery-related VTE, this did not hold true in the competing risk analysis. Our findings suggest that patients suffering from incident VTEs associated with hospitalization for medical illness other than cancer or surgery have a high risk of recurrence, even after competing risk by death is taken into account.

IV. In conclusion, a history of MI was associated with increased risk of VTE recurrence in women, whereas no association was observed in men. Our findings suggest that MI may be a persistent, rather than transient, risk factor for VTE in women. Our findings must be interpreted with caution due to the low study power, and should therefore be confirmed in larger studies.

7. Implications of results and future perspectives

The results from Papers I and II of this thesis confirm that the disease burden of VTE remains substantial. The incidence rates of VTE has increased over the last decades, and the rates of adverse events remain high, especially in the first year following a VTE.

Although the introduction of better diagnostic tools to some extent may explain the increase in PE rates, our findings suggest that there is still a need for improvement in risk stratification and prevention strategies for first time VTE. Identification of novel, preferably modifiable, risk factors at the population level is of high importance to reduce the incidence of VTE. Moreover, future studies should focus on identifying risk factors that can contribute to improved risk stratification of patients in high-risk situations (e.g. surgery or hospitalization for acute medical conditions), so that targeted thromboprophylaxis can be better utilized with a favourable benefit-to-harm ratio.

Predicting the risk of recurrence in an individual patient is a challenge. Episodes of VTE are often categorized as provoked or unprovoked, and this categorization has implications for risk of recurrence and treatment duration. However, this categorization is not always clear-cut. For instance, hospitalization may be considered as a provoking factor for first VTE. However, in Paper III we show that the risk of recurrence is highly dependent on the reason for hospitalization, as patients with a first VTE related to hospitalisation for medical illness other than cancer or surgery have a high recurrence risk, whereas those with a surgery-related first VTE have a low recurrence risk. Further, we show that women with a history of MI have an increased risk of recurrence (Paper IV), which suggests that MI may not be a considered purely as a transient provoking factor in women. In general, there is still a need to investigate risk factors for VTE recurrence. Currently existing risk prediction models for recurrence should be improved, or new models should be developed. Our studies show that in conditions with a high mortality rate, the cumulative incidence of recurrence is overestimated with conventional survival analyses. Future studies with predictive purposes should therefore consider to perform analyses which takes competing risk by death into account.

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Paper I

Paper II

Paper III

Paper IV

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