# Venous thromboembolism: Risk factors, comorbidities, and treatment-associated risk of bleeding

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**2023**

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ISBN 978-91-8069-463-6 (PRINT)
ISBN 978-91-8069-464-3 (PDF)
http://hdl.handle.net/2077/78554

Cover illustration: Lungor med lunginfarkt by Emma Sandblad, 11 years old.

Printed by Stema Specialtryck AB, Borås, Sweden

Trycksak
3041 0234

*To Staffan, Emma, and Gustav*

## ABSTRACT

*Background*: Venous thromboembolism (VTE) is the third most common cardiovascular disease, consisting mainly of deep vein thrombosis (DVT) and pulmonary embolism (PE). Since VTE often is a preventable disease, knowledge of risk factors is critical. Following a VTE, many patients are subjected to extended anticoagulant treatment. However, the bleeding risk during extended treatment is largely unknown.

*Aim*: To study risk factors in patients with VTE and to determine the occurrence of major bleeding during VTE treatment.

*Methods*: Paper *I*: 1.6 million men from The Swedish Military Service Conscription Register were grouped based on BMI and followed through nationwide registries to determine the risk of a first-time VTE. Papers *II-IV*: The National Patient Register, the National Cause of Death Register, the National Prescribed Drug Register, and the Total Population Register were used to identify almost 300,000 patients with first-time PE or DVT and 1,200,000 matched controls. PE and DVT patients and their respective controls were compared regarding comorbidities and temporary provoking factors (*II*), the prevalence of different cancers (*III*), and, between 2014–2020, the risk of bleeding during anticoagulant treatment (*IV*).

*Results*: Paper *I*: Men who were overweight or obese at enlistment had a high risk of VTE later in life. Paper *II*: Patients with PE more often had underlying cardiovascular disease, while patients with DVT were more likely to have recent musculoskeletal surgery or fracture. Paper *III*: VTE had a strong association with pancreatic, brain, or liver cancer, while the association was weak with recent diagnoses of bladder/urinary tract cancer, kidney cancer, or uterine cancer. Paper *IV*: During initial treatment (0–6 months), patients treated with apixaban had a lower bleeding risk than patients treated with warfarin or rivaroxaban. During extended treatment (6 months–5 years), both apixaban and rivaroxaban had a low bleeding risk, lower than warfarin.

*Conclusion*: The increasing prevalence of obesity might imply an increase in VTE in the coming decades. Patients with cardiopulmonary disease had a higher risk of PE than DVT. Risks of VTE differ widely for various cancers. Apixaban carried a lower risk of bleeding than rivaroxaban and warfarin in the initial treatment, while both apixaban and rivaroxaban had a low risk of bleeding, and lower than warfarin, in extended treatment. These findings are important for VTE prophylaxis and treatment in clinical praxis.



**Keywords**: Venous thromboembolism, registries, overweight, body mass index, incidence, cardiovascular disease, anticoagulants, apixaban, rivaroxaban, warfarin, hemorrhage.

ISBN 978-91-8069-463-6 (PRINT)
ISBN 978-91-8069-464-3 (PDF) http://hdl.handle.net/2077/78554

## LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I Glise Sandblad K, Jern S, Åberg M, Robertson J, Torén K, Lindgren M, Adiels M, Hansson PO, Rosengren A. Obesity in adolescent men increases the risk of venous thromboembolism in adult life.
*J Intern Med. 2020;287:734–745.*

II Glise Sandblad K, Rosengren A, Sörbo J, Jern S, Hansson PO. Pulmonary embolism and deep vein thrombosis—comorbidities and temporary provoking factors in a register-based study of 1.48 million people.
*Res Pract Thromb Haemost. 2022;6:e12714.*

III Glise Sandblad K, Hansson PO, Philipson J, Mahmoud A, Karlsson P, Rosengren A, Sörbo J. Prevalence of Cancer in Patients with Venous Thromboembolism: A Retrospective Nationwide Case-Control Study in Sweden.
*Clinical and Applied Thrombosis/Hemostasis. 2023;29:1-10.*

IV Glise Sandblad K, Schulman S, Rosengren A, Sörbo J, Philipson J, Hansson PO. Association of type of oral anticoagulation with risk of bleeding in 45,114 patients with venous thromboembolism during initial and extended treatment - A nationwide register-based study.
*J Intern Med. 2023;00:1–18.*

## SAMMANFATTNING PÅ SVENSKA

Blodproppar i benens vener (DVT) och i lungans blodkärl (LE) kallas venös tromboembolism (VTE). Det är den tredje vanligaste hjärt-kärlsjukdomen i världen, med hög dödlighet och lidande samt höga, ökande sjukdomsrelaterade kostnader. Syftet med denna avhandling var att 1) kartlägga bakomliggande sjukdomar vid venös tromboembolism (VTE), främst övervikt och olika typer av cancer, 2) skillnader i riskfaktorer mellan blodproppar i ben och lungor samt 3) förekomst av allvarliga blödningar vid behandling med blodförtunnande läkemedel efter VTE.

### Metod

*Delarbete I*: 1.6 miljoner män från Värnpliktsregistret delades upp i grupper beroende på Body mass index (BMI) vid mönstring och följdes upp i landsomfattande register för att fastställa hur många som drabbades av VTE under uppföljningstiden.

*Delarbete II*: I data från Patientregistret, Dödsorsaksregistret, Läkemedelsregistret och Totalbefolkningsregistret identifierades alla VTE-patienter mellan 1987–2018 (ca 300,000 st) och deras matchade kontrollpersoner utan VTE (ca 1,200,000 st). Patienter och kontroller jämfördes för att avgöra förekomst av samsjuklighet mellan DVT och LE.

*Delarbete III*: Samma registeruttag som i Delarbete *II*. Män och kvinnor med VTE jämfördes med sina respektive kontroller avseende förekomst av olika typer av cancer inom ett år före VTE-diagnosen.

*Delarbete IV*: Samma registeruttag som i Delarbeten *II* och *III*, men i denna studie följdes patienter med VTE 2014–2020 för att avgöra blödningsförekomst under initial behandling (0–6 månader) och förlängd behandling (6 månader upp till 5 år).

### Resultat

*Delarbete I*: Vi fann att män med övervikt och fetma vid mönstring hade hög risk för VTE senare i livet.

*Delarbete II*: Patienter med LE hade i större utsträckning bakomliggande hjärt-kärlsjukdomar, medan patienter med DVT i högre utsträckning nyligen hade genomgått ortopedisk operation eller haft en nedre extremitetsfraktur.

*Delarbete III*: Samsjukligheten mellan VTE och cancer varierade mycket mellan olika cancertyper. Patienter med VTE hade höga odds för en nylig diagnos av cancer i bukspottskörteln, hjärnan eller levern.

*Delarbete IV*: Patienter som behandlades med läkemedlet apixaban (Eliquis) hade lägre blödningsrisk än patienter med warfarin- (Waran) eller rivaroxaban- (Xarelto) behandling under de första sex månadernas behandling. Vid förlängd behandling sågs ingen säker skillnad mellan patienter som behandlades med apixaban jämfört med rivaroxaban, men båda hade en lägre risk än warfarin.

## Betydelse

Ökande förekomst av fetma i befolkningen kommer troligen att medföra en ökning av VTE de kommande decennierna. Att DVT och LE har olika samsjuklighet kan ha betydelse för vilka patienter som bör få förebyggande behandling (profylax) mot VTE eftersom LE är mer allvarligt än DVT. Risken för VTE vid olika cancerformer varierar mycket och kräver individuell bedömning. Apixaban verkar medföra lägre risk för blödning än rivaroxaban och warfarin vid initial behandling. Vid förlängd behandling är både apixaban och rivaroxaban förknippade med en låg blödningsrisk, lägre än för warfarin.

## CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| BMI | Body Mass Index |
| CDT | Catheter-directed treatment |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CT | Computed tomography |
| CTEPH | Chronic thromboembolic pulmonary hypertension |
| CTPA | Computed tomography pulmonary angiography |
| DVT | Deep vein thrombosis, djup ventrombos |
| ECMO | Extracorporeal membrane oxygenation |
| HR | Hazard ratio |
| ICD | International Classification of Diseases |
| IQR | Interquartile range |
| LE | Lungemboli |
| DOAC | Direct oral anticoagulant |
| OR | Odds ratio |
| PAR | Population attributable risk |
| PE | Pulmonary embolism |
| PPV | Positive predictive value – the proportion of subjects with a positive test result who have the disease of interest |
| PTS | Post thrombotic syndrome |
| RCT | Randomized controlled trial |
| VTE | Venous thromboembolism, venös tromboembolism |
| VKA | Vitamin-K Antagonist |

# INTRODUCTION

## Venous thromboembolism

Venous thromboembolism (VTE) occurs when a blood clot forms in a vein, most commonly as deep vein thrombosis (DVT) in the lower extremities or pulmonary embolism (PE). Most PEs embolize from a DVT in a lower extremity and travel to the lung arteries. However, they can also develop in the right atrium[1] of the heart or *in situ* in the lung vessels, i.e., as pulmonary thrombosis[2]. Venous thrombosis can also occur in other veins, such as upper extremity veins, splanchnic veins, and the cerebral venous sinuses.

### *Hemostasis*

Hemostasis is a tightly balanced, local process that produces a blood clot in areas of blood vessel injury but also limits the clot's extension and lyses the clot when vascular integrity is restored[3]. It constitutes a highly complex system of many interrelated components, including the vessel wall, platelets, coagulation factors, anticoagulant proteins, and the fibrinolytic system. If the balance in the hemostatic system is tilted, the result is either bleeding or a blood clot.

### *Blood clots*

Blood clot formation depends on the type of vessel in which the clot develops.

*Arterial blood clots* are formed when an atherosclerotic plaque ruptures and platelets are recruited to the site[4]. The platelets are activated, and additional platelets are recruited. Following the exposure of tissue factor from the atherosclerotic plaque, coagulation factors are activated, generating fibrin, and the clot develops.

By contrast, *venous thromboembolism* is often initiated in venous valve pockets, where the flow is irregular, and the oxygen tension may be low, promoting thrombi[5]. The clots are rich in fibrin and are often called red clots due to trapped red blood cells.

### *Development of VTE – Virchow's triad*

The development of VTEs is traditionally looked upon as the result of alterations in the so-called Virchow's triad; stasis/changes in blood flow, endothelial damage or dysfunction, and hypercoagulability[6]. Even though this simplified explanatory model has been questioned, both concerning its origin and accuracy[7], many risk factors of VTE can be derived from this triad hypothesis.

*Stasis:* Reduced blood flow and stasis can be caused by surgery, obesity, immobilization, and paralysis[5]. It can also explain the increased risk of left-sided DVT in pregnancy (compression of the left common iliac vein) and patients with May-Thurner

syndrome (compression of the left common iliac vein by the left common iliac artery leading to scarring and reduced blood flow in the vein) [8]. Mechanistically, the reduced blood flow is thought to lead to activation of the endothelium with expression of adhesion proteins such as von Willebrand factor and p-selectin[9]. Leucocytes and platelets are accumulated, and fibrin is formed.

*Endothelial damage:* Under physiological conditions, the endothelial surface prevents attachment of proteins required for clotting and suppresses coagulation by release of anticoagulant and profibrinolytic factors[5]. However, endothelial damage/dysfunction can lead to downregulation of their expression and upregulation of the tissue factor expression, which has a strong procoagulant action.

*Hypercoagulability:* Genetic and acquired forms of thrombophilia, advanced age, cancer, obesity, hormone contraceptives, and pregnancy are all hypercoagulable states[5]. Hypercoagulability can, as in pregnancy, be due to both an up-regulation of procoagulant factors such as factor VII, VIII, X, fibrinogen, and von Willebrand factor and a decrease of anticoagulants such as Protein S[10]. Hypercoagulability can also, as in obesity, result from lower fibrinolytic capacity due to decreased levels of plasminogen activator inhibitor (PAI-1) in combination with increased procoagulant tissue factor and increased platelet activation[11,12].

## Historical remarks

One of the first descriptions of well-documented cases of DVT originates from the 13$^{th}$ century[13]. Pregnancy and the post-partum period were early recognized as risk factors, leading to various theories on origin, including breast milk accumulating in the legs[14]. In the 19$^{th}$ and early 20$^{th}$ centuries, DVT treatment included ligating large veins such as the inferior vena cava (to prevent PE), strict bed rest, and bloodletting[13].

Heparin was discovered in the 1910s, and following its purification in the 1930s, human treatment was made possible[13]. Heparin was reported to represent a breakthrough in treatment with dramatically improved survival in patients with DVT[15]. Around the same time, the first discoveries leading to Vitamin K- antagonist (VKA) treatment were made[13]. A hemorrhagic disease was spread in cattle in the US in the early 20th century and was later found to be caused by spoiled clover. About 20 years later, dicumarol was found in moldy hay, and it was discovered that the effect of both spoiled clover and dicumarol could be reversed by Vitamin K. Dicumarol was thereafter introduced to treat VTE.

A benefit of a combination of heparin and VKA treatment was reported in the late 1940s[16]. With the introduction of LMWH in the 1980s[17] and new insights into the benefit of early ambulation and compression stockings[18], the treatment of DVT was changed from a bedridden in-hospital treatment to ambulatory outpatient treatment. Over the past decade, outpatient treatment has also been included in guidelines as a treatment option for patients with low-risk PE[19-22], facilitated by the introduction of direct oral anticoagulants, DOACs.

## Incidence, risk factors, and preventive measures

### *Incidence*

The annual incidence of VTE has been reported to be 75–269 per 100,000 persons in the Western world and Southern Latin America[23]. Studying PE separately, incidences of 23–115 per 100,000 patient-years have been reported in North America and Europe. For DVT, the corresponding numbers are 48–162 per 100,000. By contrast, yearly incidence numbers from Southeast Asia show a much lower rate of 8–17 per 100,000 population[23]. These ethnic differences have been debated since the incidence numbers may have been skewed by a probable under-diagnosis in Asian countries[24]. However, in studies on populations with different ethnicities living in the same geographical area, the differences remain, suggesting that the differences are real[24].

Regardless of nationality, the incidence increases sharply with increasing age[23,25]. Previous reports have indicated a ten times higher risk in patients above the age of 80 compared to patients between 40 and 50 years of age[23].

The incidence of VTE is increasing over time, mainly driven by the incidence of PE[20,26]. This development has been parallel to better accessibility of computed tomographic pulmonary angiography (CTPA) [26], and a part of the increase is probably due to the diagnosis of PEs that might be clinically insignificant, for example, small emboli in asymptomatic patients undergoing CT scan for cancer follow-up[27]. Other possible contributing reasons for the increased incidence are improved cancer treatment and survival[28] and the global burden of obesity[29,30], increasing the number of individuals at increased risk of VTE.

### *Risk factors*

VTE is, in many cases, a preventable disease. The development of VTE is often a consequence of the combination of underlying patient-related and situation-related risk factors[20]. Identification of high-risk individuals and situations is therefore of interest. Among the most potent patient-related risk factors are thrombophilias (notably antiphospholipid syndrome) and metastatic cancer, whereas high-risk situations include major trauma and fractures, as well as hospitalization *per se*[31].

*Obesity*

Obesity is a growing problem in large parts of the world but with a widely varying magnitude of the problem. The mean BMI in 2019 among 19-year-olds in Pacific Island countries in Oceania was above 28 kg/m$^2$, closely followed by the USA, New Zealand, Middle Eastern countries, North African countries, and the Caribbean Islands. By contrast, countries in east and central Africa, central European countries such as Romania and Bosnia, and Japan had average BMIs 9–10 kg/m$^2$ lower[32]. European guideline estimations on the effect of overweight and obesity on the risk of VTE[20] are based on studies performed decades ago[33] and might not represent the current situation, when more severe forms of obesity are increasing[34]. Also, the effect

of being overweight or obese early in life on the future risk of VTE, important for prognostication of future health care needs, has been scarcely studied.

*Cancer*

Cancer is an important risk factor for VTE, with around 20% of all VTE cases occurring in patients with cancer[35]. VTE can also be the first manifestation of occult cancer, detected in 5% of patients within a year of a seemingly unprovoked VTE[36]. The association between VTE and cancer varies with the type, stage, and treatment of cancer[28]. Reports on high thrombogenicity of specific cancer types, such as pancreatic and brain cancer, have been relatively consistent[28]. However, in other types of cancer, such as kidney and bladder cancer, data is less clear[37-39].

*Cardiovascular comorbidities*

The association between VTE and atherosclerotic diseases such as myocardial infarction has led to discussions concerning whether risk factors for arterial diseases also predispose to VTE[20]. However, although some risk factors are common to both conditions, such as obesity and cigarette smoking, the most important association seems to be increased risk of VTE, mainly PE, after hospitalization for acute cardiac disease[40-42]. The increased risk associated with cigarette smoking could be mediated by increased risk of myocardial infarction and cancer[43]. Stroke is also a well-recognized risk factor of VTE, with a high occurrence of VTE in particular within the first months[44] and with previous data indicating higher VTE rates for hemorrhagic than ischemic stroke[45].

*Chronic obstructive pulmonary disease*

PE is an important differential diagnosis in acute exacerbations of chronic obstructive pulmonary disease (COPD), with a reported prevalence of 14.4% in a meta-analysis of studies with a standardized protocol for examination of PE[46]. Previous data indicate that patients with COPD are at a higher risk of PE than DVT[47].

*Surgery, trauma*

Surgery is among the most well-recognized risk factors for VTE, and the use of pharmacologic thromboprophylaxis is widely spread. This, together with refined surgical techniques, earlier mobilization, and shorter hospital stays, has reduced the incidence of postoperative VTE. For instance, patients undergoing major orthopedic surgery before 1980 had a reported incidence of symptomatic VTE of around 30%, including cases of fatal PE[48], while the current untreated 35-day baseline risk has been calculated at 4.3% for major orthopedic surgery[49]. The usage of pharmacologic thromboprophylaxis reduces the risk by approximately 50%[49].

*Thrombophilias*

Thrombophilias can be both inherited and acquired. Among widely recognized inherited thrombophilias are factor V Leiden (the most common mutation leading to activated protein C-resistance), prothrombin G20210A mutation, deficiencies of protein C, protein S, and antithrombin[50]. Of these, factor V Leiden is the most common in Caucasians (5–10% are carriers), with a 5-fold risk increase for thrombosis in individuals with a heterozygous mutation and a 50-fold increase in patients with a homo-

zygous mutation. Prothrombin G20210A mutation exists almost exclusively in Caucasians, among whom it has a prevalence of 2%, giving a risk increase of VTE of 2-3 times in heterozygotes and 30 times in homozygotes. Protein C, S, and antithrombin deficiencies are rare but strong risk factors with several different subtypes[50]. Antiphospholipid syndrome is the most common acquired thrombophilia. It is an autoimmune disorder, which requires persisting positive antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, or anti-β2glykoprotein antibodies) in combination with clinical symptoms (thrombosis or obstetric complications) for diagnosis[51].

*Immobilization*

Short-term immobilization is a strong risk factor for VTE, contributing to the increased risk of hospitalization, trauma, surgery, and orthopedic casting. However, patients with long-term immobilization, for example, due to spinal cord injury, do not have an increased risk of VTE[52]. This has recently, following studies on hibernating bears, been proposed to be mediated by down-regulating the pro-thomboinflammatory state that immobilization normally induces.

*Sex differences*

There are important sex differences in VTE. Women have an increased risk of VTE during fertile years, whereas men have a higher risk in middle age. The excess risk in fertile women has been reported to be associated with endogenous estrogen exposure with higher VTE risk in women with late menopause and higher parity compared to early or normal menopause and lower parity[53]. Pregnancy entails an increased risk of VTE, particularly in the third trimester, with a reported 6-fold risk increase compared to time outside of pregnancy[54]. The risk was considerably lower during the first and second trimesters, while the postpartum period conferred an even higher risk increase. It has been proposed that men have a higher baseline risk of VTE than women but that female exposure to reproductive risk factors such as oral contraceptives, pregnancy/puerperium, and postmenopausal hormone therapy, out-balance this difference[55]. This aligns with the higher recurrence risk of VTE in men than women[55].

*Differences between DVT and PE*

Previous reports suggest that some risk factors are more strongly associated with DVT than with PE, or contrarily, with PE than with DVT.[41,56] For example, Factor V Leiden mutation is more often associated with DVT than with PE, which is sometimes called the Factor V Leiden paradox[56]. Although many patients with DVT have a concurrent asymptomatic PE and many patients with PE have a simultaneous asymptomatic DVT[20], there are differences in mortality between the two VTE manifestations. The overall mortality during the first year following a first-time PE has been reported to be higher than after a first-time DVT, even when excluding the first month after diagnosis[57]. This suggests that it might be of greater importance to prevent a PE than a DVT and thereby to identify which patients are at the highest risk of a PE.

### *Preventive measures*

Pharmacological thromboprophylaxis with low-molecular-weight heparin (or, in the case of orthopedic prosthetic surgery, DOACs) is the standard care in high-risk situations. Such situations include major orthopedic and non-orthopedic surgery[49,58]. In

some situations, such as certain major orthopedic surgery, major abdominal or pelvic surgery in cancer patients, postoperative thromboprophylaxis is often extended to 28-35 days[49,58,59]. For medical inpatients, there are large differences in the usage of thromboprophylaxis[60,61]. Landmark studies on the benefit of thromboprophylaxis in medical inpatients[62,63] are two decades old, and the main benefit was seen in the prevention of asymptomatic VTEs. Unfortunately, however, reports on benefits in clinical practice are not consistent[64-67], and it is unclear which medical inpatients benefit from thromboprophylaxis. Consistent with this, there is a wide array of different risk assessment tools that categorize a widely varying proportion of hospitalized patients as suitable for thromboprophylaxis[68].

Cancer is one of the most important risk factors for VTE, and consequently, primary prophylaxis has been studied in selected out-patient groups of cancer patients[69,70]. However, identifying patients who benefit most from this prophylaxis appears challenging[71]. Cancer patients have a higher risk of bleeding, a risk that may be increased with the administration of thromboprophylaxis[69]. In this context, it is important not only to consider which cancer patients have a high risk of VTE but also which patients do not.

Graduated compression stockings are mainly used for thromboprophylaxis in acutely ill patients who are perceived to be at high risk of VTE but deemed to be unsuitable for pharmacological thromboprophylaxis due to a high risk of bleeding. In theory, graduated compression stockings reduce venous stasis and could thereby reduce the risk of VTE. However, in practice, the benefit of mechanical thromboprophylaxis remains unclear[72].

## Clinical presentation and diagnosis

The clinical presentation of PE is non-specific and highly variable among patients. Nevertheless, the most common signs and symptoms are dyspnea, hypoxemia, tachycardia, and pleuritic chest pain[31]. Hemoptysis is only present in a small proportion of patients but should raise the suspicion of PE, whereas hemodynamic compromise, confusion, and sudden death are all potential but non-specific manifestations of a more extensive clot burden[31].

Patients with DVT frequently present with leg swelling, pain, localized tenderness over deep veins, redness, and prominent superficial veins[31]. In rare cases, the venous occlusion and swelling of the extremity become severe with arterial ischemia, called *phlegmasia cerulea dolens* (cyanotic leg) or *phlegmasia alba dolens* (white leg). Both these conditions are associated with high amputation and death rates[73,74].

### *Diagnostics*

Upon suspicion of PE and DVT, the first step is to assess clinical probability, either by clinical judgment based on experience or by using a prediction algorithm[20,75]. Among the most frequently used prediction models for DVT and PE is the Wells score, see Table 1.

**Table 1**. Wells Clinical Prediction Rule for DVT and PE

| **The Wells Clinical Prediction Rule for DVT** | |
|---|---|
| ***Items*** | **Points** |
| Active cancer (treatment or palliation within 6 months) | 1 |
| Paralysis, paresis or recent plaster immobilization of the lower extremities | 1 |
| Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity) | 1 |
| Pitting oedema confined to the symptomatic leg | 1 |
| Collateral superficial veins (nonvaricose) | 1 |
| Previously documented DVT | 1 |
| Alternative diagnosis at least as likely as DVT | -2 |
| *Clinical probability* | |
| Two-level score | |
| DVT unlikely | ≤1 |
| DVT likely | ≥2 |

| **The Wells Clinical Prediction Rule for PE** | | |
|---|---|---|
| **Items** | **Original version** | **Simplified version** |
| Previous PE or DVT | 1.5 | 1 |
| Heart rate >100 beats per minute | 1.5 | 1 |
| Immobilization at least 3 days OR surgery in the previous 4 weeks | 1.5 | 1 |
| Hemoptysis | 1 | 1 |
| Active cancer (treatment or palliation within 6 months) | 1 | 1 |
| Clinical signs of DVT | 3 | 1 |
| Alternative diagnosis less likely than PE | 3 | 1 |
| *Clinical probability* | | |
| Two-level score | | |
| PE unlikely | 0–4 | 0–1 |
| PE likely | ≥5 | ≥2 |

In patients stratified to the DVT or PE-unlikely group, D-dimer measurement is recommended. The negative predictive value of a low clinical probability according to Wells score in combination with a negative D-dimer is high, 99.5% (95% CI 98.4–99.9%)for PE[76]. However, the positive predictive value of D-dimer is low since D-dimer can be elevated for many other reasons such as infection, cancer, pregnancy, or simply high age[20]. Therefore, D-dimer cannot be used to confirm VTE, and if D-dimer is positive, diagnostic imaging is warranted[20,75].

In patients stratified to the DVT or PE-likely group, there is no use for D-dimer testing since the negative predictive value of a negative D-dimer in this group is not sufficiently high[76]. Instead, diagnostic imaging is required for all patients. The most frequently used imaging modality for PE is CTPA, and the most frequently used modality for DVT diagnosis in the upper or lower extremities is ultrasonography[20,75].

The introduction of CTPA as the first-line diagnostic approach to PE instead of ventilation-perfusion scans and invasive pulmonary angiography has revolutionized the diagnostic work-up of PE. CTPA is currently widely available in hospitals with an emergency department, usually on a 24/7 basis. It is sensitive and capable of detecting emboli down to the subsegmental level as well as being able to give information on differential diagnosis[20]. The diagnostic imaging of DVT has also been simplified following the introduction of ultrasound instead of phlebography (also called venography) due to its non-invasive nature and the increasing use of point-of-care ultrasound in emergency rooms[77].

## Treatment

Treatment of VTE varies depending on the urgency of the VTE and the patient's risk of bleeding. Anticoagulant treatment, which is the sole treatment for the majority of patients with VTE, prevents thrombus growth and embolization in the acute phase as well as recurrence in the post-acute phase. In this situation, it is the patients' endogenous fibrinolysis that dissolves the clot. However, in urgent situations, the thrombus must be dissolved more rapidly, and thrombolytic treatment is used. In addition, more advanced invasive treatment options can be used in select cases if clinical expertise is available.

In PE, treatment selection is based on risk stratification of short-term mortality due to PE. Patients with high-risk PE[20] (massive PE according to North American classification[22]) have hemodynamic instability. Patients with intermediate-high risk (submassive according to North American classification) PE have right ventricle strain on imaging *and* myocardial injury with elevated biomarkers (often troponins). Patients with intermediate-low risk have only one or none of the two, whereas the distinction between intermediate-low and low-risk PE is based on signs of clinical severity and comorbidities, which can be assessed by pulmonary embolism severity index (PESI/sPESI) or the Hestia criteria[20].

### *Thrombolytic treatment*

Systemic thrombolysis is recommended for patients with high-risk PE[20-22]. In a meta-analysis of randomized controlled trials including 2,057 patients, the odds ratio of death in patients receiving systemic thrombolysis compared to heparin alone was reported to be 0.59 (95% CI 0.36–0.96)[78]. The reduction was not significant when excluding patients with high-risk PE. However, the results on high-risk PE were weak since the included studies were old (three studies from the 1970s and one from 1995) with few patients (115 patients in total who received thrombolysis). Additionally, the reported benefit depended on a study of only four patients. In the PE group as a whole, the risks of death or treatment escalation, PE-related death, and PE recurrence were

reduced, whereas the risks of bleeding were tripled with thrombolytic therapy[78]. In clinical practice, thrombolysis is used in patients with high-risk PE despite the lack of strong scientific evidence due to the imminent risk of death if thrombolysis is not administered[22].

Systemic thrombolysis for patients with intermediate high-risk PE was assessed in the randomized PEITHO trial[79]. This trial showed that thrombolytic treatment plus heparin versus placebo plus heparin led to a lower risk of hemodynamic decompensation but at the cost of a higher bleeding rate and stroke (mainly hemorrhagic stroke). The conclusion of the trial was that great caution is warranted when considering thrombolytic treatment for this group of patients.

In DVT, local transcatheter thrombolytic treatment is used in severe cases such as *phlegmasia cerulea dolens* and in carefully selected young patients with extensive clots in the iliac and common femoral veins associated with severe symptoms[22]. This is a lengthy and, for many patients, demanding procedure with largely unclear benefits. In the largest randomized trial to date, pharmacomechanical catheter-directed thrombolysis in combination with anticoagulation compared to anticoagulation alone did not lead to a lower risk of post-thrombotic syndrome (PTS). Still, on average, the PTS was less severe. However, major bleeding was significantly more common in the intervention group[80].

### *Additional advanced treatment options in the acute setting*

Catheter-directed treatment (CDT) for PE, extracorporeal membrane oxygenation (ECMO), surgical embolectomy, and vena cava filters can be used in selected patients with VTE if the expertise is available.

CDT for PE is an area of high interest with several ongoing trials[81]. The indication for CDT is patients with PE who require thrombolysis but have a contraindication to this treatment or patients for which thrombolysis has failed[81]. In patients with PE associated with cardiac arrest or refractory circulatory collapse, using ECMO to maintain circulation and oxygenate critical organs can be helpful. In these cases, ECMO is often used to buy time to prepare for clot removal with CDT or surgical embolectomy[20]. Surgical embolectomy is a treatment option used almost exclusively in high-risk PE when other treatment options have failed. With this procedure, a sternotomy is performed, and the patient is on cardiopulmonary bypass during the procedure, in which a pulmonary arteriotomy is performed, and the clot is extracted[82].

Surgical embolectomy or percutaneous thrombectomy for DVT are treatment options when local thrombolysis has failed or in patients with a contraindication to thrombolysis. However, the evidence for these treatment options is weak[83,84]. In patients with PE or proximal DVT who have a contraindication to anticoagulant treatment or who have PE recurrence despite therapeutic anticoagulation, vena cava filters can be an option. However, the benefit of vena cava filters in terms of a lower incidence of PE is out-balanced by an increased risk of DVT, high complication rates, and lack of evidence of a mortality benefit[20].

### *Anticoagulant treatment*

As previously described, first-line treatment for VTE was for many decades LMWH/heparin and VKA. LMWH activates antithrombin, leading to accelerated interaction with factor Xa and, to some extent, thrombin (factor II). Unfractionated heparin (UFH) has a similar mechanism but inhibits thrombin to a greater extent than LMWH due to its longer heparin chain, enabling it to bind both antithrombin and thrombin, which is needed for the thrombin-related effect[85]. VKA inhibits vitamin K, leading to the K-vitamin dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C, S, and Z being functionally incompentent[86].

In 2014, the Swedish Medical Product Agency approved the first DOAC, rivaroxaban (Xarelto), for VTE treatment. Rivaroxaban was followed by apixaban (Eliquis), dabigatran (Pradaxa) and edoxaban (Lixiana). Rivaroxaban, apixaban, and edoxaban are direct factor Xa-inhibitors, preventing the conversion of prothrombin to thrombin, whereas dabigatran is a direct thrombin inhibitor, preventing the conversion of fibrinogen to fibrin. DOACs are not only associated with lower bleeding risks but also are easier for both patients and caregivers since they do not require monitoring with blood samples. Therefore, their introduction has led to a drastic change in the treatment patterns, see Figure 1. DOACs are now first-line treatment in most patients with VTE except in pregnant patients (requiring LMWH), breastfeeding patients (LMWH or warfarin) patients with antiphospholipid syndrome (in particular triple positive, requiring warfarin)[20], patients with certain cancers (LMWH)[59], or patients with other specific indications for warfarin treatment such as mechanical heart valves.

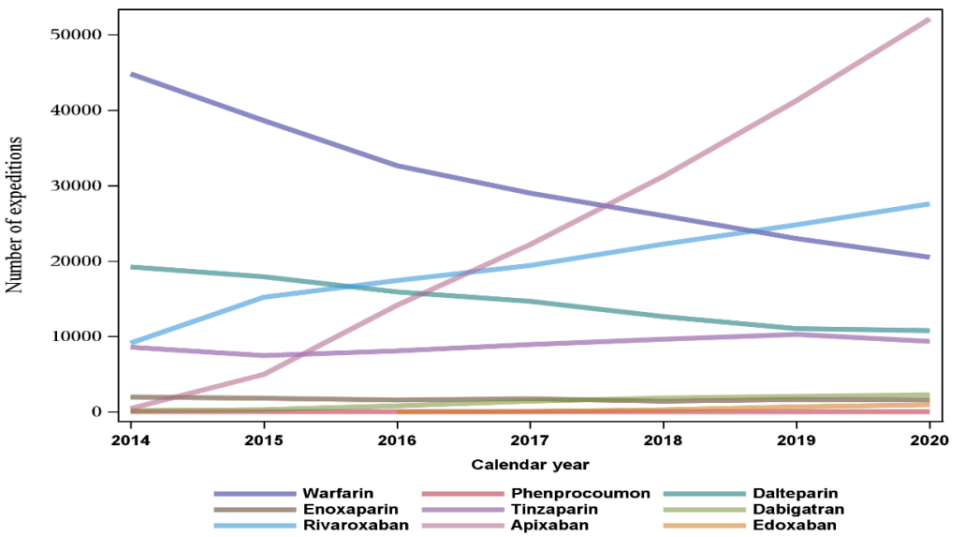


**Figure 1**. Temporal changes in expeditions of anticoagulant treatment for VTE in Sweden. Based data on filled prescriptions from the Prescribed Drug Register, Study IV.

### *Duration of anticoagulant treatment*

*Initial treatment*

Initial treatment is the minimal treatment duration needed for VTE before deciding on extended treatment or termination of treatment. Numerous trials have examined the optimal length of initial treatment after a VTE. A pooled analysis of individual participants' data from randomized trials concluded that patients with 1–1.5 months of treatment after a VTE had a higher risk of recurrence after stopping treatment than patients who completed three months of treatment[87]. There was no difference in recurrence after cessation of treatment in patients who completed three or six months or longer except for a borderline significance in patients with unprovoked VTE, where six months of treatment seemed more favorable than three months. The recurrence rate after treatment termination was highest during the first six months after cessation of treatment. Hence, in patients who do not have a high enough risk for recurrence to merit indefinite treatment, three months of treatment seems to suffice for many patients. However, in clinical practice in Sweden, many patients, particularly those who suffer from PE, receive six months of initial treatment before assessing residual symptoms, and a decision on treatment duration is made.

*Extended treatment*

Anticoagulant treatment effectively reduces the risk of recurrent thromboembolic events during treatment[88]. However, the risk of recurrence after cessation of treatment is highly dependent on the circumstances of the initial VTE[89], see Table 2. In cases

**Table 2**. Risk of recurrence after termination of anticoagulant treatment based on risk factors present at the initial VTE event. From 2019 ESC guidelines on acute pulmonary embolism[20], Reprinted with permission from Oxford University Press

| Estimated risk for long-term recurrence[a] | Risk factor category for index PE[b] | Examples[b] |
|---|---|---|
| Low (<3% per year) | Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor) | • Surgery with general anaesthesia for >30 min<br>• Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness<br>• Trauma with fractures |
| Intermediate (3–8% per year) | Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE | • Minor surgery (general anaesthesia for <30 min)<br>• Admission to hospital for <3 days with an acute illness<br>• Oestrogen therapy/contraception<br>• Pregnancy or puerperium<br>• Confined to bed out of hospital for ≥3 days with an acute illness<br>• Leg injury (without fracture) associated with reduced mobility for ≥3 days<br>• Long-haul flight |
| | Non-malignant persistent risk factors | • Inflammatory bowel disease<br>• Active autoimmune disease |
| | No identifiable risk factor | |
| High (>8% per year) | | • Active cancer<br>• One or more previous episodes of VTE in the absence of a major transient or reversible factor<br>• Antiphospholipid antibody syndrome |



PE = pulmonary embolism; VTE = venous thromboembolism.
[a]If anticoagulation is discontinued after the first 3 months (based on data from Baglin *et al.*[340] and Iorio *et al.*[341]).
[b]The categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Haemostasis.[338] The present Guidelines avoid terms such as 'provoked', 'unprovoked', or 'idiopathic' VTE.

where the initial VTE was provoked by a temporary major risk factor, such as major surgery or major trauma with fractures, the recurrence risk is low after cessation of treatment, and most patients can stop treatment after 3–6 months[87]. However, when no provoking factor can be identified (also called unprovoked or idiopathic VTE), the recurrence rate is high, and guidelines recommend considering extended therapy in most of these patients who do not have a high risk of bleeding[20-22].

The risk of recurrence in patients without provoking factors has been estimated to be 10% during the first year after cessation of treatment, 25% after five years, and 36% after ten years[90]. The overall risk of recurrence was 1.4 (95% CI 1.3–1.6) times higher in men compared to women. For patients with non-surgical provoking factors, the recurrence rate during the first year after cessation of anticoagulation has been reported to be 5.8% (95% CI 3.2–8.3%)[91]. The lowest recurrence rate after cessation of treatment has been reported for patients with an initial VTE provoked by a surgical risk factor, 1% (95% CI 0–2.3%) during the first year[91]. However, the risk of recurrence during extended treatment of an unprovoked VTE event (after initial treatment of ≥3 months) is not negligible. In a meta-analysis of prospective cohort studies and randomized controlled trials (RCTs), it was estimated to be 3.3% (95% CI 2.0%–5.1%) during the first two years and 7.1% (95% CI 3.0%–13.2%) after five years[92].

### *Risk of bleeding on anticoagulant treatment*

In decisions on treatment duration, the risk of recurrence needs to be balanced against the risk of bleeding for each patient. Given the high recurrence rates in many VTE patients and the reduced risk of bleeding of DOACs compared to VKA, a large number of patients benefit from extended treatment. However, there are still uncertainties concerning the long-term risk of bleeding in the extended treatment of VTE[93].

The risk of major bleeding (as defined by the ISTH)[94] for patients on initial anticoagulant treatment for VTE in phase III RCTs has been reported to be 1.1% for DOACs and 1.7% for Warfarin[95]. In real-world data, the risk of major bleeding (bleeding requiring hospitalization, a wider definition compared to the phase III trials) during the first six months of treatment for VTE patients without cancer has been reported to be 2.4[96]– 4.0[97] per 100 patient-years for rivaroxaban, 1.9[97]–4.2[98] per 100 patient-years for apixaban and 2.0[96]–5.5[98] per 100 patient-years for warfarin. However, available data are sparse for extended treatment. In a meta-analysis of RCTs and prospective cohort studies, the five-year cumulative incidence of major bleeding with VKA was 6.3% (95% CI 3.6%–10.0%), whereas data were insufficient to estimate bleeding incidence for patients on extended DOAC treatment beyond one year[93].

One study on real-world data on extended treatment beyond 90 days of initial treatment showed a rate of major bleeding (defined as bleeding requiring hospitalization) of 44.5 per 1000 person-years for apixaban, 50.0 for rivaroxaban, and 47.1 for warfarin[99]. However, in this study, more than one-fourth of patients had cancer, making the results difficult to generalize to non-cancer patients. Studies on the risk of major bleeding during extended treatment in different patient groups in a real-world setting are needed for better risk-benefit analysis in treatment decisions.

## Prognosis

### *Mortality*

The 30-day adjusted mortality rate ratios (MRR) compared to population controls has been reported to be 33.0 (95% CI 31.6–34.5) for VTE, with a significant difference between DVT (MRR 5.4 [95% CI 5.0–5.8]) and PE (MRR 80.9 [95% CI 76.0–86.0])[57]. From 2000 to 2015, the age-standardized annual mortality rate from PE (registered as the primary cause of death in the WHO European Region Mortality database) has decreased linearly from 12.8 (95% CI 11.4–14.2) deaths per 100,000 population in 2000 to 6.5 (95% CI 5.3–7.7) deaths per 100,000 population in 2015[100]. Among the proposed reasons for this change are improved disease management and a lower autopsy rate, the latter of which could lead to a lower detection rate. However, data on mortality trends are not unanimous. In a similar study on data from 2000 to 2017 from the WHO Mortality Database from North America, an increase in PE-related mortality in the USA among young and middle-aged adults was seen after 2006[101]. Proposed mechanisms for this are increasing inequities in risk factors and availability of health care. The age-standardized annual mortality rate in the USA in 2017 was 4.1 [95% CI 4.0-4.2] per 100,000 inhabitants for women and 4.5 [95% CI 4.4–4.7] per 100,000 for men.

### *Long-term complications*

*Complications of PE*

Persisting dyspnea is common after PE, with a reported prevalence of around 50% of PE survivors after six months to three years of anticoagulation[102,103]. In 0.5–4% of patients suffering from PE, chronic thromboembolic pulmonary hypertension (CTEPH) develops[102]. In patients with this condition, thrombi in the pulmonary vasculature are not dissolved but organized into fibrous obstructions of the arteries. Distal arteries in both affected and unaffected areas of the lungs are remodeled, leading to an increase in pulmonary artery pressure[102]. Patients develop progressive right heart failure with high mortality unless treated. Patients with CTEPH are recommended treatment with life-long anticoagulation to prevent additional thrombosis. VKA as a first-hand treatment choice is increasingly being replaced by DOACs, except in patients with antiphospholipid antibodies (10% of CTEPH patients)[104]. In cases with surgically accessible fibrotic lesions, pulmonary endarterectomy is recommended if the patient is considered operable. Pulmonary endarterectomy, in which fibrotic lesions are removed down to subsegmental arteries, is associated with improved quality of life and improved 5-year survival of 83% compared to 53% without surgery[104].

*Complications of DVT*

Post-thrombotic syndrome (PTS) is a common complication of DVT, affecting about half of all DVT patients 1–2 years after the initial event[105]. The risk of PTS is higher in patients with recurrent ipsilateral DVT and proximal DVT (in particular iliofemoral DVT). Following an acute DVT, an inflammatory response and recanalization of the vein starts. Both these events have been described to damage venous valves, resulting in valvular reflux. The reflux, in combination with residual obstruction, increases

venous pressure, leading to edema and, in more severe cases, fibrosis, hypoxia, and ulceration of the leg.

Elastic compression stockings have been used for patients with DVT to reduce the risk of PTS. However, in the randomized SOX trial[106], no benefit was shown in preventing PTS using elastic compression stockings compared to placebo stockings in patients with a first proximal DVT. Hence, guidelines do not routinely recommend compression stockings to all DVT patients[22]. However, in the event of established PTS, compression stockings are the first-line treatment.

## AIM

This thesis explored risk factors for first-time VTE and bleeding risk during anticoagulant treatment in patients with a first-time VTE.

The specific aims of the separate papers were:

- *Paper I*: To explore the relationship between BMI levels in young adulthood and later development of VTE using a long-term follow-up of a large population of men from the Swedish Military Service Conscription Register.

- *Paper II*: To determine age-specific incidence rates of PE and DVT and the prevalence of comorbidities and temporary provoking factors at the time of a first-time PE or DVT compared with a matched control population.

- *Paper III*: To determine the incidence of VTE in association with a recent diagnosis of cancer and provide information on the sex and age distributions for both all cancers and separate cancer types in patients with VTE. We also aimed to estimate sex-specific odds ratios (ORs) for various cancers in patients with VTE compared to matched population controls.

- *Paper IV*: To describe the risk of major bleeding depending on the choice of anticoagulant treatment, both during initial VTE treatment (0–6 months) and extended treatment (6 months up to 5 years) in patients with a first-time VTE. We also aimed to identify risk factors for predicting an increased risk of bleeding during initial and extended anticoagulant therapy.

# PATIENTS AND METHODS

## Study populations

### *Paper I*

Paper *I* was based on a cohort of all men enlisting for military service between 1969–2005, registered in the Swedish Military Service Conscription Register.

### *Papers II and III*

Papers *II* and *III* were based on a cohort of all VTE patients with a first-time DVT or PE in Sweden registered in the National Patient Register or National Cause of Death Register between 1987–2018 and their matched population controls from the Total Population Register.

### *Paper IV*

Paper *IV* was based on all patients with a first-time DVT or PE in the National Patient Register 2014–2020.

## Registers

### *The Swedish Military Service Conscription Register*

The register includes all men enlisting for compulsory military service in Sweden between 1969 and 2006. Exemption from conscription was granted only for 1) Swedish citizens living abroad, 2) men with certain psychiatric disorders, 3) men receiving assistance allowance (or with parents receiving care allowance for the youth), 4) men receiving support for physical impairments, and 5) men who were members of Jehovah's Witness congregations. During the period 1969–2006, about 90% of all men of eligible age were tested[107].

During conscription, height and weight were measured and used to calculate Body mass index (BMI): weight / height$^2$. Blood pressure was measured after 5–10 min of supine rest. Cognitive testing protocols changed over time but included several domains, such as spatial capacity and technical understanding. Muscle strength was previously assessed with strength in knee extension, elbow flexion, and handgrip, but since 1994, only with one vertical lifting procedure with resistance depending on the strength of the person performing the lift[107,108]. Cognitive evaluation and muscle strength test results were standardized and transformed into STAndard NINE (stanine) scores (0–9, normally distributed). Both were divided into low (0–3), medium (4–6) and high (7–9). Maximum work capacity was tested with a bicycle ergometer, divided by weight, and transformed into scores 0–9, where 0–4 was considered low, 5–6 medium, and 7–9 high.

### *The Longitudinal Integration Database for Health Insurance and Labor Market Services (LISA) register*

This register was established in 1990 and includes all registered inhabitants from 16

years of age (from 2010, all registered inhabitants from the age of 15). It includes variables such as education, migration, employment status, income, and sick leave. The completeness of education data has been reported to be >98% with an estimated accuracy for the highest achieved level of education of 85%[109].

### *The National Patient Register*

Sweden has a universal healthcare system that provides low-cost out-patient and hospital care to all citizens. The National Patient Register includes the National Inpatient Register, which has a coverage that increased gradually from 1964 and has been complete since 1987, and the National Outpatient Register, which has existed since 2001. The outpatient register has had lower coverage than the inpatient register, approximately 80% up until 2007, mainly due to missing data from private caregivers. The proportion of outpatient visits without a valid principal diagnosis has declined since then and was at only 2% in 2021[110]. The National Patient Register covers data from all hospital care and specialized outpatient clinics in Sweden, but not primary care[111].

### *The National Cause of Death Register*

Registration of death has two parts in Sweden; Notification of death, which is sent by a physician to the Swedish Tax Agency immediately following the confirmation of death, and the Medical death certificate (with information on the cause of death), which is sent to the National Board of Health and Welfare within three weeks of the death.

The National Cause of Death Register includes the date of death and cause of death for all citizens of Sweden[111]. A vast majority, around 96%, of all individuals in Sweden are assigned a specific cause of death code. A minor proportion of persons who die, mainly older individuals with multiple diseases, receive unspecific codes since the specific cause of death is difficult to determine. Individuals with obvious or suspected unnatural deaths, such as suicides or homicides, or obscure cases, such as previously healthy individuals who die suddenly, are reported to the police authorities by the physician who confirms the death. Of these, 95% undergo forensic autopsy[112], and the cause of death is reported to the National Cause of Death Register.

### *The National Prescribed Drug Register*

The National Prescribed Drug Register includes virtually all prescription medications Swedish pharmacies have dispensed since July 2005[113]. The register does not include over-the-counter medications or drugs such as antitumoral agents administered in hospital daycare facilities. Overall, the register has been reported to include 84% of all drugs sold in the country.

### *The Total Population Register*

This register consists of all Swedish inhabitants since 1968 and includes information on birthdate, date of death, emigration, marital status, and area of residence[114]. Data quality is regarded as high, particularly for births, deaths, and civil status, which professionals usually report. However, data on residence or migration might be of lower

quality since it is reported by the individual, who for various reasons might fail to report a change of residence.

## Definitions

### *Paper I*

Data from the Swedish Military Service Conscription Register 1969–2005 were used for baseline data. Information about the highest achieved parental education (a proxy for socio-economic status) was found in the LISA register. For this study, education level was categorized as low, medium, or high.

VTE outcomes were defined as follows: A primary or secondary diagnostic code in the National Patient Register or National Cause of Death Register; International Classification of Diseases (ICD) 8: PE: 450, DVT: 451. ICD 9: PE: 415B, 416W, DVT: 451 except 451A, ICD 10: PE: I26, DVT: I80 except I80.0. Before January 2006, only inpatient diagnoses were included. From January 2006, both inpatient and outpatient diagnoses were included if followed by a filling of a prescription of anticoagulant medication. Patients with a VTE diagnosis in the National Cause of Death Register did not need a prescription filling. Only the first registered diagnosis was included.

Exclusion criteria were: 1) enlistment at an early or late age (≤16 years or ≥25 years), 2) female sex, 3) individuals whose Swedish personal identification number was reused after their death or emigration, 4) missing BMI values, 5) diagnosis of VTE or stroke before enlistment, or 6) lower extremity fracture within one year prior to enlistment, see Figure 2.

Men were followed until 1) a diagnosis of PE or DVT, 2) death, 3) emigration, or 4) end of follow-up (December 31, 2014).

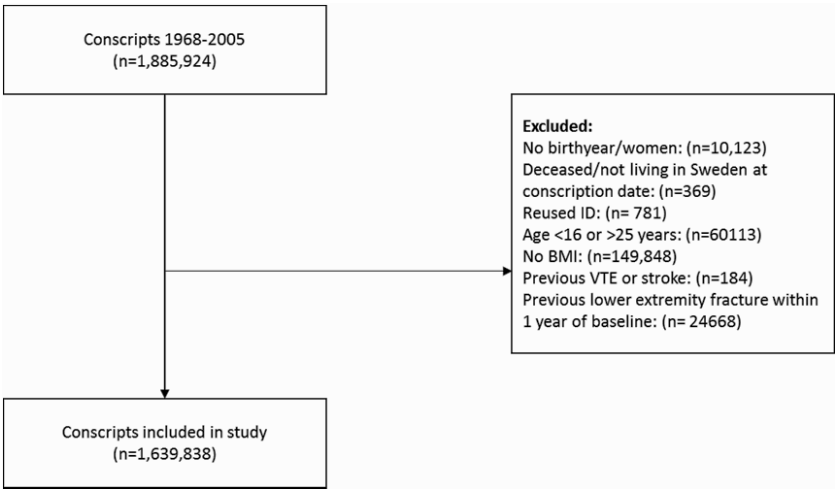


**Figure 2**. Overview of included patients and reasons for exclusion from the study. BMI= Body Mass Index. ID= Identity. VTE= Venous Thromboembolism. Reprint from Paper 1[115].

### *Paper II*

DVT and PE diagnostic codes were identical as in Paper *I*. Only first-time diagnoses were included. For diagnoses registered before July 1, 2005, a VTE diagnosis was defined as either a VTE diagnosis in the inpatient or National Cause of Death Register or one outpatient diagnosis of VTE and a subsequent, identical diagnosis within three months. For patients with VTE after July 1, 2005, the definition was the following: 1) one inpatient diagnosis and a filling of a prescription of anticoagulants within six months or 2) one outpatient VTE diagnosis and a filling of a prescription of anticoagulants within three months, or 3) one VTE diagnosis in the National Cause of Death Register. All patients with a previous VTE diagnosis from January 1, 1980, to December 31, 1986, were excluded.

Comorbidities were registered within seven years or on the same date as the VTE event, recent comorbidities within six months or on the same date, and temporary provoking factors within three months or on the same date, see Table 3 for included factors and comorbidities.

**Table 3**. Demographic factors (at the time of the VTE event), comorbidities (within seven years or on the same date as the VTE event), and temporary provoking factors (within three months or on the same date as the VTE event).

| |
|---|
| **Demographic factors** |
| Age |
| Female sex |
| **Comorbidities** |
| Heart failure |
| Ischemic heart disease |
| Atrial fibrillation |
| Ischemic stroke |
| Hemorrhagic stroke |
| Chronic obstructive pulmonary disease (COPD) |
| Cancer |
| Systemic connective tissue disorders |
| Inflammatory bowel syndrome |
| Liver disease |
| Kidney failure |
| Depression |
| Psychosis |
| Alcohol abuse |
| **Temporary provoking factors** |
| Gastrointestinal surgery |
| Obstetrical surgery |
| Surgery of the musculoskeletal system |
| Surgery, other major |
| Trauma |
| Lower extremity fracture |

Ideally, five controls matched for sex, year of birth, and county of residence, were selected from the Total Population Register. However, in some cases fewer controls were used when it was not possible to find five unique controls for every case. The same person could first be included as a control and later, after suffering a VTE, be included as a case.

### *Paper III*

This study included the same VTE population as in Paper *II*. Patients with an in- or outpatient diagnostic code of cancer within a year or on the same date as the VTE diagnosis were identified; see Table 4 for included cancer types. Among controls, individuals with a diagnostic code of cancer within or on the same date as the VTE of the corresponding case were identified.

**Table 4**. Types of cancer (registered in the National Patient Register within 1 year before, or on the same date as the VTE) included in the study.

| |
|---|
| **Cancer groups** |
| All cancers except non-melanoma skin cancer |
| **Individual cancer types** |
| Esophageal, stomach |
| Small intestinal |
| Colon |
| Rectal, anal |
| Pancreatic |
| Liver |
| Biliary |
| Lung |
| Brain |
| Malignant melanoma |
| Kidney |
| Bladder and urothelial cancer |
| Uterine |
| Ovarian |
| Cervix |
| Leukemia |
| Lymphoma |
| Multiple myeloma |
| Prostate |
| Testicular |
| Breast |

The following comorbidities were used for multivariable adjustment: heart failure, ischemic heart disease, atrial fibrillation, ischemic stroke, hemorrhagic stroke, COPD, and inflammatory bowel disease. The following temporary provoking factors were used: major surgery, lower extremity fracture, and trauma.

### *Paper IV*

Included patients came from the same dataset as in Papers *II* and *III*, with a diagnosis of VTE and a subsequent filling of a prescription of anticoagulant medication within 30 days from January 2014 to December 2020. We excluded: 1) patients with a prior VTE. 2) patients with atrial fibrillation at any time point until the day of censoring 3) patients who were pregnant at inclusion, 4) patients with a diagnosis of cancer within 1 year before the VTE, and 5) patients who filled a prescription of anticoagulant medication within 6 months prior to the VTE, see Figure 3.

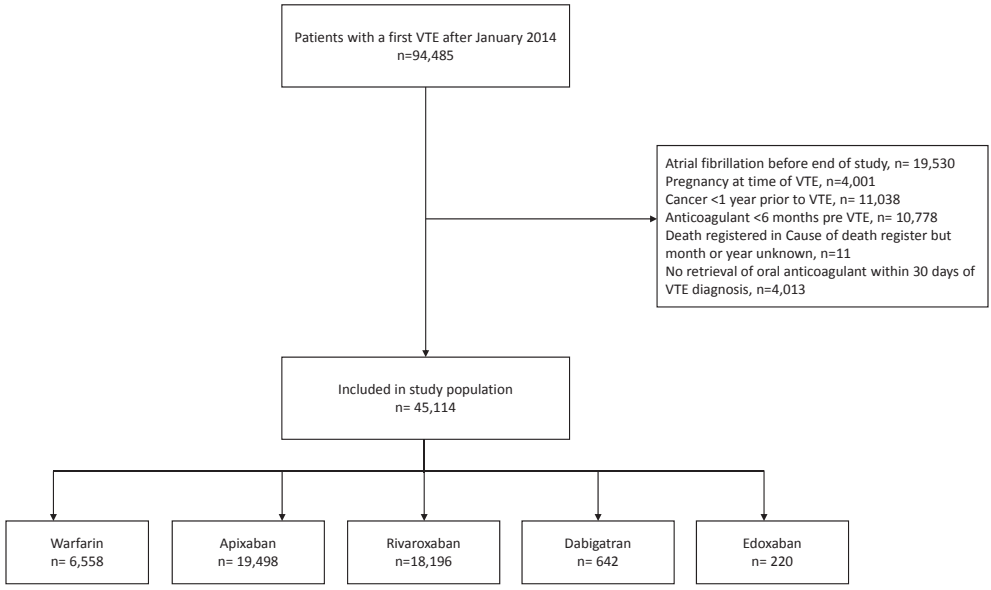


**Figure 3**. Flow chart for study inclusion and number of patients with a first venous thromboembolism (VTE) in each study group. Reprint from Paper IV[116].

Patients were considered to be on treatment if they filled a prescription within 30 days of VTE diagnosis. They were considered to have ongoing treatment if they filled at least two prescriptions of the same medication (dose adjustment allowed) per 12 months.

Major bleeding was defined as a primary inpatient diagnosis of bleeding. Fatal bleeding was defined as 1) a major bleeding in combination with death within 30 days or 2) a diagnosis of bleeding in any position on a death certificate.

Concomitant pharmacological treatment and comorbidities were registered, both for assessment of risk factors and for multivariable adjustment in calculation of hazard ratios, see Table 5.

**Table 5**. Comorbidities and concomitant pharmacologic treatments included in Paper IV

| Comorbidities | | | Concomitant pharmacological treatment |
|---|---|---|---|
| Previous bleeding (inpatient diagnosis) | Renal failure | Stroke (hemorrhagic) | Antiplatelet treatment |
| Hypertension | Liver disease | Systemic connective tissue disease | Proton pump inhibitor |
| Heart failure | Ischemic heart disease | IBD (inflammatory bowel disease) | SSRI |
| COPD | Peripheral arterial disease | Dementia | Statins |
| Diabetes | Stroke (ischemic) | | |

Patients were followed until one of the following events occurred: 1) major bleeding, 2) death, 3) diagnosis of cancer, 4) five years after the diagnosis of VTE, 5) end of treatment, or 6) end of follow-up (December 31, 2020).

## Statistical analysis

In all papers, continuous variables were presented as mean and standard deviation or median with first and third quartiles, interquartile range (IQR). Categorical data was presented as numbers with percentages.

*Paper I:* We used Poisson regression to calculate incidence rates and corresponding 95% confidence intervals (CI). Cox proportional hazard regression was used to calculate the risk of VTE during follow-up based on BMI at conscription. Covariates from baseline data were grouped in different models, and adjustment was made by combining these models in different ways.

*Paper II:* When comparing cases and controls, chi-square tests were used for dichotomous variables and t-tests for continuous variables. Tests were two-tailed, and 1% significance levels were chosen due to a large number of analyzed risk factors. Adjusted odds ratios (ORs) were calculated with conditional logistic regression according to case-control matching, with adjustment for comorbidities and temporary provoking factors. Population attributable risk (PAR) was calculated according to Bruzzi et al[117], to estimate the possible reduction of PE or DVT in the population if a risk factor is eliminated.

*Paper III:* For total incidence rates, the total number of patients with VTE and cancer was divided by the total number of Swedish inhabitants each year (equaling the patient years at risk), using data from Statistics Sweden. For incidence rates with sex and age stratification, VTE cases were divided by the number of Swedish inhabitants in the corresponding age and sex category in the same calendar year. Adjusted odds ratios were calculated using conditional logistic regression for case-control matching with 99% CI, adjusting for comorbidities and temporary provoking factors.

*Paper IV:* Cumulative incidence functions were calculated with other bleedings, death, and cancer as competing risks. Event rates for different bleedings depending on treatment choice and time period were calculated using Poisson regression. Cox proportional hazard regression was used to estimate adjusted hazard ratios for bleeding depending on the choice of anticoagulant medication and depending on different risk factors. Adjustment of hazard ratios was made for bleeding risk factors. In sub analyses with few events, we reduced the number of adjustment variables. All significance tests were two-sided and performed with a significance level of 5%.

# RESULTS

## Paper I

### *Baseline characteristics*

The study included 1,639,838 men. Of these, 79.8% had normal weight (BMI 18.5–<25 kg/m$^2$), 9.9% were overweight (BMI 25–<30 kg/m$^2$), and 2.2% were obese (BMI >30 kg/m$^2$). Men were followed for a median of 28 years (interquartile range 20–36 years).

When study subjects were stratified according to BMI, men with a high BMI had a shorter follow-up. Men with BMI ≥15–<18.8 kg/m$^2$ had a median follow-up of 31 (IQR 22–40) years, decreasing gradually to 19 (IQR 13–27) years in men with BMI ≥35–<60 kg/m$^2$. Men with normal BMIs had better cardiorespiratory fitness than thin and obese men. Muscle strength was lower in men with a low BMI than in normal or obese men. Men who were obese more often had a low intelligence quotient, hypertension, and diabetes than other study subjects.

### *VTE events*

In total, 17,805 first VTE events were registered. There was a clear increase in incidence rates with higher BMI class. In lean men with a BMI of ≥18.5 –<20 kg/m$^2$, the event rate was 32.8 per 100,000 patient-years. In obese men (class I obesity, BMI ≥30–<35), the event rate was 73.7 per 100,000 patient-years. In men with severe obesity (class II–III obesity, BMI ≥35–<60 kg/m$^2$), corresponding numbers were 112.1 per 100,000.

### *Hazard ratios*

After multivariable adjustment for baseline characteristics, obese men (BMI ≥30–<35) had an aHR of VTE of 2.9 (95% CI 2.7–3.2) and severely obese men (BMI ≥35–<60 kg/m$^2$) had an aHR of 5.0 (95% CI 4.2–5.9), compared to lean men with (BMI ≥18.5 –<20 kg/m$^2$). In a sub-analysis, men who died within two years after a VTE or who had a lower extremity fracture within three months before the VTE were excluded. This only affected aHR marginally.

## Paper II

### *Study population*

We included 298,172 patients with a first-time VTE in the National Patient Register or National Cause of Death Register. The matched control population included 1,185,079 individuals.

Patients with PE were more often women than patients with DVT (PE: 53.4% women, DVT 52.1% women) and, on average, three years older (PE: 69 years vs DVT: 66 years). Comorbidities registered within seven years and temporary provoking factors present within three months of the VTE were compared between DVT and PE patients.

Cancer was the most prevalent comorbidity (PE: 21.3%, DVT: 19.3%). Heart failure (PE: 18.9%, DVT: 10.3%) and ischemic heart disease (PE: 18.6%, DVT: 11.0%) were among the conditions that were more common in patients with PE than DVT.

### *Incidence rates*

The annual incidence rate for a first-time VTE was 105.2 per 100,000 inhabitants, 49.8 for PE, and 55.4 for DVT. The incidence rate increased markedly with age, see Figure 4. Women had a higher incidence rate of VTE before the age of 40 and 80 years and older, whereas men had higher incidence rates in ages 40–79 years.

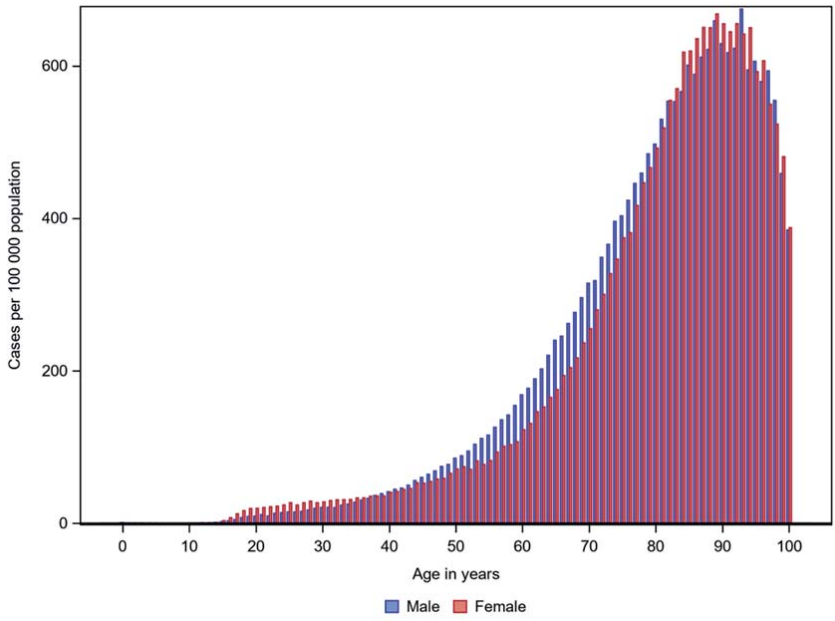


**Figure 4**. VTE incidence per 100,000 inhabitants divided into men and women aged 0-100 years. Reprint from Paper II[118].

### *Odds ratios and PAR for comorbidities and temporary provoking factors*

When comparing VTE patients to their respective matched controls, patients with PE had higher adjusted odds ratios (aOR) for cardiopulmonary diseases such as heart failure, ischemic heart disease, atrial fibrillation, and COPD, see Figure 5. Depression also had higher aORs in patients with PE than patients with DVT. Patients with DVT had higher aORs for temporary provoking factors such as musculoskeletal surgery and lower-limb fracture.

Risk factors with the highest PAR for patients with PE were cancer (13.0%), heart failure (11.7%), and ischemic heart disease (6.3%). The highest PARs for DVT were seen for cancer (11.9%) and musculoskeletal surgery (8.6%).

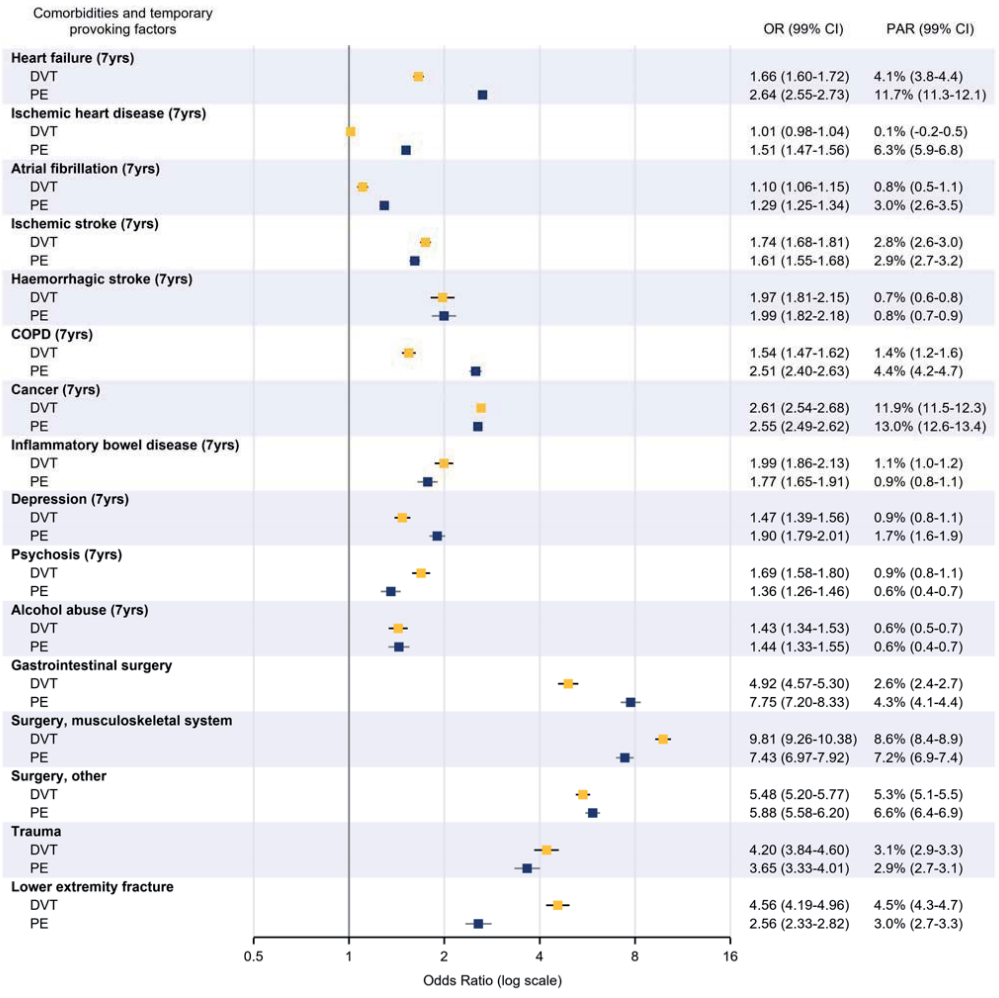


**Figure 5**. Multivariable adjusted ORs and Population attributable risk (PARs) with corresponding 99% CI for various comorbidities (registered within seven years) and temporary provoking factors (surgery, trauma, lower extremity fracture registered within three months). Reprint from Paper II[118].

## Paper III

### *Study population*

Our register data comprised 298,172 patients diagnosed with a first-time VTE between 1987–2018, and their 1,185,079 matched population controls. In the VTE population, we identified 44,685 (15%) patients with a registered cancer diagnosis within one year before the VTE. Of these, 22,000 had DVT, and 22,685 had PE. The median age was 71 years.

### *Incidence rate*

The annual incidence rate of VTE with a registered cancer diagnosis within the preceding year was 15.9 per 100,000 patient years for men and 15.7 for women. The incidence rate increased markedly after the age of 60.

In women, the most common cancer types among VTE patients were breast cancer (23.3%), lung cancer (10.3%) and colon cancer (9.2%). In men, the most prevalent cancer types among patients with VTE were prostate cancer (32.1%), lung cancer (10.5%), and bladder/urothelial cancer (8.6%).

### *Multivariable adjusted odds ratios of various types of cancer*

The adjusted odds ratios of any cancer were higher in females (aOR 5.5 [99% CI: 5.4–5.7]) than in male VTE patients (aOR 3.9 [99% CI: 3.8–4.0]) compared to their respective population controls. However, when excluding sex-specific cancers, the difference was small.

Among cancers with the highest aOR in VTE patients compared to matched controls were brain cancer (women: aOR 17.4 [99% CI 12.9–23.4], men: aOR 17.5 [99% CI 13.8-–22.2]), pancreatic cancer (women aOR: 19.6 [99% CI: 15.8–24.4], men aOR 17.2 [99% CI 13.7–21.6]) and biliary cancer (women: aOR 16.7 [99% CI 12.3–22.8], men: aOR 10.4 [99% CI 7.1–15.2]).

Among cancers with the lowest aOR, we found bladder/urothelial cancer (women: aOR 1.3 [99% CI 1.1–1.5], men: aOR 1.3 [99% CI 1.2–1.5]), malignant melanoma (women: aOR 2.5 [99% CI 2.1–3.1], men: aOR 2.7 [99% CI 2.2–3.2]). Female VTE patients also had low OR for uterine cancer (aOR 3.4 [99% CI 3.1–3.9]), whereas men had a low OR for prostate cancer (aOR 2.2 [99% CI 2.1–2.3]) compared to matched population controls.

## Paper IV

### *Study population*

The study included 45,114 patients with a first-time VTE between 2014–2020. The median age was 68 years, and 54.7% were male. The median follow-up after initiation of treatment was 0.6 years (mean 1.0 years). Among the patients, 6,558 were treated with warfarin, 18,196 with rivaroxaban, and 19,498 with apixaban. Dabigatran and edoxaban were initiated in too few patients to permit the calculation of reliable outcome data.

Patients treated with warfarin were slightly older and had more comorbidities such as renal failure, heart failure, diabetes, peripheral arterial disease, and systemic connective tissue disorder than patients on other anticoagulants. Patients on rivaroxaban were generally younger and healthier than patients on other anticoagulants.

### *Risk of major bleeding*

*Initial treatment*

During the first six months of treatment, 494 patients (1.1% of patients who started anticoagulant treatment) suffered major bleeding. The event rate was 3.9 (95% CI 3.1–4.6) for warfarin, 2.9 (95% CI 2.6–3.3) for rivaroxaban, and 2.0 (95% CI 1.7–2.3) for apixaban, per 100 patient-years.

After multivariable adjustment for comorbidities and concomitant medications, patients on apixaban had a lower risk of major bleeding compared to patients on warfarin (aHR 0.56 [95% CI 0.4–0.7]) and rivaroxaban (aHR 0.6; [95% CI 0.5–0.8]). There was no significant difference between rivaroxaban and warfarin (aHR 0.9 [95% CI 0.7–1.1]).

In a sub analysis of the first month of treatment, 44 patients on apixaban and 98 on rivaroxaban experienced major bleeding, yielding an aHR of 0.4 (95% CI 0.3–0.6). During the subsequent five months, 116 patients on apixaban and 126 patients on rivaroxaban experienced major bleeding, resulting in a non-significant risk difference of aHR 0.8 (95% CI 0.6–1.0).

*Extended treatment*

During extended treatment (from 6 months of treatment up to 5 years of treatment), a total of 267 patients (1.0% of patients who remained on anticoagulant treatment at six months) suffered major bleeding. The event rate was 1.6 (95% CI 1.2–1.9) per 100 patient-years for warfarin, 1.1 (95% CI 0.9–1.3) for rivaroxaban and 1.0 (95% CI 0.8–1.2) apixaban.

After multivariable adjustment for comorbidities and concomitant medications, the aHR was 0.7 (95% CI 0.5–1.0) for rivaroxaban and aHR 0.6 (95% CI 0.4–0.8) for apixaban vs warfarin. The difference between apixaban and rivaroxaban was non-significant, aHR of 0.9 (0.6–1.1).

### *Risk factors*

The most important risk factors associated with major bleeding during the first six months of treatment were age (per additional year), previous bleeding, liver disease, renal failure, and antiplatelet treatment. PPIs were also associated with an increased risk.

After the first six months of treatment, age (per additional year), previous bleeding, COPD, antiplatelet treatment, and selective serotonin reuptake inhibitors were the most important factors associated with increased bleeding risk.

## DISCUSSION

This thesis explored risk factors for first-time VTE and bleeding risk during anticoagulant treatment in patients with a first-time VTE.

The thesis has contributed with the following knowledge: Paper *I:* Prior to our report, overweight and obesity at a young age and its impact on future risk of VTE was scarcely studied. We showed that even mildly elevated BMI in young men was a risk factor for VTE in adult life, and the risk increased incrementally with higher BMI. Since overweight and obesity in young adulthood are rapidly increasing in many countries[32], this association may have large effects on the future VTE incidence and may be important for prognostication of the need for future health care. Paper *II*: Our study contributed a comprehensive picture of the comorbidities associated with PE and DVT, respectively, where cardiopulmonary diseases are more strongly associated with PE and recent musculoskeletal surgery, and lower extremity fractures are more strongly associated with DVT. Paper *III*: Our results confirmed the previously known, strong association between VTE and pancreatic, brain, liver, and biliary cancer. However, the risk was not as high in bladder/urothelial cancer, kidney cancer, and some gynecological cancers, which are commonly considered to be associated with a high VTE risk[35,37]. Previous risk estimates were mainly based on studies on patients on chemotherapy[37,38,119-121]. Our results indicate that at least a proportion of patients with these cancer types are at low risk of VTE. Paper *IV:* We reported a lower risk of major bleeding in VTE patients without known cancer for apixaban compared to rivaroxaban or warfarin in patients during initial treatment (0–6 months). This was in line with previous real-life data on warfarin compared to the respective DOACs[96-98], but no previous study comparing apixaban to rivaroxaban was available in this patient group. During extended treatment (6 months up to 5 years), the risk was low for both apixaban and rivaroxaban, while warfarin had a higher risk of major bleeding. We found no earlier real-life data study addressing this question in a VTE population without known cancer.

We used national registers to try to answer our scientific questions. In Paper *I*, a cohort of men was followed until the first VTE diagnosis. Papers *II–III*, a cohort of patients with a first-time VTE (cases) were compared to matched population controls regarding prior or concomitant comorbidities. In Paper *IV,* the same VTE cohort as in Papers *II* and *III* was followed prospectively after diagnosis. These methods have both advantages and disadvantages. Among the advantages of register-based studies are the following:

*Possibility to study large populations over long periods of time*. This was valuable in Paper *I*, since VTE incidence increases markedly with age. Included individuals were adolescents, and the registries gave a possibility of a median follow-up of 28 years, which would have been difficult to achieve for a large population with other study designs. Most previous studies were done on older populations[122,123], and it is valuable to have access to data from early life when studying risk factors for disease. When studying BMI at higher ages, diseases such as various cancer types[124,125] may have developed. These diseases are more frequent in obese patients and may contribute to

the increased risk of VTE, meaning that they are effect modifiers. In studies on adults, however, results on VTE risk in overweight individuals might be adjusted for cancer, and the true effect of BMI might be underestimated. When measuring weight in more advanced ages, it is also possible that diseases such as cancer might have led to weight loss, and the relationship between weight and VTE might be missed. The possibility to study a large population longitudinally was also a strength in Paper *IV* since studies of treatment effects with anticoagulants for VTE (in randomized controlled trials) commonly have a short follow-up and a limited sample size.

*Generalizability.* All Swedish citizens have access to publicly financed health care, and the national registers have high coverage. Hence, the studies include patients who would not have been included in randomized controlled trials or population studies due to severe comorbidities or incapacity to complete follow-up. However, the results may not be equally valid for populations who have been shown to have a lower VTE incidence than the Swedish population, such as Southeast Asian populations[23]. Our results may also differ from other countries due to differences in access to healthcare, leading to differences in healthcare-seeking patterns and treatments.

National registries also have some disadvantages:

*Accuracy of diagnosis*. According to previous studies on included registries, PE has a better positive predictive value (PPV) of 80.7% than DVT, with a low PPV of 59.2%[126], and inpatient diagnoses are more reliable than outpatient diagnoses[127]. For measures to increase PPV, please see the Limitations section.

*Missing data/ unmeasured exposures.* Swedish national healthcare registries lack information on data such as laboratory values, BMI, smoking, and diagnostic codes from primary care. In Paper *I*, the result is a lack of information on subsequent weight development after enlistment for military service. In Papers *II* and *IV*, the consequence is that we do not have complete data on comorbidities such as depression or hypertension, which is often cared for in primary care. We also lack granularity of data on for example, kidney failure, which is likely to be correctly registered when the patient is followed by a nephrologist, but not in elderly patients with severe comorbidities. In Paper *III*, we lack information on antitumoral treatment and the stage of cancer, which are both known to influence the risk of VTE[28,128].

*Residual confounding*. In Paper *IV*, the baseline data of patients treated with the different anticoagulants differ. We have adjusted for all comorbidities we have judged as potential confounders, but it is possible that residual confounding remains. One indication of this is the increased risk of bleeding in patients with concomitant treatment with PPI during initial treatment with anticoagulation. The cause of this is probably that PPI is prescribed to patients who are assessed to have a high bleeding risk by their doctor.

*Could our research questions have been better addressed with another study design?*

With large economic resources, Paper *I* could have been performed as a prospective cohort study with regular visits for follow-up of parameters such as weight to enable studies on time-updated data. However, it would not be possible with this study size.

Paper *II* was performed as a case-control study where we compared patients with PE and patients with DVT, respectively, to their matched population controls. We chose this design instead of comparing PE to DVT patients since patients with PE generally are older than DVT patients, which could confound the results on risk factors. However, the chosen design might be somewhat less intuitive and might be difficult to understand.

Paper *III* would have had more clinical value if we, instead of the case-control design, had studied a cohort of cancer patients with information on cancer stage from the National Cancer Register with VTE as the outcome. This would not only have rendered more easily understood results, but the National Cancer Register could also have provided information on cancer stage at diagnosis. Our results on uterine, kidney, and bladder/urothelial cancer are likely to be highly influenced by the cancer stage, as proposed by earlier studies in the California Cancer Register[39,128]. In the previous studies, these cancers were often localized at diagnosis and were associated with a low risk of VTE, whereas the same cancers were associated with a high VTE risk in more advanced stages. It would also have been interesting to have data on antitumoral treatment since this influences the risk of VTE. Inpatient medical treatment (such as chemotherapy) is mainly reported in other registers that do not have national coverage. Therefore, it would also be relevant to perform separate studies on different cancer types, including data from national quality registers such as the National Quality Registry for Hematology or the National Quality Registry for Gynecological Oncology.

Paper *IV* could have been conducted as a large, randomized, controlled trial with a long follow-up. This would not have given a true picture of clinical practice and would have required large resources, but it had reduced the risk of residual confounding. The study could also have been performed as a prospective cohort study in a quality or research register in which parameters of specific interest would be more carefully documented. These parameters could include the reason for treatment choice, data on bleeding that do not require inpatient care, details on kidney function, and use of over-the-counter medications such as NSAIDs. This approach would, however, require a lot of time and resources since there to date is no Swedish quality/ research register for VTE.

## Clinical implications

Our results on obesity in adolescence leading to an increased risk of future VTE may hopefully be an incentive for weight loss in overweight patients. It is likely that the incidence of VTE will increase with the growing prevalence of obesity. This calls for more knowledge within all areas of VTE in relation to obesity, from concomitant risk factors to treatment and prognosis.

The strong correlation between PE and cardiopulmonary diseases suggests that when patients with these comorbidities present with acute respiratory or chest symptoms, the suspicion of PE should be high. Our results could also be of importance for thromboprophylaxis. PE is a disease with higher mortality than DVT, indicating that thromboprophylaxis is of higher importance in conditions with a strong correlation with PE.

A clinical dilemma is that patients with cancer not only have an increased risk of thrombosis but also that their bleeding risk is higher. Our results on cancers with lower thrombotic risk highlight the need for an individualized approach to thromboprophylaxis and treatment of cancer-associated thrombosis based on more robust data on thrombotic risk and bleeding risk in various stages of different cancers.

With the introduction of DOACs, treatment practice has changed dramatically, largely due to the lower bleeding risk. However, both previous data and our results call for caution in treating DOACs as a group when assessing bleeding risk. This is also addressed in a randomized trial comparing bleeding risk in apixaban and rivaroxaban during initial treatment with an estimated completion date in December 2024[129]. In current clinical practice, many patients with VTE without temporary provoking factors are treated indefinitely. Our results support the view that this is a safe approach in many patients, with a low incidence of treatment-associated bleeding during extended treatment. At the same time, however, our results also indicate a need for careful consideration of the risks of anticoagulant treatment in older patients, patients with previous bleeding, and patients with liver disease.

## Limitations

As stated earlier in the discussion, the present studies have some limitations.

We lack external validation of the PE and DVT diagnoses. To increase the accuracy of diagnosis, we only included first-time VTEs. We also confirmed VTE diagnoses after July 2005 (January 2006 in Paper *I*), when the National Prescribed Drug Register was introduced, with the dispense of anticoagulant medication[127]. For diagnoses before the introduction of the National Prescribed Drug Register, only patients with inpatient diagnoses or diagnoses in the National Cause of Death Register were included in Paper *I*. In Papers *II* and *III*, we also included first-time outpatient diagnoses that were confirmed with the same diagnosis within three months. However, we do not have a validation study verifying the accuracy of these approaches.

One limitation of Paper *I* is the lack of information on the subsequent weight development of the studied men after enlistment. However, it is well known that obesity in early adulthood is strongly predictive of obesity later in life[130].

The results in Paper *II* might have been influenced by ascertainment bias. For example, heart failure patients are likely to seek medical care for shortness of breath more often than healthy persons. This might lead to a more frequent use of imaging and a higher likelihood of finding PEs. Likewise, a patient who recently had orthopedic surgery in a hip or leg is more likely to have a swollen extremity and might be referred for an ultrasound to discover a DVT. However, the opposite is also true – patients with a plausible explanation for shortness of breath or a swollen leg might not be investigated for VTE[131,132].

## CONCLUSION

This thesis concludes that the healthcare burden of VTE is likely to increase considerably with an increasing prevalence of obesity in society. Women have higher VTE incidence in fertile years and ages over 80, whereas men have a higher incidence in middle age. Cardiopulmonary diseases and PE are closely linked, whereas DVT is more closely related to musculoskeletal surgery and lower extremity fractures. Large groups of cancer patients seem to have a low risk for VTE, even in some cancer types generally considered high-risk conditions, such as kidney and bladder cancer. Apixaban is associated with the lowest bleeding risk during initial treatment compared to warfarin and rivaroxaban, but in extended treatment, this difference is only statistically significant compared to warfarin. Rivaroxaban is associated with a lower bleeding risk than warfarin in extended but not in initial treatment.

## FUTURE PERSPECTIVES

With a growing number of obese patients with VTE, the underlying mechanisms of the increased VTE risk need to be clarified, as well as the effect of different concomitant risk factors and the effect of preventive measures such as thromboprophylaxis. We need to establish the optimal dosage of anticoagulation for prophylaxis and treatment for this specific patient group as well as the long-term prognosis after VTE. There are also uncertainties regarding the consequences of obesity treatments, such as bariatric surgery, on the uptake of peroral anticoagulant treatment and the possible risk of treatment failure, which need to be addressed.

Many clinical decisions regarding patients with risk of VTE or established VTE require careful assessment of risk versus benefits with anticoagulation. Due to the lack of evidence of the benefit of clinical decision rules (in thromboprophylaxis)[68] or assessment of the risk of thrombosis versus the risk of bleeding (in decisions on treatment duration)[31], the responsible clinician is often left without much guidance. However, artificial intelligence, with its subset of machine learning, is evolving in everyday medicine. Today, it is an integrated part of areas such as the interpretation of electrocardiograms and diagnostic images[133]. The algorithms have also shown a potential to aid decisions on thromboprophylaxis[134] and VKA-dosing[135]. Hopefully, it can also be helpful in treatment decisions in patients with high bleeding risk, cancer patients, patients with previous bleeding on anticoagulation, or in decisions on extended treatment in patients where the benefit is unclear.

Although the treatment of VTE has changed considerably over the last decade with the introduction of DOACs, all currently available agents affect central factors in the coagulation cascade. Hence, the antithrombotic effect comes at a price of decreased hemostasis, leading to an increased risk of bleeding. New strategies for preventing and treating VTE with inhibition of Factor XI/XIa and FXII are being explored, which seems to decrease thrombosis without significantly affecting hemostasis[136,137]. This is particularly interesting in patients with a high bleeding risk, for whom we often need to terminate or dose-reduce anticoagulant treatment. Concomitantly, patent expirations are commencing for DOACs. With lower pricing of generic medications, DOACs will be affordable for more VTE patients worldwide, likely influencing treatment patterns.

## ACKNOWLEDGEMENT

I want to thank my main supervisor, *Per-Olof Hansson*. Always encouraging, enthusiastic, and reliable. Always up for new things, whether it's going to thrombosis conferences or starting a VTE research group. You are dedicated and get the job done no matter how much other work you have. But also very clear about priorities between family and work. You are a truly good person, and I am honored to have you as my main supervisor.

*Sverker Jern*, my main supervisor for the original Ph.D. project on diagnostics on PE in exhaled air, which was paused due to Covid-19. We met when you taught ECG when I was in medical school, and you invited me to do my master's thesis in your lab. When I moved back from Stockholm, I ran into you at the main entrance of Östra, and we decided to continue where we left off six years earlier. Our Wednesday luncheons, discussing clinical work, science, and life outside of medicine, were weekly highlights. Thank you also for all the time you put into reviewing my thesis.

*Annika Rosengren*, we ended up sitting next to each other at a dinner at Göteborgs Läkaresällskap, and you offered to introduce me to register-based research by letting me write the first paper of this thesis. That introduction was crucial to the change of the Ph.D. project when Covid-19 made it impossible to continue with the studies on exhaled air. You have exceptional writing skills, and your input in the papers of this thesis has taught me very much.

*Sofia Ekdahl*, the head of the Internal Medicine, Geriatric, and Emergency Medicine Department at Sahlgrenska University Hospital/Östra, for creating a stimulating environment that allows combining clinical and research work. And being a good human being.

*Sara Lann* and *Henrik Norrsell*, heads of the Hematology/VTE unit (353) and Acute Medicine unit (MAVA) at the Internal Medicine, Geriatric, and Emergency Medicine Department at Sahlgrenska University Hospital/Östra, for providing time to work on this project. Also for being sound colleagues and clinicians, patient and understanding leaders and good friends.

*Sam Schulman*, for helping me with articles and future research ideas even though you have no personal gain in doing so. For being warm, helpful, and inclusive. I hope that one day, I have learned enough to have the possibility to pay it forward.

*Jan Sörbo*, for sound suggestions on research work and complicated clinical cases. You are good at not complicating things; you identify what's important and what's not, which I highly appreciate.

*Per Karlsson*, for sharing your knowledge on oncology, for encouragement and valuable advice.

*Martin Adiels* and *Bengt Bengtsson*, for help with statistical analysis.

*Ulrica Forslund-Granheden*, for helping me navigate the administration of being a Ph.D. student, and *Eva Thydén*, for traveling to Gothenburg just to help me with the layout of this thesis.

*Vladimir Radulovic*, *Fariba Baghaei*, and *Anna Olsson*, for your warm welcome to the world of coagulation and thrombosis and never-ending patience with my numerous questions. *Nina Jurander* and *Linda Myrin Westesson* for all practical help at the Coagulation Unit.

*Mazdak Tavoly* and *Kristina Tempelman Svennerholm*, for great discussions on complicated clinical cases, research ideas, and collaboration on VTE guidelines and lectures. I love being challenged with your knowledge. I hope we have many, many years together ahead.

*Maria Roupe*, for being my companion in VTE teaching and in being new at the coagulation unit. Who would have thought when we worked together in Alingsås 15 years ago? Reliable, warm, and wise. Looking forward to working with you for the rest of my clinical life.

*Beatrice Aldenborg*, *Jacob Philipson*, and *Sara Hallström*, for countless lunches, walks, texts, phone calls, runs (Jacob), and dinners, for making the research weeks less lonely and life in general much more fun. I am truly grateful to have the three of you as my friends and colleagues. And *Elin Axelsson Andrén*, for lunch company, walks, laughs, and for being straight with me when I'm wrong.

*All colleagues* at Medicin, Geriatrik och Akutmottagning, Östra sjukhuset, in particular Maktgruppen, for collegiality.

My mom, *Kristina*, for always being there for me and my family with never-ending enthusiasm. In good times and bad.

My mother-in-law, *Helena*, for your help in our everyday life and for your numerous efforts to make me culturally educated. The whole *Sandblad*-family for giving a sense of belonging.

My brother, *Lars*, for always being there. For all great bike rides and runs. Great discussions on life, research, and clinical work. And my sister-in-law, *Josefina*, because you make things better for people around you. And all three of you (including *Hedvig*) for being there for my family when we need you.

*Staffan*, my love. You are may rock. You remind me of what's important in life and put things into perspective. You make me dare to make decisions that I would never have dared without you.

*Emma* and *Gustav*, because the two of you are most important persons in my life, and I love you both very, very much.

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The work was supported by grants from the Swedish state under an agreement concerning research and education of doctors (ALF), Sahlgrenska University hospital funds, The Gothenburg Medical Society, Elsa och Gustaf Lindhs stiftelse, Emelle fond, and the Swedish Heart and Lung association.

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