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Triggers and risk factors of first and recurrent venous thromboembolism

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Table of Contents

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Summary

Venous thromboembolism (VTE), encompassing both deep vein thrombosis and pulmonary embolism, is a major public health concern due to substantial morbidity and mortality. Around 50% of all VTE cases are hospital-related, and hospital-acquired VTE is considered a leading cause of VTE-related deaths. Importantly, VTE also has life-long implications, as a large proportion of VTE-patients suffer either a recurrent event or VTE-related chronic complications. The first aim of the thesis was to investigate hospitalization as a trigger factor for incident VTE. Secondly, we aimed to provide new insights to the epidemiology of recurrence, and to facilitate better recurrence prediction through identification of novel risk factors for recurrent VTE.

The study population was derived from one or more of the six surveys (Tromsø 1-6) of the Tromsø Study, with nearly 40.000 participants who were followed from 1994 through 2012. All potential cases of first lifetime and recurrent VTE events during this time-period were recorded. The target population for papers I and II were participants recruited from Tromsø 4 who had suffered a first lifetime VTE in the course of follow-up, whereas the target population for papers III and IV comprised of subjects participating in either of the first six surveys (Tromsø 1-6) who suffered an incident VTE in the period 1994-2012.

We found that hospitalization was a major trigger factor for incident VTE, and that the VTE risk was mainly influenced by the length of hospital stay rather than the frequency of hospital admissions in the 90-days prior to VTE. Furthermore, hospitalization was a high-risk situation also in the absence of immobilization, although immobilization contributed substantially to the VTE risk among hospitalized patients.

Secondly, we discovered that the rates of recurrence and mortality after a first VTE remain high, particularly in the following year after a VTE, despite recent advances in the diagnostics and treatment of VTE patients. In paper III, we found that the risk of recurrence among patients with a hospital-related first VTE appeared to be dependent on the reason for hospitalization, although not when the competing risk of death was accounted for. In the final model, patients with a VTE related to hospitalization for medical illness had a high risk of recurrence, similar to that of patients with a non-hospital-related VTE, which may imply a favorable risk-benefit-profile for prolonged treatment. Finally, we identified that d-dimer, measured at first VTE diagnosis, could be a potential biomarker to identify patients at low risk of recurrence, in whom short-term anticoagulant therapy could be sufficient.

Sammendrag

Venøs tromboembolisme (VTE) omfavner både dyp venetrombose og lungeemboli. VTE er et stort problem for samfunnshelsen på grunn av omfattende sykelighet og dødelighet. Omkring halvparten av alle VTE hendelser er sykehusrelatert, og sykehuservervet VTE regnes som en betydelig årsak til VTE-relaterte dødsfall. VTE innebærer også livslange følger, ettersom en stor andel av VTE-pasientene opplever residiv eller VTE-relaterte kroniske komplikasjoner. Det første formålet med denne avhandlingen var å undersøke sykehusinnleggelse som triggerfaktor for førstegangs VTE. Videre ønsket vi å bringe ny innsikt i epidemiologien av residiverende VTE, og fasilitere bedre prediksjon av tilbakefall gjennom identifikasjon av nye risikofaktorer for residiverende VTE.

Studiedeltakerne ble rekruttert fra en eller flere av de seks første Tromsøundersøkelsene (Tromsø 1-7), med nesten 40.000 deltakere som ble fulgt fra 1994 til utgangen av 2012. Alle potensielle tilfeller av førstegangs og tilbakevennende VTE i denne tidsperioden ble registrert. Målpopulasjonen til artikkel I og II var studiedeltakere fra Tromsø 4 som utviklet en førstegangs VTE i oppfølgingsperioden, mens målpopulasjonen til artikkel III og IV besto av studiedeltakere fra én eller flere av de første seks Tromsøundersøkelsene (Tromsø 1-6), som gjennomgikk en første VTE i perioden mellom 1994 og 2012.

Sykehusinnleggelse viste seg å være en sterk triggerfaktor for førstegangs VTE, og risikoen ble i hovedsak forsterket av lengden på sykehusinnleggelsen heller enn hyppigheten på innleggelser i 90-dagers perioden før VTE-hendelsen. Sykehusinnleggelse viste seg å være en høyrisikosituasjon også blant pasienter som ikke var immobiliserte, selv om immobilisering bidro betydelig til økt VTE-risiko hos sykehusinnlagte pasienter.

På tross av fremskritt i diagnostikk og behandling av VTE, forblir residiv- og dødsratene etter en første VTE vedvarende høye, spesielt i det første året etter en VTE. I artikkel III, så vi at residivrisikoen blant de med en sykehusrelatert første VTE tilsynelatende var avhengig av årsaken til sykehusinnleggelsen. Dette endret seg i modellen som tok høyde for forskjeller i risiko for død i de ulike undergruppene. I den endelige modellen hadde pasienter med en sykehusrelatert VTE i tilknytning til indremedisinske tilstander en høy residivrisiko, på lik linje med pasienter som ikke hadde en sykehusrelatert VTE. I artikkel IV, fant vi at bruk av d-dimer, målt på diagnosetidspunktet for første VTE, kan være en potensiell biomarkør for identifikasjon av pasienter med lav residivrisiko, hvor korttids behandling med antikoagulasjon kan være tilstrekkelig.

List of papers

The thesis is based on the following papers:

I. Hospitalization as a trigger for venous thromboembolism – Results from a population-based case-crossover study
Esben Bjøri, Håkon S. Johnsen, John-Bjarne Hansen, Sigrid K. Brækkan
Thrombosis Research 2019; 176: 115-119

II. Recurrence and mortality after first venous thromboembolism in a large population-based cohort
Nadia Arshad, Esben Bjøri, Kristian Hindberg, Trond Isaksen, John-Bjarne Hansen, Sigrid K. Brækkan
Journal of Thrombosis and Haemostasis 2016; 15: 295-303

III. Hospital-related first venous thromboembolism and risk of recurrence
Esben Bjøri, Nadia Arshad, Håkon S. Johnsen, John-Bjarne Hansen, Sigrid K. Brækkan
Journal of Thrombosis and Haemostasis 2016; 14: 2368-75.

IV. D-dimer at venous thrombosis diagnosis is associated with risk of recurrence
Esben Bjøri, Håkon S. Johnsen, John-Bjarne Hansen, Sigrid K. Brækkan
Journal of Thrombosis and Haemostasis 2017; 15: 917-24.

Abbreviations

CI – Confidence Interval

COPD – Chronic Obstructive Pulmonary Disease

CTEPH – Chronic Thromboembolic Pulmonary Hypertension

DAG – Directed Acyclic Graph

DOAC – Direct Oral Anticoagulants

DVT – Deep Vein Thrombosis

EDT – Extended Duration Thromboprophylaxis

FHVTE – Family History of Venous Thromboembolism

FVL – Factor V Leiden

GRS – Genetic Risk Score

HAT – Hospital Associated Thrombosis

HR – Hazard Ratio

ICD – International Classification of Diseases

IR – Incidence Rate

LMWH – Low Molecular Weight Heparin

MI – Myocardial Infarction

MR – Mortality Rate

OR – Odds Ratio

PTS – Post Thrombotic Syndrome

PE – Pulmonary Embolism

RAM – Risk Assessment Model

RCT – Randomized Controlled Trial

RR – Relative risk

RVT – Residual Vein Thrombosis

SLE – Systemic Lupus Erythematosus

SNP – Single Nucleotide Polymorphism

TF – Tissue Factor UNN – University Hospital of North Norway

UNN – University Hospital of North Norway

VKA – Vitamin K antagonists

VTE – Venous thromboembolism

vWF – von Willebrand Factor

1. Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) were originally viewed as separate diseases (1, 2), but subsequent to the seminal works of Rokitansky and Virchow in the 19th century (3), emerging studies revealed considerable overlap in epidemiology, etiology and treatment, and they were regarded as a single disease entity termed venous thromboembolism (VTE) (4). A DVT is a blood clot arising in the deep veins of the body, and the first compatible description of the phenomenon dates back to the middle ages, affecting Raul, a young cobbler suffering from pain and swelling in the right leg (5). A DVT usually arise in relation to the valvular sinuses in the deep veins of the body, most often in the large veins of the legs, but can also occur in the upper extremities, cerebral or abdominal veins (6). Common signs and symptoms of DVT includes pain, swelling and erythema in the affected limb (7). PE was until recently merely regarded as a complication of DVT by means of embolization of the original thrombus to the pulmonary circulation. However, emerging studies have revealed that concurrent DVT is present in less than half of all patients with PE (8), indicating that some cases of PE attend other etiologies. Several theories on other origins of PE have been postulated, including *de novo* thrombus formation in the pulmonary arteries (8, 9), or embolization from a right atrial thrombus in patients with atrial fibrillation (10). This notion is further substantiated by evidence indicating a higher risk of PE among patients with atrial fibrillation, coronary artery disease and Chronic Obstructive Pulmonary Disease (COPD) (10-12). PEs are usually recognized by dyspnea, chest pain, cough, tachypnea, tachycardia, syncope and hemoptysis (7, 13), but may also present as sudden deaths, resulting from ventilation-perfusion defects and right ventricular failure, leading to severe hypoxia, chock and cardiac arrest (13-15).

The young cobbler Raul's condition worsened progressively, despite many unspecified treatment attempts, and he was finally advised to visit the tomb of King Saint Lewis. After several days of praying to the tomb of King Saint Louis, Raul healed miraculously after applying dust from the tomb stone onto his leg ulcers (5). Since Raul's prayers back in 1271, the treatment of VTE has evolved, and the emergence of anticoagulants in the late 1930s has revolutionized the treatment of VTE. Anticoagulants, which targets various proteases (coagulation factors) in the coagulation cascade, or increase the activity of regulatory proteins, are now the principal treatment for VTE. There are three main classes of anticoagulants:

vitamin K antagonists (VKA e.g. Warfarin), heparins and direct oral anticoagulants (DOACs) (16). Treatment of VTE consists of two phases, ***active treatment*** and ***secondary prevention*** (Figure 1) (17). In the acute phase of VTE, anticoagulants prevent further growth of the thrombus and embolization (active treatment). Any treatment beyond the acute phase is aimed at preventing recurrent episodes (secondary prevention). Anticoagulants are extremely effective in preventing recurrent thrombosis (18), although at the cost of increased risk of bleeding (18, 19). Balancing the harms and benefits of secondary prevention is therefore the key in the management of VTE patients, but still remains a major challenge.

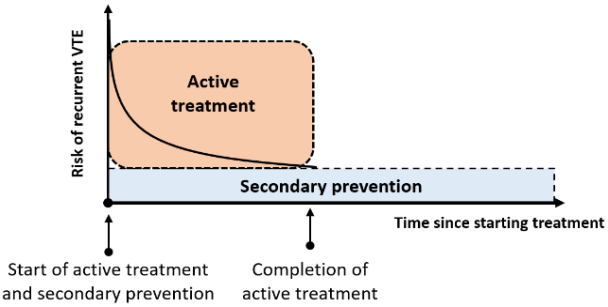

Figure 1 The two phases of anticoagulant treatment; (i) active treatment for 3 months with rapid decrease in recurrence risk, and (ii) secondary prevention with individualized duration to reduce the risk of recurrent disease. Adapted from Kearon et al (17).

1.1. Epidemiology of venous thromboembolism

VTE occurs in 1-2 per 1000 persons per year in a general population (20-23), affecting all age groups, ethnicities and both genders (21, 24). However, VTE is mainly a disease of the elderly, reflected by incidence rates ranging from 10- to 100-times greater among those >80 years of age, compared to middle aged- and young adults (Figure 2) (21, 25, 26). Notably, the disease burden of VTE is projected to more than double from 2006 to 2050 in the U.S. (27). The majority (two-thirds) of VTE cases manifest as DVT (25), although the rates of DVT and PE are comparable in studies including cases with autopsy proven diagnoses (25). The estimated number of symptomatic VTE events (incident and recurrent) in the European Union exceeds 1.1 million cases annually (28), and despite advancements in diagnostics, treatment and prophylaxis, the incidence of VTE is stable or slightly increasing (21, 23, 26, 29, 30), mainly owing to an increase in pulmonary embolism (26, 30). Moreover, increased awareness alongside better and more easily accessible

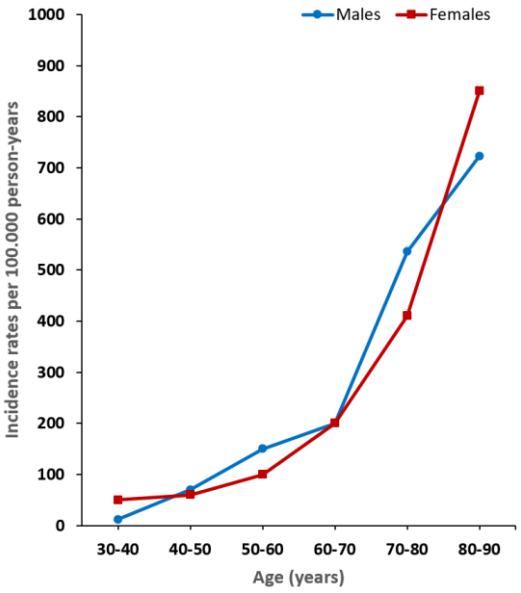

Figure 2 Age- and sex specific incidence rates of VTE. The Tromsø study 1996-2012 (26).

diagnostic procedures may have contributed to an improved detection-rate of PE. Additionally, increasing prevalence of VTE-related risk factors such as obesity, cancer and surgery may have contributed to the persistent incidence of VTE (23).

VTE is accompanied by substantial ***morbidity*** and ***mortality***, and is recognized as the third leading fatal cardiovascular disease, after myocardial infarction (MI) and ischemic stroke (16, 31). The estimated annual number of VTE-related deaths in the EU amount to more than 540.000, of which almost 60% follows undiagnosed PE (28). The acute nature of VTE is demonstrated by data suggesting that a quarter of PEs present as sudden death (32). The case-fatality rates after incident VTE cases ranges from 6% to 14% (20, 22, 33) at 1 month, with a two-fold higher mortality rate after PE than DVT (5-10% for DVT vs 10-20% for PE) (20, 22). At 1-year, the case-fatality rate approximately doubles (21-26% for DVT and 23-32% for PE) (22, 33). Interestingly, the case-fatality rates following incident PE and DVT converge at 1-year (22), indicating a substantial but elusive mortality risk related to DVT.

Besides the immediate short-term consequences, VTE-related chronic complications such as the ***post-thrombotic syndrome*** (PTS) and ***chronic thromboembolic pulmonary hypertension*** (CTEPH) are major concerns in the aftermath of a VTE. PTS is a debilitating condition resulting from valvular destruction, venous hypertension and abnormal microcirculation (34), presenting in one third to half of all DVT patients within 10-years following diagnosis (35-37), affecting nearly 400.000 patients in the EU annually (28). CTEPH arises from incomplete thromboembolic resolution following PE, resulting in increased resistance in the pulmonary circulation, which may ultimately lead to right ventricular failure (38). CTEPH is a rare complication, presenting in 0.5-5% of patients following an incident episode of PE (39-43), however, cumulative incidence rates approaching 10% have been reported (43). CTEPH is a severe condition with poor survival if left untreated (38). Patients presenting with CTEPH typically complain of exertional dyspnea and, as the disease progresses additional symptoms may arise such as exertion-related presyncope, frank syncope, and exertional chest pain (38). In advanced stages, signs and symptoms of right ventricular failure may also be present (43). Importantly, nearly half of all PE patients report functional limitations and/or decreased quality of life up to many years following the acute PE (44). Hence, the term ***post-PE syndrome***, analogous to the PTS, has been suggested to grasp the entire burden of the disease (44). CTEPH may be regarded at the ultimate manifestation of this syndrome.

1.2. Mechanistic views on venous thromboembolism

Central to our understanding of the development of a VTE, is ***Virchow's triad*** of pathophysiological alterations which includes changes in the composition of the blood (***hypercoagulability***), changes in blood flow (***stasis***) and changes to the vessel wall (***endothelial dysfunction***) (Figure 3) (16, 45). These alterations may overwhelm the local anticoagulant properties of the vessel wall and trigger ***the coagulation cascade***, a sequential process of serine protease activation, culminating in the formation of fibrin, the central stabilizing component of a blood clot (46). The coagulation system is essential for understanding the underlying mechanisms of venous thrombosis. The coagulation cascade can be subdivided into three main pathways, the extrinsic-, intrinsic- and common pathway (Figure 4) (45). Tissue Factor (TF) is the main activator of coagulation through the ***extrinsic pathway***, and is probably essential for life, because of its key role in hemostasis (46). TF is found in higher density in the brain, lung, placenta, heart and uterus, to provide additional hemostatic protection to these vital organs (46). Contact activation by FXII and FXI provides an alternate route of clotting initiation through activation of FIX in the ***intrinsic pathway*** (45, 47). Under pathological conditions, the extrinsic pathway can be activated by intravascular sources, such as circulating monocytes, microparticles, or activated endothelium expressing TF (45). Likewise, the intrinsic pathway can be activated by extracellular RNA and

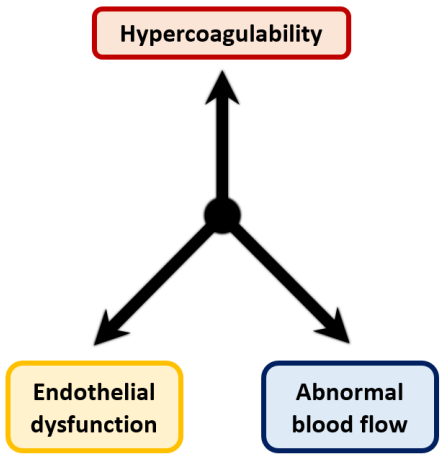

Figure 3 Virchow's triad.

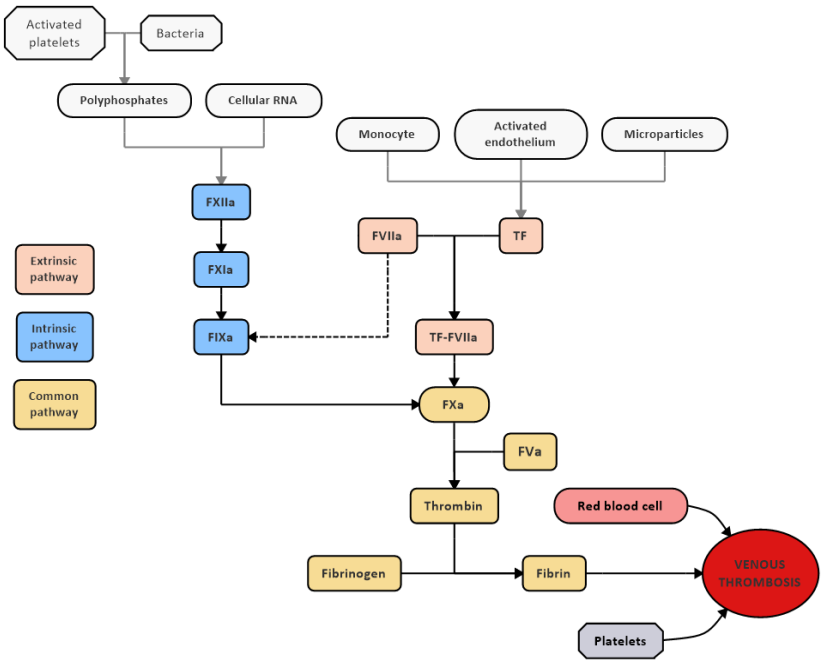

Figure 4 The extrinsic, intrinsic and common pathways of coagulation culminating in the formation of fibrin, the main stabilizing component of a blood clot.

polyphosphates shed from activated platelets or bacteria, resulting in the formation of a venous blood clot (45).

Historically, ***platelets*** have been regarded as key players in arterial thrombosis, whereas their role in VTE is assumed to be negligible. However, recent studies suggest that platelets may have a more important role in the pathogenesis of VTE than previously anticipated (48). Under normal conditions, platelets play a vital role in primary hemostasis through adhesion, activation and amplification, and aggregation (49, 50), which leads to the formation of a platelet-plug at the site of vessel injury. Additionally, platelets are highly important in the coagulation system through three main functions (46, 51), i.e. (1) provide a thrombogenic surface for assembly of the central components of coagulation, (2) by accelerating the coagulation cascade through binding of FXI via the GPIb-IX-V-receptor, and (3) by serving as an extra source for key coagulation factors, mainly factor V (FV). Recent studies highlight the role of platelets in the pathogenesis of VTE by means of genetic and acquired platelet-associated risk factors (48). However, the most important evidence is provided by randomized controlled trials (RCTs), presenting risk reductions of 25-40% for recurrent VTE among patients with an unprovoked VTE who received low-dose aspirin after anticoagulation compared with placebo (52-54).

Another key feature to the pathophysiology of venous thrombosis is that the initiation of the thrombus often occurs in relation to the pocket sinus of the ***venous valves***, where the environment becomes hypoxic due to a vortical blood flow (Figure 5) (55). Hypoxia induces endothelial activation with ensuing adherence of circulating cells and molecules that can trigger coagulation. This creates a thrombogenic surface for thrombus generation, and may explain VTEs conceived in situations with reduced blood flow, such as immobility or long-haul travel.

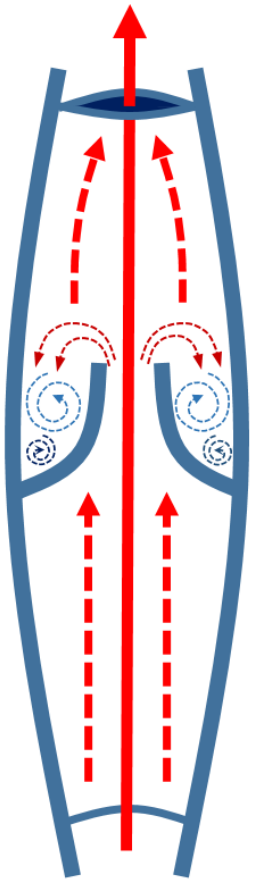

Figure 5 Venous valves with vortical blood flow in valve sinuses. Adapted from Bovill et al. (55).

A general overview of the pathophysiology of VTE is presented in figure 6. Several prothrombotic alterations, such as reduced blood flow and local hypoxia, may lead to (i) endothelial activation, with consecutive expression of the surface adhesion receptors P- and E-selectin, and von Willebrand Factor (vWF). (ii) Successive binding of

circulating leukocytes, platelets and Tissue Factor positive microvesicles (TF^+ MVs) to the activated endothelium through the PSGL-1 ligand, induces (iii) expression of TF on leukocytes with subsequent initiation of the clotting cascade and (iv) formation of a blood clot (45).

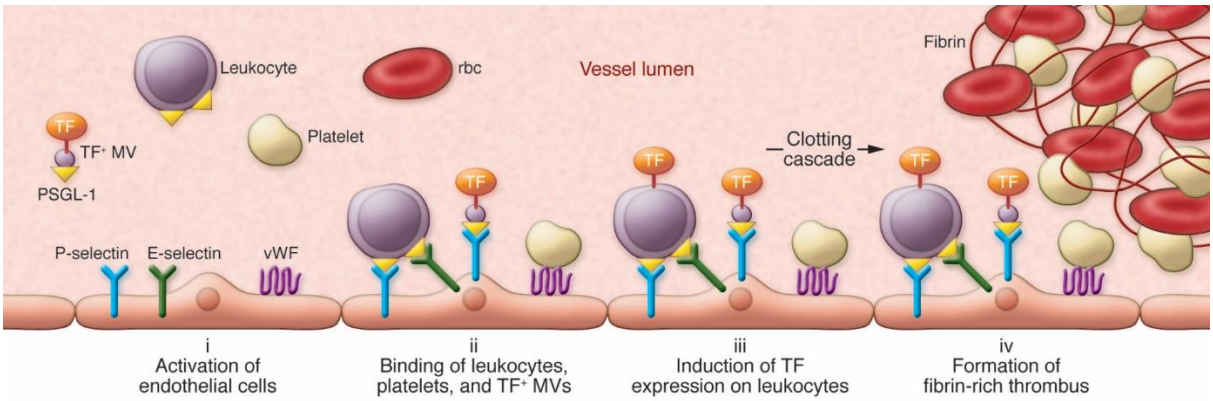

Figure 6 General overview of the pathophysiology of VTE (45). Published with permission from J Clinical Investigation.

1.2.1. Classification of VTE

VTEs are generally classified as either ***provoked*** or ***unprovoked***. If a known trigger for VTE can be identified preceding the VTE, the event is typically classified as provoked, whereas VTEs that occur in the absence of known predisposing factors are classified as unprovoked (56). Risk factors for VTE are further classified as major or minor, transient or persistent. A risk factor is considered to be ***transient*** if the effect of the risk factor is resolved following a VTE event (e.g. surgery or pregnancy), whereas a risk factor that continues to exert its effect after the event, is considered to be ***persistent*** (e.g. uncured cancer with ongoing treatment) (56). This classification has important prognostic implications, as it is strongly related to the risk of recurrence, and consequently the management of VTE patients in terms of secondary prevention. However, the classification of VTE events can often be challenging, particularly in situations where considerable uncertainty exist with regards to the association between a certain risk factor and VTE. For instance, some risk factors, such as inflammatory bowel disease with intermittent periods of remission and flare-ups, may have a fluctuating effect on VTE risk. The classification of VTE therefore places alongside a continuum from VTEs provoked by major transient risk factors associated with a low recurrence risk, through unprovoked events with intermediate recurrence risk, to cases provoked by persistent risk factors associated with the highest recurrence risks (Figure 7) (56).

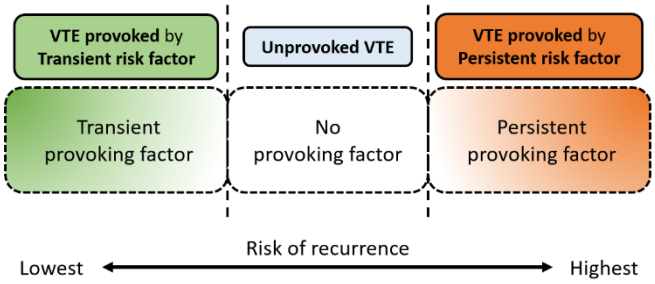

Figure 7 Continuum of VTE classification. Adapted from Kearon et al. (56).

1.2.2. Triggers, risk factors and predictors

An important distinction needs to be made between risk factors and triggers. ***Risk factors*** are typically identified from comparison of the probability of developing a disease between exposed and non-exposed individuals, and may therefore answer the question «why did I develop this disease?». ***Trigger factors*** on the other hand, are typically transient exposures with immediate and short-term effects on the risk of acute VTE, which allows us to answer the question «why did this disease occur right now?». This distinction has important implications, because the presence of a trigger factor describes a high-risk situation that warrants particular awareness and more aggressive prophylactic strategies. For instance, although obesity is

considered a risk factor for VTE, obesity *per se* does not warrant extensive VTE prophylaxis. Conversely, surgery is a major VTE trigger that merit extraordinary awareness and aggressive prophylactic regimens.

Another important distinction is between causes, risk factors and predictors. Pragmatically, a ***cause*** may be defined as something that alters the disease frequency, health status, or associated factors in a population (57), and ***risk factors*** are conditions associated with an increased risk which relation is considered to be causal (58). A ***predictor*** on the other hand is not necessarily a cause of disease, but rather a marker of an underlying process associated with an increased risk (59). The basis for this vital distinction, is that true causes for VTE (e.g. age or thrombophilia) are rather poor predictors of recurrence (59). Thus, identification of predictors of VTE are important for two main reasons; first, to help identify patients at high or low risk to guide decisions on treatment duration and secondary prophylaxis, and second, to understand the underlying mechanisms of venous thrombosis and identify true causes of VTE.

1.3. Venous thromboembolism – A multi-causal disease

The ***thrombosis potential model*** (Figure 8), proposed by professor Frits Rosendaal in the late 1990s, illustrates the key concepts in the pathogenesis of VTE (60). This model emphasizes the ***interaction*** between genetic and acquired risk factors, and that thrombosis develops once a set of sufficient causes have accumulated in a patient, so that the thrombosis threshold is exceeded. Another favorable feature of the thrombosis potential model is that it is dynamic, i.e. it allows for various forms of interaction between risk factors, such as ***additive*** or ***synergistic*** effects. One of the main reasons for this necessity is the strong age-dependency of VTE, as more risk factors needs to accumulate for thrombosis to develop in children than in adults and elderly (60). In figure 8, the green line represents the effect of a genetic risk factor (e.g. factor V Leiden (FVL)), and the red line represents the effect of age. The blue line represents the effect of FVL and age,

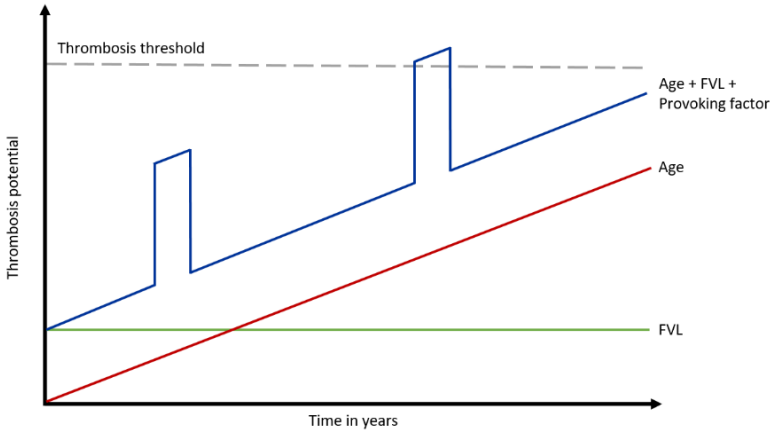

Figure 8 The thrombosis potential model. Adapted from Rosendaal (60).

together with provoking factors (e.g. surgery or immobilization) early and late in life, with the latter producing sufficient pathophysiological changes to exceed the thrombosis threshold.

1.3.1. Risk factors for VTE

A common classification of risk factors for VTE, categorizes risk factors as ***genetic*** or ***acquired***. Several acquired risk factors for VTE have been identified. As previously described, advancing ***age*** amplifies the VTE risk exponentially (20, 22, 26, 58, 61). ***Cancer*** is another major risk factor for VTE, generally associated with a 4- to 7-fold increased risk of VTE, and is estimated to attribute to 20-30% of the total VTE burden (62-65). The notion of ***medical illnesses*** as risk factors for VTE, was established already in 1810 by Ferrier, who noted that VTE occurred during debilitating infectious diseases such as typhus (3). Since then, several medical and autoimmune diseases, including congestive heart failure (66-69), myocardial infarction (12, 68, 69), acute infections (67-70), ischemic stroke (66-69), inflammatory bowel disease (69, 71-74), chronic kidney disease (75-77) and systemic lupus erythematosus (71, 72) have been recognized as risk factors for VTE. The historic view of VTE as a complication of ***surgery*** is embedded in vast amounts of evidence presenting risk estimates ranging from 6- to 22-fold for various types of surgery (63, 69, 78, 79), although the multi-causal nature of VTE has now been illuminated. Even though the underlying etiological factors of VTE were not fully understood, awareness of mobility in the prevention of thrombophlebitis was early recognized (80). ***Immobility*** has subsequently been comprehensively documented as an important risk factor for VTE, acting in a dose-response related matter depending on the length and type of immobility, spanning from use of plaster casts and long-haul travel to complete neurologic paralysis and prolonged bed-confinement (58, 66, 78, 81, 82). Other important risk factors for VTE include ***trauma*** (63, 79), use of ***central venous catheters*** (62, 79, 83, 84), ***blood transfusions*** (85), ***pregnancy*** and the ***puerperium*** (86, 87), ***oral contraceptives*** (69, 79, 88) and ***hormone replacement therapy*** (69, 89, 90). Recently, growing evidence supporting a link between anthropometric measures, such as ***obesity*** and ***body height***, and VTE has been established. Obesity is acknowledged as a growing global epidemic and a major public health concern, also with regards to VTE risk, as observational studies indicate a 2- to 3-fold increased risk for VTE in obese compared to normal-weight individuals (61, 91-93). Similar risk estimates have been presented with regards to body height, with risk

estimates ranging from 2- to 4-fold among tall individuals, depending on the reference category and stratification levels of height (94, 95).

VTE is a highly hereditary condition, and evidence from family-based studies indicate that 50-60% of the susceptibility to thrombosis can be attributed to ***genetic risk factors*** (i.e. thrombophilia) (96, 97). Currently known genetic risk factors for VTE promote thrombus formation through two main mechanisms (98), loss-of-function of anticoagulant proteins and gain-of-function of procoagulant proteins, the latter mainly resulting from impaired downregulation or increased synthesis. ***Loss-of-function*** mutations in genes encoding for anticoagulant proteins result in deficiency of either of the natural anticoagulants antithrombin, protein C and protein S. Loss-of-function mutations are generally less prevalent than gain-of-function mutations (99), but associated with an 8 to 10-fold increased thrombosis risks (98, 100). ***Gain-of-function*** mutations in procoagulants are relatively common, and generally associated with a 1.3 to 3-fold increased risk of VTE (101). These include mutations in genes encoding for factor V (FVL or APC-resistance), prothrombin (rs20210A), non-O blood type, fibrinogen and FXI. The emergence and rapid improvement of genome wide association studies during the recent decades, has enabled identification of several novel single nucleotide polymorphisms (SNPs) associated with VTE. Individually, most of the newly discovered VTE-related SNPs are associated with modest or weak risk estimates for VTE (102). Consequently, emerging studies have attempted to create genetic risk scores (GRS) based on several VTE-associated SNPs to improve the prediction of VTE. Results from a large case-control study (102), showed that a GRS based on the 5 SNPs most strongly associated with VTE performed similarly as a GRS based on 31 VTE-associated SNPs, with predictive accuracy (AUC) of 0.69 and 0.70 for a first VTE, respectively. Combining either of the GRS' with a nongenetic risk score significantly improved the predictive accuracy of the model to 0.82.

Importantly, as demonstrated by the thrombosis potential model, VTE is a ***multicausal disease*** that involve combinations of acquired and genetic risk factors, which is often set off by a trigger factor. Thus, the individual thrombosis risk may vary greatly according to the presence of concurrent risk- and trigger factors, the individual thrombosis-inducing properties of the risk factors, as well as the interaction between them. However, a fundamental challenge in the management of VTE patients and prevention of the disease, is that no obvious preceding cause or risk factor can be identified in approximately 30-50% of the cases (i.e. unprovoked VTE) (20, 26, 103). This emphasizes the complexity of the disease and that continuing efforts

are necessary to unravel the causes of VTE and to identify novel risk factors and predictors to facilitate improved strategies for prevention of thrombogenesis.

1.4. Hospitalization and venous thromboembolism

Hospitalization is a major concern with respect to VTE risk, associated with 40-60% of all VTE cases (20, 28, 62, 104), affecting surgical and medical patients equally (62). Furthermore, more than 70% of all VTE-related deaths are estimated to result from ***hospital-acquired VTE*** (28). PE has been shown to account for 5-10% of all in-hospital deaths (105, 106), making it a prominent cause of preventable deaths in hospitalized patients. Importantly, three-quarters of these deaths occur in medical patients (107), even though VTE has traditionally been considered as a complication of surgery. Moreover, hospital-associated VTE is shown to be the leading cause of disability-adjusted life-years lost in low- and middle-income countries, and the second leading in high-income countries, responsible for more disability-adjusted life-years lost than nosocomial pneumonia, catheter-related blood stream infections, and adverse drug events (108).

The annual incidence of in-hospital VTE is reported to be 960 per 10.000 person-years, exceeding 100-times that of community residents (109). Previous case-control studies have reported a 7 to 21-fold increased risk of VTE following recent hospitalization (58, 63, 78), and results from a recent cohort reported that the risk of experiencing a first or recurrent VTE was 35-fold increased during the 92-days following hospitalization (104). Notably, VTEs occur more frequently ***after*** than ***during*** hospitalization (104, 110), and within a relatively short time-frame from hospital discharge (104, 110, 111), indicating that thrombosis might have been initiated already during hospitalization, although clinically silent upon hospital discharge. Furthermore, the hospital-related VTE risk may be influenced by both the length of hospital stay and the frequency of hospital admissions (111-113), as well as the reason for hospitalization (70, 107, 114-116) and patient-related risk factors, such as age (70, 114-116), obesity (116-118) and genetic abnormalities (107, 119). Importantly, the risk of VTE in hospitalized patients increases dramatically as the number of concurrent risk factors accumulates (68, 70, 107, 120).

Despite that hospitalization is widely acknowledged as a high-risk situation, there is still an underuse of thromboprophylaxis. Results from the ENDORSE study, a large multinational

cross-sectional study, showed that only 60% of surgical patients and 40% of medical patients considered to be at risk of VTE received thromboprophylaxis according to the ACCP guidelines (121). Similar or worse results have been presented in previous studies among hospitalized medical patients (122-125). Given that hospital-acquired VTE is a largely preventable condition, risk assessment upon hospital admission to aid decisions on use of thromboprophylaxis should be mandatory. Furthermore, since both disease entity and severity, degree of mobility, in-hospital procedures, and length of hospital stay influences the VTE risk, the patient needs to be reassessed periodically with regards to VTE risk throughout the hospital stay, and upon hospital-discharge. In 2010, The National Venous Thromboembolism Prevention Program was launched in England. This program warrants a mandatory VTE risk assessment for all adult patients on admission to an acute NHS hospital (126). In the first 9 months following implementation, documented VTE risk assessment improved from below 40% to over 90%, resulting in a 12% reduction in the relative risk of hospital-associated thrombosis (HAT), corresponding to a 15% reduction in HAT attributable to inadequate thromboprophylaxis (127). Furthermore, following implementation, there was a 15% reduction in the mortality rates with VTE as the primary cause of death in hospitals achieving >90% risk assessment (128). However, no effect was found on non-fatal VTE readmissions up to 90 days after discharge. Likewise, in a study from the United States (104), hospital-related VTE attack rates (incident or recurrent VTE in-hospital or within 92-days post discharge) remained essentially unchanged after implementation of a near universal VTE prophylaxis regimen. Considering that the prevalence of hospitalization and hospital-related risk factors (e.g. active cancer, surgery and leg paresis) are increasing (23, 129), that the population attributable risks for VTEs related to hospitalization, surgery or active cancer remain high (23), and that near universal strategies for thromboprophylaxis have produced modest risk reductions (104, 127), current attempts to prevent hospital-related VTEs have likely been inadequate. There has been numerous attempts to create risk assessment models (RAMs) to enable better risk stratification among hospitalized patients to aid decisions on thromboprophylaxis (107, 130-137). However, current RAMs lack generalizability and adequate validation (138), some are highly complex and inconvenient to use, and most lack integrated bleeding risk assessment. Furthermore, the decision to prescribe thromboprophylaxis in medically ill hospitalized patients is complicated by a high frequency of comorbidities and generally older age, leading to major concern with regard to bleeding

risk, which may partly explain the low adherence to practice guidelines described above. Given the large potential to reduce morbidity and mortality from VTE, the Steering Committee of the International Society on Thrombosis and Haemostasis called out for routine VTE-risk assessment in all patients admitted to hospital in 2016 (139). However, the need for better and more accurate tools to enable accurate risk stratification to ensure the safety of prophylactic therapy is urgent.

Although hospitalization is acknowledged as a major risk factor for VTE, few studies have addressed hospitalization as a trigger factor for VTE. Consequently, we do not know whether hospitalization acts a proxy for the underlying VTE risk already accumulated upon hospital admission, or whether it reflects exposure to additional hospital-related risk factors. Studies on hospitalization as a trigger for VTE are therefore necessary to answer the question «why did this VTE event occur right now?». Moreover, hospitalization is often accompanied by ***immobilization***, which is associated with a 1.5- to 2.5-fold increased VTE risk in hospitalized patients (81), and up to a quarter of medical patients with hospital-acquired VTE have been shown to be immobilized preceding the event (130, 140). Previous studies have not been able to elucidate the role of immobility in the hospitalized setting due to lack of data on immobility and varying definitions, as well as differences in prophylaxis policies. In a previous case-crossover study, any non-surgical hospitalization or nursing home facility stay was found to be a significant trigger associated with a 4.2-fold higher risk of VTE (141). Interestingly, adjustment for other hospital-related factors like major surgery, infection, blood transfusion, use of central venous catheters, injuries and medication, did not markedly influence the risk estimates, although many of these factors most likely are in the causal pathway. Recent results from the ARIC study (142), confirmed that hospitalization with infection was a trigger of VTE, and results from two recent case-crossover studies derived from the Tromsø study, showed that immobilization had a synergistic effect when combined with hospitalization for infection and stroke (143, 144).

1.5. Recurrent venous thromboembolism

VTE is a chronic condition that ***recurs*** in 30-40% of VTE patients within 10-years (36, 145-148). The recurrence risk is highest in the initial 6 to 12 month period following the incident event with reported cumulative recurrence rates ranging from 7% to 10% at 6 months (35, 145, 147,

149-151), and from 7% to 14% at 1-year (35, 145, 147, 150-152). Moreover, the absence of a plateau in the cumulative recurrence curve reinforces the notion that VTE is a chronic disease with a persistent recurrence risk, even a decade after the index event (36). The reported recurrence rates vary widely. Current estimates rely partly upon data from previous decades, often restricted to a particular clinical setting (e.g. hospital or community) (35, 153, 154), and with differences with regard to start of follow-up (e.g. time of diagnosis or following completion of 3-12 months of anticoagulation) (35, 154, 155). Subsequently, there have been advancements in the treatment and prevention of VTE. The introduction of low molecular weight heparins (LMWH) in the early 1990s improved the efficacy of antithrombotic therapy (primarily by ease of use) (4), and has contributed to reducing the duration of hospital stays following VTE, with ambulatory treatment now becoming the main strategy for many VTE patients (30, 151). Later on, the emergence of direct oral anticoagulants (DOACs) around 2010 has improved the safety of anticoagulant therapy, and they now serve as first-line treatment for VTE (156, 157). Additionally, progress in the prevention of VTE, such as increased awareness and improved prophylactic strategies (e.g. risk assessment, use of medical or mechanical prophylaxis and early and frequent mobilization), have contributed to reduce the incidence of first and recurrent VTEs, despite an increase in the prevalence of risk factors (126, 127, 129, 158). Consequently, as previous reports on the rates of recurrence might portray an inaccurate outline of the current situation, updated estimates from more recent studies are needed.

1.5.1. Case-fatality and long-term complications following recurrent VTE

The ***case-fatality rates*** following recurrent VTE are substantial. In a large review of 13 prospective cohorts and 56 randomized controlled trials (159), the reported rate of fatal recurrent VTE during the initial 3 months of anticoagulation was 0.4%, with a case-fatality rate of 11.3%. After the initial phase of anticoagulation however, the rate of fatal recurrent VTE rapidly declines, with a reported rate of 0.3 per 100 patient-years (159, 160), corresponding to a case-fatality rate of 3.6-5.1% (159, 160). The case-fatality rates following recurrent VTE are particularly high among elderly patients, with reported rates of 20.5%, with even higher rates among those with unprovoked VTE (23%) and cancer-related VTE (29%) (161).

In addition to the risk of immediate mortality, recurrent VTEs are associated with greater risk of ***long-term complications*** of VTE, such as ***PTS*** and ***CTEPH*** (162). Previous studies

have reported a 6-fold higher risk of developing PTS following recurrent DVT (35), whereas previous PE has been associated with a 19-fold higher odds of CTEPH after acute PE (40). These findings have important implications, as PTS and CTEPH is associated with considerable morbidity and mortality, and further emphasizes the need for improved preventive measures to reduce the risk of recurrent VTE.

1.5.2. Clinical risk factors for recurrence

Currently, patient characteristics (e.g. age, sex) and clinical features related to the index event (e.g. PE vs. DVT, provoked vs. unprovoked) are most reliable for recurrence prediction, whereas laboratory markers (i.e. genetic risk factors and biomarkers) are less useful for assessing recurrence risk. Most studies report that the ***clinical manifestation*** of VTE as either proximal DVT or PE does not influence the probability of recurrence (145, 148, 153, 163-165), although, some studies report higher recurrence rates in patients with DVT (147, 166). Some of these differences could potentially be attributed to differences with regard to inclusion/exclusion of patients with isolated distal DVT and those with concomitant DVT and PE, as distal DVT is generally associated with a lower recurrence risk than proximal DVT and PE (148, 153, 163-165). Importantly, the initial presentation of VTE as PE or DVT is strongly predictive of the clinical manifestation of the recurrent event, as studies indicate a 3- to 5-fold higher probability of recurrence manifested as PE rather than DVT in patients with initial PE, and vice versa for patients with a first DVT (11, 36, 148, 163, 167). These findings have vital implications, as patients with incident PE are more likely to suffer a recurrent PE, meaning that they are also at higher risk of succumbing a fatal recurrence than patients with DVT. Moreover, although patients with a first proximal DVT are more likely to suffer a recurrent VTE than patients with a first distal DVT, up to one-third of patients with an unprovoked distal DVT experience a recurrence within 20-years (148), with a similar risk of suffering a recurrent PE as patients with proximal DVT (165).

Male sex is a strong indicator of recurrence risk, generally associated with a 2-fold increased risk of recurrent VTE (36, 145, 148, 168-171). ***Obesity*** has been proposed as a causal risk factor for VTE by means of three main mechanisms; (1) increased intraabdominal pressure predisposing to stasis in the lower extremities, (2) coagulation and fibrinolytic abnormalities producing a hypercoagulable state, and (3) low-grade inflammation which can promote endothelial activation (92, 172, 173). The notion of obesity as a causal risk factor for VTE is

substantiated by evidence from Mendelian randomization studies (174-176). However, the recurrence risk related to obesity is conflicting, as some studies report no association (145, 177-179), while other studies indicate a moderate to high recurrence risk in obese individuals (172, 180, 181). ***Residual vein thrombosis*** (RVT) refers to the persistence of thrombotic material inside a vein following treatment of a DVT, which may form a substrate for thrombosis formation. RVT is a clinically reliable predictor which is associated with an approximately doubled risk of recurrent VTE (182-185). However, the risk estimates differ according to detection criteria and measurement timing, and in various subgroups of VTE patients (184). Sex-specific risk factors such as ***pregnancy*** (145, 186, 187) ***oral contraceptives*** (145, 168, 187-189) and ***hormone replacement therapy*** (168, 187-189) are associated with a 30-60% lower recurrence risk. However, resumption of hormone replacement therapy in women with a previously verified VTE has been shown to increase the recurrence risk dramatically (190), and women who suffer a VTE are therefore strongly discouraged to resume hormonal treatment. Accordingly, hormone related risk factors (including pregnancy and the puerperium) may explain some of the observed sex differences in recurrence risk but not in risk of incident VTE, indicating a higher intrinsic VTE risk among men (191). Interestingly, although ***age*** is considered a major risk factor for incident VTE, conflicting evidence exist with regards to the association between age and recurrence risk, as some studies report positive associations (36, 145, 165, 169), while others do not (148, 153, 154, 192).

As previously described, the classification of VTE as ***provoked*** or ***unprovoked*** is strongly related to recurrence risk, and therefore has important prognostic implications. The recurrence risk among patients with an unprovoked first VTE is generally 2- to 3-times greater than that of patients who suffer a first VTE provoked by a transient risk factor (164, 165, 182, 193, 194). The recurrence risk for ***transient*** risk factors are generally low, as long as the risk factor is removed and the effect reversible (145, 153, 193-195). On the other hand, patients with VTE provoked by ***persistent*** or irreversible risk factors are generally at high risk of recurrence (59, 145, 196). However, previous studies vary widely with respect to the classification of VTE events as provoked or unprovoked, and whether risk factors are considered to be transient or persistent. Consequently, the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis recently published universal guidelines for the classification of VTE as unprovoked or provoked by major or minor risk factors (56). The goal was to improve consistency of classification of patients into one of

these categories, as this would benefit clinical practice and research. However, this classification may not be clinically useful as there exist considerable diversity in recurrence risk within each subgroup (151, 178, 197-199). Thus, continued efforts are needed to provide more refined risk estimation within subgroups of provoked and unprovoked VTE, to tailor prophylactic regiments at an individual level.

1.5.3. Genetic risk factors and recurrence

Given the high heritability of VTE, the role of genetic risk factors in predicting recurrent disease has received vast attention. During the 1990s, thrombophilia screening became popular under the rationale that identification of underlying genetic predisposition to thrombosis, would identify patients at high risk of recurrence who would benefit from extended anticoagulation (200). However, emerging evidence revealed that most genetic risk factors for VTE seemingly have a weak impact on recurrence risk (171, 194, 200-207), a phenomenon known as «***the thrombophilia paradox***» (59). Consequently, the concept of thrombophilia screening was abandoned (200). Recently, this concept has again been materialized accompanying the derivation of ***genetic risk scores*** (GRS) combining multiple VTE-associated SNPs to improve recurrence prediction (204, 206, 208). Nevertheless, the prevalence of multiple concurrent prothrombotic genetic abnormalities is low (204, 206), and the benefit of such a model is therefore limited to a small subgroup of VTE patients, indicating that universal screening for thrombophilia is still not warranted. Notably, a more simplified approach using ***family history of VTE*** (FHVTE) as a proxy for the genetic burden of VTE, may be clinically valuable for recurrence prediction, as FHVTE is reported to be associated with a near two-fold increased recurrence risk (183, 203). However, advances in genetic research recent decades may help unravel the genetic basis of recurrent VTE (209), as demonstrated in a recent genome wide association study, which identified a novel genetic marker of VTE located on chromosome 18, associated with a 1.7-fold increased recurrence risk (210).

1.5.4. Hospital-related VTE and risk of recurrence

As previously described in this thesis, the role of hospitalization in VTE is extensive. Recent data suggest that more than half of all VTE cases are hospital-related (28, 104), and hospital-acquired VTE is a paramount cause of mortality, accounting for more than two-thirds of VTE-related deaths (28). The transient nature of hospitalization could imply a low recurrence risk, however, recent hospitalization (within the 3 months prior to the VTE) was not associated with

recurrence risk (HR: 0.98, 95% CI: 0.70-1.37) in a previous cohort from Olmsted County, USA. (145). In fact, patients who acquired a first VTE during hospitalization had an almost 50% (HR: 1.46, 95% CI: 1.08-1.98) increased recurrence risk as compared to patients with community acquired VTE. Similar results were found in the Worchester VTE study (178), in which hospitalization due to non-surgical illness before the index event was associated with a 30% (HR: 1.30, 95% CI: 1.03-1.63) increased recurrence risk.

Hospitalized patients compose a heterogeneous population, and the recurrence risk among hospitalized individuals may therefore relate to the circumstances of the event including the reason for hospital admission, hospital- and patient-related risk factors. Hospitalization for ***surgery*** is one of the strongest risk factors for a first VTE, and VTE occurs in approximately 0.5-2% of patients post-operatively (114). However, surgery is generally associated with a low recurrence risk (145, 153, 193-195), although somewhat diverging depending on the type of surgery (195). Consequently, patients with a first VTE after hospitalization for surgery do not have a high recurrence risk because the thrombotic state post-operatively is ***transient*** and reversible. Conversely, ***cancer***, another major risk factor for first VTE, involves a ***persistent*** or ***progressively*** elevated recurrence risk in the range between 2- to 7-fold compared to cancer-free VTE patients (145, 153, 178, 211, 212). The recurrence risk among patients with active cancer can be further stratified on whether treatment requires chemotherapy (145), and according to the type of cancer, tumor site, stage and stage progression (145, 211, 213). Moreover, survival is significantly worse for cancer patients who suffer a recurrent VTE, particularly among patients with recurrent PE (213). Interestingly, a number of studies present similar recurrence rates following VTE provoked by ***non-surgical*** risk factors as those following unprovoked VTE (178, 193, 197, 214), indicating that certain non-surgical risk factors (e.g. acute medical illness) considered to be transient, may instead have a persistent nature. For instance, results from a multicenter trial comparing secondary prophylaxis with VKA for 6 weeks or 6 months (36), showed similar recurrence rates among patients with VTE related to infection or immobilization as among those with unprovoked VTE. Several other ***medical conditions*** have been associated with increased recurrence risk including chronic lung-, heart- and renal disease, inflammatory bowel disease and neurologic disease (145, 212, 215). These are chronic conditions shown to be associated with coagulation and fibrinolytic abnormalities (71, 73, 216-218), endothelial dysfunction (71, 73, 216-218), increased platelet activation (73, 216, 217) and inflammation (71, 73, 216, 217), which could

elicit a persistently elevated thrombosis potential. Moreover, hospitalized patients often present with ***comorbidities***, which may interact and amplify recurrence risk in these patients. However, in a previous study (219), patients with any, a single or two or more comorbidities did not have a significantly increased recurrence-risk compared to patients without any known comorbidities (219).

Importantly, the survival after a hospital-related VTE may also vary according to the same factors influencing the recurrence risk, meaning that the reported recurrence rates might be overestimated due to differential losses to follow-up caused by the ***competing risk of death*** (220, 221). Currently, few studies have addressed the role of the competing risk of death when estimating the recurrence risk among patients with hospital-related VTE. Ay and colleagues demonstrated that the 1–KM method slightly overestimated the 1- and 2-year cumulative incidence of VTE among cancer-patients compared to models accounting for the competing risk of death, and that the magnitude of bias was a direct function of the competing mortality (221). Furthermore, in a recent study, the reported 5-year cumulative recurrence rates dropped from 43.4% to 33.8% in patients with incident cancer-associated VTE, whereas the rates remained essentially unchanged among those with incident idiopathic (27.3% to 26.2%) and secondary non-cancer associated VTE (18.1% to 16.8%), when the competing risk of death was taken into account (149). Accordingly, competing risk models appear to be beneficial to produce accurate and unbiased risk estimates in subgroups of VTE-patients with a high risk of a competing event (e.g. death). As decisions on treatment duration are based on the balance between risk of recurrence and risk of bleeding, precise recurrence estimates are crucial to identify the optimal equipoise of anticoagulation. Therefore, future studies that incorporate competing risk models, especially in high-risk situations for both VTE and death, as imposed by hospitalization or hospital-related risk factors such as cancer or medical illness, are needed.

1.5.5. D-dimer and risk of recurrent VTE

The distinction between risk factors and predictors is particularly evident in the case of ***biomarkers***, as biomarkers are rarely causal factors in the pathogenesis of a disease, but rather a reflection of an ongoing disease process. In recent years, vast resources have been dedicated towards identification of novel biomarkers to enable prediction of VTE recurrence. ***D-dimer***, a degradation product from cross-linked fibrin, reflects an activated coagulation and

fibrinolysis, and is a highly sensitive biomarker of VTE. D-dimer is vital in the diagnostic work-up of patients with suspected VTE, with a negative predictive value of nearly a 100% (222). Furthermore, d-dimer is the most established biomarker of recurrent VTE, and studies have shown that elevated d-dimer after discontinuation of anticoagulation is associated with a 2- to 4-fold increased recurrence risk (223-227). However, d-dimer is positively correlated with several clinical characteristics and medical conditions, including age, sex, cancer, heart disease, infection and inflammatory diseases (228-233), and therefore has a low specificity for VTE. For a biomarker to be clinically useful for prediction purposes, high specificity is a key to avoid the possibility that a negative results is impeded by other conditions. However, results from a prospective interventional study (234), showed that patients with elevated post-anticoagulation d-dimer randomly assigned to resume anticoagulation had a significantly lower recurrence risk than those who did not resume anticoagulation, demonstrating that d-dimer could potentially be used to guide decisions on the duration of anticoagulant treatment, despite lack of specificity. Nevertheless, because d-dimer is a non-specific biomarker, the clinical utility to identify patients at high risk of recurrence is limited as d-dimer may be elevated due to other conditions. However, whether d-dimer may be used to identify patients at low risk of recurrence in whom anticoagulant therapy may be safely discontinued is debated. Furthermore, as d-dimer is widely available already at the time of incident VTE diagnosis, it would be reasonable to explore whether these d-dimer measurements could be used for prediction purposes, as it would reduce the need for additional out-patient clinic visits and save time and resources for the health care system.

1.6. Mortality after incident venous thromboembolism

Besides the high risk of recurrence and chronic complications (i.e. PTS and CTEPH) in the aftermath of a VTE event, VTE is accompanied by substantial ***mortality*** and reduced short- and long-term survival. Extrapolated data from 6 EU countries indicate that there are more than 540.000 VTE-related deaths in the EU per annum (28), making VTE responsible for more than 1 out of 10 deaths each year, putting further emphasis on VTE as a tremendous burden on public health. Previous data on survival after VTE are scattered, ranging from 72% to 94% at 30 days (22, 32, 33, 152), from 63.6% to 99.1% at 1-year (22, 32, 33, 35, 152, 235) and from 53.5% to 93.4% after 5-years (32, 35, 235). The mortality rates vary widely depending on the

clinical presentation of VTE as either PE or DVT, especially in the short-term, with reported case-fatality rates around two-fold higher at 1-month in patients with PE compared to patients with DVT (20, 22). Similar as the risk of recurrence, survival after VTE is dependent on the circumstances surrounding the incident VTE event, as well as patient-related risk factors. Survival is particularly poor in VTE-patients with concomitant cancer, medical illness or neurological disease (20, 22, 32, 35, 236, 237), and patient-related risk factors associated with reduced survival after VTE includes advancing age, male sex, and low BMI (32).

Current reports on the rates of both recurrence and mortality after incident VTE are widespread. The diverging results may partly be explained by differences with regard to the time-period in which the studies were conducted, dissimilarities in study design, study population, inclusion and exclusion criteria, start and length of follow-up (i.e. before or after termination of anticoagulant therapy), and outcome ascertainment. However, it is not well known whether recent advances in diagnosis, treatment, prophylaxis and management of VTE patients have influenced the rates of adverse events after a first VTE. Updated reports on recent trends in recurrence and mortality after VTE are therefore crucial to determine whether these advancements have had an impact on the total public health burden of VTE.

2. Aims of the thesis

The specific aims of the thesis were:

A. To investigate the impact of hospitalization as a trigger of VTE, and to explore the influence of immobility on this relationship in a population-based case-crossover study of VTE patients. We also investigated the influence of hospital-related factors, such as length of hospital stay and frequency of hospital admissions, on the risk of VTE.

B. 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.

C. 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 risk factors such as surgery, cancer or other medical conditions on the risk of recurrence in models with and without death as a competing event.

D. To investigate the association between d-dimer, measured at the time of first VTE diagnosis, and the risk of recurrent VTE.

3. Methods

3.1. Study population – The Tromsø study

The Tromsø study is a single center prospective population-based study with repeated health surveys of the inhabitants of Tromsø, in the North of Norway (238). Overall, seven surveys (Tromsø 1-7) have been conducted, starting with Tromsø 1 in 1974, followed by the second (1979-80), third (1986-87), fourth (1994-95), fifth (2000-01), sixth (2007-08) and seventh survey completed in 2015-16. The study originated in an attempt to combat the high mortality of cardiovascular diseases in the northern part of Norway, and was therefore initially termed the Tromsø Heart study. However, the study has evolved over four decades and now includes a wide range of diseases (238). The study offers several favorable features, including a longitudinal design, long-term follow-up, repeated measurements, high attendance rates and single center follow-up.

The study population for papers I and II of this thesis was recruited from the fourth survey of the Tromsø study, while the source population for papers III and IV comprised of subjects participating in either of the first six (Tromsø 1-6) surveys of the Tromsø study. Overall, 39,825 unique individuals participated in at least one of the surveys, of which 27,158 subjects were recruited to Tromsø 4. The average participation rate was 78.5% across the six surveys, and 77% of the eligible population participated in Tromsø 4. VTE registration started on January 1, 1994 and ended on December 31, 2012. All potential cases of first lifetime and recurrent VTE events during this time-period were recorded.

3.2. Outcome ascertainment – Venous Thromboembolism

All possible VTE events in the study-period (January 1, 1994 through December 31, 2012) were identified and validated by trained personnel using the hospital discharge diagnosis registry, the radiology procedure registry and the autopsy registry at the University Hospital of North of Norway (UNN). UNN is the sole provider of all VTE-related health care and diagnostic radiology procedures for VTE in the area. The discharge diagnosis codes of interest were the International Classification of Diseases (ICD)-codes 325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994-98, and the ICD-10 codes I26, I80, I81, I82, I67.6, O22.3, O22.5, O87.1 and O87.3 for the period 1999-2012. A diagnosis of VTE was verified and recorded when the presence of clinical signs and symptoms was combined with objective confirmation tests (i.e. compression ultrasonography, venography, spiral computed tomography, perfusion-

ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment. For cases derived from the autopsy registry, a VTE-event was only recorded when the autopsy-record indicated PE as the sole cause of death or as a significant contributing cause of death. Patients with concurrent DVT and PE were registered as having PE. Recurrent episodes of VTE were identified and validated using the same criteria as described above for first lifetime VTE events. For papers II, III and IV, information on mortality was derived from the Norwegian Population Registry by use of the unique national person identification number.

3.3. Baseline measurements and design

The baseline data for each participant of the Tromsø study was obtained by physical examination, blood samples and self-administered questionnaires upon study inclusion in the Tromsø study. Body height and weight were measured in participants wearing light clothing and no shoes, and was used to estimate the body mass index (BMI, kg/m^2) as the body weight (kg) divided by height squared (m^2).

Study I followed the design of a case-crossover study (Figure 9). Information regarding all VTE cases enrolled in study I were acquired by review of medical records. Trained personnel systematically collected information on potential trigger factors in the 90-days immediately preceding the VTE event (defined as the risk period), as well as four consecutive 90-day periods (i.e. control periods) prior to the risk period, except from a 90-day wash-out period in-between the risk- and control periods. Additional information regarding diagnostic procedures, surgical and medical treatment, laboratory tests and diagnosis during hospital admissions, day-case and outpatient clinic visits in any of the control or risk periods were recorded. Exposures that extended over several days, were registered and considered to have occurred if any of the days of exposure fell within the specified 90-day period.

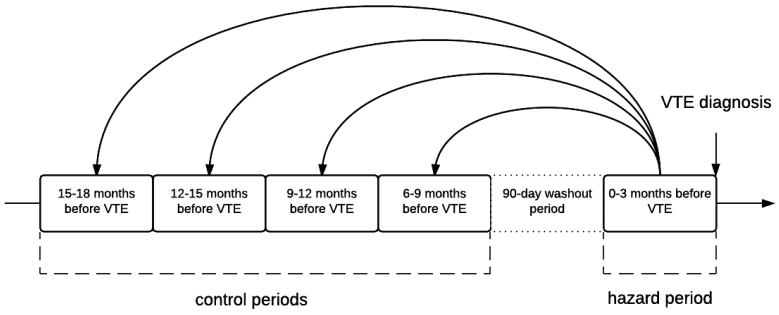

Figure 9 The case-crossover design

For studies II, III and IV, the medical records for each potential VTE case derived from the hospital discharge registry, the autopsy registry and the radiology procedure registry at UNN were reviewed by trained personnel. The participants were followed from the date of their first VTE until the first occurring event of either recurrent VTE, death, migration or end of study (Figure 10). Information on clinical risk factors, comorbidities, provoking factors and laboratory markers at the time of and eight weeks preceding the VTE event was extracted from the medical records using standardized forms. Clinical risk factors included obesity (BMI>30 kg/m^2 according to the WHO definition (239)), previous VTE, use of estrogen, family history of VTE, varicose veins, as well as pregnancy and the puerperium. Comorbid conditions encompassed myocardial infarction or a stroke within the last 12 months preceding the VTE, chronic obstructive pulmonary disease, myeloproliferative disorders, systemic lupus erythematosus and chronic infections. A VTE was considered provoked if preceded by (i) surgery, trauma or acute medical illness within the 8 weeks preceding the event, (ii) marked immobilization such as bedrest >3 days, confinement to wheelchair or long distance travel exceeding 4 hours within the last 14 days prior to the VTE, (iii) active cancer at the time of VTE, or (iv) any other factor specifically described in the medical records, such as other immobilization (e.g. plaster cast), or other provoking factors (e.g. central venous catheters). D-dimer was assessed as part of the diagnostic work-up of patients with suspected VTE. All blood samples were analyzed at the Department of Clinical Chemistry at the UNN. Two different assays were used in the study period; The NycoCard D-dimer (Nycomed Pharma, Oslo, Norway) in the period 1994-98 and the STA®Liatest® D-Di FM from Stago (Diagnostica Stago, Asnières, France) in the remaining period from 1998-2012.

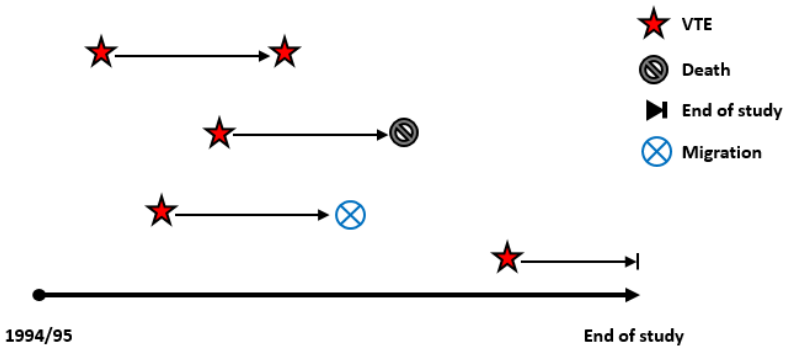

Figure 10 Follow-up of participants in papers II, III and IV

4. Main results

4.1. Paper I – Hospitalization as a trigger of venous thromboembolism – Results from a population-based case-crossover study

Previous studies have reported that around 50% of patients with venous thromboembolism (VTE) has undergone recent hospitalization. However, studies on the impact of hospitalization as a trigger factor for VTE, and the influence of immobility on this relationship are limited. The aim of this study was to investigate the impact of hospitalization with and without concurrent immobilization as a trigger factor for VTE using a case-crossover study of 530 cancer-free VTE patients. Hospitalizations were registered during the 90-day period preceding the VTE diagnosis (hazard period), and in four preceding 90-day control periods. A 90-day washout period between the control- and hazard periods was implemented to avoid potential carry-over effects. Overall, 159 (30%) of the VTE-patients had been hospitalized in the hazard period, corresponding to an odds ratio (OR) of 9.4 (95% confidence interval (CI): 6.8–12.8) for hospitalization. The risk increased slightly with the total number of days spent in hospital (OR per day: 1.11, 95% CI: 1.04–1.18), and with the number of hospitalizations (OR 8.9, 95% CI: 6.4–12.4 for 1 hospitalization and OR 12.3, 95% CI 6.4–23.6 for ≥2 hospitalizations). After adjusting the number of hospitalizations for the total number of days spent in hospital, there was no significant difference in the VTE risk between those with one compared to patients with two or more hospitalizations (OR: 1.8, 95% CI: 0.6-5.2). Hospitalization without immobilization was 6-times (OR: 6.3, 95% CI: 4.4–9.2) more common, whereas hospitalization with immobilization was near 20-times (OR: 19.8, 95% CI: 11.5–34.0) more common in the 90-days prior to a VTE compared to the control periods. These findings imply that hospitalization is a major trigger factor for VTE also in the absence of immobilization. However, immobilization contributes substantially to the risk of VTE among hospitalized patients. Furthermore, the hospital-associated VTE-risk is mainly dependent on the length of hospital stay rather than the frequency of admissions.

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

The rates of recurrence and mortality after a first episode of VTE vary considerably in previous reports. Advances in the management and treatment of VTE during the last 15 years may have influenced the rates of clinical outcomes. The purpose of this study was to estimate the rates of recurrence and mortality after a first VTE in a large cohort of 710 VTE patients recruited from a general population. Patients with a first, symptomatic, objectively confirmed VTE were included and followed in the period 1994–2012. Recurrent episodes of VTE were identified from multiple sources and carefully validated by review of medical records. During a median follow-up of 7.7 years (range 0.04-18.8 years), 114 patients experienced a recurrent VTE, and 333 patients died. The overall recurrence rate was highest during the first year following incident VTE diagnosis, corresponding to an annual rate of 7.8% (95% CI: 5.8-10.6), whereas VTE recurred at an annual rate of 3% (95% CI: 2.4-3.8) in the remaining 17 years of follow-up. The overall 1-year all-cause mortality rate (MR) was 29.9 (95% CI: 25.7-34.8) per 100 person-years, and was particularly high among patients with cancer-related VTE (MR: 114.4 per 100 person-years, 95% CI: 94.0-139.3). Consequently, the cumulative incidence rates of recurrence dropped from 26.4% to 11.4% in competing risk of death analysis. Our results highlight, that despite recent advances in the management of VTE patients, the rates of adverse events remain high, particularly in the following year after a VTE, and the trend persists for at least a decade beyond the incident event.

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

Hospitalization is a well-established risk factor for incident VTE. However, the recurrence risk, particularly in patients hospitalized for conditions other than cancer or surgery, is uncertain. Furthermore, the cumulative incidence of recurrence in hospital-related VTE may be influenced by the competing risk of death. We aimed to elucidate the risk of recurrence and mortality among patients with a first hospital-related VTE with and without death as a competing event. We collected information on hospital-related risk factors in 822 patients with a first-lifetime VTE derived from the Tromsø study. Recurrent VTEs and deaths during follow-up (1994-2012) were recorded. During a median follow-up of 2.8-years, VTE recurred in 132 patients and 442 patients died. A hospital-related VTE *per se* was not associated with increased risk of recurrent thrombosis (HR: 0.99, 95% CI: 0.69-1.41). However, stratification on hospital-related factors revealed considerable differences in recurrence risk. The 5-year cumulative incidence of recurrence was 27.4%, 11.0% and 20.2% in patients with incident VTEs related to cancer, surgery or other medical illness, and 18.4% in patients with a non-hospital related first VTE. The corresponding relative risk estimates showed a 73% (HR: 1.73, 95% CI: 1.06-2.81) higher risk, and a 47% (HR: 0.53, 95% CI: 0.28-0.99) lower risk among patients with a first VTE related to hospitalization for cancer or surgery, whereas patients with a VTE related to other medical illness had a similar risk (HR: 1.02, 95% CI: 0.61-1.72) as patients with a first VTE that was not hospital-related. All subgroups displayed an increased mortality risk, except for those with a surgery-related first VTE. Consequently, the cumulative recurrence rates dropped in analyses accounting for the competing risk of death, showing a 5-year cumulative recurrence rate 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, whereas the 5-year cumulative recurrence rate remained high (16.4%) among patients with a first VTE that was non-hospital-related. Our findings suggest that patients with a first VTE related to hospitalization for other medical illness have a high recurrence risk, even in the presence of competing risk of death, indicating that prolonged anticoagulation similar to that recommended for unprovoked VTE may be warranted.

4.4. Paper IV – D-dimer at venous thrombosis diagnosis is associated with risk of recurrence

D-dimer is essential in the diagnostic work-up of patients with suspected VTE, and measurements of d-dimer after discontinuation of anticoagulant therapy is used to aid decisions on treatment prolongation. However, whether d-dimer measured at first VTE diagnosis can be used to assess recurrence-risk is unknown. We set out to explore the association between d-dimer, measured at first VTE diagnosis and risk of recurrent VTE. We collected information on clinical risk factors and laboratory markers in 454 cancer-free patients with a first VTE enrolled in the Tromsø study, and recorded all recurrent VTEs and deaths during follow-up (1994-2012). During a median 3.9 years of follow-up, 84 patients experienced a recurrent VTE. The absolute recurrence risk was 1.7 (95% CI: 1.0-2.9) per 100 person-years in the lower quartile of d-dimer, and 4.9 (95% CI: 3.9-6.1) per 100 person-years in the upper three quartiles combined, yielding an absolute risk difference of 3.2 per 100 person-years. Accordingly, patients with a low d-dimer (≤1500 ng/mL) presented with a 54% (HR: 0.46, 95% CI: 0.25-0.82) lower recurrence risk compared to patients with a high d-dimer (>1500 ng/mL). Stratification according to the manifestation (DVT or PE) and classification (unprovoked vs. provoked) of the index event, revealed that the association was particularly pronounced among patients with a low d-dimer and a first DVT and among those with an unprovoked VTE. Patients with a first DVT and a d-dimer ≤1500 ng/mL displayed a 68% (HR: 0.32, 95% CI: 0.14-0.71) lower risk of recurrence, whereas patients with a first unprovoked VTE had a 66% (HR: 0.34, 95% CI: 0.15-0.74) lower recurrence-risk, compared to corresponding patients with a high d-dimer. These findings advocate that a clinical decision to avoid prolonged anticoagulant treatment could potentially be considered based on low D-dimer at the time of VTE diagnosis

5. General discussion

In most epidemiological studies, observations are made on a study sample, and based on these observations, inference is drawn onto the population from which the study sample comes from. Since we only observe a small part of the target population, we cannot be sure that these observations applies to the entire population, and consequently there will always be some degree of uncertainty. The research methodology is the key in reducing this uncertainty so that inference drawn from a study can be as valid and precise as possible.

5.1. Methodological considerations

5.1.1. Study design

Study I in the present thesis followed the design of a ***case-crossover study***. The case-crossover design is a type of self-controlled case series method where cases are selected based on the outcome of interest, and each case serves as his or her own control (240). A hazard period is then defined based on assumptions of the target person-times at risk from previous studies and presumed biological mechanisms. Control periods are designated for comparison, and a wash-out period is fitted between the hazard and control periods to avoid potential carry-over effects. The exposures of interest are recorded in the risk period and in each of the comparison periods to compare frequency of exposures in the risk period compared to control periods. The results are expressed in terms of odds ratios (OR), and interpreted as the «odds of being exposed to X in the risk period, compared to the control period(s)». This allows for answering two important questions: (I) «*was the event triggered by something unusual that happened just before the event?*» and, (II) «*how unusual was this?*» (240). Case-crossover studies are therefore especially suited to study triggers of disease, and allows us to separate acute effects from more chronic effects of a given exposure. The key driver of statistical power in case-crossover studies are the number of discordant pairs, i.e. the number of periods discordant with respect to the presence or absence of the exposure. The key strengths of the case-crossover design is the so called self-matching, in which is each case serves as their own control, thereby implicitly controlling for confounding by factors that are ***fixed within***, but ***vary between*** individuals. The main limitation of case-crossover studies is confounding by factors that change over time. Other limitations include that potential trigger factors needs to be well defined in order to avoid misclassification and recall bias, challenges in determining the length of a hazard period, and selecting representative control periods. Importantly, to

avoid risk of confounding by ***factors that vary over time*** within individuals, comparison periods should be fitted as close to the risk period as possible. Furthermore, an inherent weakness of this design is the risk of ***survival bias***, as only cases who survive a disease to receive a diagnosis may contribute to the results, meaning that those who die before receiving the correct diagnosis and in whom autopsy is not performed, are left out. The case-crossover design mostly resembles a ***case-control study***, in which cases and controls are compared with respect to a given exposure. The main drawback of a case-control study is that information on potential exposures are retrieved after the outcome and this information may therefore be influenced by the outcome by means of ***reverse causation*** or ***recall bias***. Case-crossover studies may also be susceptible to recall bias, especially when the information is gathered by means of self-administered questionnaires or interviews. However, in paper I, information on potential trigger factors were derived from medical records, and recall bias was therefore not an issue.

Papers II-IV in the present study follows the design of a ***cohort study***. In a cohort study, information on exposure and various predefined characteristics are collected for each participant at the time of enrollment, with subsequent follow-up and outcome registration or censoring (e.g. death, migration, or end of the study). Upon study completion, comparisons are made between exposed and non-exposed individuals with respect to the outcome. The prospective design allows for estimating incidence rates (IR) as a measure of the ***absolute risk***, which can be used to derive relative risk estimates, usually expressed in terms of relative risks (RR) or hazard ratios (HR), as measures of the strength of association between a given exposure and the outcome. The cohort design offers a major advantage in that the exposure information is obtained prior to the outcome, thereby satisfying the only absolute criterium among Hills criteria for causality, namely ***the temporal sequence*** between exposure and outcome (i.e. temporality). Satisfying the criterium of temporality also rules out reverse causation, a special type of temporal bias, in which the outcome influences exposure status (241). Furthermore, most cohort studies offer an adequate sample size, which (given a representative sample) improves the ***internal validity***, and permits ***generalization*** of the results onto the source population or even on to other similar populations (i.e. ***external validity***). There are several disadvantages of a cohort study. Most important, a cohort study is not sufficient to establish causality, because it does not provide the necessary experimental evidence required to infer causal associations (57). For this matter, you need a ***randomized***

controlled trial (RCT). RCT studies are recognized as the gold standard for making causal inference in epidemiology, as the process of randomization makes the comparison groups similar in all other aspects apart from the exposure/intervention, thereby drastically reducing confounding and bias. However, RCTs are expensive and time-consuming, and may have limited generalizability in situations where strict inclusion- and exclusion criteria are applied. Furthermore, RCTs may be not be feasible due to ethical concerns. Among other drawbacks of the cohort design is that it requires a high number of participants and long-term follow-up for an appropriate amount of outcomes to accumulate to yield adequate ***statistical power*** to detect small differences between comparison groups. This also makes it both time-consuming and costly, and it also makes cohort studies poorly suited to study rare diseases with a low incidence rate.

5.1.2. Validity and generalizability

Validity may refer to screening tests, as the tests ability to distinguish between subjects with and without disease, which again is reflected by the sensitivity and specificity of a test (242). Alternatively, validity may also refer to the degree to which the results from a study may be generalized beyond the study population. In this sense, validity is usually separated into two components, internal and external validity (243). ***Internal validity*** concerns whether or not an observed association is true for the population studied, whereas ***external validity***, often referred to as ***generalizability***, concerns whether or not an observed association can be transferred to other populations outside the study population as well (243). Most violations of internal validity can be classified into three general categories, i.e. confounding, selection bias and information bias (243). The Tromsø study is derived from a general population and the participation rates were high. Notably, the participation rates among young males <40 years and among elderly >80 years were low (238), which may reduce the validity of our results for these age groups. However, in all studies included in the present thesis, patients were selected based on the occurrence of a first-lifetime VTE. The age distribution of the source population is therefore less important because the results are not inferred onto the source population, but rather patients who suffer a first VTE.

5.1.3. Confounding and interaction

In epidemiology, ***confounding*** refers to a situation where a non-causal association between a given exposure and outcome is observed as a result of the influence of a third variable, i.e. a

confounder (241). A confounder is defined according to three main criteria (244, 245), (i) it has to be associated with both exposure and the outcome, (ii) it has to be unevenly distributed between the groups of interest and, (iii) it cannot be an intermediate step in the causal pathway from the exposure to the outcome. Confounding can influence the risk estimates so that the «true» effect is either over- or underestimated, or it can even reverse the apparent direction of effect (243).

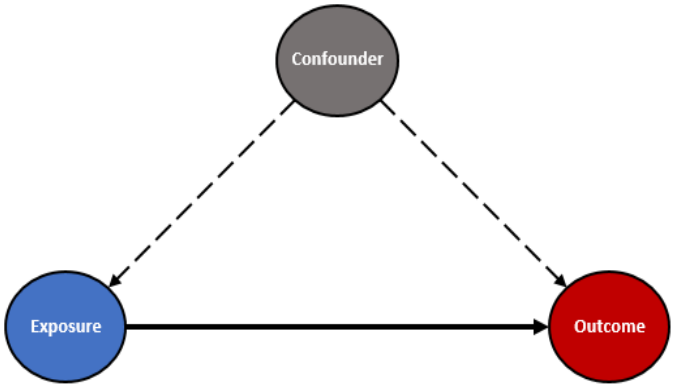

Figure 11 Confounding.

Use of ***directed acyclic graphs*** (***DAGs***) may help visualize the concept of confounding (Figure 11). The black arrow between exposure and outcome represents a ***causal pathway***. The confounder is associated with both the exposure and the outcome, illustrated by the dashed lines, but importantly, not an intermediate step in the causal pathway between exposure and the outcome.

There are three main strategies for dealing with confounding, i.e. randomization, stratification/restriction, and statistical adjustments/regression techniques (57). In RCTs, the risk of confounding is reduced through the process of randomization, which makes the groups equal on all other characteristics than the intervention. Since cohort studies are by nature non-randomized with respect to allocation of exposure classification, stratification/ restriction or regression techniques are the predominant methods for dealing with confounding. ***Regression techniques*** is the most frequently used method to reduce confounding in cohort studies (246). This entails statistically «conditioning» or «adjusting» on the confounder which removes the association (i.e. closes the path in the DAG) between the confounder and the exposure or outcome and reduces bias. When using regression to adjust for a confounder, you get an estimate of the association between the independent and dependent variables that is conditioned for the effect of all the other variables you include in your model. The main advantage of using regression to adjust for a confounder is that it takes data from all subjects into account (246). ***Stratification*** is a second method for approaching confounding in cohort studies. Stratification entails dividing your data into subgroups on the variable you believe to be confounding the association of interest. In studies on VTE, stratifications on sex and whether the event was classified as provoked or unprovoked are common. The main

advantage of stratification is that you create subgroups that are more similar with regards to baseline characteristics than the population as a whole (246). ***Matching*** may be viewed as a special type of stratification. Potential confounders in papers II, III and IV in the current thesis, are age and sex. These were therefore included as covariates in the statistical models, thereby conditioning for the effect of age and sex on the examined associations. Alternative ways of dealing with age as a confounder would be by using age as a time scale or by stratification/restriction. When using age as a time scale comparisons are made between individuals who contribute with the same age interval, rather than the same study interval, which is generally shown to yield less bias than using time-on study as the time scale (247). However, when the baseline hazard is an exponential function of age, the two approaches yield identical estimates (247). For the three papers on recurrence (Paper II-IV) in the thesis, time to event was used as time scale rather than age, as time to event is more important for recurrence, since the recurrence risk is strongly related to the time after a first VTE. In paper II, we conducted subgroup analysis stratified on patient sex to account for any possible confounding or interaction, as men are generally considered to be at higher risk of recurrence than women.

In studies II, III, and IV, comparison of the baseline characteristics and distribution of risk factors indicated that there were only small differences between the comparison groups and therefore a low potential for confounding. Nevertheless, there were some dissimilarities that needs to be addressed. In paper III, 6% of those with non-hospital-related VTE reported to have a positive family history of VTE, as oppose to 1% of those with a hospital-related VTE, indicating potential differences in genetic susceptibility for VTE. However, the low prevalence of a positive FHVTE in both groups advocates that extensive confounding due to such differences is unlikely. In paper IV, patients with a d-dimer value in the lowest quartile tended to be treated with anticoagulants for a shorter duration of time compared to those with a d-dimer in the upper three quartiles. This could potentially be explained by a higher prevalence of women with estrogen-related first VTEs and patients with distal DVT among those with a low d-dimer, as these patients have previously been shown to have a low recurrence risk (146, 163, 168, 189, 248). However, subgroup analysis excluding women with estrogen-related VTE, and analysis restricted to patients with proximal DVT, produced essentially similar results. Furthermore, including the length of anticoagulant therapy in a multivariate model had negligible influence on the results, indicating a low risk of confounding on this account.

Residual confounding refers to a situation where the effect of a confounder is not fully resolved due to incomplete adjustments (241). Residual confounding can occur in cohort studies when there are unknown, unmeasured or misclassified confounders, or when the stratification categories are broad. Despite rigorous efforts to minimize confounding, residual confounding will always remain a challenge in observational studies.

The term ***interaction*** may refer to either (i) statistical interaction or, (ii) biological interaction, which are profoundly different. ***Statistical interaction***, also known as ***effect modification***, is used to describe a situation in which two or more independent variables are correlated, such that the effect of the exposure variable on the outcome differs across the level of another covariate, i.e. an ***effect modifier*** (241). Statistical interaction is dependent on the statistical model relative to the nature of the interaction (i.e. additive, multiplicative, synergistic, antagonistic, etc.) (57). Statistical interaction needs to be distinguished from the phenomenon of confounding, as it rarely influences the «true» association, but rather produces risk variation across levels of the effect modifier. ***Biological interaction*** however, refers to a situation in which two or more causes of disease together exert their effect on disease risk (249), which results in departure from additivity of disease risk (249, 250). Biological interaction can be approached in several ways, e.g. by assessing the synergy index, or by calculating the relative excess risk due to interaction or the proportion attributable to interaction.

5.1.4. Bias and misclassification

Bias may be defined as «*any systematic error in the design, analysis or conduct of the study that results in the mistaken estimate of an exposures effect on the risk of a disease*» (242). Most biases in epidemiology occur under the caption selection- or information bias.

Selection bias refers to any systematic error in the enrolment or retention of study participants, which influences the association between exposure and outcome (241). Selection bias occurs when the study-subjects are not representative of the target population about which conclusions are to be drawn (251). Selection bias can be particularly severe in RCTs because of high non-participation, strict inclusion or exclusion criteria, and because the intervention may only be appropriate for a part of the target population (57). Cohort studies are also vulnerable to selection bias due to ***self-selection***, in which the subjects who volunteer to participate differ from those who don't. In the Tromsø study, selection bias is likely

minimized due to the high participation rates, with an average of 78.5% across Tromsø 1-6. However, selection bias caused by non-responders will always be an issue. As previously mentioned, many of the non-attendees in the Tromsø study were young single males. Additionally, the participation rates among patients >80 years were low (238). As participation required physical presence at the study site, elderly people with poor health could have had trouble to attend. High rates of non-responders in these groups may reduce the generalizability of our results onto these age groups. In the studies included in the thesis however, the participants were selected based on the occurrence of a first VTE event. Since all incident and recurrent VTE events were identified from a single hospital, which is the exclusive provider of all VTE-related health care and diagnostic radiology procedures within a 250-km radius, complete identification of all outcomes is conceivable, and the chance of selection bias is likely minimized. Nonetheless, missed outcomes due to patients treated and diagnosed elsewhere, or that patients with classical signs and symptoms were diagnosed and treated in primary care, could be a potential source of bias. However, any bias due to the latter is highly unlikely, as the diagnosis and treatment of VTE relies on strict criteria and requires diagnostic procedures only available at hospitals.

The best way to reduce selection bias in cohort studies is by careful selection of comparison groups. The goal is to find a comparison group that is as similar as possible to the exposure group on all other variables, except from the exposure (252). In choosing comparison groups, restriction is a powerful way of reducing selection bias, in which the groups you are to compare are selected based on a set of predefined characteristics. By restricting, you will reduce differences related to these characteristics and have more similar comparison groups.

Differential losses to follow-up is another form of selection bias, which occurs in epidemiological studies when the participants lost to follow-up differ from the subjects remaining under observation (241). This problem is particularly evident in the case of cancer and VTE, where ***the competing risk of death*** has been shown to produce an overestimation of the associated risk (221). In conventional survival analysis, death is usually handled as a censoring event, meaning that those who die do not contribute with more person-time beyond that point. Importantly, a requisite of survival analysis is the assumption of ***random censoring*** (also called non-informative censoring), meaning that all study subjects should have the same probability of being censored at any time. Because patients with and without cancer

differ with regards to mortality risk, they also differ with regard to the probability of being censored by death. Consequently, the person-times at risk among patients with cancer-related VTE is reduced due to non-random censoring by death, producing an overestimation of the recurrence risk. One way of handling the competing risk of death is the statistical method proposed by Fine and Grey by use of sub-distribution hazard, which treats death as a competing event rather than a censoring event (253). This method was used in papers II-IV in the thesis, and produced weaker risk estimates compared to regular Cox proportional hazard methods, indicating that overestimation due to differential loss to follow-up had occurred.

Index event bias, also known as ***collider stratification bias***, is a type of selection bias that is common in studies on disease recurrence, as subjects are selected based on the occurrence of an index event (254). This selection induces dependence between risk factors and influences the distribution of risk factors among the enrolled participants, which may affect the association between the independent exposure variables and the outcome. Index event bias will often bias studies toward the null, causing the contribution of the risk factors to be substantially underestimated or even reversed (254). Index event bias may help clarify why true causes of VTE, such as age and thrombophilia, are rather poor predictors of recurrence, a phenomenon known as «***the Paradoxes of Recurrence***» (59). Index event bias is of particular concern in paper III of the thesis when comparing the recurrence risk among patients with hospital- and non-hospital related VTE. As previously described, hospitalized patients are often exposed to multiple concurrent risk factors, whereas those with non-hospital related VTE compose largely of patients with unprovoked VTE. This selection particularly influences the distribution of risk factors among the enrolled participants. Moreover, as almost half of all VTE cases have an unknown etiology, there could be residual confounding due to unknown risk factors operating to cause the disease (254).

Information bias refers to an error in the methods used for gathering information about the study participants that results in inaccurate or erroneous information regarding exposures or outcome (242). Information bias may lead to ***misclassification***, which refers to the incorrect allocation of study participants according to exposure or disease status. Misclassification predominantly occurs when the means of gathering information on the study participants are inadequate so that the information on exposure/outcome is incorrect (242). Misclassification can be random/non-differential or non-random/differential. ***Non-differential misclassification*** is a misclassification of the exposure status that is independent

of the outcome, and results in equal amount of participants being misclassified in each direction. ***Differential misclassification*** on the other hand, occurs when the misclassification of exposure or the outcome is dependent of the other, resulting in either an apparent association or an apparent lack of association that is untrue (57, 242). In the Tromsø study, self-administered questionnaires were used to obtain information on a broad spectrum of variables and characteristics of the participants. A particular problem with this way of gathering information is that it may introduce misclassification, as some questions may be open for interpretation, they may be misunderstood or skipped entirely. Furthermore, the potential for ***recall bias*** in questionnaires is considerable if the participant has an inaccurate recollection of exposure information, or the exposure information may be influenced by the outcome. The latter is a particular problem of case-control studies, in which exposure information is collected after the outcome, as this could give rise to differential misclassification. In cohort studies however, information bias will normally be non-differential because of the temporal sequence between registration of exposure and outcome, meaning that any observed association will tend to be diluted. The vulnerability for information bias in self-administered questionnaires can be reduced by using validated questionnaires.

In all four studies of the thesis, information on the most important exposure variables and clinical risk factors was derived from retrospective review of medical records. The information therefore relied on thorough reporting from the doctors, nurses and other health care professionals. Any information not reported in the medical records could not be taken into account, and could potentially have led to exposure misclassification because the exposure variable or risk factor was considered absent. However, most of the main exposure variables in each paper were hospital-related risk factors, such as cancer, surgery and other medical illness. These are major clinical events, and it is unlikely that these were underreported and thereby a source of misclassification. Immobilization on the other hand, might be more vulnerable to misclassification. Immobilization was of particular interest for paper I in the thesis. For this paper, information on immobility was mainly extracted from the nurse's report in the patient's medical records. The nurse's report is a thorough day-to-day record, encompassing daily functioning, activity level, mobility and ambulation, nutrition, sleep, fluid balance and bowel function, among other things. These records are standardized and reported by each nurse during a work-shift. Consequently, there is a high probability that any conceivable information on immobility for each patient was detected and recorded,

particularly among those who were severely immobilized. However, in patients with moderate restrictions of mobility, there might have occurred some underreporting. In this context, any misclassification due to missed information on immobilization would lead to an underestimation of the observed association between hospitalization, immobility and VTE.

Information gathered on ***laboratory markers*** may be another potential source of exposure misclassification, as the blood sample extraction and laboratory analysis may be prone to technical errors. In paper IV, the laboratory marker d-dimer was the main exposure variable and was investigated as a predictor of recurrence. Information on d-dimer was extracted from medical records, and represents blood samples taken and analyzed at first VTE diagnosis. These tests were also subject to measurement errors. However, these are most likely random errors and would therefore serve as a source of non-differential misclassification. Furthermore, we had a large cohort of 454 VTE cases and d-dimer was modeled in relatively broad categories by dividing the study population into quartiles, which would serve to reduce the effect of any such measurement errors.

In all the studies of the present thesis, misclassification of VTE cases as false-positives were largely avoided by using strict criteria for case validation, combining signs and symptoms with objective confirmation tests with a subsequent diagnosis that required treatment. Identical criteria were used for identification and validation of incident and recurrent VTE events. In the case of recurrences, all patients presenting with new or reoccurring signs and symptoms of DVT or PE, whether or not this event was clinically and phenotypically similar as the index event, and whether it affected the same vein or not, were regarded as a recurrent event. Accordingly, we could not completely differentiate between a recurrence and a relapse, which could give rise to some outcome misclassification. Moreover, the hospital registries used for case validation were retrospectively reviewed, meaning that any information not reported in the medical records was lost, which could potentially lead to misclassification.

5.1.5. Missing data

Missing data is a concept all studies have to deal with, and the prime concern is whether the missing observations bias the available data (255). There are three main approaches for handling missing data: (i) omitting variables with many missing observations, (ii) omitting individuals with incomplete data, and (iii) estimating what the missing values were (i.e. imputation). In paper IV, approximately 16% of the eligible population were excluded due to

missing data on d-dimer. This could potentially introduce bias. However, comparison of the patient characteristics and the incidence rates of recurrence among those with and without missing values, showed that the groups were essentially similar in most respects, indicating that the missing value was presumably at random, and any misclassification that might have occurred due to missing d-dimer values is likely non-differential.

As information on the most important exposure variables in the papers of the present thesis relied on comprehensive and exact documentation from health care professionals in medical records, some independent variables may also be prone to missing data. For instance, in VTE cases that occurred in the presence of an obvious provoking factor (e.g. surgery or trauma), the treating physician might not have considered to ask the patient about family history of VTE, hormone replacement therapy or other minor risk factors considered to be insignificant at that time-point. Again, as the main exposure variables were major clinical events (e.g. hospitalization, cancer, surgery, other medical illness), they were less likely to be missed by the treating physicians, and the probability of differential misclassification on account of missing data on these variables is therefore expected to be low.

5.2. Discussion of main results

5.2.1. Hospitalization as a trigger of venous thromboembolism

In paper I, we reported that hospitalization was a major trigger factor for VTE, associated with a 9-fold higher risk of VTE. Importantly, hospitalization was a trigger factor also in the absence of immobilization, emphasizing that hospitalization is a high-risk situation even in patients who are hospitalized without restricted mobility. Although the role of hospitalization as a risk factor for VTE has been extensively studied, the role of hospitalization as a trigger factor for VTE is not well documented. Most previous studies on hospitalization and risk of VTE are case-control or cohort studies that are designed to answer the question «why me?». However, it is equally important to answer the question «why did this disease occur right now?», for which case-crossover studies are especially suitable. Results from a nested case-control study of 624 patients with a first VTE and 635 patients without VTE, reported that institutionalization (hospital- or nursing home confinement) was independently associated with an 8-fold increased risk of VTE (63). In the AT-AGE study, a case control study of elderly individuals, hospitalization was associated with a 15-fold higher risk of VTE within the first 2 weeks following hospital-discharge (78), and in a recent cohort study, the risk of VTE was 35-fold higher in the 92 days following hospitalization (104). Few studies have addressed the role of hospitalization as a trigger of VTE. In a previous case-crossover study, immobility defined as any non-surgical hospitalization or skilled nursing home facility stay, was found to be a significant trigger associated with a 4.2-fold higher VTE risk (141). Interestingly, this association was not markedly influenced by adjustments for other hospital-related factors, such as major surgery, infection, blood transfusion, use of central venous catheter, injuries and medication. Compared to our results, these risk estimates were considerably lower, however, the studies differ profoundly with regards to patient selection and exposure definition, which could potentially explain some of the observed differences.

Although hospitalization was a major trigger for VTE in the absence of immobility, the VTE risk was augmented in patients who were concurrently immobilized, as the OR for hospitalization with immobilization was essentially 3-times higher than the OR of hospitalization without immobilization. Even though immobility often concur with hospitalization, the role of immobility in the hospitalized setting has previously not been well addressed, mainly due to lack of data and varying definitions of immobility. In a meta-analysis

on immobilization and VTE-risk among hospitalized inpatients (81), immobilization was associated with a relative risk of 1.5 across 7 cohort studies and a 2.5-fold higher odds of VTE across 3 case-control studies. Results from two previous case-control studies on elderly patients (66, 78), reported that immobility mediated the risk of VTE in a dose-response related manner, depending on both the type and duration of immobility, with the highest risk estimates among patients who were bedridden in hospital. Furthermore, three recent case-crossover studies derived from the Tromsø study, emphasized the mediating effect of immobility alongside hospitalization with infection, stroke or myocardial infarction (143, 144, 256). Notably, patients who are immobilized in-hospital more often receive thromboprophylaxis than those who are not (257), which could lead to an underestimation of the observed risk.

Hospitalization per se is not likely a causal factor for VTE, but certainly a strong predictor and may therefore act as a *proxy* for other causal hospital-related risk factors. However, both hospitalized medical- and surgical patients, constitute a heterogeneous population ranging from those receiving weeks of ICU care to those briefly admitted to general wards for elective diagnostic procedures. Consequently, the individual VTE risk associated with hospitalization depends upon patient-related risk factors (i.e. age, sex, obesity, comorbidities, thrombophilia), as well as the reason for hospital-admission (i.e. acute medical or surgical illness, infection, cancer, trauma), in-hospital medical or surgical procedures and degree of mobility. Furthermore, the risk can be directly related to the number of present risk factors (68, 70, 79, 107). However, the separate as well as the mutual interaction between genetic and acquired risk factors is complex (258, 259), as many risk factors act synergistically amplifying the risk multiplicatively rather than the additively (258, 259). This highlights the multi-causality of VTE and that interaction between risk factors is especially relevant in the hospitalized setting, as multiple concurrent risk factors (e.g. surgical- or medical illness and immobility) are particularly common among hospitalized individuals. Appropriate risk stratification among hospitalized patients is extremely challenging, and identification of risk factors, or in particular, combination of risk factors which have a high thrombotic potential in hospitalized individuals is crucial for disease prevention. This concept and the multi-causal nature of hospital-acquired VTE may be illustrated in a thrombosis potential model (Figure 12). In this example, a hospital-admission early in life produced a transient increase in the thrombosis potential, yet insufficient to exceed the thrombosis threshold. Later in life, aging

together with a hospital-admission accompanied by immobilization, produced a synergistic amplification in the thrombosis potential, and the employment of a central venous catheter during hospitalization triggered an overshooting of the thrombosis threshold.

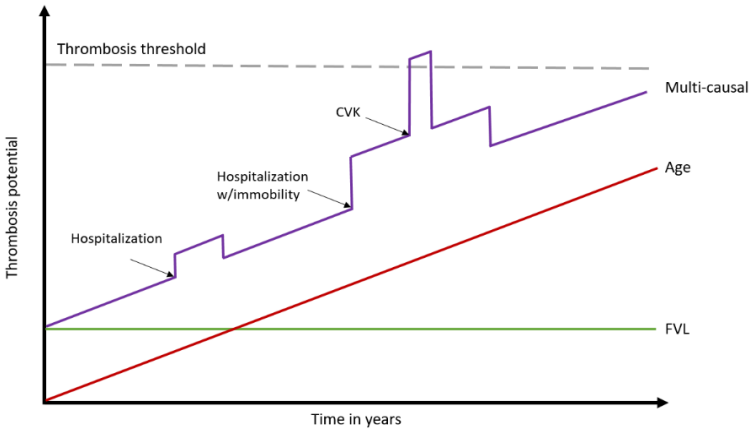

Figure 12 The thrombosis potential model in a hospitalized setting. Adapted from Rosendaal (60).

Importantly, we found that the triggering effect of hospitalization was associated with the length of hospital stay, but not with the frequency of hospital admissions in the 90-days prior to VTE diagnosis, highlighting hospitalization as a high risk situation that is mainly dependent on duration rather than the frequency of exposure. Few observational studies have explored the role of duration and frequency of hospital stay with respect to VTE risk. In a previous case-control study of older adults (112), hospitalization for 4 to 6 days and for more than 7 days was associated with a 2.4- and 3.4-fold increased risk of VTE, compared to patients who were hospitalized for 0-3 days. Furthermore, results from a matched case-control study (111), showed that each additional hospital admission in the 90 days preceding VTE diagnosis approximately doubled the risk of VTE, and the risk increased with 17% for each additional day spent in hospital. In comparison, we found that the VTE risk increased with 11% per one day increase in total days spent in hospital during the 90-days prior to VTE diagnosis, and the risk was 5-fold in those with hospital admissions for≥5 days compared to those with shorter hospital stays (i.e. 1–4 days). However, there were no substantial differences in VTE-risk in those with a single hospitalization (OR: 8.9) compared to those with ≥2 hospitalizations (OR: 12.3) prior to their VTE. Furthermore, after conditioning on the length of hospital stay there was no differences in the risk of VTE in those with one compared to ≥2 hospitalizations. In a recent study (260), Amin et al found that length of hospital stay was associated with VTE both during hospital stay, as well as within the 6 months beyond hospital-discharge in patients hospitalized for acute medical illness. Importantly, the study showed that a higher proportion of patients with longer duration of hospital stay received thromboprophylaxis, which could indicate that the true association between length of hospital stay and risk of VTE might be underestimated. Furthermore, the study showed that increased length of hospital stay was

associated with older age and greater comorbidity, and presumptively, length of stay likely correlates with disease severity and immobility, which may be assumed to mediate the VTE-risk among these patients.

In summary, our findings highlight that hospitalization is a major trigger of VTE also in the absence of immobilization. However, the VTE risk among hospitalized patients is strongly augmented by concurrent immobilization. Furthermore, the hospital-related VTE risk is mainly dependent on the length of hospital stay rather than the frequency of admissions.

5.2.2. Recurrence and mortality after incident venous thromboembolism

In paper II, we presented results on recurrence and mortality rates among patients who had experienced a first lifetime VTE recruited from a large cohort derived from the general population. The crude recurrence rate was 3.9 per 100 patients-years, but was 4-fold higher in the initial 6 months after a first VTE compared to the period 5-10 years after VTE (IR: 9.2 vs 2.3 per 100 person-years, respectively). The cumulative recurrence rates were 4.3% at 6 months, 7.2% at 1-year, 18.8% at 5-years and 28.3% at 10-years, respectively, but varied according to patient sex (35.4% in men vs. 22.0% in women at 10-years) and classification of the initial VTE event as unprovoked, provoked or cancer-related (17.9% vs. 16.7% vs. 26.4% at 5-years, respectively). In a previous cohort of patients with a first VTE in the period 1960-1999 from Olmsted County (145), the reported cumulative recurrence rates were 30.4% at 10-years. The corresponding cumulative recurrence rates were 12.9% at 1-year, and results from the more recent (1999-2003) Worchester study (155), showed that the cumulative incidence of recurrence was 10.9% at 1-year. In comparison, the 1-year probability of recurrence was 7.2% in our study, which is almost half of that reported in the former cohort from Olmsted County. We found that >60% of the VTE patients were treated with anticoagulants for 3 months or more, and almost 30% were treated more than 6 months after the incident VTE. Moreover, the majority of patients with isolated calf DVT in our study received anticoagulant treatment. Accordingly, the improved short-term recurrence rates may to some extent be attributable to improved treatment strategies recent years. Conversely, our results on long-term recurrence rates are largely similar to those of previous studies, which provides further evidence for a «***catch-up***» effect or «***rebound phenomenon***», in which recurrences appear to aggregate shortly after anticoagulant treatment is terminated (36, 150, 261-263). However, it is not

certain whether this reflects a return to the previous prothrombotic state (i.e. catch-up), or a transient overshooting with subsequent normalization of coagulation (i.e. rebound) (264). Consequently, recent advances in treatment and diagnosis of VTE have not improved the rates of long-term recurrences following a VTE, which persists even a decade after a VTE.

The mortality rates were high, especially among cancer patients, who presented cumulative all-cause mortality rates of 19.4% and 62.0% at 30-days and 1-year, respectively. The corresponding rates were 9.0% at 30-days and 16.6% at 1-year among cancer-free patients. Accordingly, when the competing risk of death was taken into account, the cumulative recurrence rates dropped substantially among cancer patients, from 26.4% at 5-years in conventional 1-KM analysis to 11.4% in the competing risk analysis.

In accordance with previous studies (147, 163, 265), the clinical manifestation of the primary VTE as DVT or PE predicted the phenotype of the recurrent event, with a 2.4-fold higher risk of recurrent PE than DVT among patients with index PE. Likewise, patients with a first unprovoked VTE were more likely to have a second unprovoked VTE, however, VTE recurred at similar rates as provoked and unprovoked in patients with a first VTE that was provoked. This observation could potentially be explained by provoking factors or comorbidities which could invoke a persistently elevated thrombosis potential, or by other factors which increases the baseline thrombosis potential, such as residual vein thrombosis or local damage at the initial thrombus site which may lead to impaired endothelial function with subsequent loss of anticoagulant properties in the vessel wall. The thrombosis potential model may be used to demonstrate this concept. After a first episode of VTE, three things can happen to the thrombosis potential: it can either increase, stay the same or decrease (59). This concept relates to the nature and influence of different risk factors on the course of the disease. In the case of transient risk factors (e.g. surgery or pregnancy) (Figure 13, panel A), the thrombotic potential is lowered immediately once the risk factor is removed, given that the effect of the risk factor is reversible. However, when a VTE event is unprovoked or provoked by a persistent or irreversible risk factor, the thrombotic potential may either stay the same or even increase. In patients with unprovoked VTE (Figure 13, panel C), the causes of the index event persist, and the thrombosis potential stays the same. In the presence of a persistent risk factor such as cancer (Figure 13, panel B), the post-VTE thrombotic potential may stay the same, or even increase due to metastasis, disease progression or disease-related risk factors such as chemotherapy. Additionally, local damage at the initial thrombus site with

subsequent endothelial dysfunction, may influence the recurrence risk as a result of an elevated baseline thrombosis potential as illustrated in panel B and C. This notion may be supported by findings from a recent study, showing a similar recurrence risk among patients with VTE provoked by minor persistent or transient risk factors as in those with a unprovoked VTE (266), but could also suggest a higher intrinsic baseline thrombus potential among these patients. Likewise, in a retrospective study of cancer-free VTE patients (197), the risk of recurrence following travel-related VTE, normally classified as a minor transient risk factor, was found to be comparable to that of unprovoked VTE, thus substantiating the claim of a high baseline thrombosis potential in patients with VTE provoked by minor risk factors, which could be further elevated by disease-related factors induced by the first VTE event. Furthermore, even in patients with VTE provoked by surgery, a major transient risk factor, the recurrence rates exceeds the rates of incident VTE in a general population, indicating that the risk does not fully return to baseline after a first VTE (198), which could further support this hypothesis.

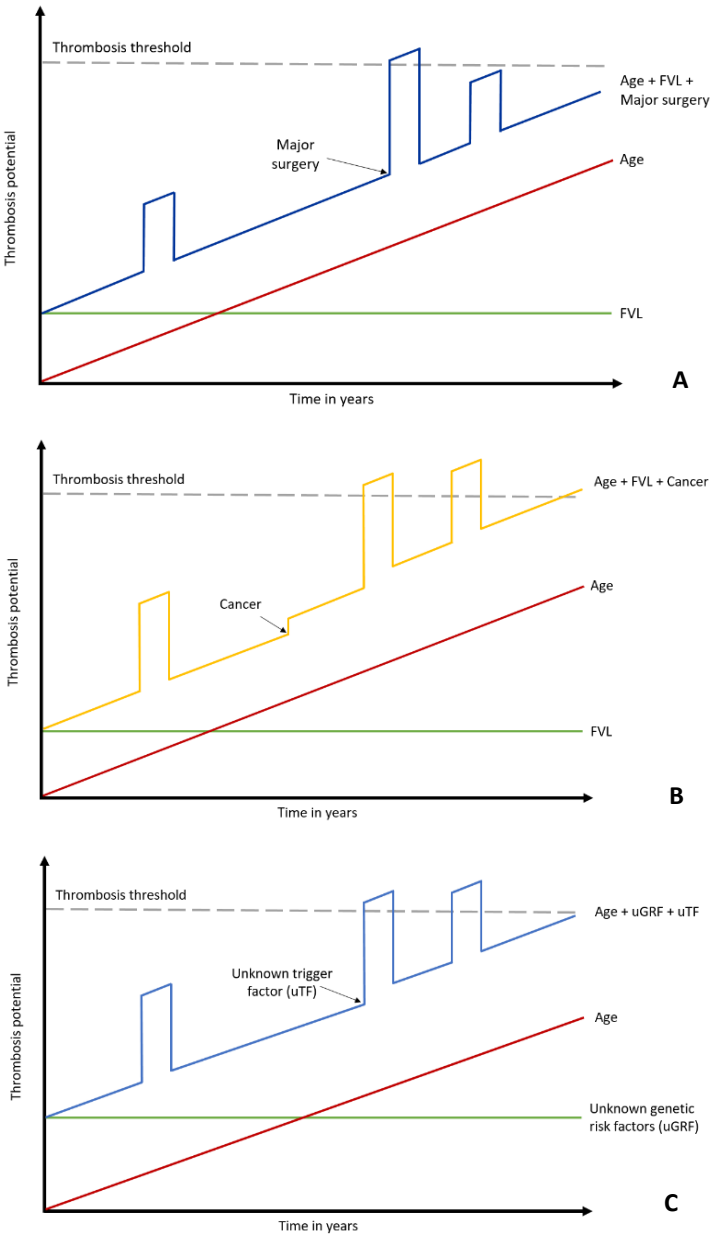

Figure 13 The thrombosis potential model demonstrating the influence of a transient (A) and persistent (B) provoking factor, alongside unprovoked VTE (C) on the risk of recurrence. Adapted from Cannegieter and van Hylckama Vlieg (59) and Rosendaal (60).

5.2.3. Hospital-related venous thromboembolism and risk of recurrence

In paper III, we found that the risk of recurrence among patients with a hospital-related first VTE was similar to those with a non-hospital-related VTE (including unprovoked VTEs), but varied considerably according to the reason for hospitalization in conventional Kaplan-Meier analyses. The recurrence risk was similar in patients with a VTE related to hospitalization for medical illness and in those with non-hospital-related VTE, and in accordance with previous studies (145, 153, 193, 194, 196, 211), patients with a cancer-related VTE had a high recurrence risk, whereas those with a surgery-related index event had a low recurrence risk.

The mortality rates following a hospital-related VTE were 3-times higher than among patients with VTE not related to hospitalization, and they were elevated in all subgroups of hospital-related VTE, except in patients with VTE related to surgery. Our findings of a 6- and 2-fold higher mortality risk among patients with cancer and acute medical conditions are consistent with previous studies (20, 32, 35, 236, 267, 268). Accordingly, the cumulative incidence of recurrence were lower in competing risk of death analysis, particularly among those with cancer-related VTE. In this analysis, patients with cancer-related VTE presented with lower cumulative recurrence rates than those with VTE related to hospitalization for other medical illness, as well as in patients with VTE not related to hospitalization. In the presence of competing risk of death, the cumulative recurrence rate is dependent on both the hazard of recurrence and the hazard of dying. Consequently, differential losses to follow-up due to dissimilarities in mortality risk between the groups compared might bias the risk estimates towards an overestimation of the recurrence risk (220, 221, 269). Our results confirmed this observation, however, the degree of the competing risk of death varied between subgroups, and as expected, the largest change in risk estimates was observed in patients with cancer, where the cumulative recurrence rate dropped from 27.4% at 5-years in conventional analysis to 11.7% in analysis accounting for the competing risk of death. These results emphasize the importance of competing risk regression to produce accurate risk estimates in situations where the comparison groups differ with regards to a competing event.

In paper I, we showed that hospitalization was a major trigger factor for VTE associated with a 9-fold higher risk. The low recurrence risk among patients with VTEs provoked by transient reversible risk factors is widely acknowledged. Accordingly, the transient nature of hospitalization could imply a low recurrence risk. However, in paper III, a recent (within 8 weeks) hospitalization *per se* was not associated with the risk of recurrent VTE (HR: 0.99),

which is also in line with the results from a previous cohort study (145). However, there appeared to be considerable heterogeneity depending on the reason for hospitalization. Patients with a VTE related to hospitalization for medical illness other than cancer or surgery, had a high recurrence risk in both conventional and competing risk analysis, which could imply a persistently elevated thrombosis risk following the first VTE. Two previous observational studies have indicated a higher recurrence risk among patients with VTE related to hospitalization for medical illness (147, 149). Furthermore, in a recent study using data from 2 RCTs comparing Rivaroxaban with Aspirin for extended VTE treatment (266), the recurrence rates did not significantly differ between patients with incident VTE provoked by a minor persistent- or a minor transient risk factor and in those with unprovoked VTE (HR: 0.82 and HR: 0.68, respectively). In this study, inflammatory bowel disease, lower extremity paralysis or paresis and congestive heart failure, (among others) were classified as minor persistent risk factors, whereas immobilization, travel >8 hours and lower limb trauma with transient impaired mobility (among others) were classified as minor transient risk factors. The diversity in recurrence risk within each subgroup of provoked and unprovoked is further emphasized by recent findings from the MEGA-study (199), which found that men with a VTE provoked by other factors than surgery and a high d-dimer level had a high absolute recurrence risk of 6.8% per year, which was essentially similar to that among men with an unprovoked VTE and a high d-dimer level. Conversely, women with a first unprovoked VTE and a low d-dimer had an absolute recurrence risk of 2.3% per year, which was virtually similar as that of patients who had a first provoked event.

There are several identified pathophysiological mechanisms supporting the notion of a prothrombotic state related to medical illness, as chronic heart- and lung disease, as well as autoimmune and inflammatory conditions, have been shown to influence the balance between coagulation and fibrinolysis (71, 73, 216-218), as well as endothelial- and platelet function (71, 73, 216-218). Additionally, these are chronic conditions which cause a persistent or intermittent inflammatory state (71, 73, 216, 217), which may add to the elevated thrombosis potential. Furthermore, disease specific mechanisms, such as hypoxia in COPD patients (216) and right ventricular failure with subsequent venous stasis in patients with congestive heart failure (217, 218), may add to the VTE risk, and flare-up periods (73, 74, 215) or exacerbations (270, 271) that lead to re-hospitalization may in itself cause a transiently elevated thrombosis risk or induce additional VTE risk factors such as immobilization. In a

previous case-cohort study (149), interim rehospitalization for medical illness after a first VTE was reported to be associated a 6-fold increased risk of VTE recurrence, and the risk remained increased for at least 92-days following discharge. In our study, 31.1% and 21.6% of the hospital-related VTEs were related to surgery and acute medical conditions, respectively. In comparison, among patients with a hospital-related first VTE who suffered a recurrence, 13.7% of the recurrences were related to surgery and 17.6% were related to acute medical illness. Consequently, it is likely that re-exposure to potential triggers occur more frequently among medical- than surgical patients, which could further explain the high recurrence rates observed among medically ill patients.

Current guidelines recommend short-term (3 months) over indefinite anticoagulant treatment in patients with a VTE provoked by a non-surgical transient risk factor (157). Considering that VTEs related to hospitalization for medical illness might invoke a more persistent underlying VTE risk, prolonged treatment similar to those recommended for unprovoked VTE might be justified.

5.2.4. D-dimer and risk of recurrence

In paper IV, we found that patients with a low d-dimer level (≤1500 ng/mL) at first VTE diagnosis had a markedly lower recurrence risk compared to patients with a high d-dimer (>1500 ng/mL), with an absolute risk difference of 3.2 (IR: 1.7 vs. 4.9) per 100 person-years for a d-dimer above and below 1500 ng/mL, respectively. The association was particularly pronounced among patients with a low d-dimer and a first DVT and among those with an unprovoked event, displaying a 68% and 66% lower recurrence risk compared to corresponding patients with a high d-dimer, respectively. Although the predictive value of d-dimer measured after withdrawal of anticoagulant treatment is extensively documented (224, 227, 234, 272), to our knowledge, no previous study has addressed the predictive ability of d-dimer, measured at index VTE diagnosis, on the risk of recurrence. The absolute recurrence rates in the lowest d-dimer category in the present study concur with other studies on the recurrence rates among patients with a normal d-dimer (i.e. <500 ng/mL) assessed after withdrawal of anticoagulant therapy (224, 234, 272). However, whether d-dimer levels measured after anticoagulation can be used to select patients at low risk of recurrence who may safely stop anticoagulant therapy is debated (248). In our study, the overall absolute

recurrence rates in patients with a low d-dimer was 1.7% at 1-year and 8.5% at 5-years. The corresponding rates among patients with a first unprovoked VTE and a low d-dimer was 1.4% and 10.5% at 1- and 5-years, respectively. Importantly, these rates are below the rates considered acceptable to justify stopping anticoagulation (5% at 1-year and 15% at 5-years) according to the recommendation from the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis (273). However, because of limited statistical power in subgroups, some of the confidence intervals exceeded the upper limit of the recommended rates, meaning that these findings should be interpreted with some caution. Furthermore, we do not know whether the patients with a low pre-treatment d-dimer are the same patients as those with negative d-dimer after discontinued anticoagulation, especially in view of studies indicating a transient period of rebound hypercoagulability following withdrawal of anticoagulation (264, 274, 275), with a successive increase in d-dimer formation accompanied by thrombin generation.

Our findings could have important implications. First, as d-dimer is widely available for most patients at the time of VTE diagnosis, the potential use of d-dimer to identify patients at low recurrence risk may have great clinical utility for the initial decision on treatment duration and further follow-up of the patients. Current risk prediction models, such as the Vienna prediction model (146), the DASH prediction rule (276), and the Men continue and HER DOO2 rule (277), all make use of d-dimer tests during or after anticoagulation, together with clinical predictors, to discriminate between patients at high and low risk of recurrence among those with a first unprovoked VTE. The clinical components in these prediction models can usually be assessed at the initial patient examination. Thus, if pre-treatment d-dimer assessment can replace current use of post-anticoagulation d-dimer in future prediction models to detect patients at low risk of recurrence, it may prove valuable for the patients, as well as for the clinician and the health care system. For the patients, information on the disease prognosis may provide appreciated reassurance and, as the need for additional blood sampling is reduced, they will avoid additional discomfort, as well as additional sick leave to attend follow-up outpatient visits. For the clinicians, it may provide the opportunity to make decisions on treatment duration upon hospital discharge, and reduce the need for additional outpatient care after discontinued treatment, saving both time and resources for the health care system.

Current treatment guidelines recommend an initial 3 months of therapy, followed by bleeding risk assessment to consider indefinite treatment in patients with a first unprovoked

VTE (157). To aid this decision, the guidelines suggest stopping anticoagulation and repeating d-dimer measurements after 1 month. Importantly, withholding anticoagulation for 1 month in patients with a high recurrence risk before repeating d-dimer measurements, implies a transient elevation of recurrence risk during this period without anticoagulant protection. Thus, if d-dimer levels at incident VTE diagnosis could be used to detect high risk patients as well, the transient increase in recurrence risk accompanied by withheld anticoagulation could be avoided. In the present study, we found a high recurrence risk among patients with a high d-dimer, which was similar across the upper 3 quartiles, with a 10-year cumulative incidence approaching 35%, compared to 14.4% in quartile 1. The corresponding estimates at 1- and 5-years were 6-9% and 23-24% in the upper quartiles, compared to 1.7% and 8.5% in quartile 1. The results were similar or even more pronounced among those with a first DVT or unprovoked VTE, although not as consistent in subjects with provoked VTE and PE. Accordingly, the majority of recurrences occur beyond the initial year after a VTE, indicating that VTE prevention strategies needs to be tailored for the long-term. Our findings and those of others (223, 224, 227, 234, 272), show that d-dimer can be useful to distinguish patients at high and low risk of recurrence, and could therefore also potentially be used to aid decisions on prolonged treatment. Ideally, given the high rates of recurrence in the long-term, all patients with a high d-dimer would be offered indefinite antithrombotic therapy. However, the decision to sustain treatment is complicated by the increased risk of bleeding accompanied by anticoagulation. In a recent study, elevated d-dimer >8.3 μg/mL (upper 20th percentile) was associated with a 2.6-fold increased risk of major bleeding in the initial 3 months of anticoagulation after VTE (278). This implies that particular attention and careful consideration of the risk-to-benefit ratio are warranted among those with the highest d-dimer. The latest guidelines are the first to implement DOACs as the primary choice of anticoagulation for most patients. The introduction of DOACs has improved the safety of anticoagulant therapy considerably, with a substantial decrease in the risk of bleeding (156). Consequently, the improved safety of DOACs could have implications for the decision on treatment duration and secondary prophylaxis, as more patients could be treated indefinitely with an acceptable risk of bleeding.

In the present study, patients with a low d-dimer (≤1500 ng/mL) appeared to be treated for a shorter duration of time with anticoagulants compared to those with a high d-dimer (>1500 ng/mL). This could potentially be explained by a higher prevalence of women

with estrogen-related first VTEs and patients with distal DVT among those with a low d-dimer, as these patients have previously been shown to have a low recurrence risk (146, 163, 168, 189, 248). Our results could therefore have been driven by such low-risk subgroups. To test this hypothesis, we conducted sensitivity analyses excluding patients with estrogen-related VTE and analysis restricted to those with proximal DVT. The results showed no substantial differences compared to the results of the overall analysis and analysis of all DVT patients, indicating that no bias had occurred on account of these subgroups. Additionally, adjusting for length of anticoagulation and accounting for the competing risk of death produced essentially similar results.

Another issue of concern in this study, was that two different d-dimer assays were used in the study period, i.e. the NycoCard D-dimer (Nycomed Pharma, Oslo, Norway) and the STA®Liatest® D-Di FM from Stago (Diagnostica Stago, Asniereès, France). The two tests are principally different as the NycoCard assay is based on the immunometric flow-through principle, whereas the Sta-Liatest is based on the immunoturbidimetric method. The Sta-Liatest has consistently been reported to produce excellent analytical properties (279-281), whereas conflicting results exist regarding the NycoCard d-dimer assay (282-284). Analytical differences between these tests could potentially have biased our results. However, the NycoCard d-dimer assay was used in the period 1994-1998, and the Sta-Liatest was used in the remaining period from 1998-2012. Over 90% of the VTE events occurred in the time-period in which the Sta-Liatest was used, and the majority of d-dimer measurements were therefore assessed using the Sta-Liatest. Furthermore, we performed sensitivity analysis restricted to include only measurements using the validated Sta-Liatest, which revealed no significant differences in our results, meaning that comprehensive misclassification due to poor analytical properties of the NycoCard assay is unlikely.

In summary, a low d-dimer measured at incident VTE diagnosis identified a quarter of the patients as having a low recurrence risk. Stratified analysis revealed that the association was particularly pronounced among those with a first DVT or an unprovoked index event. These findings suggest that d-dimer, measured at first VTE diagnosis could potentially be used to guide decisions on duration of antithrombotic therapy. However, this study has novel and unchallenged findings, and future studies are needed to confirm these results.

6. Conclusions

→ We found that hospitalization was a major trigger factor for VTE, and that the risk mainly depended on the length of hospital stay rather than the exposure frequency (i.e. the number hospitalizations). Furthermore, hospitalization was a major trigger also in the absence of immobilization, although, the VTE risk among hospitalized patients was augmented by concurrent immobilization, putting further emphasis on hospitalization as a high-risk situation even in the absence of immobilization.

→ We found that the rates of adverse events following a first VTE remain high, despite recent advances in the diagnosis and management of VTE patients. VTE recurs at particularly high rates in the first year following diagnosis. However, the rates remain high for at least 10-years following the index event, supporting the notion that VTE is a chronic disease with a high recurrence risk.

→ The risk of recurrence after a first hospital-related VTE appeared to be dependent on the reason for hospital-admission in conventional Cox modelling. However, competing risk analysis revealed a considerable overestimation due to the competing risk of death, especially in patients with cancer-related VTE. Our findings suggest, that patients with incident VTEs related to hospitalization for medical illness other than cancer or surgery, are at particularly high recurrence risk, even in the presence of competing risk of death. These findings could imply that prolonged treatment regimens similar to those recommended for unprovoked VTE might be warranted among these patients.

→ A low d-dimer (≤ 1500 ng/mL) measured at incident VTE diagnosis was associated with a low recurrence risk in a quarter of the VTE patients. The association was particularly pronounced among patients with incident DVT and in those with an unprovoked first VTE. Our findings suggest that d-dimer, measured at first VTE diagnosis, may be used to identify VTE patients at low risk of recurrence and guide decisions on short-term treatment in these patients. However, these findings needs to be confirmed in future studies.

7. Final remarks and future perspectives

Hospitalization is widely acknowledged as a high-risk situation with respect to VTE. However, the underlying mechanisms have not been fully elucidated, and hospital-related VTE remains a major challenge. Although mandatory risk assessment programs upon hospital-admission have reduced the rates of hospital-associated VTE (126, 127), current risk assessment strategies do not embrace all patients at risk, as around half of all VTE cases remains associated with current or recent hospitalization (28, 104). Current guidelines recommend thromboprophylaxis during the period of immobilization or hospitalization in acutely ill hospitalized medical patients at increased risk of thrombosis, but recommend against extending prophylaxis beyond the initial period of immobilization or hospital stay (285, 286). However, the findings in this thesis emphasize a high VTE-risk also in hospitalized patients without concurrent immobilization. Furthermore, the VTE-risk extends beyond hospital-discharge, as a large proportion of hospital-related VTE cases occur after hospitalization (104, 110, 287, 288). Importantly, all these events might be considered secondary and therefore largely preventable. Extended duration thromboprophylaxis (EDT) beyond hospital-discharge mitigate the VTE-risk in hospitalized medical patients, although at the expense of increased rate of major bleeding to such a degree that EDT is not universally warranted in unselected medical patients (289-298). Consequently, there is a large potential to reduce the burden of VTE by means of improved prevention strategies among hospitalized patients, as well as in the initial period following hospital-discharge. However, there is urgent need for accurate risk stratification tools to identify subgroups of hospitalized patients with a positive risk-benefit ratio for EDT without the excess risk of bleeding.

Recent advances in the diagnosis and treatment of VTE may have improved the short-term outcomes after VTE. However, our findings, in accordance with those of others (35, 145, 147, 149, 151, 152, 299), show that the rates of recurrence and death remain particularly high in the following year after a first VTE diagnosis. Importantly, the rates also remain high in the long-term, as more than two-thirds of all recurrent VTE cases accumulate in the subsequent decade. Although there are prospects of novel anticoagulant agents which do not promote any bleeding risk (300, 301), currently, the ultimate challenge in the treatment and prevention of VTE is to identify the optimal equipoise of anticoagulant therapy. Current guidelines recommend short-term (3 months) over indefinite anticoagulant treatment in patients with a VTE provoked by a non-surgical transient risk factor (157). Recent studies emphasize the

diversity of recurrence risk also within subgroups of provoked and unprovoked VTE (178, 198, 199), meaning that this dichotomy might not be clinically useful and more refined risk stratification is necessary (302). Considering our findings, that VTE related to medical conditions might invoke a more persistent recurrence risk, prolonged treatment similar to that recommended for unprovoked VTE might be justified. Furthermore, the introduction of DOACs has improved the safety and convenience of anticoagulation, which could entail an improved benefit-to-harm ratio in favor of prolonged anticoagulation.

Identification of VTE patients at high risk of recurrence is extremely challenging, particularly among those with unprovoked VTE. Existing risk assessment models (RAMs) to distinguish patients with unprovoked VTE at high and low risk of recurrence have low predictive capability and ease of use, and are therefore of limited clinical utility. Genetic risk scores for recurrence prediction show promise (204, 206, 208), as do some biomarkers, although none have yet prevailed. Combining a GRS with biomarkers and clinical characteristics in future RAMs could improve recurrence prediction, and would ideally, also offer integrated bleeding risk assessment. Our findings of a low recurrence risk in patients with a low d-dimer at the time of first VTE diagnosis could potentially be useful in such RAMs, as it is widely available already at the time of VTE diagnosis, and would provide the opportunity to make definite decisions on treatment duration upon hospital-discharge. However, these are novel findings that has to be confirmed in future studies. We are currently working on externally validating these findings in collaboration with a research team within the Østfold Hospital Trust.

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Full Length Article

Hospitalization as a trigger for venous thromboembolism – Results from a population-based case-crossover study

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ABSTRACT

Background: Previous studies have reported that around 50% of patients with venous thromboembolism (VTE) has undergone recent hospitalization. However, studies on the impact of hospitalization as a trigger factor for VTE are limited.

Objectives: To investigate the impact of hospitalization with and without concurrent immobilization as a trigger factor for VTE.

Methods: We conducted a case-crossover study of 530 cancer-free VTE patients. Hospitalizations were registered during the 90-day period preceding the VTE diagnosis (hazard period), and in four preceding 90-day control periods. A 90-day washout period between the control- and hazard periods was implemented to avoid potential carry-over effects. Conditional logistic regression was used to calculate odds ratios (OR) of VTE according to hospitalization.

Results: In total, 159 (30%) of the VTE-patients had been hospitalized in the hazard period, and the OR of hospitalization was 9.4 (95% CI: 6.8–12.8). The risk increased slightly with the total number of days spent in hospital (OR per day: 1.11, 95% CI: 1.04–1.18), and with the number of hospitalizations (OR 8.9, 95% CI: 6.4–12.4 for 1 hospitalization and OR 12.3, 95% CI 6.4–23.6 for ≥2 hospitalizations). Hospitalization without immobilization was 6-times (OR: 6.3, 95% CI: 4.4–9.2) more common, whereas hospitalization with immobilization was near 20-times (OR: 19.8, 95% CI: 11.5–34.0) more common in the 90-days prior to a VTE compared to the control periods.

Conclusions: Hospitalization is a major trigger factor for VTE also in the absence of immobilization. However, immobilization contributes substantially to the risk of VTE among hospitalized patients.

1. Introduction

Venous thromboembolism (VTE), a conceptual term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with severe complications [1–5]. Population based studies have indicated that around 40–60% of the VTE cases can be attributed to current or recent hospitalization or nursing home residency [5,6]. Case-control studies have reported a 7 to 21-fold increased risk of VTE following recent hospitalization [7,8]. Moreover, a longitudinal study from Olmsted County (US), reported that the risk of experiencing a first or recurrent VTE was 35-fold increased during the 92 days following a hospitalization [9]. Although hospitalization is acknowledged as a risk factor for VTE, the role of hospitalization as a trigger factor for VTE has not been extensively studied.

Hospitalization is often accompanied by immobilization. Immobilization is associated with a 2 to 11-fold increased risk of VTE among hospitalized patients [10,11], and up to 25% of medical patients developing a hospital-related VTE has been shown to be immobilized preceding the event [12,13]. Thus, the increased risk of VTE observed in hospitalized patients may be partly explained by immobilization. Most previous studies have not been able to disentangle this relationship due to lack of information on immobilization, and some studies have even used hospitalization as a proxy for immobilization [14]. The influence of immobilization on the risk of hospital-related VTE, and to what extent hospitalization without concurrent immobilization serves as a trigger of VTE, have not been well addressed.

In the present study, we set out to investigate the impact of hospitalization as a trigger of VTE, and to explore the influence of

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immobilization on this relationship in a population-based case-crossover study of VTE patients. We also investigated the influence of hospital-related factors, such as length of hospital-stay and frequency of hospital admissions, on the risk of VTE. Our hypothesis was that hospitalization is a major trigger for VTE also in the absence of immobilization, and that the triggering effect is influenced by the length of hospital-stay and the frequency of hospital-admissions.

2. Methods

2.1. Study population and outcome assessment

The source population comprised of subjects participating in the fourth survey of the Tromsø study, a single-center, population based, prospective cohort study, with repeated health surveys of the inhabitants in the municipality of Tromsø, Norway. The fourth survey was conducted in 1994/95, and included 27,158 inhabitants above 24 years. Further details about the Tromsø study can be found elsewhere [15]. All participants gave an informed written consent, and the study was approved by The Regional Committee of Medical and Health Research Ethics. Participants were followed from the inclusion date (1994/95) through December 31, 2012, and all first-lifetime symptomatic, objectively confirmed VTE events (n = 707) during the course of follow-up were recorded by thorough identification and validation as previously described [16]. These 707 patients formed the basis of our case-crossover study.

2.2. Study design

In the case-crossover design, each case serves as his or her own control (self-matching), thereby controlling for risk factors that are constant within an individual (e.g. inherited thrombophilia), but vary between study objects. We defined the 90-day period prior to the VTE as the hazard period, and 4 consecutive 90-day periods preceding the hazard period as control periods (C1–C4). A 90-day wash-out period was implemented between the risk and control periods, to avoid potential carry-over effects (Fig. 1). This allows for comparison of exposure-frequency in the hazard period to control periods, and makes the design especially suited to study the effect of transient exposures (e.g. hospitalization) on acute events (e.g. VTE). Patients with cancer in the hazard period were excluded (n = 177), as cancer progression may change an individual's VTE risk even over a short time-period, and thereby potentially introduce confounding. Consequently, 530 cancer-free VTE patients were included in our case-crossover study.

2.3. Measurements

Trained personnel reviewed the medical records for each VTE case, and systematically collected information on potential trigger factors for each of the 90-day periods using standardized forms. Moreover, diagnostic procedures, surgical and medical treatment, laboratory tests and diagnosis during hospital admissions, day-case and outpatient clinic visits in any of the control or hazard periods were recorded. Exposures extending over several days, were registered and considered to have occurred if any of the days of exposure fell within the specified 90-day period.

Hospitalization was defined as being admitted to the hospital for > 48 h in the control or hazard periods. Hospital admissions > 80 days were not registered as hospitalizations, as these were likely to be admitted to rehabilitation wards. The date of hospital admission and hospital discharge was used to estimate the length of hospital stay for each hospital contact. Re-admissions during each 90-day period were registered individually, and the total number of hospitalizations and total number of days spent in hospital was calculated for each 90-day period. Hospitalizations were categorized according to the main diagnosis assigned by the treating physician(s) using the 9th and 10th revisions of *the International Classification of Diseases and Related Health Problems* (ICD-9 and ICD-10). Each hospital admission was assessed individually, and patients could therefore contribute with multiple hospitalizations within each case or control period. Patients were classified in 7 broad categories, i.e. infection, chronic obstructive pulmonary disease (COPD), heart failure, acute coronary syndrome (ACS), neurologic disease, surgery (i.e. both major or minor, or admission to any surgical ward) or trauma, and others.

Immobilization was defined as the presence of one or more of the following; confinement to bed ≥3 days, ECOG score of four, or other immobilizing factors specified in the patient's medical record (e.g. transient or persistent use of wheelchair, cast immobilization, etc.). CRP was analyzed in serum with a particle-enhanced immunoturbidimetric assay at the Department of Clinical Chemistry.

2.4. Statistical analysis

All statistical analysis were performed using STATA version 14.0 (Stata Corporation LP, College Station, Texas, USA). Baseline characteristics are given as means ± 1SD or percentages. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CI) for hospitalization in the hazard and control periods, as well as for the influence of duration of hospital stay and number of hospital admissions on the risk of VTE. Duration of hospital stay was analyzed as a continuous variable, and the OR was expressed per 1-day increase in hospital stay. To separate the effect of total days in hospital from frequency of admissions on the VTE risk, we performed a separate analysis adjusting the number of hospital admissions for the length of hospital stay. In order to address the impact of hospitalization as a trigger in the absence of immobilization, we performed an analysis

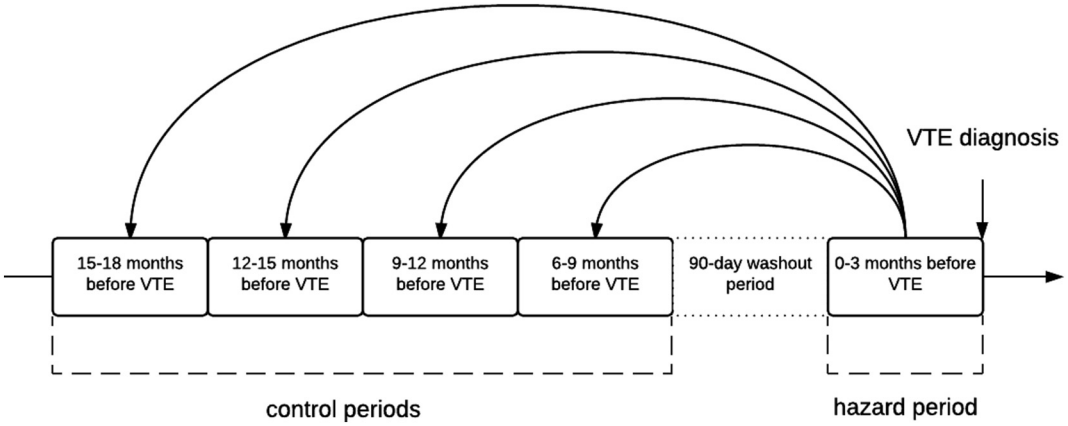

Fig. 1. The case-crossover study design.

Table 1
Characteristics of venous thromboembolism (VTE) patients (n = 530).

Age (years)	68.4 ± 14.0
Sex (% women)	54.2 (287)
Obesity (% obese)	17.7 (94)
Deep vein thrombosis (%)	55.8 (296)
Pulmonary embolism (%)	43.0 (228)
Location at VTE onset	
Community	84.0 (445)
Hospital	10.6 (56)
Nursing home	5.4 (29)

Values are means ± 1 SD or percentages with numbers in brackets.

with exposure categorized as not hospitalized, hospitalized without immobilization and hospitalized with immobilization. Since surgery is recognized as a strong trigger for VTE, we performed a separate analysis restricted to patients who did not have surgery.

Hospitalization with immobilization could possibly reflect a more severe underlying condition and a worse health condition in general. To test this hypothesis, we estimated the mean maximum CRP-level (mg/L) during hospitalization in patients with and without immobilization, as a proxy for the inflammatory state. Furthermore, to examine the potential role of confounding by occult cancer, we performed sensitivity analysis excluding patients who developed cancer in the following year after VTE.

3. Results

Characteristics of the 530 VTE patients are given in Table 1. The mean age was 68 years, 54.2% were women and 17.7% were obese. There were 296 (55.8%) DVTs and 228 (43.0%) PEs with or without concurrent DVT. Among the VTE's, 84.0% (445) were community acquired, 10.6% (56) acquired their VTE in-hospital, and 5.4% (29) were nursing home residents. An overview of the categorization of hospital admissions according to the main diagnosis assigned by the treating physician in the hazard and control periods is provided in Table 2. There were no substantial differences in the reason for hospitalization in the hazard compared to the control periods, except that hospitalization with heart failure was more common in the hazard period than in control periods (4.0% vs. 0.6%).

The OR according to hospitalization, length of hospital stay and number of hospitalizations, in hazard and control periods are shown in Table 3. Overall, 30.0% (n = 159) of the patients had been hospitalized at least once in the hazard period (n = 530), compared to 6.2% (n = 132) in the control periods (n = 2120). The hospital admissions were evenly distributed among the four control periods, with 5.9% (n = 31) occurring in C1, 5.5% (n = 29) in C2, 6.4% (n = 34) in C3 and 7.2% (n = 38) in C4, respectively. Multiple hospitalizations were more common in the hazard period than in the control periods (5.5% vs. 1.6%), and patients were generally hospitalized for a longer time in the hazard period than in the control periods (median of 11 days, IQR: 6–18 vs. median of 6 days, IQR: 3–12). The OR for hospitalization as a trigger of VTE was 9.4 (95% CI: 6.8–12.8) (Table 3). The OR increased according to the number of hospitalizations within each period from 8.9 (95% CI: 6.4–12.4) in those with one hospitalization to 12.3 (95% CI 6.4–23.6) in those with ≥2 hospitalizations. After adjusting the number of hospitalization for the total number of days spent in hospital, there was no significant difference in the VTE risk between those with one compared to patients with two or more hospitalizations (OR: 1.8, 95% CI: 0.6–5.2). Overall, there was an 11% increased odds per one day increase in the total number of days spent in hospital (OR: 1.11, 95% CI: 1.04–1.18), and the OR for hospitalization ≥5 days was 5.2 (95% CI: 1.8–15.1), compared to patients hospitalized for 1–4 days (Table 3). These results remained unchanged after adjustment for the frequency of hospital admissions (data not shown).

Table 2
Characteristics of hospitalizations in case and control periods.

	Control period (n = 158)	Hazard period (n = 201)
Infection	15.8% (25)	13.4% (27)
COPD[a]	4.4% (7)	2.5% (5)
Heart failure	0.6% (1)	4.0% (8)
Acute coronary syndrome	9.5% (15)	6.0% (12)
Neurologic disease	9.5% (15)	8.5% (17)
Surgery or trauma	32.9% (52)	34.3% (69)
Others	27.2% (43)	31.3% (63)

Values are percentages with numbers in brackets.
[a] COPD: chronic obstructive pulmonary disease.

The ORs according to hospitalization with and without immobilization are shown in Table 4. Overall, 74 (46.5%) of the 159 patients hospitalized in the hazard period were considered to be immobilized, compared to 34 (25.8%) of the 132 patients hospitalized in the control periods. Hospitalization without immobilization was 6-times (OR: 6.3, 95% CI: 4.4–9.2) more common, whereas hospitalization with immobilization was near 20-times (OR: 19.8, 95% CI: 11.5–34.0) more common in the 90-days prior to a VTE compared to the control periods. The results were essentially similar when the analyses were restricted to those who did not have surgery in the hazard period, with an OR of 5.0 (95% CI: 3.2–7.9) and 14.4 (95% CI: 7.4–27.9) for hospitalization without and with immobilization, respectively (Table 4).

Immobilization during the hospital stay could reflect a more severe underlying condition, and therefore we recorded the maximum CRP levels measured during the hospital stay for each patient. The mean maximum CRP-level was 109 ± 96 mg/L in hospitalized patients who were immobilized and 82 ± 89 mg/L in hospitalized patients who were not immobilized. Sensitivity analysis excluding patients who developed cancer in the following year (n = 18) after VTE produced essentially similar results (data not shown).

4. Discussion

In the present case-crossover study, we found that hospitalization was a major trigger associated with a 9-fold higher risk of VTE. The triggering effect of hospitalization was mainly dependent on the length of hospital stay, but not the frequency of hospital admissions. The risk of VTE increased with 11% per one day increase in total days spent in hospital during the 90-day hazard period, and the risk was 5-fold in those with hospital admissions for ≥5 days compared to those with shorter hospital stays (i.e. 1–4 days). Furthermore, we found that hospitalization without immobilization was over 6-times more common, and that hospitalization with immobilization was near 20-times more common, in the 90-day period preceding a VTE compared to the control periods. The results were comparable when the analyses were restricted to patients who did not undergo surgery. Our results indicate that hospitalization is a major trigger factor for incident VTE also in the absence of immobilization. Moreover, our findings confirm that concomitant immobility increases the risk of VTE among hospitalized patients.

Several studies have investigated hospitalization as a risk factor for VTE. In a nested case-control study of 625 patients with a first lifetime VTE and 625 patients without VTE, hospital or nursing home confinement (institutionalization) was an independent risk factor for VTE, with an OR of 8.0 [7]. When the analysis was stratified according to institutionalization with or without recent surgery, the odds of VTE was almost 22-fold and 8-fold increased, respectively, compared to patients with neither institutionalization nor recent surgery. In the AT-AGE study, a case-control study of elderly individuals, hospitalization was associated with an almost 15-fold increased risk of VTE within the first 2 weeks after hospital-discharge [8]. The risk was similar in surgery-

Table 3
Odds ratios (ORs) of exposure in hazard period as compared to control periods.

	Control periods (n = 2120)	Hazard period (n = 530)	OR (95% CI)	OR[c] (95% CI)
Hospitalized (n)	132	159	9.4 (6.8–12.8)	
Length of hospital stay (IQR)[a]	6 (3 − 12)	11 (6–18)	1.11 (1.04–1.18)	
Hospital stay ≥5 days[b]	75	134	5.2 (1.8–15.1)	
Number of hospitalizations				
0	1988	371	Ref.	
1	109	130	8.9 (6.4–12.4)	Ref.
≥2	23	29	12.3 (6.4–23.6)	1.8 (0.6–5.2)

[a] Median (interquartile range, IQR).
[b] Compared to patients hospitalized for 1–4 days.
[c] Adjusted for the length of hospital stay.

Table 4
Odds ratios (ORs) of VTE according to hospitalization with and without immobilization.

	Control periods	Hazard period	All	Restricted to non-surgical[a]
	(n = 2120)	(n = 530)	OR (95% CI)	OR (95% CI)
Not hospitalized	1988	374	Ref.	Ref.
Hospitalized without immobilization	98	85	6.3 (4.4–9.2)	5.0 (3.2–7.9)
Hospitalized with immobilization	34	74	19.8 (11.5–34.0)	14.4 (7.4–27.9)

[a] Analysis restricted to patients hospitalized for reasons other than surgery.

and non-surgery-related hospitalizations (OR: 6.6 and 5.5, respectively), when compared to individuals without hospitalization. Furthermore, in a recent cohort study with hospitalization as a time-varying covariate, the risk of VTE was 35-fold increased in the period up to 92 days following a hospitalization [9].

Case-crossover studies are suitable to study triggers of acute diseases, since they are designed to answer the question “why did this disease occur right now?”. This is in contrast to case-control and cohort studies which compare the risk between individuals, and thereby are designed to answer the question “why me?”. Although previous studies have addressed hospitalization as a risk factor for VTE, few studies have investigated the role of hospitalization as a trigger of VTE using a case-crossover design. In one previous case-crossover study, any non-surgical hospitalization or skilled nursing home facility stay was found to be a significant trigger associated with a 4.2-fold higher risk of VTE [14]. Interestingly, adjustment for other hospital-related factors like major surgery, infection, blood transfusion, use of central venous catheters, injuries and medication, did not markedly influence the risk estimates, even though many of these factors most likely are in the causal pathway.

Few observational studies have evaluated the influence of length of hospitalization and frequency of hospital admissions on the risk of VTE. In a case-control study of older adults (≥60 years) [17], Yousuf et al. found that hospitalization for 4–6 days and for ≥7 days was associated with a 2.4- and 3.4-fold increased risk of VTE compared to patients who were hospitalized for 0–3 days. In a matched case-control study of outpatients with a VTE diagnosis during the 90-days following hospital discharge [18], increasing number of hospitalizations and increasing length of hospital stay was both associated with post-discharge VTE diagnosis. The VTE risk doubled for each additional hospital-admission and increased by 17% for each additional day spent in the hospital. In the present study, we found that the risk of VTE increased with 11% per one day increase in total days spent in hospital during the 90-day hazard period, and the risk was 5-times higher in those with hospital admissions ≥5 days compared to 1–4 days. Conversely, we did not find any substantial differences in the VTE-risk in those with multiple hospitalizations compared to those with a single hospitalization prior to their VTE. Furthermore, after conditioning on the length of hospital stay there was no differences in the risk of VTE in those with one compared to ≥2 hospitalizations, placing further emphasis on hospitalization as a high risk situation that is mainly dependent on the length of hospital stay rather than the frequency of admissions.

Immobilization is a strong trigger of VTE which often concurs with hospitalization. Few studies have been able to disentangle the effect of immobilization from that of hospitalization, and hospitalization has frequently been used as a proxy for immobilization when studying the risk of VTE, as high-quality data on immobilization is often lacking. A previous meta-analysis on immobilization and VTE-risk among hospitalized inpatients reported a relative risk of 1.5 across 7 cohort studies and an OR of 2.5 across 3 case-control studies [10]. In our study, hospitalization with immobilization was 3-times more common prior to a VTE than hospitalization without immobilization, supporting that immobilization contributes substantially to the risk of VTE among hospitalized patients. In agreement with our findings, two previous case-control studies on elderly patients, reported that immobility mediated the risk of VTE in a dose-response related manner, depending on both the type and duration of immobility [19], and that the risk was highest among patients who were bedridden in hospital [8,19]. Our study showed that hospitalization without immobilization was 6-times more common prior to a VTE compared to equivalent control periods. This highlights that hospitalization is a high-risk situation even in the absence of immobilization, and that thromboprophylaxis should be considered also among non-immobilized patients. The VTE risk associated with hospitalization is dependent on the reason for hospitalization (e.g. surgery, cancer, infections or acute medical conditions) [6,20–23], as well as patient-related risk factors (e.g. age, obesity, comorbidities and genetic risk profile) [20–23]. Moreover, the risk can be directly related to the number of risk factors present [20,22,24], as thrombosis develops once the accumulation of risk factors in an individual is sufficient to exceed the thrombosis threshold [25]. Appropriate risk stratification among hospitalized patients is therefore challenging, and further research is needed to develop risk stratification models that can accurately identify subjects at high risk of hospital-related VTE.

In addition to being a risk factor in itself, immobilization may reflect a more severe underlying disease and a generally worse health condition. Accordingly, we found a higher mean CRP-level in hospitalized patients who were immobilized compared to hospitalized patients who were not immobilized, indicating that there could be a difference in disease severity among these patients. Consequently, there could also

be differences in the use of thromboprohylaxis in patients with and without restricted mobility, as immobilized patients with severe conditions are more likely to receive anticoagulant treatment. In the present study, 36.1% of the patients who were hospitalized without being immobilized, and 50.9% of those who were hospitalized with immobilization prior to their VTE received thromboprophylaxis, suggesting that our risk estimates may have been underestimated. Our data strongly indicates confounding by indication for thromboprophylaxis. Consequently, we could not adjust our analysis for thromboprophylaxis as this would introduce bias.

There are several strengths of the present study. The case-crossover design is especially suited to study triggers of disease, as information on different exposures are collected for several pre-defined time periods, allowing for comparison of exposure and exposure frequencies across different time periods in relation to the disease. Furthermore, since each subject serves as its own control, potential confounders such as chronic diseases and conditions are controlled for by the design. The present study included a large sample size of VTE patients recruited from a general population, which strengthens the external validity of our results. Moreover, the case-crossover design may partly adjust for the heterogeneity of the hospitalized population, as each subject serves as his/her own control [26]. In contrast to many other studies, we had information on immobilization during the hospital stay. A limitation of the case-crossover design is that it is susceptible to confounding by factors that change over time within individuals. However, this can be minimized by fitting the control periods as close to the hazard periods as possible. Moreover, all information in this study was collected retrospectively using hospital records, and the data therefore relies on thorough registration by the treating physicians and other health care professionals. Consequently, any other factors not accounted for in the medical records could potentially have influenced our results. Occult cancer could be a potential confounder in this study. However, sensitivity analysis excluding patients who developed cancer in the following year after VTE produced essentially similar results, indicating a low probability of confounding by occult cancer.

In conclusion, hospitalization is a major trigger factor for VTE also in the absence of immobilization. However, immobilization contributes substantially to the risk of VTE among hospitalized patients. Furthermore, the hospital-associated risk of VTE is mainly dependent on the length of hospital stay rather than the frequency of admissions. Our findings highlight that hospitalization is a high-risk situation also among patients who are not immobilized.

Addendum

E. Bjøri: data analysis and writing of manuscript. H.S. Johnsen: data interpretation and revision of content. J.B. Hansen: conception and design of study, data collection and interpretation, and writing of manuscript. S.K. Brækkan: conception and design of study, data collection and interpretation, and writing of manuscript.

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Disclosures

None.

Conflict of interest

The authors declare no conflicts of interest.

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Paper II

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ORIGINAL ARTICLE

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

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Essentials

- Reports on recurrence and mortality after a first venous thromboembolism (VTE) vary considerably.
- We describe rates of recurrence and mortality in patients with a first VTE from the Tromsø study.
- The overall recurrence rate was 3.9 per 100 person-years, but this varied widely with time.
- Despite advances in VTE management, the rates of adverse events are still fairly high.

Summary. *Background:* Previous reports on recurrence and mortality rates after a first episode of venous thromboembolism (VTE) vary considerably. Advances in the management and treatment of VTE during the last 15 years may have influenced the rates of clinical outcomes. *Aim:* To estimate the rates of recurrence and mortality after a first VTE in patients recruited from a large population-based cohort. *Method:* From the Tromsø study, patients (n = 710) with a first, symptomatic, objectively confirmed VTE were included and followed in the period 1994–2012. Recurrent episodes of VTE were identified from multiple sources and carefully validated by review of medical records. Incidence rates and cumulative incidence rates with 95% confidence intervals (CIs) of VTE recurrence and mortality were calculated. *Results:* The mean age of the patients was 68 years (range 28–102 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 0.04–18.2 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 person-years (PY), whereas the recurrence rate in the remaining follow-up period (1–18 years) was 3.0 (95% CI 2.4–3.8) per 100 PY. 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. *Conclusion:* Despite advances in VTE management, the rates of adverse events remained fairly high, particularly in the first year following a first VTE.

Keywords: cancer; epidemiology; mortality; recurrence; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) is a common term for deep vein thrombosis (DVT) and pulmonary embolism (PE). The annual incidence of VTE is approximately 1–3 per 1000 in the adult population of high-income countries [1–4], and the risk increases exponentially with age [5]. With high rates of recurrence and mortality, as well as increased long-term morbidity and functional disability, VTE remains a major public health concern with a substantial disease burden [6].

Previously reported rates of recurrence and survival after a first VTE vary widely, ranging from 0.6% to 5% at 30 days, and from 25% to 40% at 10 years, for VTE recurrence [3,7–16], and from 77% to 97% at 1 week, and from 61% to 75% at 8 years, for survival [3,7,16–18]. The differences in the reported rates may, to some extent, be ascribed to differences in study design (e.g. clinical trials, cohorts or registry databases with limited case validation), clinical setting (hospital or community setting), and the time period over in which the study was conducted. Advances in diagnostics, management and treatment of VTE in recent years may have influenced the rates of adverse outcomes after VTE. The introduction of low molecular weight heparins for the treatment of acute VTE in the early 1990s [19] has reduced the length of

hospital stays after VTE, and a larger proportion of the VTE cases are currently treated as outpatients [20,21]. Furthermore, increased awareness of VTE risk and the use of thromboprophylaxis in high-risk situations may have impacted on recurrence and mortality rates. Finally, the more widespread use of spiral computed tomography (CT) to diagnose PE, and the concomitant increased detection of subsegmental PE [22], may have influenced the overall outcome rates after a first VTE.

VTE is a multifactorial disease that occurs frequently in association with cancer and other comorbidities. A high mortality rate resulting from other conditions will result in an overestimation of the cumulative incidence of recurrence in patients with a first VTE, as death is a competing event [23,24]. Few studies have assessed and compared the cumulative incidence of recurrence in the presence of competing risk of death in subgroups of patients with a first VTE [25,26]. Moreover, many of the previous studies were carried out several decades ago [7,13,17], were restricted to either the hospital or community setting [7,15,27], or included their patients after completion of anticoagulant treatment (i.e. 3–12 months after the first event) [7,27,28]. We therefore aimed 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.

Methods

Study population

Patients with a first lifetime VTE were recruited from the fourth survey of the Tromsø Study, a population-based cohort study in which 26 855 subjects age 25–97 years were enrolled in 1994–1995 and followed up to December 2012, as previously described in detail [29]. The study was approved by the regional committee for research ethics, and all participants gave their informed, written consent to participate. In total, 710 incident symptomatic VTE cases were included in the study. Recurrent VTE events and all-cause mortality among the incident cases were recorded until the end of follow-up on 31 December 2012.

Identification and validation of VTE

All first lifetime episodes of VTE were identified by searching the hospital discharge registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway, from the date of enrolment in the Tromsø Study (1994–1995) to 31 December 2012. The University Hospital of North Norway is the only hospital in the region, and all hospital care and relevant diagnostic radiology for VTE in the Tromsø community is provided exclusively by this hospital. We used a broad search strategy, and the relevant discharge codes were ICD-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994–1998, and ICD-10 codes I26, I67.6, I80, I81, I82, O22.3, O22.5, O87.1 and O87.3 for the period 1999–2012. The hospital discharge registry included both outpatient clinic visits and hospitalizations. An additional search of the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE, either as a cause of death or as a significant condition, were identified. We also searched the radiology database in order to identify potential cases of symptomatic objectively confirmed VTE that may have been missed because of coding errors in the hospital discharge registry. Trained personnel systematically reviewed all relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during the 18-year period, and cases with objectively confirmed VTE were identified.

The medical records for each potential VTE case derived from the hospital discharge registry, the autopsy registry and the radiology procedure registry were reviewed by trained personnel for case validation. 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: (i) signs and symptoms consistent with DVT or PE were present; (ii) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral CT, perfusion–ventilation scan, pulmonary angiography, or autopsy); (iii) the medical record indicated that a physician had made a diagnosis of DVT or PE; and (iv) the patient received treatment with anticoagulants (heparin, warfarin, or a similar agent), thrombolytics, 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 the cause of death or as a significant condition contributing to death.

A VTE event was classified as cancer-related, provoked, or unprovoked, 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). Non-melanoma skin cancer (ICD-10 code C44) was not registered as cancer. VTEs occurring in patients with active cancer were classified as cancer-related regardless of other risk factors. In patients without cancer, a VTE occurring in the presence of one or more provoking factors was defined as provoked. The following were regarded as provoking factors: recent hospitalization, surgery, or trauma (within 8 weeks before the event), an acute medical condition (acute myocardial infarction, acute ischemic stroke, or acute infections), immobilization (bed rest for > 3 days, wheelchair use, or

long-distance travel for ≥ 4 h within the last 14 days), or another factor specifically described as provoking by a physician in the medical record (e.g. intravascular catheter). VTEs occurring in patients without cancer or any provoking factor were classified as unprovoked.

Outcomes

We recorded all VTE recurrences and deaths among the study participants during follow-up. 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.

Statistical analyses

Statistical analyses were carried out with STATA version 14.0 (Stata Corporation, College Station, TX, USA). Descriptive statistics for baseline data were reported as percentages or means (with standard deviations), as appropriate. For analyses of recurrence, the patients (n = 710) were followed from the date of their first VTE until the date of VTE recurrence, date of migration, date of death, or study end (31 December 2012), whichever came first. Crude recurrence rates were calculated by dividing the number of recurrent events by the total person-years (PY) at risk, and expressed per 100 PY. Moreover, recurrence rates were calculated for the various subtypes of VTE (cancer-related, unprovoked, and provoked) in different time intervals (0–6 months, 6 months to 1 year, 1–5 years, 5–10 years, and > 10 years) after the first event. 1-Kaplan–Meier estimates with 95% confidence intervals (CIs) were used to report the cumulative incidence of recurrence over time in men and women, and according to subtype and location (DVT and PE) of the index VTE. Cox proportional hazards regression was used to calculate the hazard ratios (HRs) of recurrence and mortality in men and women and according to the classification (cancer-related, provoked, and unprovoked) and localization (DVT and PE) of the first VTE adjusted for age and sex.

For analyses of mortality, subjects were followed from the date of the first VTE until the date of death or study end (31 December 2012). Subjects who died on the same day as the VTE (n = 18) were given 1 day of follow-up in the analyses. Crude mortality rates were calculated as the number of deaths divided by the total PY at risk, and expressed per 100 PY. Similarly, we estimated mortality rates according to type and localization of the first VTE in different time intervals, and Kaplan–Meier curves were used to visualize survival over time for men and women and according to subtypes of VTE.

The cumulative incidence of VTE recurrence is dependent on both the risk of recurrence and the risk of dying, and, consequently, recurrence risks are overestimated when the mortality rate is high. We therefore estimated the cumulative incidence of recurrence in the presence of competing risk of death by using the stcrreg and stcurve cif commands in STATA.

Results

Patient characteristics

The clinical characteristics assessed at the time of incident (n = 710) and recurrent (n = 114) VTE events are summarized in Table 1. The mean age at the time of the first

Table 1 Baseline and clinical characteristics of incident (n = 710) and recurrent venous thromboembolism (VTE) cases (n = 114); the Tromsø Study 1994–2012

Variables	Incident (n = 710)	Recurrent (n = 114)
Age (years), mean ± SD	68.7 ± 13.5	70.6 ± 12.0
Gender (male), no. (%)	329 (46.3)	61 (53.5)
PE, no. (%)	295 (41.5)	46 (40.3)
DVT, no. (%)	415 (58.4)	68 (59.6)
Proximal leg DVT, no. (%)	314 (44.2)	58 (50.8)
Calf vein DVT, no. (%)	131 (18.4)	19 (16.6)
VTE at other site, no. (%)	32 (4.5)	4 (3.5)
Unprovoked, no. (%)	295 (41.5)	55 (48.2)
Cancer-related, no. (%)	166 (23.3)	28 (24.5)
Treatment duration with AC (months), no. (%)		
0–3	247 (34.7)	29 (25.4)
3–6	229 (32.2)	13 (11.4)
6–12	137 (19.2)	14 (12.2)
> 12	65 (9.1)	53 (46.5)
Provoking factors, no. (%)		
Acute medical condition *,†	102 (14.3)	13 (11.4)
Surgery†	107 (15)	12 (10.5)
Trauma†	56 (7.9)	3 (2.6)
Immobilization	135 (18.9)	20 (17.4)
Bed rest for ≥ 3 days	47 (6.6)	8 (7.0)
Long-haul travel‡	6 (0.8)	3 (2.6)
Other immobilization	82 (11.5)	9 (7.8)
Other provoking factor	36 (5.0)	5 (4.4)
One provoking factor	182 (25.6)	24 (21.1)
More than one provoking factor	99 (13.9)	11 (9.6)
Clinical risk factors, no. (%)		
Recent hospitalization†	288 (40.5)	45 (6.3)
Nursing home	39 (5.5)	8 (7)
Estrogen usage §	40 (5.6)	2 (1.7)
Heredity¶	20 (2.8)	3 (2.6)
Obesity	116 (16.3)	19 (16.6)
Comorbidity**	157 (22.1)	24 (21.0)
Pregnancy/puerperal period	3 (0.4)	–

AC, anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation. *Acute myocardial infarction, ischemic stroke, or major infectious disease. †Within 8 weeks prior to the VTE event. ‡Travel exceeding 4 h within the last 14 days. §Hormone replacement therapy/oral contraceptives. ¶Heredity: family history of VTE in first-degree relative before the age of 60 years. **Comorbidity within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).

VTE was 68.7 ± 13.5 years (range 28–102 years), and the proportion of men was 46.3%. Furthermore, 42% of the incident VTE events were classified as unprovoked, 23% as cancer-related, and 35% as being provoked by a factor other than cancer. The mean age at recurrence was 70.6 years (range 36–97 years), and the proportion of men was 46.5%. Among the recurrences, 48.2% were classified as unprovoked, 24.5% as cancer-related, and 27.3% as being provoked by factors other than cancer.

Recurrent VTE

Of the 710 incident VTE cases, 114 patients had a recurrent VTE event (PE in 46 and DVT in 68) during a median of 2.7 years of follow-up (range 1 day to 18.1 years). The overall recurrence rate was 3.9 (95% CI 3.3–4.7) per 100 PY; 4.5 (95% CI 3.5–5.8) in men, and 3.4 (95% CI 2.6–4.4) in women. The incidence rates of recurrence per 100 PY were 8.5 (95% CI 5.5–13.2) for cancer-related VTE, 3.4 (95% CI 2.5–4.7) for provoked VTE, and 3.6 (95% CI 2.7–4.6) for unprovoked VTE.

The recurrence rate varied widely during follow-up, as it was highest in the beginning and declined in later years. The overall recurrence rates per 100 PY were 9.2 (95% CI 6.2–13.3) in the first 6 months, 6.3 (95% CI 3.8–10.3) in the period 6 months to 1 year, 3.5 (95% CI 2.6–4.6) in the period 1–5 years and 2.3 (95% CI 1.5–3.7) in the 5–10 years after the index event (Table 2).

The cumulative incidence rates of overall VTE recurrence were 1.7% (95% CI 1.0–3.1) at 1 month, 4.3% (95% CI 3.0–6.2) at 6 months, 7.2% (95% CI 5.4–9.7) at 1 year, 18.8% (95% CI 15–22) at 5 years and 28.3% (95% CI 23–33) at 10 years of follow-up (Table S1). The 10-year cumulative incidence rates of recurrence were 35.4% in men and 22.0% in women (Fig. 1A), which corresponded to a 1.3-fold (95% CI 0.96–2.03) higher risk of recurrence in men than in women.

The cumulative incidence of VTE recurrence according to classification of the initial event is shown in Fig. 2A. The 5-year cumulative incidence rates were 17.9% in unprovoked, 16.7% in provoked and 26.4% in cancer-related VTE, respectively (Fig. 2A; Table S1). When competing risk of death was taken into account, the corresponding figures were 16.1% in unprovoked, 14.4% in provoked and 11.4% in cancer-related incident VTE (Fig. 2B).

The recurrence risk was higher in patients with initial DVT than in patients with PE throughout the 10-year period (Fig. 1B). The HR of recurrence was 1.4-fold higher (HR 1.45, 95% CI 0.96–2.18) in those with DVT than in those with PE. Furthermore, patients with a first PE were 2.4-fold more likely to develop a second PE rather than a DVT, and vice versa (Table 3). Among the 34 patients with a first PE, 24 (70.6%) had recurrent PE and 10 (29.4%) had recurrent DVT. Correspondingly, among the 80 patients with a first DVT, 22 (27.5%) had recurrent PE and 58 (72.5%) had recurrent DVT. Likewise, patients with a first unprovoked VTE were more likely to have their second event unprovoked (Table 4). Among those with a first unprovoked VTE, 66.7% experienced a second unprovoked event, 20.4% had a provoked VT, and 12.9% had a cancer-related VTE as the recurrent episode. Those with a first provoked VTE were just as likely to have a second provoked or unprovoked VTE (47.5% versus 45%, respectively), and 7.5% had a cancer-related VTE as the recurrent episode (Table 4).

All-cause mortality

During follow-up, 333 of the 710 VTE patients died. The overall mortality rate during a median of 3.4 years of follow-up (range 1 day to 18 years) was 9.7 per 100 PY (95% CI 8.7–10.8). The crude mortality rate was higher in women (11.0 per 100 PY, 95% CI 9.5–12.7) than in men (8.3 per 100 PY, 95% CI 7.1–10.0); however, the CIs overlapped. Correspondingly, the cumulative probability of survival beyond 10 years was higher in men (48.4%, 95% CI 41.5–55.0) than in women (41.1%, 95% CI 35.1–47.1) (Fig. 3A). The higher mortality rate among women was explained by their higher age at the

Table 2 Incidence rates (IRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) recurrence (per 100 person-years) in different time intervals after VTE and according to classification of the index VTE; the Tromsø Study 1994–2012

Time	Overall VTE *n* IR (95% CI)	Cancer-related VTE *n* IR (95% CI)	Provoked VTE* *n* IR (95% CI)	Unprovoked VTE *n* IR (95% CI)
0–6 months	27 9.2 (6.2–13.3)	9 17.8 (9.2–34.3)	11 10.4 (5.7–18.8)	7 5.0 (2.4–10.6)
6 months to 1 year	16 6.3 (3.8–10.3)	6 18.1 (8.1–40.3)	5 5.4 (2.2–13.0)	5 3.9 (1.6–9.4)
1–5 years	47 3.5 (2.6–4.6)	4 3.5 (1.3–9.5)	14 2.6 (1.5–4.4)	29 4.1 (2.8–5.8)
5–10 years	18 2.3 (1.5–3.7)	–	8 2.4 (1.2–4.8)	10 2.5 (1.3–4.7)
After 10 years	6 2.4 (1.0–5.3)	1 20.5 (2.8–145.9)	2 1.8 (0.4–7.5)	3 2.1 (0.6–6.7)

*Without cancer.

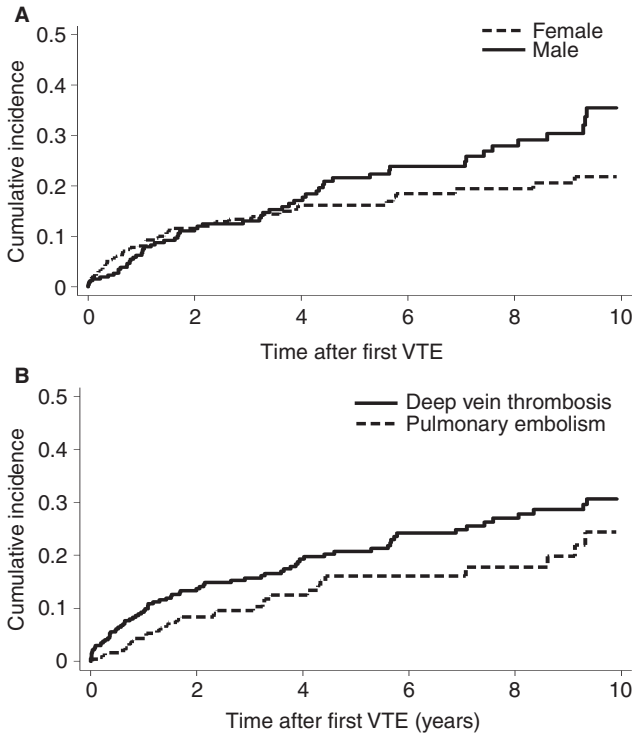

Fig 1. Cumulative incidence of venous thromboembolism (VTE) recurrence. (A) 1-Kaplan–Meier curves for men and women. (B) 1-Kaplan–Meier curves according to initial deep vein thrombosis and pulmonary embolism.

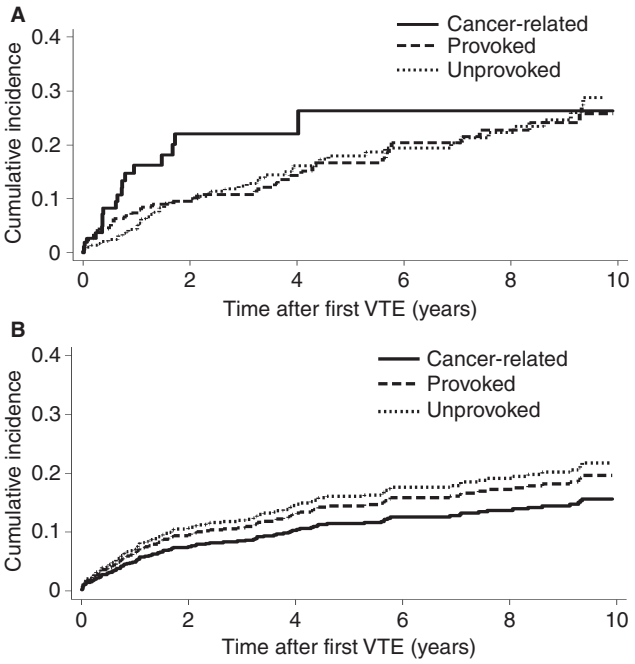

Fig 2. Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the index event. (A) 1-Kaplan–Meier curves. (B) Cumulative incidence after taking competing risk of death into account.

Table 3 Recurrence sites (%) according to site of the index venous thromboembolism

	Second event		
First event	Pulmonary embolism	Deep vein thrombosis	Total
Pulmonary embolism	24 (70.6)	10 (29.4)	34
Deep vein thrombosis	22 (27.5)	58 (72.5)	80
Total	46 (40.3)	68 (59.6)	114

Table 4 Classification of recurrences (%) according to the classification of the index venous thromboembolism

	Second event			
First event	Unprovoked	Provoked*	Cancer-related	Total
Unprovoked	36 (66.7)	11 (20.4)	7 (12.9)	54
Provoked*	18 (45.0)	19 (47.5)	3 (7.5)	40
Cancer-related	1 (5.0)	1 (5.0)	18 (90.0)	20
Total	55 (48.2)	31 (27.2)	28 (24.6)	114

*Without cancer.

index date, as the HR of death for men versus women changed from 0.78 (95% CI 0.63–0.97) to 0.96 (95% CI 0.77–1.21) after adjustment for age.

The mortality rate was highest in the first 6 months after the VTE event, and declined rapidly thereafter (Table 5). The 1-year mortality rate in patients with cancer-related VTE was 114.4 (95% CI 94.0–139.3) per 100 PY.

The cumulative incidence of all-cause mortality after VTE is shown in Table S2. The 10-year cumulative incidence of mortality was highest among those with cancer-related VTE (88.3%), and lowest among those with unprovoked VTE (41.5%) (Fig. 3B).

Discussion

The present study was conducted to determine recurrence and mortality rates after a first event of VTE in a cohort of patients recruited from the general population in the period 1994–2012, including both the community and hospital setting. The overall recurrence rate was 3.9 per 100 PY, but varied widely with time, from 9.2 per 100 PY in the first 6 months to 2.3 per 100 PY in the 5–10 years after the first VTE event. The overall 10-year cumulative incidence rates of recurrence were 35.4% in men and 22.0% in women. The cumulative incidence of recurrence was high among cancer patients, particularly in the first year (16.3%). However, after competing risk of death was taken into account, the cumulative incidence rates of recurrence were 4.9% at 1 year and 11.4% at 5 years in cancer patients, whereas the corresponding rates in non-cancer patients were 6.3% and 14.4%. The 30-day and 1-year cumulative all-cause mortality rates after VTE were 19.4% and 62.0% in cancer patients, and 9.0% and 16.6% in cancer-free patients, respectively.

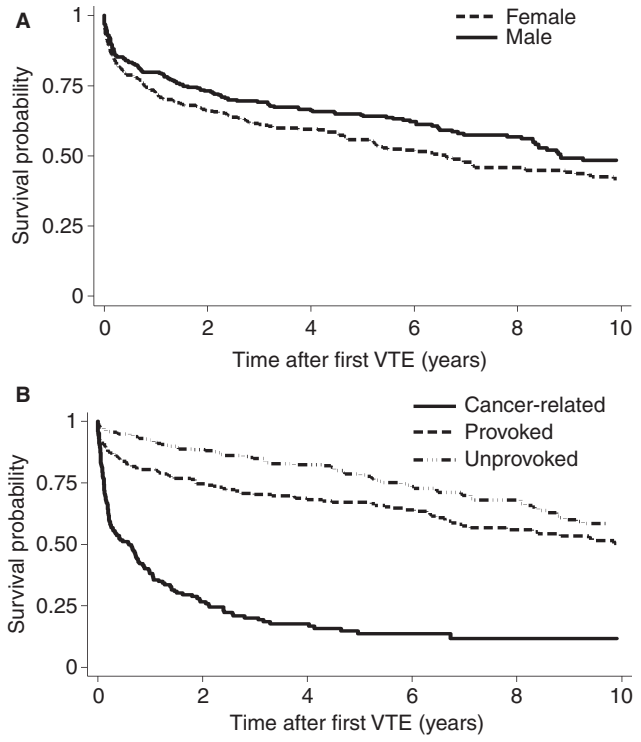

Fig 3. Survival probability after venous thromboembolism (VTE). (A) Kaplan–Meier curves in men and women. and (B) VTE by classification of the initial event.

Advances in diagnostic tools and the management and treatment of VTE in recent years may have influenced the outcome rates after a first VTE. Few studies have recently described this in a setting that covers provoked and unprovoked first events derived from both the hospital and community setting with long-term follow-up starting from the date of first VTE. Our recurrence rates were only marginally lower than those reported by Heit *et al.* [13], who investigated recurrence among 1791 patients with a first VTE in the period 1960–1999. They reported overall cumulative incidence rates of recurrence of 12.9% at 1 year and 30.4% at 10 years, whereas the corresponding numbers in our study were 7.2% and 28.3%. In the Worcester study [28], conducted in the period 1999–2003, the 1-year cumulative incidence of recurrence was 10.9%, but they did not report on long-term follow-up. Improved treatment strategies may, to some extent, explain the lower 1-year cumulative recurrence risk observed in our study than in the previous studies. Nevertheless, in the long term, our cumulative incidence of recurrence was similar to that in previous studies, suggesting a catch-up effect after the initial period [15,30]. Thus, despite advances in diagnosis and treatment in recent years, the rates of recurrence after VTE were still high, particularly in the long term.

The recurrence rate was highest during the initial 6 months after the VTE in all subgroups, despite the fact that most patients received anticoagulant therapy in this period. This highlights the importance of including patients at the time of the event, particularly for descriptive epidemiologic purposes, as studies that start their follow-up after the withdrawal of anticoagulants will lose a significant amount of cases that occur in the initial phase.

In agreement with previous studies [25,26], the 5-year cumulative risk of recurrence was highest among cancer patients. The mortality rate is high among cancer patients, and, in the presence of competing risk of death, the cumulative incidence of recurrence is dependent on both the risk of recurrence and the risk of dying [23,24,31]. Therefore, when competing risk of death was taken into account, the estimated 5-year cumulative risk of recurrence changed from 26.4% to 11.4% in cancer patients, and the risk of recurrence in cancer patients was actually lower than in those with unprovoked and provoked VTE (16.1% and 14.4%, respectively).

In our study, patients with a first DVT had a 1.4-fold higher risk of recurrence than those with a first PE. This finding is in agreement with a Canadian study of 646 patients with first unprovoked VTE showing that subjects with DVT had a two-fold higher risk of recurrence than

Table 5 All-cause mortality rates (MRs) per 100 person-years in different time intervals after venous thromboembolism (VTE) and according to classification of the index event; the Tromsø Study 1994–2012

Time	Overall VTE *n* MR (95% CI)	Cancer-related VTE *n* MR (95% CI)	Provoked VTE* *n* MR (95% CI)	Unprovoked VTE *n* MR (95% CI)
0–6 months	134 44.7 (37.7–52.9)	79 153.3 (122.9–191.1)	40 37.2 (27.3–50.7)	15 10.6 (6.4–17.6)
6 months to 1 year	35 13.3 (9.5–18.5)	20 57.1 (36.8–88.5)	8 8.3 (4.1–16.7)	7 5.2 (2.4–10.9)
1–5 years	95 6.2 (5.1–7.6)	33 28.9 (20.5–40.6)	28 4.8 (3.3–6.9)	34 4.0 (2.9–5.7)
5–10 years	56 5.8 (4.5–7.6)	1 2.6 (0.3–18.8)	23 5.8 (3.8–8.7)	32 6.0 (4.2–8.5)
After 10 years	13 3.5 (2.0–6.1)	1 10.7 (1.5–76.0)	6 4.1 (1.8–9.1)	6 2.8 (1.2–6.4)

CI, confidence interval. *Without cancer.

those with PE [32]. Likewise, the study by Prandoni *et al.* [18] found that DVTs were 1.4-fold more likely to recur than PEs. Potential explanations for this phenomenon may be more efficient clot resolution in the lungs, owing to high fibrinolytic activity [33], in contrast to venous valve damage and development of the post-thrombotic syndrome, which frequently occurs among patients with DVT [7]. Moreover, the introduction of CT to diagnose PE may have led to increased detection of subsegmental PEs, which have a better prognosis with regard to recurrence [22].

In accordance with previous studies [18,34,35], the type of the first VTE was a predictor for the type of recurrence, as patients with a first PE were 2.4-fold more likely to have a second PE rather than a DVT. Moreover, we showed that those with a first unprovoked VTE were more likely to have a second unprovoked VTE, whereas those with a first provoked VTE were just as likely to have a provoked or unprovoked VTE as their second event. The latter may be explained by an altered baseline risk following the first provoked VTE, e.g. residual vein thrombosis [36,37] or other pathophysiologic changes in the veins caused by the first VTE increasing the chance of having a recurrent thrombosis, even in the absence of provoking factors.

Most previous studies have reported a two-fold to four-fold higher recurrence rate among men than among women [27,34,38]. In our study, we confirmed this trend, but the relative risk of recurrence was only 30% higher in men than in women, and the difference was not statistically significant. As the source population for our VTE cases was restricted to subjects aged $\geq$ 25 years, our study population did not contain the very young women with a first VTE often related to oral contraceptives or pregnancy. Generally, the young women with hormone-related VTE have a low recurrence risk [39], and, as a result, the risk difference between men and women will be higher in a VTE population that contains these women. The cumulative incidence curves for recurrence in men and women started to separate 3 years after the initial event in our study, which may partly explain why higher relative risk differences in men versus women are reported in studies with a later start of follow-up (after withdrawal of anticoagulants).

The 1-year mortality rates after VTE remained high (24% in all VTE patients and 62% in cancer-related VTE patients), and were remarkably similar to those reported in a previous Norwegian study of 740 VTE patients recruited in the period 1995–2001 [40]. We observed a higher survival rate among men in our crude analyses, but this was explained by age differences among men and women at the time of the index event. Subjects with provoked VTE had poorer survival than those with unprovoked VTE, which can probably be explained by a higher age and more comorbidities among those with provoked VTE.

The strengths of our study include the unselected VTE patients recruited from the general population covering both the community and the hospital setting, thoroughly identified and individually validated first and recurrent events, the relatively long follow-up, and data collected from a recent calendar period. Patients were treated according to standard practice. As our study center is the only diagnostic and treatment facility for all patients in the area, few cases were lost to follow-up, and we therefore believe that our observations reflect the true clinical course of VTE. Moreover, few previous studies have compared the cumulative incidence of recurrence among subgroups in the presence of competing risk of death. Unfortunately, the study population was too small to for trends in recurrence and mortality over time to be investigated, and we did not have sufficient information on causes of death. Moreover, the VTE population was only representative for the population aged $\geq$ 28 years. However, as the incidence increased sharply with age, our VTE population covered the vast majority of the total VTEs in the general population. Unfortunately, we did not have detailed information on the duration of anticoagulant treatment after VTE. However, adjustment for the planned duration, which, in most cases, is expected to reflect the actual duration, did not have a major impact on the difference in recurrence risk between unprovoked and provoked VTE.

Despite advances in VTE management in recent years, 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 the development of risk prediction models with high precision, in order to identify high-risk individuals with a favorable benefit-to-harm ratio for anticoagulant treatment.

Addendum

N. Arshad analyzed data and wrote the manuscript. E. Bjøri interpreted data and revised the manuscript. K. Hindberg provided statistical support, interpreted data, and revised the content. T. Isaksen collected data and revised the manuscript. J.-B. Hansen was responsible for the concept and design of the study, data collection and interpretation, and revision of the manuscript. S. K. Brækkan was responsible for the concept and design of the study, data collection and interpretation, and writing of the manuscript.

Disclosure of Conflict of Interests

K.G. Jebsen TREC is supported by an independent grant from the K. G. Jebsen Foundation.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the index VTE. The Tromsø Study 1994–2012.

Table S2. Cumulative incidence of all-cause mortality according to time since venous thromboembolism and classification of the index event. The Tromsø Study 1994–2012.

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Paper III

Journal of Thrombosis and Haemostasis, **14**: 1–8 DOI: 10.1111/jth.13492

ORIGINAL ARTICLE

Hospital-related first venous thromboembolism and risk of recurrence

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Essentials

- Recurrence risk after a hospital-related venous thromboembolism (VTE) is underinvestigated.
- We explored this association in a cohort of patients with a first VTE from the Tromsø study.
- Stratification on hospital-related factors revealed considerable differences in recurrence risk.
- The recurrence risk was high in cases with a VTE related to hospitalization for medical illness.

Summary. *Background:* Hospitalization is a well-established risk factor for first venous thromboembolism (VTE), but 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. *Objectives:* 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. *Methods:* Information on hospital-related risk factors was collected in 822 patients with a first-lifetime VTE derived from the Tromsø study. Recurrent VTEs and deaths were recorded during follow-up (1994–2012). *Results:* 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. *Conclusions:* 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.

Keywords: epidemiology; hospitalization; recurrence; risk factors; venous thromboembolism.

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Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), are frequently associated with considerable morbidity and mortality [1–3]. VTE is particularly common among hospitalized patients, with incidence rates (IRs) exceeding 100 times greater than those in community residents [4]. Moreover, 40–50% of the VTE cases can be attributed to hospitalization, with hospitalization for surgery and medical illness accounting for similar proportions [5].

After an incident episode of VTE, 30–40% experience a recurrent event within 10 years, and the risk is highest during the first 6–12 months [2,6–9]. The risk of recurrence is dependent on the clinical characteristics of the initial event. Patients with a first VTE provoked by a transient risk factor (e.g. surgery) are at low risk of recurrence [6,8,10–13], whereas VTEs provoked by a persistent risk factor, such as active cancer, have a high risk of recurrence [6,8,12,14,15]. When no provoking risk factor (transient or persistent) can be identified, the event is classified as unprovoked, and these patients have an intermediate to high risk of recurrence [9–13,16,17]. However,

categorization along this continuum may be difficult, particularly for patients where considerable uncertainty exists regarding the prognostic importance of a risk factor.

Hospitalization in itself is an interim exposure and may therefore be considered as a transient risk factor, assumed to yield a low risk of recurrence. However, the risk of recurrence after a first hospital-related VTE, particularly hospitalization for conditions other than cancer or surgery, has not been extensively studied. Moreover, as the mortality rate is expected to be higher among patients with co-morbidity, the cumulative incidence of recurrence may be influenced by the competing risk of death, particularly in these patients [18]. In the present study, we therefore aimed 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.

Methods

Study population

The source population comprised subjects participating in the first (1974), second (1979/80), third (1986/87), fourth (1994/95), fifth (2001/02) and sixth (2007/08) surveys of the Tromsø study. The Tromsø study is a single-center, population-based, prospective cohort study, with repeated health surveys of inhabitants in the municipality of Tromsø in the north of Norway. Further details about the Tromsø study can be found elsewhere [19]. The Regional Committee of Medical and Health Research Ethics approved the study, and written consent was collected from all participants. Overall, 39 825 unique individuals, aged 25–97 years, participated in at least one of the surveys, which yielded an average participation rate of 78.5% for all surveys. Participants that were still alive and living in the municipality of Tromsø by 1 January 1994 (n = 33 885) were followed through to 31 December 2012, and all potential cases of first lifetime VTE were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North of Norway. This is the only hospital in the region and serves as the exclusive provider of all diagnostic radiology procedures and VTE-related healthcare in the area. Trained personnel reviewed the medical records for each potential VTE case and extracted information for case-validation. A VTE event was considered verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography and autopsy) and resulted in a VTE diagnosis that required treatment, as previously described [20]. Using the criteria described above, 822 subjects with a validated first lifetime VTE event were identified and included in our study.

Patient characteristics

Information on clinical and provoking factors at the time of and 8 weeks preceding the VTE event, were extracted by review of medical records using standardized forms. We defined a VTE as being hospital related when patients were hospitalized within 8 weeks preceding the VTE (including patients hospitalized at the time of VTE), had undergone surgery (with or without subsequent hospitalization) within 8 weeks preceding the event or had active cancer. When none of these factors could be identified, the event was classified as non-hospital-related. Cancer was registered as the provoking factor only when patients had active cancer at the time of the initial event. Bedrest was defined as confinement to bed in hospital > 3 days, whereas other immobilization was defined as transient or persistent use of a wheelchair or long haul travel > 4 h (i.e. by airplane, train, car or boat). Hospital-related VTE was classified into three main categories according to the main provoking factor for the first VTE following the algorithm: cancer > surgery > hospitalization for other medical illness.

Clinical factors included were obesity, use of estrogens, family history of VTE, pregnancy, puerperium or other co-morbidities. Participants were classified as obese according to the World Health Organization definition (BMI > 30 kg m^{-2}) [21]. Co-morbidity was defined as a myocardial infarction or a stroke within the last 12 months preceding the VTE, chronic obstructive pulmonary disease (COPD), myeloproliferative disorders, systemic lupus erythematosus or a chronic infection.

Outcomes

All cases of recurrent VTE were recorded in the period 1994–2012. The diagnosis of recurrent VTE was made using the same criteria as described for validating first lifetime VTE events. Information on mortality was collected from the Norwegian Population Registry.

Statistics

Statistical analyses were performed using STATA version 14.0 (Stata Corporation LP, College Station, TX, USA). The significance level was set to 0.05. For analyses of recurrence, subjects were followed from the date of their first VTE to the first occurring event of a recurrent VTE (n = 132), death (n = 307), loss to follow-up as a result of migration (n = 19) or end of follow-up (31 December 2012) (n = 364). Crude IRs of recurrent VTE were calculated and expressed per 100 person-years at risk. Kaplan–Meier failure estimates were calculated and visualized according to hospital-related classification of the first

VTE (no hospitalization, cancer, surgery or hospitalization because of other medical conditions). Moreover, Cox proportional hazards regression models were performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of VTE recurrence according to individual characteristics associated with the incident VTE event. The HRs were estimated in two models, allowing for adjustment of the other provoking factors in those with multiple provoking factors. Model 1 included age and sex, and Model 2 was a multivariable model that included age, sex and all the characteristics of interest (i.e. surgery, acute medical condition, cancer and bedrest > 3 days). Furthermore, crude mortality rates per 100 person-years and HRs of death were calculated using the same models as described above. The proportional hazards assumption was tested for all variables using Schoenfeld residuals.

Generally, hospitalized patients have poorer prognosis than outpatients and healthy subjects. Because the mortality rates were likely to differ among those with and without hospital-related factors, the rates of VTE recurrence in these patients could potentially be overestimated as a result of competing risk of death. In order to account for death as a competing event, cumulative incidence functions were performed and visualized using the user-contributed stcompet suite and the stcrreg cif curve in STATA (Stata Corporation LP).

Results

Of the 822 patients with validated first lifetime VTE, 19 died on the same day as the VTE occurred and were therefore excluded from follow-up. The baseline characteristics and the distribution of risk factors among patients with and without hospital-related first VTE are shown in Table 1. The patients with hospital-related VTE were on average 4 years older (mean age = 68.9 ± 13.5 vs. 64.9 ± 14.7) and more likely to be female (54.4% vs. 49.5%) than those with a non-hospital-related VTE. Only 1.0% of the hospital-related events occurred in patients with a reported history of first-degree relatives suffering from a VTE before age 60, whereas 5.9% of the non-hospital-related events occurred in patients with a known family history of VTE. Furthermore, co-morbid conditions were more common among the hospital-related events as opposed to the non-hospital-related events (24.3% vs. 18.8%). The durations of anticoagulant treatment within subgroups of patients with hospital-related VTE are shown in Table S1.

Recurrence

During the course of 3423 person-years of follow-up, 132 subjects experienced a recurrent episode of VTE. The mean observation time was 4.3 years, ranging from 1 day to 18.8 years. The overall crude IR of recurrence was 3.9 per 100 person-years (95% CI, 3.3–4.6). Characteristics of the

Table 1 Characteristics of subjects with hospital-related and non-hospital-related first venous thromboembolism

	Hospital-related	
	Yes (n = 412)	No (n = 410)
Age (years)	68.9 ± 13.5	64.9 ± 14.7
Sex (% women)	54.4	49.5
Obesity (% obese)	15.5	18.8
Location at onset		
Hospital	38.3	–
Nursing home	2.9	4.4
Community	58.8	95.6
Deep vein thrombosis	59.2	57.6
Pulmonary embolism	40.8	42.4
Treatment duration with AC		
0–3 months	36.4	16.8
3–6 months	36.7	48.0
6–12 months	20.6	27.6
> 12 months	6.3	7.6
Clinical risk factors		
Estrogens	3.4	8.3
FHVTE	1.0	5.9
Co-morbidity	24.3	18.8
Pregnancy/postpartum	0.7	0.7
Surgery	31.1	0
Trauma	9.5	7.0
Acute medical condition	21.6	5.6
Cancer	46.4	0
Confined to bed > 3 days	11.9	1.5
Other immobilization	15.8	7.6
Other provoking factor	7.0	2.9

Values are means ± 1 SD or percentages. AC, anticoagulants; FHVTE, family history of venous thromboembolism .

VTE recurrences are shown in Table S2. A hospital-related VTE *per se* was not associated with increased risk of recurrent thrombosis (HR, 0.99; 95% CI, 0.69–1.41) in the age- and sex-adjusted model (Table 2). However, the recurrence risk varied greatly according to the classification of the first hospital-related event (Fig. 1A). After 5 years of follow-up, the cumulative incidence of recurrence was 27.4% (95% CI, 17.3–41.6) in patients with a first VTE associated with cancer. Patients with a surgery-related first VTE had the lowest risk of recurrence after 5 years (11.0%; 95% CI, 5.5–21.1), whereas patients hospitalized because of other medical illness and non-hospital-related first events had a 20.1% (95% CI, 12.2–32.0) and 18.4% (95% CI, 14.5–23.1) cumulative recurrence risk after 5 years, respectively. The recurrence rate was highest during the first 12 months, especially for cancer-related events and events associated with other medical illness. When this relationship was expressed in a Cox proportional hazard model (Table 2), cancer patients had a 73% higher risk of recurrence (HR, 1.73; 95% CI, 1.06–2.81) and patients with surgery-associated events had 47% lower risk of recurrence (HR, 0.53; 95% CI, 0.28–0.99) than those without hospital-related events. Patients hospitalized with a medical illness other than cancer or surgery appeared to have similar risk of recurrence (HR, 1.02; 95% CI, 0.61–1.72) to those with a

Table 2 Incidence rates and risk of recurrent venous thromboembolism (VTE) by classification of hospital-related first VTE

	n	Recurrences	IR (95% CI)*	HR (95% CI†)
Non-hospital-related	410	81	3.7 (3.0–4.6)	Reference
Hospital-related‡	412	51	4.1 (3.1–5.4)	0.99 (0.69–1.41)
Cancer-related	191	22	8.8 (5.8–13.3)	1.73 (1.06–2.81)
Surgery-related	97	11	1.9 (1.0–3.4)	0.53 (0.28–0.99)
Other medical illness	124	18	4.7 (3.0–7.4)	1.02 (0.61–1.72)

CI, confidence interval; HR, hazard ratio; IR, incidence rates. *Per 100 person-years. †Adjusted for age and sex. ‡Hospital-related includes patients hospitalized within 8 weeks preceding the VTE, who are further classified into three main categories according to the main provoking factor following the algorithm: cancer > surgery > hospitalization for other medical illness.

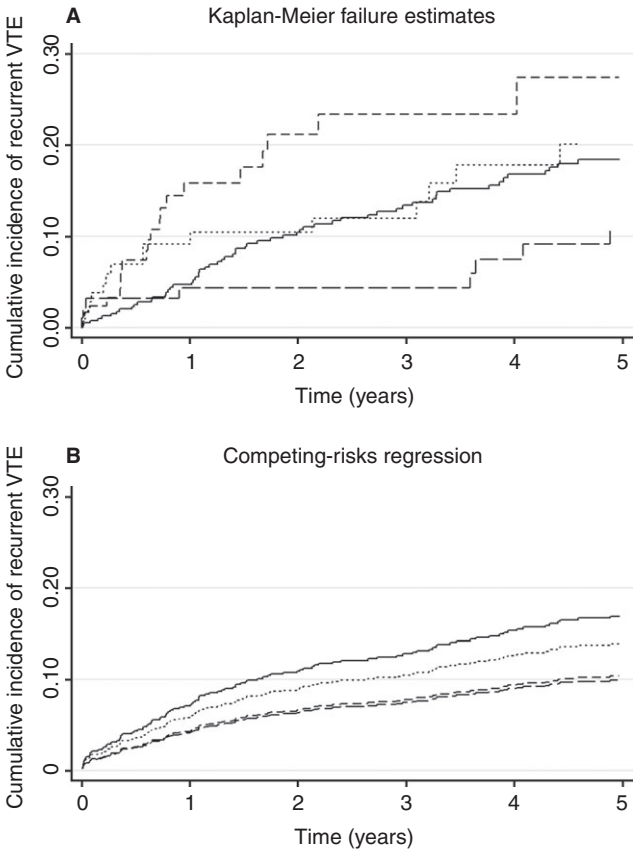

Fig. 1. Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the first VTE event in crude analyses (A) and with death as a competing event (B). ———, non- hospital-related; – – –, cancer related; — — —, surgery-related; ·····, other medical illness.

non-hospital-related VTE. Further adjustment for duration of anticoagulant treatment did not influence the risk estimates (data not shown).

The IRs and HRs of VTE recurrence according to individual characteristics associated with the first VTE are presented in Table 3. In the multivariable model, in which all characteristics were mutually adjusted for, surgery was significantly associated with decreased risk of VTE recurrence, displaying a 61% (HR, 0.39; 95% CI, 0.21–0.71) lower risk compared with those without a surgery-associated first VTE (Table 3). Cancer, on the other hand, was significantly associated with an almost 2-fold increased risk of recurrence in this model (HR, 1.95; 95% CI, 1.21–3.15).

Mortality

In total, 442 patients died during the course of 3896 person-years of follow-up. Estimated mortality rates and HRs of death according to classification of the first event are shown in Table 4. Overall, patients with a hospital-related VTE had a 2.8-fold higher risk of death (HR, 2.76; 95% CI, 2.26–3.37). Compared with non-hospital-related events, patients with a first VTE event related to cancer or other medical illness had a 7.4-fold and 2.2-fold higher risk of death, respectively (HR, 7.39; 95% CI, 5.84–9.35; and HR, 2.20; 95% CI, 1.68–2.88), whereas patients with a first VTE event related to surgery had a 13% lower risk of death (HR, 0.87; 95% CI, 0.60–1.26). In multivariable analyses of the individual components, cancer (HR, 6.09; 95% CI, 4.95–7.49), bedrest > 3 days (HR, 2.47; 95% CI, 1.77–3.46) and acute medical conditions (HR, 1.36; 95% CI, 1.05–1.78) were all significantly associated with increased risk of death (Table 5).

Competing risk of death

Cumulative incidence functions (Fig. 1B) showed that patients with a non-hospital-related first VTE had the highest risk of recurrence, with a cumulative incidence of 16.4% (95% CI, 12.8–20.4) after 5 years, when death was included as a competing event. In comparison, patients with other medical illness had a cumulative incidence of 14.4% (95% CI, 8.4–21.9) after 5 years, whereas cancer and surgery-related events had a similar cumulative incidence of 11.7% (95% CI, 7.6–17.0) and 9.7% (95% CI, 4.5–17.4) after 5 years, respectively. Sub-distribution HRs of VTE recurrence according to characteristics associated with the first VTE are shown in Table 3.

Discussion

In the present study, subjects with a hospital-related first VTE had a similar risk of recurrence to those with a non-hospital-related VTE. However, Kaplan–Meier failure

Table 3 Incidence rates and risk of venous thromboembolism (VTE) recurrence according to individual characteristics associated with the first VTE

	Recurrences	IR (95% CI)*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	SHR (95% CI)†
Surgery	12	1.8 (1.0–3.2)	0.45 (0.25–0.81)	0.39 (0.21–0.71)	0.52 (0.28–0.93)
Acute medical condition	18	5.7 (3.6–9.0)	1.35 (0.82–2.22)	1.32 (0.78–2.25)	1.10 (0.66–1.84)
Bedrest > 3 days	7	6.6 (3.1–13.7)	1.66 (0.78–3.57)	1.85 (0.81–4.21)	0.83 (0.38–1.83)
Cancer	22	8.8 (5.8–13.3)	1.87 (1.17–2.99)	1.95 (1.21–3.15)	0.66 (0.41–1.06)

CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, sub-distribution hazard ratio (competing risk analysis).*Per 100 person-years. †Model 1: adjusted for age and sex. ‡Model 2: adjusted for surgery, acute medical condition, bedrest > 3 days, cancer, age and sex.

Table 4 Mortality rates and risk of death by classification of hospital-related first venous thromboembolism

	n	Deaths	MR (95% CI)*	HR (95% CI)†
Non-hospital-related	410	148	5.8 (4.9–6.8)	Reference
Hospital-related‡	412	294	21.9 (19.5–24.5)	2.76 (2.26–3.37)
Cancer	191	171	65.5 (56.4–76.1)	7.39 (5.84–9.35)
Surgery	97	34	5.4 (3.8–7.5)	0.87 (0.60–1.26)
Other medical illness	124	89	19.8 (16.1–24.4)	2.20 (1.68–2.88)

CI, confidence interval; HR, hazard ratio; MR, mortality rates. *Per 100 person-years. †Adjusted for age and sex. ‡Hospital-related includes patients hospitalized within 8 weeks preceding venous thromboembolism, who are further classified into three main categories according to the main provoking factor following the algorithm: cancer > surgery > hospitalization for other medical illness.

estimates revealed considerable heterogeneity among the hospital-related events with regards to recurrence risk. Patients with index events related to hospitalization for medical illness other than surgery or cancer had a similar risk of recurrence to patients with a non-hospital-related first VTE after 5 years of follow-up. In accordance with previous studies [6,8,10–13,15], patients with cancer-related first events were found to have a high risk of recurrence, whereas patients with surgery-related first episodes of VTE had a low risk of recurrence after 5 years of follow-up. A hospital-related first VTE was associated with a 3-fold higher risk of death compared with non-hospital-related VTE, and except for surgery-related events, all subgroups of hospital-related VTE displayed an increased mortality-risk. Consequently, the cumulative recurrence rates decreased when competing risk of death was taken into account. This was particularly pronounced for cancer-related VTE, which was lower than the cumulative risk among non-hospital-related cases and events related to hospitalization for other medical illnesses.

The IR of VTE among hospitalized patients is > 100-fold higher than among community residents [4] and the risk of a first VTE is significantly increased during the initial 3-month period after a hospital stay [8]. For transient risk factors, the risk of VTE recurrence is generally low as long as the risk factor is removed and the effect of the risk factor is reversible [8,11,12]. Thus, the transient nature of hospitalization could imply a low recurrence risk among those with a first hospital-related VTE. In our study, however, hospitalization within 8 weeks preceding an incident VTE event, including patients admitted at the time of the event, was not associated with a lower risk of recurrence. Accordingly, a previous study of 1791 patients with a first VTE recruited and followed in the period 1966–1990, showed no association between recent hospitalization (3 months preceding the first VTE) and risk of recurrence (HR, 1.01) [8].

Although the recurrence risk did not differ among hospital-related and non-hospital-related first VTEs, the reason for hospitalization preceding the first event appeared to have a major impact on recurrence risk. As shown in previous studies [6,8,10–12,14–16], surgery, a transient and reversible risk factor, was associated with a low risk of recurrence in both conventional and competing risk analyses. Cancer, a persistent and mostly irreversible risk factor, was associated with a high risk of recurrence in conventional Kaplan–Meier analyses. However, competing risk analyses revealed that this risk was substantially

Table 5 Mortality rates and risk of death according to individual characteristics associated with the first venous thromboembolism

	Deaths	MR (95% CI)*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Surgery	60	8.5 (6.6–10.9)	0.77 (0.59–1.02)	0.62 (0.47–0.82)
Acute medical condition	84	23.1 (18.7–28.6)	1.72 (1.35–2.18)	1.36 (1.05–1.78)
Bedrest > 3 days	47	40.9 (30.7–54.4)	3.01 (2.21–4.09)	2.47 (1.77–3.46)
Cancer	171	65.5 (56.4–76.1)	6.09 (4.95–7.49)	6.09 (4.94–7.51)

CI, confidence intervals; HR, hazard ratio; MR, mortality rate. *Per 100 person-years. †Model 1: adjusted for both age and sex. ‡Model 2: adjusted for surgery, acute medical condition, bedrest > 3 days, cancer, age and sex.

overestimated as a result of the high mortality rate among cancer patients.

Whether hospitalization for medical illnesses other than cancer or surgery should be regarded as a temporary risk condition with a low recurrence risk is not well studied. Heit and colleagues [22] found a non-significant 15% increased risk of recurrence among those with a first VTE related to hospitalization for acute medical illness compared with all other VTEs (i.e. hospitalized for other conditions and non-hospitalized). A study of 1626 VTE patients followed for a median of 50 months after withdrawal of anticoagulation, reported that patients who had been bedridden for > 1 week because of a medical disease preceding the first VTE were more likely to develop recurrence than those with recent trauma or surgery [9]. However, this study did not distinguish between hospitalized and non-hospitalized patients. In our study, we showed that patients with a first VTE related to hospitalization for medical illness other than cancer or surgery had similar risk of recurrence to subjects with a non-hospital-related VTE, and that the cumulative incidence of recurrence remained high even after the competing risk of death was taken into account.

The relatively high rates of recurrence after a first VTE related to hospitalization for a medical illness point towards a persistent nature of the VTE risk in these subjects. Several chronic conditions, such as chronic heart and lung diseases, as well as inflammatory and autoimmune disorders, are associated with coagulation and fibrinolytic abnormalities [23–27], endothelial dysfunction [23–27], increased platelet activation [24,25,27] and inflammation [23–25,27], which may induce a prothrombotic state. Moreover, disease-specific mechanisms, such as hypoxia in COPD patients [24] and right ventricular failure with subsequent venous stasis in patients with congestive heart failure, [25,26] may add to the VTE risk, and flare-up periods [27–29] or exacerbations [30,31] that lead to re-hospitalization may induce additional prothrombotic risk factors, such as immobilization. The latter is supported by Heit *et al*. [22], who studied hospitalization as an interim exposure after a first VTE and found that patients hospitalized for a medical illness had an almost 6-fold increased risk of VTE recurrence during the hospital stay, and a 2.6-fold increased risk within 92 days post-dismissal.

Previous studies have shown both in-hospital and post-hospital discharge [32], as well as cancer and several other medical co-morbidities, to be associated with high mortality rates after a first VTE [1,7,33,34], whereas the opposite findings have been reported for various types of surgery [33]. Accordingly, in the present study, increased mortality rates were found for all subgroups of VTE patients, except for those with surgery-related events. Our estimated 6.1-fold higher mortality risk among cancer patients vs. cancer-free subjects is consistent with previous studies in which risk estimates ranging from 4.5 to 9.5 were reported [1,7,33,34]. Moreover, our findings of a 2-fold increased risk of death among patients with acute medical conditions is in agreement with previous studies showing that heart diseases, neurologic diseases and chronic lung , renal and liver diseases are associated with a 2- to 4-fold increased risk of death in patients with VTE [33,35,36].

In the presence of competing risk of death, the cumulative incidence of recurrence is dependent on both the hazard of recurrence and the hazard of dying, and consequently, recurrence risks are overestimated when the mortality rate is high [37–39]. Accordingly, the cumulative incidences of recurrence were lower in all subgroups after competing risk analysis in our study. In patients with a first VTE related to hospitalization for medical illness, the 5-year cumulative recurrence dropped from 20.1% to 14.4%, suggesting a moderate role of hospital-related mortality in estimating recurrence risk among these patients. The change was much more pronounced in cancer patients (dropped from 27.4% to 11.7%), and the 5-year cumulative incidence was comparable to that of surgery-related first VTE (11.7% vs. 9.7%). This result is in contrast to the study by Heit *et al*. [22], which reported a 5-year cumulative incidence of 34% in cancer-related VTE and 17% in secondary non-cancer VTE (including subjects hospitalized for surgical or medical conditions) in competing risk analysis. The diverging results may in part be explained by the vast difference in mortality rates between the studies, particularly among cancer patients, as well as differences in the length of follow-up and definition of active cancer.

Current guidelines recommend short-term (3 months) anticoagulant treatment over longer-term treatment in patients with a DVT or PE provoked by a non-surgical transient risk factor [40]. Although hospitalization for a medical condition other than cancer or surgery is a transient condition, the high recurrence risk among these patients suggests a more persistent underlying VTE risk that may justify similar treatment recommendations to those for unprovoked VTE, as well as increased awareness of recurrence risk in high-risk situations such as re-hospitalization.

The strengths of the present study include the recruitment of patients with first VTE from a general population, the prospective design and long-term follow-up. Because a single hospital serves the entire study population the chance of missing outcomes is very low. Moreover, the combination of multiple approaches to identify cases, comprehensive medical records review and firm criteria for VTE assessment yields thorough validation of first and recurrent VTE events. Advances in prevention, diagnosis and treatment of VTE may have influenced outcomes during the last two decades and our data have the advantage of being collected from a recent time period compared with previous studies [6,8,22]. The study has limitations. Information on patient characteristics was collected from medical records and relied on the reporting by physicians, nurses and other healthcare professionals. However, the main exposures in this study are major

clinical events for which one would expect a low degree of under-reporting and misclassification. Unfortunately, because of the low number of events we had limited statistical power in subgroups and our findings should therefore be interpreted with caution. Moreover, we did not have the possibility to further investigate the recurrence risk among different disease entities in patients with a first VTE related to hospitalization for medical illness.

In conclusion, 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 of death is taken into account.

Addendum

E. Bjøri was responsible for data analysis and writing the manuscript. N. Arshad was responsible for data interpretation and revising the manuscript. H. S. Johnsen was responsible for data interpretation and revising the content. J.-B. Hansen was responsible for the conception and design of the study, data collection and interpretation, and writing the manuscript. S. K. Brækkan was responsible for the conception and design of the study, data collection and interpretation, and writing the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Duration of anticoagulant therapy stratified by subgroups of venous thromboembolism (VTE).
Table S2 Characteristics of recurrent venous thromboembolism (VTE) in patients with hospital-related and non-hospital-related first VTE.

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Paper IV

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ORIGINAL ARTICLE

D-dimer at venous thrombosis diagnosis is associated with risk of recurrence

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Essentials

- Whether D-dimer at incident venous thromboembolism (VTE) can predict recurrence-risk is unknown.
- We explored this association in 454 cancer-free patients with a first lifetime VTE.
- A low D-dimer at first VTE diagnosis was associated with a low recurrence risk.
- The association was predominant in patients with deep vein thrombosis and unprovoked VTE.

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Summary. *Background:* Venous thromboembolism (VTE) is a common disease with a high recurrence rate. D-dimer measured after cessation of anticoagulant therapy predicts recurrence, and is used to decide on treatment prolongation. However, whether D-dimer measured at first VTE diagnosis can be used to assess recurrence-risk is unknown. *Aims:* To investigate the association between D-dimer, measured at first VTE diagnosis and risk of recurrent VTE. *Methods:* Information on clinical risk factors and laboratory markers were collected in 454 cancer-free patients with a first VTE. Recurrent VTEs and deaths during follow-up (1994–2012) were recorded. *Results:* During a median follow-up of 3.9 years, 84 patients experienced a recurrent VTE. The crude recurrence rate was 1.7 (95% confidence interval [CI], 1.0–2.9) per 100 person-years in the lower quartile of D-dimer ($\leq$ 1500 ng mL^{-1}), and 4.9 (95% CI, 3.9–6.1) per 100 person-years in the upper three quartiles combined, yielding an absolute risk difference of 3.2 per 100 person-years. Patients with D-dimer $\leq$ 1500 ng mL^{-1} had 54% lower recurrence-risk than patients with D-dimer > 1500 ng mL^{-1} (HR, 0.46; 95% CI, 0.25–0.82). The association was particularly pronounced among patients with unprovoked events and deep vein thrombosis, showing a 66% (HR, 0.34; 95% CI, 0.15–0.74) and 68% (HR, 0.32; 95% CI, 0.14–0.71) lower recurrence risk among patients with D-dimer $\leq$ 1500 ng mL^{-1}, respectively. *Conclusions:* A low D-dimer ($\leq$ 1500 ng mL^{-1}) measured at first VTE diagnosis was associated with a low recurrence risk, particularly among patients with DVT and unprovoked events. Our findings suggest that a clinical decision to avoid prolonged anticoagulant treatment could be considered based on low D-dimer at the time of VTE diagnosis.

Keywords: epidemiology; D-dimer; prediction; recurrence; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE), a conceptual term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious disease that recurs in up to 30–40% of patients within 10 years following the first event [1–5]. Recurrent events can be effectively prevented through secondary prophylaxis with anticoagulants [6,7], although at the cost of an increased risk of bleeding [8]. The challenge therefore lies in identifying patients who may benefit from extended thromboprophylaxis, but with minimal risk of bleeding complications. Likewise, to avoid unnecessary exposure to bleeding risk, it is desirable to identify subjects with low risk of VTE recurrence in whom short-term treatment with anticoagulants would be sufficient.

D-dimer, a global biomarker of coagulation activation and fibrinolysis, is commonly used in clinical algorithms for

the diagnostic work-up of patients with suspected VTE [9,10]. Several studies have shown that elevated D-dimer levels measured during or after cessation of anticoagulant therapy are associated with increased risk of recurrence in patients with unprovoked VTE [11–13] and are therefore regularly applied to assess individual recurrence risk and guide decisions on treatment prolongation [14–17]. However, this strategy is resource demanding both for the patient and the healthcare system because of additional blood sampling and outpatient clinic visits for evaluation of recurrence risk. Information on D-dimer is widely available for most VTE patients at the time of diagnosis. Therefore, there is a clinical rationale to explore whether D-dimer, measured at the time of first VTE diagnosis (i.e. before initiation of anticoagulant therapy), can be used to distinguish between patients at high and low risk of recurrence. Our hypothesis was that low plasma D-dimer concentration at VTE diagnosis could identify subjects at low risk of recurrence. Therefore, we aimed to investigate the association between D-dimer, measured at the time of the first VTE diagnosis, and risk of recurrent VTE.

Methods

Study population

The source population comprised subjects participating in ≥ 1 of the six currently conducted surveys of the Tromsø study (hereby referred to as Tromsø 1–6), who were still alive and living in Tromsø by 1 January 1994 (n = 33 885). The Tromsø study is a single-center, population-based prospective cohort study, with repeated health surveys of inhabitants in Tromsø, Norway. Detailed information about the Tromsø study can be found elsewhere [18]. The study was approved by the Regional Committee of Medical and Health Research Ethics, and all participants gave their informed written consent. The overall attendance rates were high, ranging from 85% in Tromsø 2 to 66% in Tromsø 6, with an average of 78.5% for the six surveys.

Participants were followed from the date of inclusion in 1994 through to the end of the study on 31 December 2012. All potential cases of first lifetime VTE during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North of Norway (UNN), which is the exclusive provider of all in- and outpatient VTE-related diagnostic procedures and VTE-related healthcare in the Tromsø region. Trained personnel reviewed the medical records for each potential VTE case and extracted information for case validation, as well as information on clinical risk factors and laboratory markers, using standardized forms. A VTE event was considered verified and recorded when presence of clinical signs and symptoms of DVT or pulmonary embolism were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography or autopsy) and resulted in a VTE diagnosis that required treatment, as previously described [19]. Applying these criteria, we identified 822 subjects with a thoroughly validated first lifetime VTE diagnosis. D-dimer has low specificity for the diagnosis of VTE as it is often elevated in conditions such as malignancy, infections or inflammatory states [20–22]. Consequently, we excluded VTE patients with active cancer (n = 124) and patients already hospitalized for other conditions when the VTE occurred (n = 158). Moreover, patients with missing D-dimer values (n = 86) were excluded, which left us with 454 included VTE patients in our study.

Patient characteristics

Information on clinical and provoking factors at the time of and 8 weeks preceding the VTE event was obtained for all eligible patients. The VTE event was classified as provoked if preceded by (i) major surgery, trauma or an acute medical condition (acute myocardial infarction, ischemic stroke or major infectious disease) within 8 weeks prior to the event, (ii) marked immobilization (confinement to bed >3 days, confinement to wheelchair or long-distance travel exceeding 4 hours within the last 14 days prior to the event) or (iii) any other factor specifically described in the medical records to have provoked the VTE (e.g. intravascular catheter). If no provoking factor could be identified, the VTE was classified as unprovoked.

Clinical risk factors included were obesity, family history of VTE, use of estrogens, pregnancy, puerperium or other co-morbidities. The classification of obesity was made according to the definition from the World Health Organization (BMI > 30 kg m^{-2}) [23]. Family history of VTE was defined as having a first-degree relative who suffered from a VTE before the age of 60 years. Co-morbidity was defined as having a myocardial infarction or a stroke within the last 12 months preceding the VTE, chronic obstructive pulmonary disease, myeloproliferative disorders, systemic lupus erythematosus (SLE) or chronic infection.

D-dimer measurements

D-dimer levels were assessed as part of the diagnostic work-up of patients with suspected VTE, and a negative test was defined as a D-dimer value < 500 ng mL^{-1}. All blood samples were analyzed at the Department of Clinical Chemistry at the University Hospital of North Norway. In the period 1994–98 the NycoCard D-Dimer (Nycomed Pharma, Oslo, Norway) assay, based on the immunometric flow-through principle, was used to assess D-dimer. In the remaining period (1998–2012) D-dimer was assayed with the STA®-Liatest® D-Di FM from Stago (Diagnostica Stago, Asnieères, France). This test quantitatively measures D-dimer levels by the immunoturbidimetric method (liquid reagent).

Outcome registration of recurrent VTE and deaths

All recurrent VTE events during follow-up in the period 1994 through to 2012 were identified and validated using the same criteria as described for the validation of first lifetime VTE events. Information on mortality was obtained from the Norwegian Population Registry.

Statistics

For analyses of recurrence, subjects were followed from the date of their first VTE to the first occurring event of either recurrent VTE, death or loss to follow-up as a result of migration, or end of follow-up (31 December 2012). The study population was divided into quartiles based on D-dimer levels (quartile 1, ≤ 1500 ng mL^{-1}; quartile 2, 1600–3000 ng mL^{-1}; quartile 3, 3100–7000 ng mL^{-1}; quartile 4, ≥ 7100 ng mL^{-1}). Crude incidence rates (IRs) of recurrent VTE were calculated across categories of D-dimer and expressed per 100 person-years at risk. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). In the analysis across quartiles of D-dimer, the highest quartile was set as the reference. To test our hypothesis that low levels of D-dimer could identify patients at low risk of recurrence, we dichotomized the D-dimer variable by merging the upper three quartiles and used this upper category as the reference group. The HRs were estimated in two models; the first was adjusted for age and sex, and the second was additionally adjusted for duration of anticoagulant treatment. The proportional hazards assumption was tested for all variables using Shoenfeld residuals. Cumulative incidences were calculated and visualized in 1-Kaplan-Meier (1-KM) plots, both for overall VTE and in subgroups of VTE (i.e. among provoked and unprovoked first VTE events, and among first DVTs and PEs). In analyses according to clinical presentation, patients were classified as having isolated DVT or PE (with or without concurrent DVT).

In the presence of competing risk by death the cumulative incidence of recurrence is dependent on both the hazard of VTE and the hazard of death, and consequently the 1-KM is often overestimated in the regular analyses [24–26]. In order to evaluate the influence of the competing risk by death, sub-distribution hazard ratios (SHRs) and cumulative incidence functions (CIFs) were performed and visualized for overall VTE recurrence using the stcrreg and the stcrreg cif curve commands in Stata. All statistical analyses were performed using Stata version 14.0 (Stata Corporation LP, College Station, TX, USA).

Previous studies have shown that women with estrogen-related VTE and patients with distal DVT have a low risk of recurrence [16,27–30]. As these conditions may also be associated with low D-dimer levels, we performed sensitivity analyses in patients without estrogen-associated VTE, as well as in patients with proximal DVT, in order to rule out potential confounding by such low-risk groups.

Results

Baseline characteristics and distribution of risk factors according to quartiles of D-dimer are presented in Table 1. Compared with the upper three quartiles, subjects in the lowest quartile tended to be younger and more likely female, and a slightly higher proportion were obese. Additionally, patients in the lowest quartile tended to be treated with anticoagulants for a shorter duration of time (< 6 months) than patients in the upper three quartiles. Co-morbidities and acute medical conditions were less common among patients with a D-dimer in the lowest quartile.

Of the 454 eligible patients with a validated first lifetime VTE, 84 patients experienced a recurrent VTE event during a median of 3.9 years of follow-up. Crude recurrence rates and hazard ratios of recurrent VTE according to quartiles of D-dimer are presented in Table 2. Compared with quartile 4, patients with a D-dimer value in quartile 2 (HR, 0.88; 95% CI, 0.50–1.58) and quartile 3 (HR, 1.00; 95% CI, 0.56–1.57) had a similar risk of recurrence, whereas patients with a D-dimer below 1500 ng mL^{-1} had a 55% lower risk of recurrence (HR, 0.45; 95% CI, 0.23–0.89). The results were essentially similar in the competing risk model. The 10-year cumulative incidence of recurrence was 33.2% (95% CI, 21.2–49.5), 34.2% (95% CI, 23.0–48.7) and 34.8% (95% CI, 21.6–52.9) among patients with a D-dimer value in quartile 2, 3 and 4, respectively, and 14.4% (95% CI, 8.4–23.8) in patients with a D-dimer value in quartile 1 (Fig. 1A). The corresponding 1- and 5-year cumulative incidence estimates were 1.7% (95% CI, 0.4–6.6) and 8.5% (95% CI, 4.5–15.8) in quartile 1, 6.0% (95% CI, 2.8–13.0) and 22.9% (95% CI, 15.1–33.9) in quartile 2, 7.8% (95% CI, 4.0–15.0) and 23.7% (95% CI, 15.6–35.1) in quartile 3, and 9.0% (95% CI, 4.8–16.6) and 23.0% (95% CI, 15.4–33.6) in quartile 4. In competing risk analyses (Fig. 1B), the 10-year cumulative incidence estimate of recurrence dropped by almost 10% in the upper three quartiles (quartile 2: 24.2%, quartile 3: 26.2% and quartile 4: 24.8%), whereas it remained essentially unchanged in patients with a D-dimer in the lowest quartile (14.1%). Analyses restricted to the time after termination of anticoagulant therapy produced similar results (Figure S2).

Risk estimates of recurrent VTE according to a D-dimer cut-off of ≤ 1500 ng mL^{-1}, for overall VTE and in subgroups of VTE patients, are shown in Table 3. For overall VTE, the crude incidence rate was 1.7 (95% CI, 1.0–2.9) per 100 person-years in the lower quartile (≤ 1500 ng mL^{-1}) and 4.9 (95% CI, 3.9–6.1) per 100 person-years in the upper three quartiles combined, yielding an absolute risk difference of 3.2 per 100 per year. The overall recurrence risk was 53% lower in patients with a

Table 1 Baseline characteristics across quartiles (Q) of D-dimer

	Q1 (n = 122)	Q2 (n = 105)	Q3 (n = 116)	Q4 (n = 111)
D-dimer range (ng mL^{-1})	≤ 1500	1600–3000	3100–7000	≥ 7100
Age (years)	62.0 ± 16.23	66.1 ± 13.6	66.4 ± 14.5	69.1 ± 14.3
Sex (% women)	59.8%	46.7%	45.7%	49.6%
Obesity (% obese)	21.3%	18.1%	19.0%	13.5%
Deep vein thrombosis	58.2%	57.1%	60.3%	49.5%
Pulmonary embolism	41.8%	42.9%	39.7%	50.5%
Treatment duration with AC				
0–3 months	21.3%	14.3%	20.7%	11.7%
3–6 months	54.1%	52.4%	44.8%	44.1%
6–12 months	21.3%	25.7%	26.7%	35.1%
> 12 months	3.3%	7.6%	7.8%	9.0%
Duration of symptoms				
0–2 days	36.9%	34.3%	29.3%	41.4%
3–7 days	27.1%	39.1%	38.8%	31.5%
>7 days	32.9%	22.9%	29.3%	20.7%
Clinical risk factors				
Estrogens	9.8%	5.7%	8.6%	6.3%
FHVTE	6.6%	6.7%	4.3%	4.5%
Co-morbidity (%)	14.8%	21.9%	18.1%	20.7%
Pregnancy/postpartum	1.6%	1.0%	0.0%	2.7%
Surgery (%)	13.1%	10.5%	16.4%	12.6%
Trauma (%)	13.1%	6.7%	9.5%	9.9%
Acute medical condition (%)	2.5%	7.6%	9.5%	14.4%
Confined to bed > 3 days preceding	1.6%	1.0%	3.4%	2.7%
Other immobilization	15.6%	6.7%	10.4%	12.6%
Other provoking factor	4.1%	2.9%	3.5%	2.7%

Values are means ± 1 SD or percentages. AC, anticoagulants; FHVTE, family history of VTE; VTE, venous thromboembolism.

Table 2 Incidence rates and risk of recurrent venous thromboembolism (VTE) by quartiles (Q) of D-dimer

D-dimer (ng mL^{-1})	Recurrences	IR (95% CI)*	HR (95% CI)	SHR (95% CI)
Q4 (≥ 7100)	23	5.43 (3.61–8.17)	Ref.	Ref.
Q3 (3100–7000)	24	4.65 (3.11–6.93)	1.00 (0.56–1.77)	1.07 (0.60–1.90)
Q2 (1600–3000)	23	4.60 (3.06–6.92)	0.88 (0.50–1.58)	0.98 (0.64–1.76)
Q1 (0–1500)	14	1.71 (1.02–2.90)	0.45 (0.23–0.89)	0.53 (0.27–1.06)

HRs are adjusted for age and sex. CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, sub-distribution hazard ratio.*Per 100 person-years.

D-dimer ≤ 1500 ng mL^{-1} as compared with patients with a D-dimer > 1500 ng mL^{-1} (HR, 0.47; 95% CI, 0.26–0.84) in the age- and sex-adjusted model. Stratification by provoked and unprovoked VTE, and by DVT and PE, revealed that the association was particularly pronounced among unprovoked events and among patients with incident DVT, showing a 64% (HR, 0.36; 95% CI, 0.17–0.77) and 69% (HR, 0.31; 95% CI, 0.14–0.70) reduced risk of recurrence, respectively. D-dimer ≤ 1500 ng mL^{-1} was also associated with lower risk estimates in patients with provoked VTE (HR, 0.69; 95% CI, 0.27–1.72) and patients with PE (HR, 0.78; 95% CI, 0.33–1.87), but the results were not statistically significant (Table 3). Additional adjustment for duration of anticoagulant treatment had negligible effect on the risk estimates (Table 3, Model 2).

Cumulative incidence of VTE recurrence according to quartiles of D-dimer in patients with unprovoked VTE and DVT are shown in Fig. 2. Among patients with unprovoked VTE, a similar pattern to that for overall VTE was observed (Fig. 2A), with considerably higher 10-year cumulative incidences among patients with D-dimer levels above than below 1500 ng mL^{-1} (quartile 2, 39.7%, 95% CI 23.9–60.9; quartile 3, 39.8%, 95% CI 24.7–59.6; quartile 4, 26.4%, 95% CI 15.3–43.2; vs. quartile 1, 12.8%, 95% CI 6.5–24.4). In quartile 1, the 1- and 5-year cumulative incidences of recurrence were 1.4% (95% CI, 0.2–9.3) and 10.5% (95% CI, 5.1–20.9), respectively. Among patients with DVT, the 10-year cumulative incidence of recurrence ranged from 14.6% (95% CI, 7.1–28.7) among patients with a D-dimer value below 1500 ng mL^{-1} to 51.3% (95% CI, 31.5–74.6) in patients with a D-dimer ≥ 7100 ng mL^{-1} (Fig. 2B). In subjects with provoked VTE and PE, the cumulative incidence of recurrence was essentially similar to that of overall VTE in those with D-dimer ≤ 1500 ng mL^{-1} (16.7% and 13.6%), but the effect across quartiles was not as consistent as for unprovoked VTE and DVT (Figure S1).

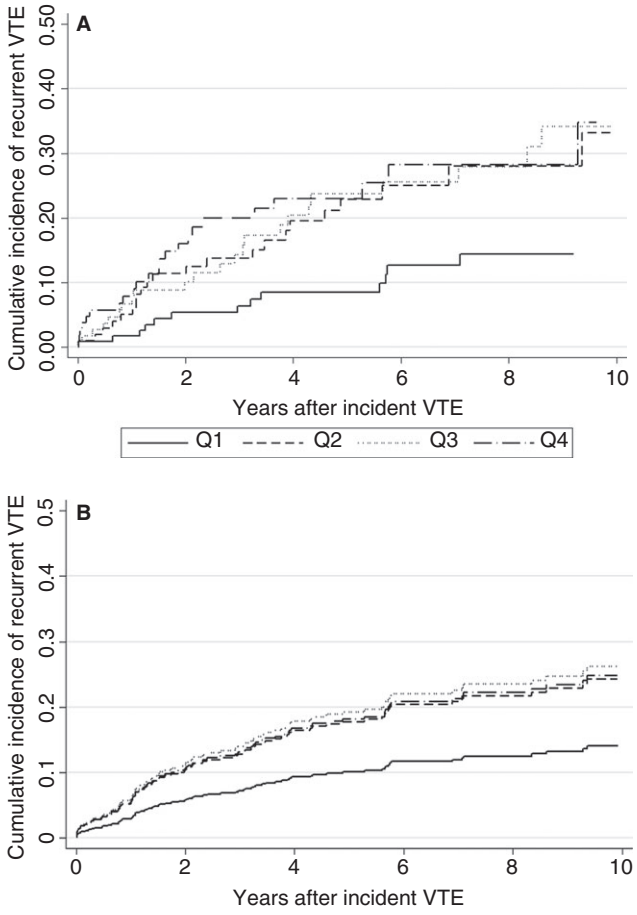

Fig. 1. Cumulative incidence of venous thromboembolism (VTE) recurrence stratified by quartiles of D-dimer in crude analyses (Panel A) and with death as a competing event (Panel B).

Analysis restricted to patients without estrogen-related VTE and analysis of patients with proximal DVT showed similar results (Table S1).

Discussion

In the present study, we investigated whether D-dimer measured at the time of VTE diagnosis, before initiation of anticoagulant therapy, was associated with risk of recurrence. We found that subjects with a D-dimer value ≤ 1500 ng mL^{-1} had a substantially lower risk of VTE recurrence compared with patients with a D-dimer > 1500 ng mL^{-1}. The overall incidence rate of recurrence was 1.7 per 100 person-years in those with D-dimer ≤ 1500 ng mL^{-1}, and the 10-year cumulative incidence was 14%. The association between low D-dimer and recurrence was particularly pronounced among patients with incident DVT and in patients with a first unprovoked VTE event, who had a 69% and 64% lower risk of recurrence, respectively. The corresponding absolute risk differences were 4.1 and 3.5 per 100 persons per year. Our findings suggest that a low D-dimer measured at the time of VTE diagnosis may aid decisions on short-term treatment, particularly in patients with unprovoked VTE. However, our findings need to be confirmed in additional observational studies and tested in clinical randomized studies.

To our knowledge, no previous study has investigated the association between D-dimer measured at the time of VTE diagnosis and the risk of recurrent events. In THE-VTE study [31], patients with an elevated D-dimer level (> 500 ng mL^{-1}), measured 2–3 months after discontinuation of anticoagulation, had a more than 2-fold higher risk of recurrence than patients with a normal D-dimer level, and the absolute recurrence rate was 1.8 per 100 person-years in those with normal D-dimer. In a cohort of 610 VTE patients [32], D-dimer levels measured shortly after discontinuation of anticoagulant therapy were related to risk of recurrence, with the risk being 40% and 70% reduced in patients with a D-dimer in the range

Table 3 Incidence rates and risk of recurrent venous thromboembolism (VTE) by categories of D-dimer

D-dimer (ng mL^{-1})	Recurrences	IR (95% CI)*	HR (95% CI)†	HR (95% CI)‡
Overall				
Q2–Q4 (≥ 1600)	70	4.86 (3.85–6.14)	Ref.	Ref.
Q1 (0–1500)	14	1.71 (1.02–2.90)	0.47 (0.26–0.84)	0.46 (0.25–0.82)
Unprovoked				
Q2–Q4 (≥ 1600)	46	5.43 (4.07–7.25)	Ref.	Ref.
Q1 (0–1500)	8	1.57 (0.79–3.14)	0.36 (0.17–0.77)	0.34 (0.15–0.74)
Provoked				
Q2–Q4 (≥ 1600)	24	4.05 (2.71–6.03)	Ref.	Ref.
Q1 (0–1500)	6	1.95 (0.88–4.35)	0.69 (0.27–1.72)	0.68 (0.27–1.73)
DVT				
Q2–Q4 (≥ 1600)	50	5.77 (4.37–7.61)	Ref.	Ref.
Q1 (0–1500)	7	1.40 (0.67–2.95)	0.31 (0.14–0.70)	0.32 (0.14–0.71)
PE				
Q2–Q4 (≥ 1600)	20	3.49 (2.25–5.40)	Ref.	Ref.
Q1 (0–1500)	7	2.20 (1.05–4.62)	0.78 (0.33–1.87)	0.66 (0.27–1.63)

CI, confidence interval; HR, hazard ratio; IR, incidence rate. *Per 100 person-years. †HRs are adjusted for age and sex. ‡HRs are adjusted for age, sex and duration of anticoagulant treatment.

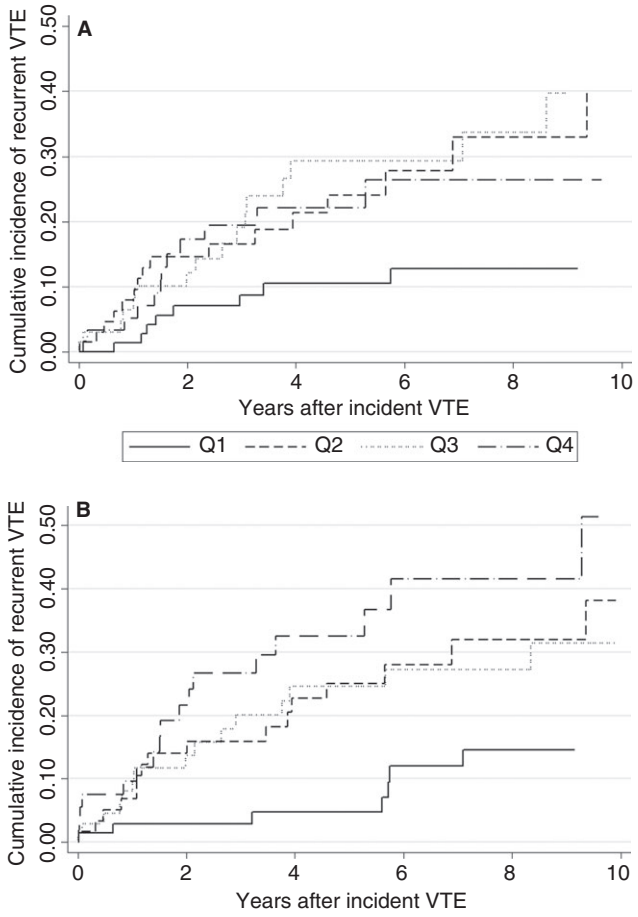

Fig. 2. Cumulative incidence of venous thromboembolism (VTE) recurrence stratified by quartiles of D-dimer in patients with unprovoked VTE (Panel A) and in patients with deep vein thrombosis (DVT) (Panel B).

250–750 ng mL^{-1} and < 250 ng mL^{-1}, respectively, as compared with patients with a D-dimer ≥ 750 ng mL^{-1}. Furthermore, a 2.6-fold increased risk of recurrence was found for patients with elevated compared with normal D-dimer in a patient level meta-analysis investigating the ability of D-dimer to assess recurrence risk after unprovoked VTE [13]. The annualized recurrence rates ranged from 2.0 to 4.2, and from 7.4 to 10.2, per 100 for those with normal compared with elevated D-dimer, respectively [13]. In the PROLONG study [33], elevated D-dimer measured 1 month after discontinuation of treatment was associated with a 2.5-fold increased risk of adverse outcomes (recurrent VTE or major bleeding), and the absolute rates were 4.4 and 10.9 per 100 person-years for patients with normal and elevated D-dimer, respectively.

Current treatment guidelines for VTE recommend at least 3 months of anticoagulant therapy [34], with subsequent evaluation of the risk–benefit ratio for extended therapy in patients with unprovoked DVT or PE. Whether D-dimer levels measured 1 month after anticoagulation withdrawal can be used to select patients with unprovoked VTE who can stop anticoagulant therapy is debated [27]. In our study, patients with a D-dimer level ≤ 1500 ng mL^{-1} measured in the acute phase of VTE had a low absolute risk of recurrence. Noticeably, the recurrence rates observed in the lowest D-dimer category in our study were similar to [31] or lower than [13,33] the rates among patients with normal D-dimer (i.e. < 500 ng mL^{-1}) in studies that measured D-dimer after treatment withdrawal. The absolute recurrence rates in those with D-dimer ≤ 1500 ng mL^{-1} were 1.7% at 1 year and 8.5% at 5 years for overall VTE, and correspondingly 1.4% and 10.5% in those with unprovoked VTE. Of note, these rates are below the rates considered acceptable to justify stopping anticoagulation (5% at 1 year and 15% at 5 years) according to the recommendation from the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis [35]. However, because of limited statistical power in subgroups, some of the confidence intervals exceeded the upper limit of the recommended rates, and our findings should therefore be interpreted with some caution.

As information on D-dimer is widely available for most VTE patients at the time of diagnosis, the potential use of D-dimer to identify patients at low risk of recurrence may have great clinical utility for the initial decision on treatment duration and further follow-up of the patients. Current risk prediction models for VTE recurrence among patients with a first unprovoked VTE, such as the Vienna prediction model [16], the DASH prediction rule [15] and the Men continue and HER DOO2 rule [17], all make use of D-dimer measurements during or after anticoagulation, together with clinical predictors, to distinguish patients at high and low risk of recurrence. The clinical elements included in these rules can usually be assessed at the initial patient examination. Thus, if D-dimer assessment before start of anticoagulation can be utilized in similar upcoming prediction models to identify patients at low risk of recurrence, it may prove valuable for both clinicians and patients. For the clinicians, it may provide the opportunity to make decisions on treatment duration upon hospital discharge, and reduce the need for additional outpatient care after discontinued treatment. For the patients, information on the prognosis of the disease may provide well-appreciated reassurance and, as the need for additional blood sampling is reduced, the patients will be less subjected to additional discomfort.

Women with estrogen-related first VTEs and patients with distal DVT have previously been shown to have a low risk of recurrence [16,27–30]. To investigate whether the observed association could be driven by such low-risk patient groups, we performed separate analyses excluding women with estrogen-associated first VTEs, as well as analysis restricted to patients with proximal DVT. The results of these sub-studies were essentially similar to those of the overall analysis and analysis of all DVT patients, respectively. Furthermore, neither adjustment for duration of anticoagulant treatment nor analysis of

the cumulative incidence with and without death as a competing event after cessation of anticoagulant treatment noticeably altered the results.

Recruitment of VTE patients from a general population, high attendance rates, prospective design and long-term follow-up are among the main strengths of the present study. Furthermore, all VTE-related health care in the municipality of Tromsø is provided by a single hospital, which together with comprehensive case validation through a multimodal approach, firm criteria and extensive review of medical records, enhances the probability of a complete and accurate VTE register. The study also has some limitations. Around 16% of the eligible patients were excluded because of missing D-dimer values. However, patient characteristics and incidence rates of recurrence were essentially similar in those with and without missing values of D-dimer, indicating that the missing value was presumably at random, and thereby would not be likely to introduce selection bias. Second, two different assays were used to assess D-dimer levels during the study period. Although the Sta-Liatest has consistently reported excellent analytical properties [36–38], there are conflicting results regarding the NycoCard D-dimer assay. However, the majority of the D-dimer measurements were assessed using the Sta-Liatest (Diagnostica Stago®) and when we restricted our analysis to include only measurements from the validated Sta-Liatest (Diagnostica Stago®) the results remained essentially the same (data not shown). It is therefore unlikely that comprehensive misclassification has occurred as a result of the poor analytical properties of the NycoCard D-dimer assay. Unfortunately, we did not have information on post-anticoagulation D-dimer values in our study. Thus, we could not assess whether patients with a low D-dimer at the time of first VTE diagnosis had a negative D-dimer (< 500 ng mL^{-1}) after anticoagulation.

In conclusion, a low D-dimer (≤ 1500 ng mL^{-1}) measured at the time of first VTE diagnosis identified a quarter of the patients as having a low risk of recurrence. The association was particularly pronounced among patients with a first unprovoked event and in patients with DVT. Our findings suggest that D-dimer, measured at VTE diagnosis, may be used to identify VTE patients at low risk of recurrence and guide decisions on short-term anticoagulation in these patients. Further studies are needed to confirm our findings and to investigate whether D-dimer, measured at the time of first VTE diagnosis, could replace or improve the contemporary use of post-anticoagulation D-dimer measurements in existing prediction models.

Addendum

E. Bjøri contributed to data analysis and writing the manuscript. H. S. Johnsen contributed to data interpretation and revision of content. J.-B. Hansen contributed to the conception and design of the study, data collection and interpretation, and revision of content. S. K. Brækkan contributed to the conception and design of the study, data collection and interpretation, and writing the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Incidence rates and risk of recurrent venous thromboembolism (VTE) by quartiles (Q) of d-dimer in analyses restricted to non-estrogen-related VTE and proximal deep vein thrombosis (DVT).
Figure S1. Cumulative incidence of venous thromboembolism (VTE) recurrence stratified by quartiles of D-dimer in patients with incident pulmonary embolism (Panel A) and in patients with a first provoked VTE event (Panel B).
Figure S2. Cumulative incidence of venous thromboembolism (VTE) recurrence stratified by quartiles of D-dimer after estimated termination of anticoagulant therapy in crude analysis (panel A) and with death as a competing event (Panel B).

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