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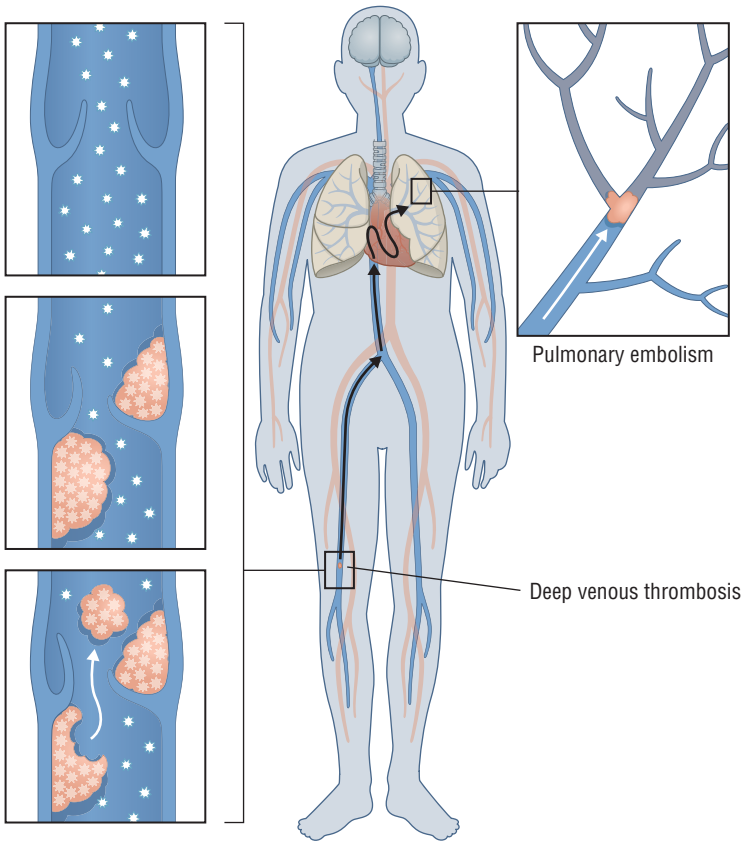

Doctoral Dissertation, Higher Doctorate (Doctor of Science)

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DEPARTMENT OF CLINICAL EPIDEMIOLOGY

STUDIES ON THE ASSOCIATIONS AMONG VENOUS THROMBOEMBOLISM, CANCER, ARTERIAL CARDIOVASCULAR EVENTS, AND MORTALITY

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Lars Hvilsted Rasmussen

Dekan/Dean

Preface

This dissertation is based on studies conducted during my employment at Department of Clinical Epidemiology, Aarhus University Hospital, and Department of Clinical Medicine, Aarhus University (and also at the affiliated unit at Aalborg University Hospital during 2000 to 2013).

I thank my wonderful and knowledgeable colleagues at Department of Clinical Epidemiology for many interactions and discussions over more than two decades.

I have had the pleasure of working with many talented colleagues from Denmark, the Netherlands, Italy, the US, and Germany in preparing the dissertation papers. I appreciate the cooperation of all the co-authors and thank them warmly for their efforts.

A special thank you goes to Lene Mellemkjær, Jørgen H. Olsen, Paolo Prandoni, and John Baron for stimulating discussions and input on key studies of cancer and cardiovascular disease. In connection with the current dissertation, I have had a particularly close collaboration with Kirstine Søgaard. She has made critically important contributions to three of the papers covered in the dissertation.

My colleagues Erzsébet Horváth-Puhó, Dóra Kormendine Farkas and Lars Pedersen have played an important role in establishing the department's high level of biostatistical expertise and in providing invaluable biostatistical input to several of the dissertation's studies. I greatly appreciate our collaboration.

In the preparation of the final version of the dissertation, I greatly value the input of in particular Jan Vandenbroucke and Hans Erik Bøtker with whom I have worked for many years. They have raised both the epidemiological and clinical level of the dissertation.

Over the years, I have had many valuable discussions with other great colleagues at Aarhus University, I thank them all, Hendrik Vilstrup, Jens Otto Lunde Jørgensen, and Jørgen Frøkiær.

I am also very indebted to Kenneth Rothman, Jørn Olsen and Timothy Lash, with whom I have had many invaluable discussions on epidemiological and scientific topics over several decades.

In the summer of 2019 I became aware of the possibility of submitting a dissertation to Aalborg University covering our group's studies on venous thromboembolism. The dissertation has been a joint project with Hanne Schlosser, my close colleague for more than 23 years. She tirelessly and with great energy and enthusiasm typed many drafts of the dissertation and patiently adapted to my working habits. Thank you.

I am especially indebted to Tove Nilsson, who has been a key figure in the development of Department of Clinical Epidemiology. Tove's efforts and my many discussions with her over wide-ranging topics over our many years together molded the department into its current form.

Thank you to Ken Peter Kragsfeldt for the excellent illustrations in the dissertation.

I would like to express my deep gratitude to Drs. John Anderson† and Harald Fuglsang for support and discussions in the early stages of my career.

My deepest thanks go to my family, Sissel, Trine, Troels, Anne, and Birgit, without whose support during the years this dissertation would have not been possible. Also a warm thank you to my children's partners, Søren, Kathrina, and Mitya, and our grandchildren, Vilda, Sofia, Tóra, and Katarina.

Egå, February 2021, Henrik Toft Sørensen

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This dissertation is based on the following papers:

Paper I.

Sørensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *New England Journal of Medicine*. 1998;338:1169-73.

Paper II.

Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *New England Journal of Medicine*. 2000;343:1846-50.

Paper III.

Sørensen HT, Pedersen L, Mellemkjaer L, Johnsen SP, Skriver MV, Olsen JH, Baron JA. The risk of a second cancer after hospitalization for venous thromboembolism. *British Journal of Cancer*. 2005;93:838-41.

Paper IV.

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

Paper V.

Sørensen HT, Horvath-Puho E, Søgaard KK, Christensen S, Johnsen SP, Thomsen RW, Prandoni P, Baron JA. Arterial cardiovascular events, statins, low-dose aspirin, and subsequent risk of venous thromboembolism: a population-based case-control study. *Journal of Thrombosis and Haemostasis*. 2009;7:521-8.

Paper VI.

Cronin-Fenton DP, Søndergaard F, Pedersen L, Fryzek JP, Cetin K, Acquavella J, Baron JA, Sørensen HT. Hospitalization for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *British Journal of Cancer*. 2010;103:947-53.

Paper VII.

Sørensen HT, Horvath-Puho E, Lash TL, Christiansen CF, Pesavento R, Pedersen L, Baron JA, Prandoni P. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. *Circulation*. 2011;124:1435-41.

Paper VIII.

Sørensen HT, Sværke C, Farkas DK, Christiansen CF, Pedersen L, Lash TL, Prandoni P, Baron JA. Superficial and deep venous thrombosis, pulmonary embolism, and subsequent risk of cancer. *European Journal of Cancer*. 2012; 48:586-93.

Paper IX.

Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130:829-36.

Paper X.

Cannegieter SC, Horváth-Puhó E, Schmidt M, Dekkers OM, Pedersen L, Vandenbroucke JP, Sørensen HT. Risk of venous and arterial thrombotic events in patients diagnosed with superficial vein thrombosis: a nationwide cohort study. *Blood*. 2015;125:229-35.

Paper XI.

Søgaard KK, Farkas DK, Pedersen L, Sørensen HT. Splanchnic venous thrombosis is a marker of cancer and a prognostic factor for cancer survival. *Blood*. 2015;126:957-63.

Paper XII.

Søgaard KK, Adelborg K, Darvalics B, Horváth-Puhó E, Beyer-Westendorf J, Ageno W, Sørensen HT. Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: a population-based cohort study. *Lancet Haematolology*. 2018;5:e441-e449.

Chapter 1. Aims

The subject of this dissertation is venous thromboembolism, associated mortality, and its connection with the common serious conditions of cancer and arterial cardiovascular events.

The dissertation focuses on:

1. The bidirectional link between venous thromboembolism and cancer (papers I, II, III, VI, VIII, and XI).
2. The bidirectional link between venous thromboembolism and arterial cardiovascular events (papers IV, V, VII, X, and XII).
3. Mortality associated with venous thromboembolism (papers II, IX, and XI).

The dissertation also outlines briefly the clinical presentation, diagnosis, and treatment of venous thrombosis, as they relate to these three topics.

The choice of this subject arose from the disease burden of venous thrombosis[1] and pulmonary embolism and their association with cancer and cardiovascular diseases. Venous thromboembolism represents a huge burden globally, with approximately 10 million cases occurring every year. It is the third most common vascular disease after acute myocardial infarction and stroke.[1]

Venous thromboembolism is also a major health challenge in first world countries, such as Denmark. In six European countries with a population of 300 million inhabitants, approximately 466,000 cases of deep venous thrombosis and 296,000 cases of pulmonary embolism are estimated to occur each year, as well as 370,000 venous thromboembolism-related deaths.[2] More than 10% of hospital deaths are related to pulmonary embolism, and autopsy studies have shown that many cases of pulmonary embolism are not diagnosed *in vivo*.[3,4] The yearly economic burden of venous thromboembolism is substantial, estimated at 7-10 billion USD in the United States.[5] Surprisingly, venous thromboembolism is not included in the Global Burden of Diseases, Injuries and Risk Factors for Study.[6]

[1] The terms deep venous thrombosis and deep vein thrombosis are used interchangeably in the literature. We have used deep venous thrombosis for consistency.

Arterial cardiovascular disease is the leading cause of death in both developing and developed countries. The annual total number of deaths due to cardiovascular disease is more than 17.9 million, or approximately 30% of all deaths. Approximately seven million of these deaths are due to ischemic heart disease, 5.7 million are due to cerebrovascular disease, particularly stroke, and approximately 2.2 million are due to hypertensive disorders and congestive heart failure. Cardiovascular disease is also an important cause of severe disability among survivors of acute myocardial infarction and stroke.[7] The World Health Organization (WHO) reported in 2015 that more than 82% of all cardiovascular deaths occur in low and middle income countries.[7]

Annually, cancer causes more than 7.7 million deaths worldwide and approximately 30% of the 16 million annual deaths from all causes.[7,8] Across all age groups, cancer is now ranked second behind heart disease as a leading cause of death globally.[7,8] Cancer shares major risk factors with cardiovascular disease, such as smoking and obesity. Cigarette smoking alone is estimated to cause approximately 22% of all cancer deaths. Of all cancer deaths, 70% occur in low and middle income countries.[8]

Clinical medicine in the Western world is confronting an evolving set of diseases, as smoking becomes less prevalent in many countries and obesity more common. The proportion of people aged ≥65 years in Western Europe and North America will increase from 18% in 2012 to 26% in 2025. The gain in life expectancy is greater than the gain in disease-free lifespan.[9] From 2000 to 2015, total life expectancy increased by five years, but was accompanied by only 4.6 years of healthy life expectancy.[10] Currently, 16%-20% of a person's life is spent with late life morbidity.[9] As the diagnosis and treatment of chronic disease continues to improve, the number of patients with multimorbidity (*i.e.*, the coexistence of several chronic diseases, such as cardiovascular disease and cancer) will increase dramatically.[10-12] The implications of these developments have been the focus of editorials in highly respected journals, such as *JAMA, The Lancet* and the *BMJ*.[13-15] In addition, as individuals live longer with multiple chronic diseases, each requiring treatment with new, or at least evolving, medical interventions, the major clinical challenges of polypharmacy and iatrogenic harms emerge—an example being anticoagulation treatment.[16-19]

Clearly, research and treatment will remain suboptimal if they continue to focus only on individual diseases or episodes of illness, individual treatments, or mortality without attention to long-term morbidity, comorbidity, and quality of life.[17] Perhaps the most pressing challenge facing health care systems such as Denmark's is the aging of its population in the face of significant pressure to contain costs. Danish and Nordic medical databases contain the longitudinal data needed to understand these complex issues and

allow multimorbidity to be captured and described in a comprehensive, valid, and population-based manner.[20-22] These databases allowed this dissertation to focus on the interplay between venous thrombosis, pulmonary embolism, cancer, acute myocardial infarction, stroke, and mortality.

A large proportion of diseases worldwide share several risk factors and are also potentially preventable. For example, the risk of venous thromboembolism subsequent to surgery has decreased over the last few decades due to improved thromboprophylaxis, but also due to improved surgical procedures, shorter hospital stays, and earlier mobilization.[23]

In the United Kingdom, a systematic approach to preventing hospital-associated venous thromboembolism has reduced the number of deaths within three months after discharge by approximately 15%.[24] Still, little is known about the long-term prognosis of venous thromboembolism, which is now regarded as a chronic disease. An improved understanding of the link between venous thromboembolism, cancer, and arterial cardiovascular events would have an important public health and clinical impact.

Chapter 2. Introduction

Clinical picture and diagnosis of venous thromboembolism

A venous thrombosis is an obstructive clot in a vein resulting from an imbalance in procoagulant, anticoagulant, and fibrinolytic factors.[25] A venous thrombosis in a leg may break off and travel to the lungs, causing a pulmonary embolism (Figure 1). The clinical manifestation of deep venous thrombosis in the legs includes pain, redness, edema, swelling, tenderness, and noticeable collateral superficial veins.[2] The calf is the most prevalent site of deep venous thrombosis. Signs and symptoms of pulmonary embolism include sudden onset of dyspnea, or deterioration of existing dyspnea, tachypnea, chest pain, weakness from hypotension, shock, syncope, hemoptysis, arrhythmia, and cardiac arrest.[26-28]

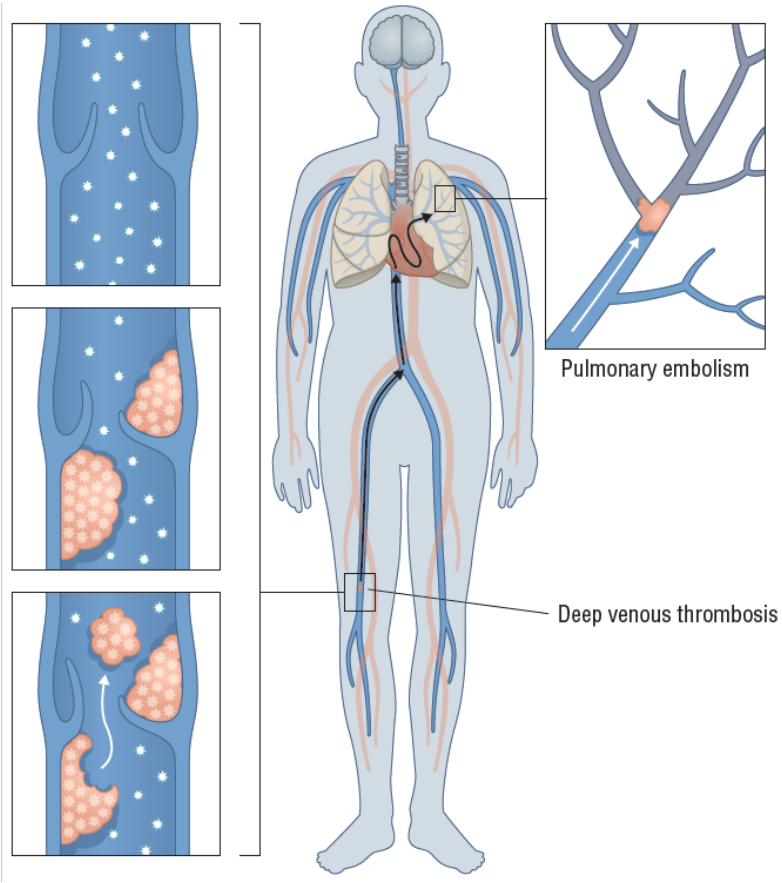

Figure 1. The link between deep venous thrombosis and pulmonary embolism.

Deep venous thrombosis is often asymptomatic or may cause only a few non-specific symptoms. Among patients diagnosed with a pulmonary embolism, 50%-80% have been found to have asymptomatic venous thrombosis.[29,30] In many patients, the first symptom is thus a pulmonary embolism. Pain and tenderness,

the most frequent symptoms associated with deep venous thrombosis, are also present in many other chronic diseases and conditions, such as cellulitis, erysipelas, edema, superficial vein thrombosis, lymphedema, and varicose veins, and are common in the general population.[26] Homan's sign has been used as a classical clinical sign of deep venous thrombosis, but is present in only one-third of patients with this diagnosis and is also present in 50% of patients who have Homan's sign but not this condition.[31]

History of diagnostic techniques

Diagnosing venous thromboembolism on the basis of clinical manifestations alone is thus often inaccurate because of the lack of specificity of symptoms and clinical findings.[32] Using only a clinical diagnosis of deep venous thrombosis will lead to overestimation of the disease and potential initiation of anticoagulation treatment, which carries the risk of severe side effects such as life-threatening (or even fatal) bleeding. The introduction of venography in 1940 and pulmonary angiograms in 1963 represented major advances in diagnostic technology. The landmark study by Haeger published in 1969 showed that only 46% of patients with a clinical diagnosis of deep venous thrombosis had this condition verified by venography.[33]

Venography now is performed rarely because it is invasive and expensive, requires expertise, and is associated with risk of kidney impairment due to use of contrast media.[34] The introduction of computed tomography angiography, magnetic resonance venography, and positron emission tomography improved diagnostic accuracy, but also exposed patients to radiation and risks associated with contrast materials (except for magnetic resonance venography).[34-36]

One-fifth of patients with pulmonary embolism have been reported to die within a few days after diagnosis. Due to this serious prognosis, early and accurate diagnosis is important.[37] While very accurate tests exist, they are invasive. Inexpensive and easily conducted tests with acceptable specificity and sensitivity, available with no diagnostic delay, are preferable.

In the diagnosis of venous thrombosis, compression venous ultrasonography has largely replaced venography in clinical practice. Ultrasound is a fast, non-invasive, and inexpensive examination, though somewhat less valid. For isolated calf deep venous thrombosis, its sensitivity and specificity are 70%-75%.[38] For proximal deep venous thrombosis, its sensitivity and specificity are higher than 95%.[39]

D-dimer is a product of cross-linked fibrin that is elevated in patients with acute venous thrombosis, but also in many other patients.[40,41] Overall, D-dimer testing has good sensitivity, but poor specificity, making it

most useful as a clinical exclusion tool. The performance of clinical decision rules in D-dimer testing varies across various patient groups. Lower test validity for both clinical decision rules and D-dimer testing has been found in patients with cancer and those who are hospitalized.[42-46] The clinical value of D-dimer testing therefore lies in its high negative predictive value.

Current clinical diagnostic algorithm(s)

Although the signs and symptoms of venous thromboembolism are non-specific, they are used to determine the pretest probability of venous thromboembolism, which takes into account symptoms, presence of risk factors, and potential alternative diagnoses.[39] Recent recommendations stress the importance of categorizing patients based on likelihood of venous thromboembolism using validated clinical decision rules, prior to diagnostic testing.[47,48] Appropriate clinical decision-making is based on a combination of clinical assessment with risk stratification, D-dimer testing, and subsequent imaging (Figure 2).

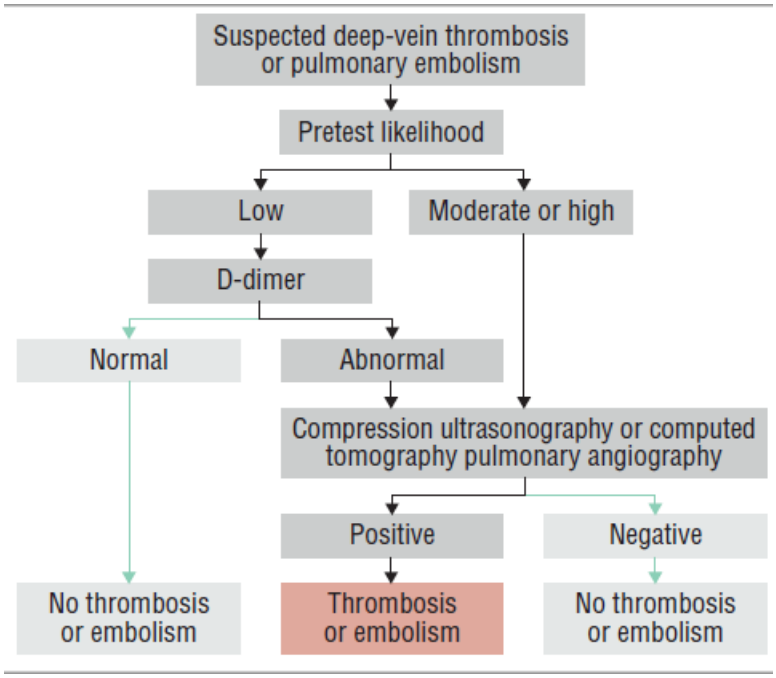

Figure 2. A diagnostic algorithm for suspected venous thromboembolism.

Diagnostic algorithms now have been developed for both deep venous thrombosis and pulmonary embolism. The Wells and Geneva scores initially were based on a three-level rule of low, immediate, and high clinical probability, but later were dichotomized, classifying patients as having high or non-high probability.[49] The Wells and revised Geneva scores have been studied in more than 50,000 patients with

suspected pulmonary embolism.[50] Information on the Wells, OUDEGA, and Geneva scores can be found in the paper by Wells *et al*[48] and for selected score systems in the appendices.

Compression ultrasonography is used in the diagnostic pathway when patients present with a potential deep venous thrombosis. If a diagnostic algorithm like the one presented above is followed, the risk of venous thromboembolism is less than 1% with a negative test.[51,52] In a high-risk patient, a negative test can be followed by a second ultrasound one week later. This approach has been evaluated in 45 studies including more than 15,718 patients.[53,54]

Pulmonary embolism can be safely excluded in patients with low probability of disease (<5%) based on the highly sensitive D-dimer test.[55] Otherwise, a ventilation/perfusion scan may be preferred over multidetector computed tomography angiography because of lower radiation exposure. A pulmonary embolism will produce a defect in perfusion but not ventilation. In patients with >50% probability of pulmonary embolism, computed tomography angiography is recommended as the first test.[47,48] For patients with an immediate risk of pulmonary embolism (20%), D-dimer can be used to exclude pulmonary embolism, most often followed by computed tomography angiography if the D-dimer is elevated. This approach has been evaluated in 75 studies including 44,834 patients.[53,54]

A cancer-specific risk model for venous thromboembolism was developed by Khorana, using clinical and laboratory parameters. Please see the appendices. The model included cancer site stratified according to risk, body mass index, and platelet, leukocyte, and hemoglobin levels to predict venous thromboembolism in patients receiving chemotherapy.[56,57] In the original model, the risk score had a high negative predictive value of 98.5% in patients at low risk, but a poor positive predictive value of 7.1% in patients at high risk.[53] Subsequently, the model has been expanded to include P-selectin and D-dimer levels, with a negative predictive value of 99.0% in patients with the lowest risk score and a positive predictive value of 42.9% in patients with a high risk score.[58]

Incidence of venous thromboembolism

Incidence is defined as the number of new cases of a disease in a population during a given period.[59] Several studies have examined the basic epidemiology of venous thromboembolism but interpretation of their data is challenging. As deep venous thrombosis and even pulmonary embolism are often asymptomatic, produce few symptoms, or are diagnosed at autopsy, incidence estimates are dependent on methods used in the diagnostic work-up and the validity of data collection methods.[60] These factors have

changed over time, and several of the available incidence studies were conducted decades ago. Moreover, only a few studies are truly population-based and only some include autopsy diagnoses.

Population-based studies

Data from the United States indicate that the incidence of pulmonary embolism with venous thrombosis ranges from 29 to 78 per 100,000 person-years and that of venous thrombosis alone ranges from 45 to 117 cases per 100,000 person-years.[61-68] Venous thromboembolism is predominantly a disease of elderly people and is rare among children.[69] Incidence in childhood is reported to be 1 in 100,000, compared to 1 in 100 in persons aged over 84 years.[66,70] For both men and women, age is a strong predictor of incidence, but the overall adjusted annual incidence rate is somewhat higher for men than women.[66] The incidence of deep venous thrombosis has been reported to be higher than the incidence of pulmonary embolism.[61,69,71-73] The incidence trend over time in the Norwegian Tromsø study showed an approximately 27% overall adjusted increase in venous thromboembolism between 1996 and 2012, rising from 158 per 100,000 person-years in 1996 to 201 per 100,000 person-years in 2011. This was mainly due to an increase in the incidence of pulmonary embolism with and without concurrent venous thrombosis.[74] A likely explanation for the observed increase in pulmonary embolism incidence may be improvements in diagnostic imaging during the time period.

Brahmandam *et al*. examined national trends in hospital admissions, outcomes, and the economic burden of venous thromboembolism in the United States.[75] They reported 3,368,409 admissions for venous thromboembolism (54% female, median age 62.9 years) and an average of 818 admissions per 100,000 population per year, with a temporally increasing admission rate for pulmonary embolism, but not for deep venous thrombosis. Old age, race, female gender, pulmonary embolism, and high comorbidity, measured by the Charlson Comorbidity Index, were predictors of in-patient mortality.

For Denmark, Munster *et al*. provided recent incidence estimates.[76] They examined temporal trends in the incidence of Danish patients hospitalized with first- time venous thromboembolism between 2006 and 2015 and identified 67,426 patients from medical registries. Rates were standardized to the national age and gender distribution in 2006. Age- and sex-standardized incidence rates increased from 12.6 per 10,000 person-years in 2006 to 15.1 in 2015. This corresponds to an increase of 20%. The increase was due to a 74% increase in incidence of pulmonary embolism. No increase was observed for deep venous thrombosis,[76] similar to findings in an earlier Norwegian study.[74]

Population-based data on the prevalence of venous thromboembolism in the Danish, and other, populations are lacking. As part of this dissertation, we thus calculated in Denmark. Prevalence is the total number of individuals who have a disease at a particular point in time and is a function of incidence and prognosis.[59] In Denmark the *one-year prevalence* of venous thromboembolism (*i.e.*, the number of persons ever diagnosed with venous thromboembolism during a year) is presented in Table 1 (unpublished data).

Table 1. Yearly prevalence of venous thromboembolism by age and gender, Denmark, 2000-2016.

	Age (years)										Gender				Number of patients with a history of a VTE* episode		Population at risk on 1st of July
	-40		41-50		51-60		61-70		>70		Female		Male				
2000	723	(4.8)	610	(4.2)	900	(4.5)	1,023	(3.5)	2,172	(3.7)	2,827	(4.0)	2,601	(3.9)	5,428	(4.0)	5,445,120
2001	759	(5.0)	586	(4.0)	895	(4.5)	1,022	(3.5)	2,343	(4.0)	2,884	(4.1)	2,721	(4.1)	5,605	(4.1)	5,464,649
2002	748	(5.0)	685	(4.7)	979	(4.9)	1,145	(3.9)	2,530	(4.4)	3,251	(4.6)	2,836	(4.3)	6,087	(4.4)	5,482,437
2003	765	(5.1)	637	(4.3)	1029	(5.1)	1,175	(4.0)	2,580	(4.4)	3,271	(4.6)	2,915	(4.4)	6,186	(4.5)	5,493,628
2004	808	(5.4)	714	(4.9)	998	(5.0)	1,335	(4.6)	2,797	(4.8)	3,514	(5.0)	3,138	(4.7)	6,652	(4.9)	5,506,278
2005	930	(6.2)	787	(5.4)	1143	(5.7)	1,442	(4.9)	2,918	(5.0)	3,827	(5.4)	3,393	(5.1)	7,220	(5.3)	5,518,995
2006	886	(5.9)	837	(5.7)	1159	(5.8)	1,576	(5.4)	3,081	(5.3)	4,008	(5.7)	3,531	(5.3)	7,539	(5.5)	5,535,337
2007	948	(6.3)	903	(6.1)	1150	(5.7)	1,675	(5.7)	3,176	(5.5)	4,263	(6.0)	3,589	(5.4)	7,852	(5.7)	5,554,923
2008	891	(5.9)	832	(5.7)	1098	(5.5)	1,661	(5.7)	3,170	(5.5)	4,042	(5.7)	3,610	(5.5)	7,652	(5.6)	5,581,346
2009	944	(6.3)	977	(6.6)	1184	(5.9)	1,853	(6.3)	3,511	(6.0)	4,435	(6.3)	4,034	(6.1)	8,469	(6.2)	5,604,697
2010	1,051	(7.0)	1,034	(7.0)	1234	(6.2)	1,944	(6.7)	3,579	(6.2)	4,584	(6.5)	4,258	(6.4)	8,842	(6.4)	5,623,946
2011	850	(5.7)	907	(6.2)	1089	(5.4)	1,870	(6.4)	3,564	(6.1)	4,362	(6.2)	3,918	(5.9)	8,280	(6.0)	5,642,059

	Age (years)										Gender				Number of patients with a history of a VTE* episode		Population at risk on 1st of July
	-40		41-50		51-60		61-70		>70		Female		Male				
2012	930	(6.2)	943	(6.4)	1289	(6.4)	2,168	(7.4)	4,040	(7.0)	4,787	(6.8)	4,583	(6.9)	9,370	(6.8)	5,657,757
2013	995	(6.6)	1,102	(7.5)	1470	(7.3)	2,390	(8.2)	4,391	(7.6)	5,164	(7.3)	5,184	(7.8)	10,348	(7.5)	5,672,534
2014	979	(6.5)	1,157	(7.9)	1508	(7.5)	2,433	(8.3)	4,653	(8.0)	5,321	(7.5)	5,409	(8.2)	10,730	(7.8)	5,695,499
2015	938	(6.2)	1,016	(6.9)	1444	(7.2)	2,284	(7.8)	4,774	(8.2)	5,234	(7.4)	5,222	(7.9)	10,456	(7.6)	5,723,834
2016	889	(5.9)	966	(6.6)	1496	(7.5)	2,192	(7.5)	4,838	(8.3)	5,089	(7.2)	5,292	(8.0)	10,381	(7.6)	5,755,415

*Abbreviation: VTE, venous thromboembolism

Seasonal variation

A few studies have examined seasonal variation in incidence of venous thromboembolism. Bounameuaux reported no seasonal variation in venous thromboembolism incidence in a small Swiss study.[77] In contrast, a French study based on 127,318 hospital admissions reported 15% more admissions during the winter than during the summer months for both deep venous thrombosis and pulmonary embolism.[78]

We used Danish registries to identify all patients with deep venous thrombosis, pulmonary embolism, splanchnic venous thrombosis, cerebral venous thrombosis, and retinal venous thrombosis during 1977 to 2016. We estimated the peak to trough ratio and timing of the peak of both diagnoses and deaths associated with a venous thromboembolism diagnosis summed over all years of the study period. In the peak to trough ratio, a departure from 1 measures the intensity of any seasonal pattern. The estimated peak to trough ratio was 1.09 (95% confidence interval: 1.07-1.11) for deep venous thrombosis and 1.22 (95% confidence interval: 1.19-1.24) for pulmonary embolism. The corresponding ratios for splanchnic venous thrombosis, cerebral venous thrombosis, and retinal venous thrombosis were 1.10 (95% confidence interval: 1.01-1.20), 1.19 (95% confidence interval: 1.00-1.40), and 1.12 (95% confidence interval: 1.07-1.17), respectively.[79] The occurrence of all types of venous thromboembolism peaked during winter or fall. In a time-trend analysis, we found that the peak to trough ratio increased for splanchnic vein thrombosis, cerebral venous thrombosis, and retinal venous thrombosis. For associated mortality, the peak to trough ratio was larger for deep venous thrombosis (1.15 [95% confidence interval: 1.07-1.23]) than for pulmonary embolism (1.04 [95% confidence interval: 1.01- 1.08]). Based on these results, we concluded that the excess winter risk, though modest, was more marked for pulmonary embolism than for deep venous thrombosis. We also concluded that the winter peak in mortality following pulmonary embolism was smaller than for deep venous thrombosis.[79]

Costs

As mentioned in Chapter 1, the cost associated with venous thrombosis is substantial. Recently, Gustafsson *et al*.[80] examined the societal costs of venous thromboembolism and subsequent major bleeding events in Denmark. The study population included 74,137 venous thromboembolism patients. The three-year attributable societal venous thromboembolism costs were 40,024 EUR, (34,509 EUR for deep venous thrombosis and 50,083 EUR for pulmonary embolism). Over half (53%) of these costs occurred during the first year of follow-up. The cost estimate for major bleeding was 51,168 EUR, with 46% of the costs occurring in the first year.[80]

Risk factors

Our current basic framework of thinking about mechanisms leading to arterial and venous thrombosis are based on the 'triad' proposed by the German pathologist Virchow in 1856. He suggested that stasis, vessel wall injury, and changes in blood composition are the three major causes of thrombosis (Figure 3).[81] On October 13, 2014, the date of Virchow's birth, the International Society of Thrombosis and Haemostasis established 'World Thrombosis Day.'

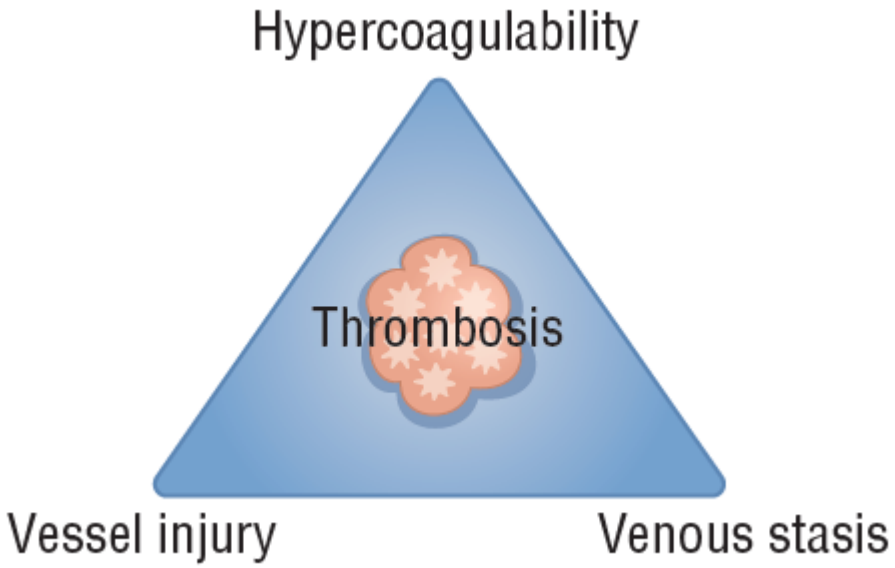

Figure 3. Virchow's triad.

Coagulation is a process that leads to fibrin formation and involves controlled interaction between protein coagulation factors. Coagulation and thrombosis in a pathological setting lead to localized intravascular clotting and potential vessel occlusion. Existing evidence suggests that thromboses may arise via different mechanisms in arterial vs. venous vascular settings. Blood components and flow are especially important for venous thrombosis (red clots in Figure 4).[82] In contrast, vessel wall changes are important for rupture of an atherosclerotic plaque and atherosclerotic progression, resulting in arterial thrombosis or artery stenosis (white clots in Figure 4).[83] There is increasing evidence that the atherosclerosis process starts very early in life (maybe even *in utero*, as suggested by Barker).[84]

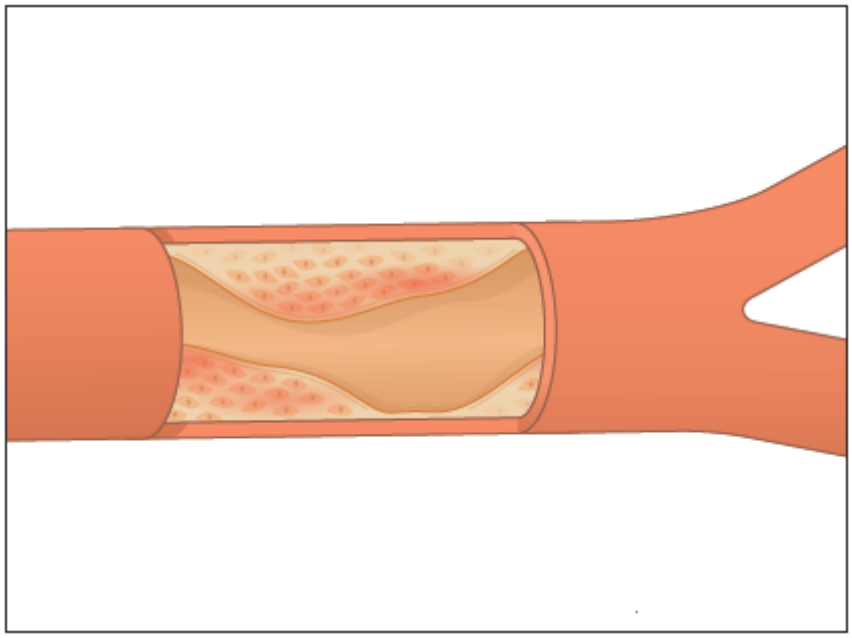

Figure 4. Atherosclerotic plaque with arterial stenosis.

Venous thrombosis can be considered a multi-causal disease, requiring the presence of more than one risk factor for development of thrombosis.[85] It is well established that venous thromboembolism has both genetic and acquired causes.[27] Rosendaal suggested that risk factors for venous thromboembolism may be divided into acquired risk factors, genetic risk factors, and risk factors with an unclear origin.[86] Rosendaal also suggested categorizing risk factors as “fixed” and “transient”. Such stratification is important because it may determine duration of treatment. In addition, transient risk factors have a better prognostic impact than fixed factors.

The most important coagulation disorders arise from defects in the naturally occurring inhibitors of coagulation (deficiencies in anti-thrombin, protein C, or S) and from resistance to activated protein C. This resistance is caused by the factor V Leiden mutation (the most common) or the G20210A prothrombin gene mutation. Heterozygous anti-thrombin deficiency and homozygous factor V Leiden are the strongest genetic risk factors. The relative risk of coagulation disorders has been reported to be 20-50-fold higher in persons with these risk factors.[87,88]

There is a clear inverse association between prevalence of, and strength of, the genetic variations.[89] The common variants are Factor V Leiden, non-O blood group, and the prothrombin 20210A mutation.

A substantial number of epidemiological studies have established genetic and environmental risk factors for venous thromboembolism, and it is beyond the scope of this dissertation to go into the details of the literature. Our contribution to the epidemiological literature on risk factors is shown in Table 2.

Table 2. Causes of venous thrombosis examined in studies conducted by our group.

Genetic	
	• Blood groups A and AB in pregnancy[90]
	• Familial[91]
	• Gender[92]
Acquired and others	
	• Acromegaly[93]
	• Acute infections[94]
	• Antipsychotics[95]
	• Atrial fibrillation[96]
	• Cancer (Papers I, II, III, VI, VIII, and XI)[97-107]
	• Chronic kidney disease[108]
	• Celiac disease[109]
	• Cushing's syndrome[110]
	• Diverticular disease[111]
	• Elevated B12 levels[112]
	• Endogenous testosterone[113]
	• Erythropoiesis-stimulating agent[114]
	• Glucocorticoids[115]
	• Hip and knee replacement[116-119]
	• Hip fracture[120]
	• HIV[121]
	• Hyperthyroidism[122]
	• Implantable cardioverter defibrillators[123]
	• Inflammatory bowel disease[124,125]
	• Liver disease[126]

- Mastocytosis[127]
- Migraine[128]
- Monoclonal gammopathy of undetermined significance[129]
- Multiple sclerosis[130]
- Myocardial infarction (Papers IV, V, VII, X, and XII)[131-134]
- Non-steroidal anti-inflammatory drugs[135]
- Obesity[136]
- Pregnancy[137,138]
- Primary chronic immune thrombocytopenia[139]
- Rheumatoid arthritis and systemic lupus erythematosus[140]
- Seasonality[79]
- Smoking during pregnancy[141]
- Splenectomy[142]
- Statins (Paper V)[132,143,144]
- Stress disorders[145]
- Stroke (Paper IV, V, X, and XII)[131-134,146]
- Tamoxifen[147]
- Third-generation oral contraceptives[148,149]

Evidence is strong that lack of movement, caused by diseases and diagnostic or therapeutic procedures leading to immobilization, as well as local trauma, are among the strongest risk factors for venous thromboembolism.[31,86] Hospital patients have been reported to be at 100 times higher risk of venous thromboembolism than the general population.[150] The risk of venous thrombosis is much higher in the paretic leg in stroke patients than in the non-paretic leg.[151] Many hospital patients have at least one established risk factor for venous thromboembolism, but up to 40% have at least three.[152]

Based on relative risk estimates, risk factors vary from weak to very strong.[153] Among the strongest acquired risk factors are orthopedic surgery, neurosurgery, major abdominal surgery, trauma, multiple fractures, and metastatic cancers.[37,154] Somewhat less severe risk factors include antiphospholipid syndrome, the puerperium, hospitalization without severe immobilization, varicose veins, use of oral glucocorticoids, use of nonsteroidal anti-inflammatory drugs, non-metastatic cancers, pregnancy, use of oral contraceptives, smoking, post-menopausal hormone replacement therapy, obesity, and long-distance traveling.[37,115,135,155-162]

Treatment of venous thromboembolism

It is beyond this dissertation to review the treatment of venous thromboembolism in detail, except to note that treatments have evolved over the last few decades and are important for understanding venous thromboembolism prognosis. An important milestone was approval by the US Food and Drug Administration of intravenous heparin and oral anticoagulation use in 1954. Intravenous heparin was later replaced by low molecular weight heparin.

In the treatment pathway, use of low molecular weight heparin is routinely followed by vitamin K antagonists or a direct oral anticoagulant that is a direct factor Xa inhibitor (rivaroxaban, apixaban, edoxaban) or a direct thrombin inhibitor (dabigatran-etexilat).[47]

Treatment of venous thromboembolism can be divided into an initial period (first 5-10 days), a long-term period (end of acute treatment up to 3-6 months), and an extended period (after 3-6 months).[163] Short-term anticoagulation reduces clot extension and propagation. It also prevents pulmonary embolism, and thereby potential circulatory collapse and death. Long-term treatment may prevent recurrent venous thromboembolism, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and death.[47]

During the last decade, direct oral anticoagulants have been widely used in treating venous thromboembolism due to their advantages over anticoagulation with vitamin K antagonists. These advantages include rapid onset of action and a predictable pharmacokinetic profile that allows simplified drug administration at a standardized dose without laboratory monitoring.[164]

Several clinical trials have indicated that direct oral anticoagulants are at least as effective and safe as warfarin.[165] They are recommended by both the American College of Chest Physicians and the European Society of Cardiology.[166-168] One unsolved problem at present is that there are no antidotes to reverse their effect, in contrast to the vitamin K antagonists where the simple administration of vitamin K acutely reverses anticoagulation, as needed in case of bleeding.[164]

As anticoagulation treatment has the serious adverse side effect of bleeding, its benefits should be carefully weighed against this risk in determining choice of anticoagulant and duration of therapy. In low-risk patients, anticoagulation is recommended for only three months because well-conducted randomized trials

have shown that the major bleeding risk associated with extending anticoagulation treatment beyond this period outweighs the risk of recurrent venous thromboembolism.

Thrombolysis is recommended for patients with a massive pulmonary embolism, including patients with hypotension and right ventricular dilatation and those with deep venous thrombosis and threatened limb loss.[166,167,169,170] The benefit of thrombolysis should be weighed against the severely increased risk of major bleeding. [164,171,172] Several contraindications exist, including active bleeding and recent stroke.

Depending on local expertise and facilities, surgery may be considered in hemodynamically unstable patients. The Pulmonary Embolism Severity Index and other scoring systems appear capable of adding information to reliably identify patients at low risk of pulmonary embolism and free of serious comorbidity.[173] Because the Pulmonary Embolism Severity Index integrates pulmonary embolism severity and comorbidity to assess overall 30-day mortality, it may provide useful information for selecting patients suitable for systemic thrombolytic therapy or surgical therapy, after diagnostic imaging (such as echocardiography and computed tomography angiography) in the hemodynamically unstable patient.

Following the initial event, pulmonary endarterectomy can be beneficial in selected patients with persistent pulmonary hypertension.[167] Consequently, routine follow-up three to six months after the index event is mandatory, not only to assess venous thromboembolism recurrence risk, but also to manage persistent symptoms and functional limitations after pulmonary embolism. Development of chronic thromboembolic pulmonary hypertension is caused by persistent obstruction of the pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodeling of the pulmonary microvascular bed. Surgical pulmonary endarterectomy is the first-choice treatment for operable chronic thromboembolic pulmonary hypertension. In contrast to surgical embolectomy for acute pulmonary embolism, treatment of chronic thromboembolic pulmonary hypertension requires a true bilateral endartectomy through the medial layers of the pulmonary arteries during deep hypothermia and intermittent circulatory arrest.[174]Inferior vena cava filters may be considered in patients with an acute pulmonary embolism and absolute contraindications to anticoagulation, and in cases when pulmonary embolism recurs despite therapeutic anticoagulation.[175]

Benefits versus risks

It is clinically accepted that selected patients with uncomplicated deep venous thrombosis and pulmonary embolism can be treated in an outpatient setting.[153,176-179] The classification of venous thromboembolism as

provoked or unprovoked may assist clinical decision-making.[153] Patients with unprovoked venous thromboembolism have a 10% risk of venous thromboembolism recurrence after one year and 30% after five years, and extended therapy should be considered.[166-168,180] In contrast, the risk of recurrence after treatment is lower in patients with venous thromboembolism associated with surgery.[47,166]

In Chapter 3 we will discuss the strong association of cancer with venous thrombosis. Here we describe the specific clinical challenges of treating the thromboembolism in patients with both diseases.[181-188] A recent Cochrane review included 17 randomized controlled trials of 5,167 patients with cancer and venous thromboembolism.[188] Eight studies encompassing 2,327 patients examined the effectiveness of low molecular weight heparin with that of vitamin K antagonists. Five studies including a total of 982 patients compared direct oral anticoagulants to vitamin K antagonists. Two studies with a total of 1,455 patients compared direct oral anticoagulants to low molecular weight heparin, and one randomized trial of 284 patients compared once weekly subcutaneous injection of idraparinux with standard treatment followed by treatment with warfarin or acenocoumarol for three or six months. For long-term treatment of venous thromboembolism in patients with cancer, low molecular weight heparins are associated with reduced risk of venous thrombosis compared to vitamin-K antagonists. Direct oral anticoagulants may reduce the risk of venous thrombosis but increase the risk of bleeding compared to low molecular weight heparins.[188]
To supplement the safety profile of non-vitamin K antagonists and anticoagulants, we recently conducted a cohort study examining the risk of thromboembolic and bleeding complications during oral anticoagulation therapy in patients with atrial fibrillation. Patients were stratified by presence of cancer (n=11,855) and absence of cancer (n=56,264) before start of oral anticoagulation treatment. One-year risk of thromboembolic events in atrial fibrillation patients was very similar in those with (6.5%) and without (5.8%) cancer. The rate of bleeding complications was also similar. The absolute risk of thromboembolic or bleeding complications was nearly the same in patients with and without cancer who redeemed prescriptions for vitamin-K antagonists and non-vitamin K antagonist oral anticoagulants.[189]

Chapter 3. Venous thromboembolism and cancer

Introduction

The association between cancer and venous thromboembolism has been apparent in anecdotal case reports for almost 200 years. In 1823, Jean-Baptiste Bouillaud (1796-1881) reported an association between cancer and thrombosis, but it fell to Trousseau (1801-1867) in 1865 to describe the syndrome that was attributed to him (Trousseau's Syndrome). In 1867, Trousseau himself actually died from venous thromboembolism and in a postmortem (upon which he had insisted) visceral cancer was found.[190]

As mentioned in Chapter 2, in 1856 Rudolf Virchow described the triad that underlies thrombosis: endothelial injury, stasis, and abnormalities in the blood clotting system.[81] The pathogenesis and pathways of cancer associated with venous thromboembolism are multiple, interrelated, and complex. From a clinical point of view, all factors involved in Virchow's triad are associated with risk of venous thrombosis in cancer patients, including endothelial damage, hypercoagulability, and stasis.

Over the past several decades, a substantial amount of evidence has shown that pro-thrombotic activation may promote tumor growth and dissemination in cancer patients.[191-193] Cancer cells also may contribute to a hypercoagulable state through production of coagulant factors (Figure 5).[192]

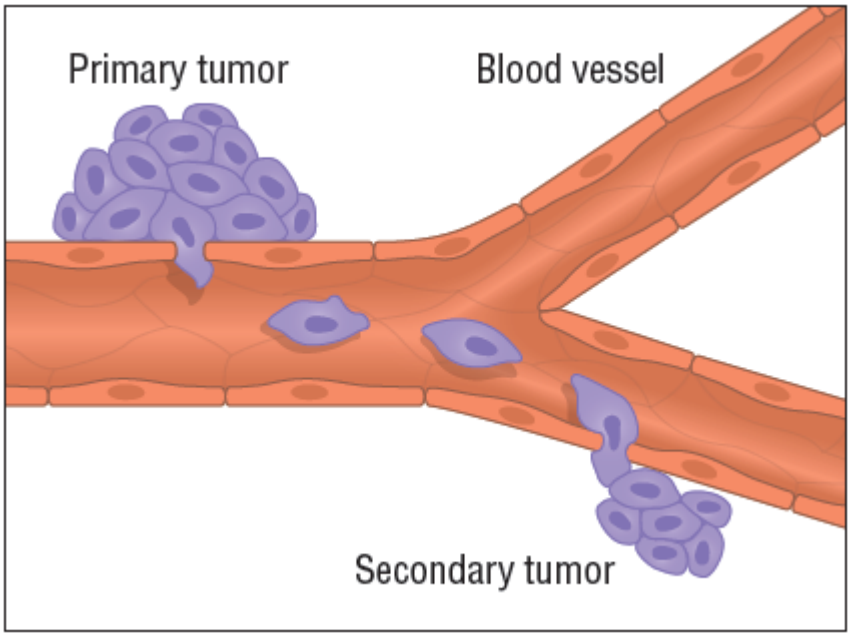

Figure 5. Cancer spread.

Many cancer types require surgery, followed by radiation and chemotherapy. Cancer may also contribute to development of stasis because of immobilization and vascular compression occurring when a tumor reduces blood flow. Over the past three decades, major advances have been made in our understanding of the impact of genetic factors on risk of venous thromboembolism in general, but most relevant studies have not involved cancer patients. Therefore, the role of genetic factors in cancer-related venous thromboembolism remains relatively poorly understood. However, it is already known that prothrombotic genotypes, such as factor V Leiden, the prothrombin G20210A mutation, and non-O blood groups, are associated with an increased risk of venous thromboembolism in cancer patients. There also is some evidence of interaction between cancer and prothrombotic genotypes.[194-196] Two SNPs in the F5 gene (FVL and FRS4524) have been shown to be capable of discriminating patients at venous thromboembolism risk in the first 6 months following a cancer diagnosis.[194] Other genetic characteristics of cancer have been found to increase venous thromboembolism risk in cancer patients. For example, studies have shown that mutations in K-ras are associated with increased risk of venous thromboembolism in colon and lung cancer.[197,198]

It is beyond the scope of this dissertation to review these biochemical pathways in detail. Overall, cancer growth is associated in particular with development of a hypercoagulable state, and fibrin also may be involved in tumor adhesion, spread, and metastases.[192,199-201] Cancer patients have an increased inflammatory response, which may have an impact on fibrin clot formation. Laboratory tests have shown that fibrin formation and dissolution occur continuously at different rates in patients with and without cancer. These biochemical factors, reduced blood flow, and endothelial dysfunction may be activated through immobility, chemotherapy, surgery, and infection.[192]

Not only are cancer patients at increased risk of venous thromboembolism, it is one of their leading causes of death (Paper II).[97,185] This has led to a substantial research over the last few decades on four generic clinical issues:

1. Short- and long-term risk of cancer after a venous thromboembolism episode;
2. Risk of venous thromboembolism in cancer patients;
3. Localization of venous thrombosis and risk of cancer;
4. Diagnostic work-up for cancer patients with venous thromboembolism.

Short- and long-term risk of cancer after venous thromboembolism

Strong clinical epidemiological evidence has accumulated indicating that venous thromboembolism may be the first manifestation of occult cancer. This hypothesis was suggested as early as 1935 and 1944 by Illtyd James, Matheson, Cooper, and Parker.[202,203] However, until a few decades ago, the idea was controversial,[204-207] with some studies indicating an association while others did not.[205,207-209] A follow-up study conducted by Gore *et al*. in 1982 reported a higher rate of cancer detected within 2 years of follow-up in patients with unexplained pulmonary embolism.[210] In 1992, Prandoni *et al.* reported in a study based on 250 patients that the incidence of cancer was higher in patients with an otherwise unprovoked thrombosis than in patients with thrombosis secondary to a transient or provoked factor.[211] Because the concept remained controversial after Prandoni's study, it was followed by three large studies, two of which were published simultaneously in 1998. These are discussed briefly below.

In Paper I, we reported results from a population-based cohort study using Danish registry data.[97] The study included 15,348 patients with deep venous thrombosis and 11,305 with pulmonary embolism. We observed 1,737 cases of cancer in the cohort with deep venous thrombosis, yielding an overall standardized incidence ratio of 1.3 (95% confidence interval: 1.21–1.31). Among the 11,305 patients with pulmonary embolism, we found a similar standardized incidence rate ratio of 1.3 (95% confidence interval: 1.22-1.41). The risk was substantially elevated during the first six months of follow-up, but declined thereafter. However, the relative risk was constantly elevated (slightly above 1.0) even one year after the thrombotic event. This moderate overall excess risk was evenly distributed among the various types of cancer, with robust associations with pancreatic, ovarian, primary liver cancer, and brain cancer. After the first year of follow-up, no clear excess persisted even for the cancer sites with the strongest initial association. We found no substantial differences between smoking-related cancers and cancers without a known relation to smoking. An important finding was that 40% of patients receiving a diagnosis of cancer within one year after their thromboembolic event were observed to have distant metastases at that time. This points to the severe prognosis for cancer patients with venous thromboembolism. In the sub-cohort of 3,762 patients with recurrent episodes of deep venous thrombosis or pulmonary embolism, the relative risk of all types of cancer combined was as high as 3.2 (95% confidence interval: 2.0-4.8) during the first year of follow-up and 1.3 (95% confidence interval: 1.2-1.5) thereafter.

Baron *et al*. similarly used Swedish registries to study cancer incidence in 61,998 patients without a previous cancer diagnosis who were admitted for venous thromboembolism to a hospital in Sweden during 1965 - 1983.[212] They also computed standardized incidence ratios using general population cancer rates for

comparison. The standardized incidence ratio for the 2,509 cancers diagnosed during the first year of follow-up was 4.4 (95% confidence interval: 4.2-4.6). As in the Danish study, they found incidence rates most elevated for liver, pancreatic, ovarian, and brain cancer, and non-Hodgkin's lymphoma. After one year of follow-up, 6,081 cancers were diagnosed, with a standardized incidence ratio of 1.3. Even 10 years later, the cancer incidence ratio remained elevated at 1.3 (95% confidence interval: 1.3-1.4).

In contrast to the Danish study, the Swedish study included patients who had undergone surgical procedures in the preceding months, as well as patients with all other discharge diagnoses. Risk estimates were similar for patients with and without a surgical procedure and were slightly lower (standardized incidence ratio of 4.1 [95% confidence interval: 3.9-4.4]) for patients with other discharge diagnoses.

The two Scandinavian studies were followed in 2004 by a Scottish cohort study of 59,534 patients with venous thrombosis or pulmonary embolism diagnosed between 1982 and 2000. The patients were followed for cancer occurrence until the end of 2000. The standardized incidence ratio in the first 6 months after venous thromboembolism diagnosis was 4.2 (95% confidence interval: 3.9-4.5), confirming the findings from the two Scandinavian studies. Three studies with a similar study design thus showed nearly the same results, with increases in specific cancer types (liver, pancreas, ovary, and brain cancer, and lymphoma).[213]

It also has been suggested that patients with idiopathic or primary venous thromboembolism have a higher risk of occult cancer than patients with a venous thrombotic event secondary to a provoking risk factor.[211,214] As discussed above, Baron *et al*. challenged this assumption and also reported an increased relative risk of cancer in patients with another discharge diagnosis than venous thromboembolism at the time of the venous thromboembolism.[212] This elevated risk was confirmed later in a series of studies of Danish patients with chronic diseases.[215-217]

Heightened diagnostic efforts may explain the association between venous thromboembolism and cancer in the short term. Data from a clinical trial (SOMIT),[218] which focused on extensive diagnostic work-up, are somewhat consistent with the possibility that the elevated short-term risk of cancer detected in patients with venous thromboembolism is potentially due to lead time bias. However, the two Scandinavian studies clearly showed no compensatory deficit in relative risk estimates after one year of follow-up, as would be expected if the association were explained by lead time bias.[97,212] The risk of cancer was elevated many years after the venous thrombotic event, with unclear reasons for this long-term elevated risk. The elevated risk after more than one year of follow-up demonstrated by both the Swedish and Danish studies

has created scientific debate.[219] Prandoni *et al*. concluded from their small study that the risk of venous thromboembolism was similar to the risk in the general population after six months. However, the risk estimate was imprecise and indeed very similar to the one in the Scandinavian studies (hazard ratio 1.09 [95% confidence interval: 0.59-1.34]). In reviewing several possible explanations for the long-term elevated venous thromboembolism risk, Baron *et al*.[212] suggested that slow-growing tumors that remain subclinical for a long period can cause thrombosis. However, they regarded this explanation as unlikely because most cancers do not have a prolonged subclinical course. They noted that factors associated with thrombosis also may promote carcinogenesis, and prostaglandins could be involved in both thrombosis and cancer etiology.[220] Furthermore, use of oral contraceptives, smoking, and obesity as potential shared risk factors could not fully explain the elevated risk.

In their 2008 systematic review of available studies, Carrier *et al*.[214] reported a 6.1% (95% confidence interval: 5.0-7.1) rate of undiagnosed cancer at the time of a first thromboembolic event. After one year, the cumulative rate was 10.0% (95% confidence interval: 8.6%-11.3%). To capture the substantial improvement in use of imaging that occurred after our 1998 study, we performed an updated analysis based on Danish patients with venous thromboembolism diagnosed between 1994 and 2009 (Paper IX).[101] Similar to our earlier study (Paper I),[97] we computed cancer occurrence in the venous thromboembolism cohort and compared it to the expected number of cancer cases based on national incidence rates (Paper VIII).[101] During the first year of follow-up, we observed a standardized incidence rate ratio of 2.75 (95% confidence interval: 2.60-2.90) for deep venous thrombosis and 3.27 (95% confidence interval: 3.03-3.52) for pulmonary embolism. After the first year of follow-up, the standardized incidence rate ratios declined to 1.11 (95% confidence interval: 1.07-1.16) and 1.15 (95% CI 1.09-1.22), respectively. We still found strong associations between venous thromboembolism and subsequent diagnosis of cancers of the liver, lung, ovaries, and pancreas, and non-Hodgkin's lymphoma (Paper VIII).[101]

Patients with cancer are at increased risk of a new primary cancer compared to the general population. However, until 2005 it was not clear whether venous thromboembolism in patients with cancer was associated with an elevated risk of a secondary cancer. Therefore we conducted a study on this topic based on Danish registry data. The risk of a second cancer in the cohort of 6,285 cancer patients that we identified as having a venous thromboembolism episode(Paper III)[99] was compared to the risk in 30,713 patients without venous thromboembolism matched based on age, gender, cancer type, and year of diagnosis (Paper III).[99] Overall, the relative risk of a secondary cancer diagnosis was 1.3 (95% confidence interval: 1.1-1.4) after venous thromboembolism. However, the excess risk varied with amount of time elapsed from the

initial cancer diagnosis to the thromboembolic event. If the venous thromboembolic event occurred within the first year, the relative risk of a second cancer was 1. However, if the venous thromboembolic event occurred more than one year after the initial cancer diagnosis, the overall relative risk of a second event was 1.4 (95% confidence interval: 1.2-1.7), with strong associations for cancer of the gastrointestinal tract, ovary, and prostate. We therefore concluded that the association between venous thromboembolism and subsequent incident cancer extended to patients who already had a cancer diagnosis.

Although it is known that venous thromboembolism can be a presenting symptom of cancer, the association between lower limb arterial thrombosis and cancer has remained unclear. We therefore examined cancer risk and prognosis in 6600 patients with lower limb arterial thrombosis.[221] We observed 772 subsequent cancers in the cohort. During the first six months of follow-up, the standardized incidence ratio of any cancer was 3.3. The standardized incidence ratio remained elevated during 7 to 12 months (1.42) and also beyond 12 months. The strongest associations were found for lung cancer and other smoking-related cancers. Lower limb arterial thrombosis also was associated with increased all-cause mortality after colon, lung, urinary bladder, and breast cancer, but not after prostate cancer. The risk of any cancer was 2.5% after six months of follow-up. We therefore concluded that lower limb arterial thrombosis may also be a marker of occult cancer, especially lung cancer, and an adverse prognostic factor for mortality in common cancers.

Specific location of venous thrombosis and cancer risk

Patients with cancer and venous thrombosis have a higher prevalence of thrombosis at other sites in the legs and lungs.[222] However, it is not clear if venous thrombosis at these locations may also be a marker of occult cancer.

Superficial venous thrombosis

Few data are available on the association of superficial venous thrombosis with risk of occult cancer. We therefore studied 7,663 patients with superficial venous thrombosis in a 2012 analysis and found a standardized incidence ratio of 2.46 (95% confidence interval: 2.10-2.86). The relative risk was only slightly lower than for persons with deep venous thrombosis and pulmonary embolism (Paper VIII).[101] In contrast, Prandoni *et al*. followed 737 patients with superficial venous thrombosis and 1,438 controls in another study and reported a hazard ratio of 0.86 (95% confidence interval: 0.55-1.35).[223] Heterogeneity in these results may be explained by differences in study design, setting, definitions of venous thrombosis, or chance.

Upper extremities

Deep venous thrombosis in the upper extremities is reported to account for 4% of all cases of venous thrombosis [224] and is often associated with use of the central venous catheters for chemotherapy and antibiotics. However, at the time of a first thromboembolic event, risk of venous thrombosis in the upper extremities also is increased in the absence of a central venous catheter. A 2003 study reported an 18-fold increased risk of upper extremity deep venous thrombosis in cancer patients compared to non-cancer patients.[225] We and others have shown that deep venous thrombosis in the upper extremities also may be a marker of occult cancer.[103]

Splanchnic venous thrombosis

Cancer is a well-established predictor of venous thrombosis in the abdomen. [222,226] Among patients with splanchnic venous thrombosis and patients with myeloproliferative disease, 25% and 8%, respectively, have been reported to have a cancer diagnosis.[227] As data were sparse on the association between splanchnic venous thromboembolism and subsequent cancer risk, we conducted a cohort study (Paper XI)[102] based on 1,191 patients with splanchnic venous thrombosis. We followed the patients for subsequent cancer diagnoses and computed both absolute risk and incidence rate ratios. After median follow-up of 1.6 years, we observed that splanchnic venous thromboembolism was a strong marker of occult cancer. Compared to the general population, the three-month cancer risk was 8% and the standardized incidence rate ratio was 33 (95% confidence interval: 27-40). We found a particularly increased risk of liver cancer, pancreatic cancer, and myeloproliferative neoplasms. The incidence rate ratio remained 2-fold increased after one or more years of follow-up.

Other sites

Few data exist on the association between cerebral venous thrombosis and occult cancer.[226] A study based on 152 patients reported that 7% of patients with cerebral venous thromboembolism are carriers of the JAK2 V617F mutation. A cerebral venous thromboembolism thus could be a first symptom of a myeloproliferative neoplasm.[228] We studied the risk of occult cancer in 9,589 patients with retinal venous thrombosis and found that it is not a clinically important marker of occult cancer.[229] The same was true of venous thrombosis during pregnancy.[230]

Risk of venous thromboembolism in cancer patients

In recent decades, a substantial number of studies—varying in data collection methods, study design, and settings—have examined the association between cancer and subsequent venous thromboembolism risk.

We found that 20% of Danish venous thrombosis patients have a diagnosed cancer at the time of their venous thromboembolism diagnosis (Paper V).[132] Available studies have shown that cancer is associated with a 5- to 10-fold increased risk of venous thromboembolism, with the highest venous thromboembolism risk in the period just after a cancer diagnosis. In the Multiple Environmental and Genetic Assessment case-control study, based on 3,200 patients, the odds ratio for developing venous thromboembolism in the first 3 months following a cancer diagnosis was 53, decreasing to 14.3 in the subsequent nine months.[231] The literature has consistently shown a very high risk of venous thromboembolism associated with pancreatic, brain, lung, ovary, lymphoma, kidney, stomach, and bone cancers.[37,232-238]

Few true population-based cohort data exist. In 2010, we investigated venous thromboembolism risk in 57,591 cancer patients and 287,476 members of the general population. We found that the risk depended most on cancer stage, with relative risks of 2.9, 2.9, 7.5, and 17.1 among patients with stage I, II, III, and IV disease, respectively (Paper VI).[100] The risk was particularly high in the first year after the cancer diagnosis. Other predictors of venous thromboembolism were site of cancer and the type of cancer-directed treatment. A study from the California Cancer Registry reported similar findings.[233]

Horsted *et al*. examined the incidence of venous thromboembolism in a meta-analysis of eight different types of cancer.[239] They reported an annual risk of 0.5%-20% depending on cancer type and time since cancer diagnosis.[239]

Recently, we conducted a cohort study of 32,141 Danish patients with hematological cancers and matched them to 1-5 persons from the general population. Ten-year absolute risks were 5.2% for venous thromboembolism (hazard ratio 3.37 [95% confidence interval: 3.13-3.64]), 52% for ischemic stroke (hazard ratio 1.22 [95% 1.12-1.33]), 3.2% for acute myocardial infarction (hazard ratio 1.36 [95% confidence interval: 1.25-1.49]), and 5.8% for bleeding (hazard ratio 2.39% [95% confidence interval: 2.26-2.53]). We therefore concluded that patients with hematological cancer have a substantially higher risk of both arterial and venous thrombotic events and bleeding than the general population.[103]

Currently we are conducting a new study on the risk of venous thromboembolism in 499,092 cancer patients and 1,497,276 members of a comparison cohort drawn from the general population. The study period is 1997-2017. The proportion of persons diagnosed with venous thromboembolism during the six months prior to the cancer diagnosis/index date was 0.93 in the cancer cohort and 0.16 in the comparison cohort (hazard ratio 6.0 [95% confidence interval: 5.7-6.2]). Cumulative incidence of venous

thromboembolism 12 months after the cancer diagnosis/index date was 2.3% in the cancer cohort and 0.35% in the comparison cohort (hazard ratio 8.4 [95% confidence interval: 8.1-8.7]). Risk factors associated with venous thrombosis in cancer patients were male gender, cancer site, presence of distant metastases, chemotherapy, and history of prior venous thromboembolism. The one-year risk of venous thromboembolism in the cancer cohort increased from 1% in 1997 to 3.2% in 2017, probably due to improved imaging and longer survival (paper in draft at time of submission of dissertation, later a revised version was accepted by *Blood*).

Overall, existing studies have shown that among cancer patients the following treatments are risk factors for venous thromboembolism: surgery, chemotherapy, hormonal therapy, anti-angiogenic drugs, immune modulatory agents, thrombocytosis, erythropoiesis-stimulating agents, blood transfusion, and the use of intravenous catheters.[114,240-245]

Diagnostic workup for occult cancer

As many studies have confirmed the association between symptomatic cancer and venous thromboembolism, the issue arises whether patients with venous thromboembolism should be screened for occult cancer. Since venous thromboembolism can be the first manifestation of an undiagnosed cancer, screening for occult cancer might improve cancer-related mortality. This question has been heavily debated. In total, three randomized trials have not supported the effectiveness of screening patients with venous thromboembolism for occult cancer. The SOMIT study was a multicenter randomized trial comparing a strategy of extensive screening versus no further testing for cancer in venous thromboembolism patients.[218] A total of 201 patients with idiopathic venous thromboembolism for whom a routine initial evaluation did not yield a diagnosis of cancer were randomized to the two regimens (n=99 and n=102) and followed for up to two years. In the extensive screening group, 13 patients (13.1%) were diagnosed with cancer. Ten cases were revealed through computed tomography of the abdomen and pelvis. Subsequent cases of cancer (1%) were diagnosed during follow-up. The 13 malignancies diagnosed in the extensive screening group at the time of screening produced an initial screening sensitivity of 93%. In the control group, 10 (9.8%) cases of cancer were diagnosed during follow-up. As expected from screening theory,[246] screening led to earlier detection of cancer. Cancer-related mortality occurred in 2 (2%) of the 99 patients in the extensive screening group compared to 4 (3.9%) of the 102 control patients. The absolute risk difference was 1.9% (95% confidence interval: -5.5-10.9). The risk of occult cancer was higher in elderly patients and in those without thrombophilic conditions. Due to the relatively small sample size, the study results were inclusive.

Carrier *et al.*'s 2015 Canadian SOME trial included 854 patients randomized to limited cancer screening alone or in combination with comprehensive computed tomography of the abdomen and pelvis. The overall rate of occult cancer detection was 3.9% over 12 months.[247] There were no important differences between the two group in time to a cancer diagnosis (4.2 versus 4.0 months) or in cancer-related mortality (1.4% versus 0.9%).

The 2016 French MVTEP study was based on 399 patients[248] who were randomized to a limited screening strategy alone or in combination with 1-F-fluorodeoxyglucose positron emission tomography/computed tomography.[249] As expected, a slightly higher rate of occult cancer was detected with extensive screening strategies. However, these strategies were not associated with improved patient outcomes, including earlier stage tumors or lower cancer-related mortality.

In Robin *et al's* recent meta-analysis of 1,830 patients included in prospective studies, occult cancer was detected either at screening or during a two-year follow-up period in 98 patients (5.4%, 95% confidence interval: 4.4% to 6.5%). Of the 56 patients (48.2%) diagnosed with cancer in the extensive screening group, 27 died during follow-up, compared with 23 out of 42 patients (54.8%) in the limited screening group (hazard ratio 0.83; 95% confidence interval: 0.48-1.45). Similar results were found in subgroup analyses conducted according to time of cancer diagnosis (*i.e.*, at screening vs. during follow-up) and according to whether cancer was diagnosed during limited or more extensive testing. Robin *et al.* concluded that extensive screening for occult malignancy in patients with unprovoked venous thromboembolism was not effective in reducing overall mortality. As well, diagnosing an occult cancer in patients with an unprovoked venous thromboembolism was associated with a poor outcome.[249]

Another recent comprehensive meta-analysis of 2,316 venous thromboembolism patients from 10 prospective studies reported that the prevalence of occult cancer was 5.2% over one year of follow-up.[250] As expected, an intensive screening strategy was associated with 2-fold higher probability of cancer detection at the initial screening. However, despite the higher rate of cancer detection with extensive screening, these strategies have not been associated with improved cancer-related mortality. According to this meta-analysis, 58% of patients received extensive screening for venous thromboembolism and the cancer rate in the following year was 5.2%. A strong risk factor for cancer was old age. As expected, the extensive screening strategy detected more cancer than limited screening. However, the data were inconclusive as to whether this translated into improved patient outcomes. Overall, the available evidence

does not clarify whether an extensive screening strategy is preferred over a limited screening strategy in patients with venous thromboembolism.

Recent guidelines recommend limited cancer screening, including a medical history and physical examination, basic laboratory investigations, x-rays, and age- and gender-specific cancer screening for breast, cervical, colon, and prostate cancer.[251] However, it is not entirely clear from the existing literature whether some subgroups of patients may benefit from a more extensive diagnostic work-up for cancer.[249] Newly developed and validated clinical predictor rules may be increasingly used as a tool for stratifying patients with unprovoked venous thromboembolism according to their underlying risk of occult cancer.[252]

Chapter 4. Venous thromboembolism, atherosclerosis, and arterial cardiovascular events

Introduction

Venous and arterial thrombosis have traditionally been regarded as two different diseases from clinical and epidemiological points of view. As explained above, arterial thrombosis is caused primarily by plaque rupture when shear stress is high, while venous thrombosis occurs in the veins, where flow and pressure are low compared to the arterial system.[253] Moreover, arterial thrombosis is associated with platelet activation and venous thrombosis is associated with activation of the clotting system.[82,254] However, existing atherosclerosis involves an activation of platelets and blood coagulation, as well as fibrin turnover, suggesting that activated platelets and coagulation factors could play a role in thrombi formation in the venous system. In addition, arteriosclerosis and venous thromboembolism share several risk factors.

A few decades ago, anticoagulation therapy was found effective both in treating deep venous thrombosis and preventing arterial embolism in patients with atrial fibrillation, challenging the long held view that venous and arterial thrombosis are two different diseases.[255,256] Antiplatelet treatment also has some effect on both venous thrombosis and arterial diseases.[257,258] Similarly, a number of observational studies demonstrated an up to 40%-50% reduced risk of venous thromboembolism after use of statins. The mechanism behind the statin finding is unclear, as dyslipidemia is not associated with increased risk of venous thromboembolism or hypercoagulability. However, there is increasing evidence for the protective effect of statins on venous thrombosis. Kunutsor *et al.* conducted a systematic review and meta-analysis of observational cohort studies and randomized trials to evaluate the extent to which statins are associated with first-time venous thromboembolism.[259] Thirty-six studies (13 cohort studies and 23 randomized trials) were included in their analysis. The pooled relative risk of venous thromboembolism was 0.75% (95% confidence interval: 0.65-0.87) in studies in which statin use was compared to no statin use. An analysis of a sub-group of statins showed that rosuvastatin was associated with a lower risk of deep venous thrombosis than other types of statins (0.57 [95% confidence interval: 0.42-0.75]). No effect was evident for pulmonary embolism. We confirmed these findings in a recent large cohort study based on 601,011 statin initiators and 1,803,033 members of a comparison cohort drawn from the general population during 2005-2015. We found a reduced risk of unprovoked venous thromboembolism (adjusted hazard ratio 0.92 [95% confidence interval: 0.89-0.95]) and no indication of a healthy user effect.[144]

Prandoni *et al.* initiated research on the potential association between venous and arterial thrombosis when they undertook a cohort study focusing on the prognosis of patients with unprovoked and secondary venous thrombosis. They examined the risk of developing recurrent venous thromboembolism and post-thrombotic sequelae, leading to the idea that venous thrombosis and arterial disease were closely associated.[260] They found that a substantial number of patients died because of an acute myocardial infarction or stroke. These observations spurred them to initiate a case-control study in which they examined carotid arteries by compression ultrasonography, comparing 299 patients with deep venous thrombosis without clinical signs of atherosclerosis to 150 controls.[261] They controlled for several potential confounders. The study showed that patients with unprovoked venous thrombosis had an increased prevalence of carotid plaques, compared to the controls (prevalence odds ratio risk; 2.3). This study led to a substantial amount of extended research on the association between venous and arterial thrombosis. Key studies are reviewed below.

In a small case-control study, Hong *et al*. reported a higher prevalence of coronary artery calcium detected by computed tomography in patients with unprovoked venous thrombosis compared with a matched control group of patients without venous thromboembolism (51.7% vs. 28.1%).[262] In a cross-sectional study of approximately 24,000 consecutive autopsies, Eliasson *et al*.[263] reported a higher prevalence of venous thrombosis in patients with coronary thrombosis. Subsequently, the hypothesis was presented that obesity and metabolic syndrome are important components of the pathways between the two diseases.[264-266] These observations also led to a substantial amount of research on the potential pathophysiological pathways between the two diseases, to examine whether venous thromboembolism is a risk factor for subsequent atherosclerosis and arterial events, and whether atherosclerotic events are risk factors for venous thromboembolism. The two questions may have important implications for prophylaxis of both venous thrombosis and atherosclerosis.

A conceptual model explaining the association was suggested by Lijfering,[267] who provided several potential explanations for the association between venous and arterial thrombosis, as follows:

Lijfering *et al*.[267] proposed that potential causal mechanisms be divided into direct and indirect causes. He suggested that the associations between venous and arterial thrombosis could be mediated by several indirect causal mechanisms, which could be studied and interpreted in both directions:

1. Arterial thrombosis causes venous thrombosis or venous thrombosis causes arterial thrombosis – direct causality.
2. Atherosclerosis increases risk of venous thromboembolism due to shared risk factors– indirect causality.
3. Venous thromboembolism is associated with development of atherosclerosis, thereby increasing the risk of arterial thrombosis – direct causality.
4. Venous thromboembolism increases the risk of atherosclerosis due to shared risk factors and thereby leads to arterial events – indirect causality.

Potential shared risk factors

Several studies have investigated whether shared risk factors or common causal mechanisms underlie the association between venous and arterial thrombosis. Smoking is a strong risk factor for arterial cardiovascular disease[268] and also has been investigated as a potential risk factor for venous thromboembolism. A meta-analysis of 32 studies with 3,966,184 participants found that venous thromboembolism risk in both former and current smokers is slightly increased (relative risks 1.10 and 1.23, respectively).[269] Other studies have indicated that the association is present only between cigarette smoking and provoked venous thromboembolism.[270] This may indicate that smoking-related diseases, such as cancer and atherosclerosis, mediate the increased risk of venous thromboembolism among smokers.

Ageno *et al.* published a meta-analysis in 2008 based on 21 observational studies. They reported that hypertension was associated with an increased risk of venous thrombosis (odds ratio 1.51).[271] In a later meta-analysis, Mahmoodi *et al*.[270] also reported an association between hypertension and venous thromboembolism. However, after controlling for age, gender, and body mass index, the positive association disappeared and even became inverse for systolic blood pressure.

Hypertension, diabetes, and obesity are closely linked. As expected, evidence is increasing that both obesity and hypertension are risk factors for venous thromboembolism. In addition, two meta-analyses have reported that diabetes mellitus is a risk factor for venous thromboembolism.[271,272] However, Mahmoodi *et al*. found no association between diabetes mellitus and venous thromboembolism after controlling for obesity and other confounding factors.[270] Therefore, it is likely that at least some of the association between diabetes and venous thromboembolism is mediated through obesity --a strong risk factor for venous thromboembolism, even stronger than for myocardial infarction. Obesity is estimated to account for approximately one-third of unprovoked cases of venous thromboembolism.[268,273-276] In addition to body

mass index, total body fat, waist and hip circumference, and waist to height ratio are risk factors for venous thromboembolism. The mechanisms underlying these strong associations have only been partially examined, but factors associated with low-grade inflammation and increased intra-abdominal pressure have been suggested as possible pathways.[277-280]

Childhood weight trajectories influence cardiometabolic traits and potentially the risk of venous thromboembolism later in life. We therefore recently conducted a large cohort study to examine whether being overweight and experiencing changes in weight status during childhood are associated with venous thromboembolism risk in adulthood. Our study included 313,998 schoolchildren with computerized health records linked to medical registries. We found that an above-average body mass index at age 7 or 13 years was associated with increased venous thromboembolism risk in adulthood. Children with a persistently above-average body mass index at 7 and 13 years of age had an additionally increased risk of venous thromboembolism in adulthood. In contrast, venous thromboembolism risks among overweight children who normalized their body mass index by age 13 years were comparable to those with a consistently normal weight. We found no association between low birth weight and venous thromboembolism in adulthood. Controlling for birth weight did not change our estimates.[281]

Data on physical activity and venous thromboembolism are inconsistent. A few studies have reported a lower venous thromboembolism risk; some studies have reported no effect after adjusting for body mass index; and a few studies have even reported that rigorous exercise increased the risk of venous thromboembolism in obese persons and in the elderly.[282-287]

While several studies examined the association between hyperlipidemia and venous thromboembolism risk with inconsistent results, the majority of studies found that high levels of cholesterol and triglycerides are not associated with increased venous thromboembolism risk.[266,270,288,289] Recently, a comprehensive analysis of 421,537 participants in the UK Biobank and 75 cohort studies with 731,728 participants examined whether established cardiovascular risk factors also are associated with venous thromboembolism risk. The analysis confirmed that old age (hazard ratio 1.81-2.67 per decade), smoking (hazard ratio 1.23-1.38), and obesity (hazard ratio 1.37-1.43 per 1 standard deviation higher body mass index) are consistently associated with an elevated risk.[290]

In summary, venous thromboembolism and arterial cardiovascular events clearly share common etiologic risk factors. However, available data are not entirely consistent and the mechanisms remain poorly understood.

Venous thromboembolism, atherosclerosis, and subsequent arterial vascular events

The association between venous thromboembolism and subsequent arterial events has been examined in several studies (Figures 6 and 7). One of the largest was a 20-year follow-up study conducted by our group, which investigated the risk of acute myocardial infarction and stroke in 25,199 patients with deep venous thrombosis, 16,925 patients with pulmonary embolism, and 163,556 persons from a general population cohort. We found that deep venous thrombosis was associated with increased risk of acute myocardial infarction and stroke the first year after a thrombotic episode, with a relative risk of 1.60 for acute myocardial infarction and 2.19 for stroke. In pulmonary embolism patients, corresponding relative risks were 2.60 for acute myocardial infarction and 2.93 for stroke. The relative risk decreased after 20 years of follow-up, but the risk was still increased by 20%-40%. The relative risk was the same for both provoked and unprovoked deep venous thrombosis and pulmonary embolism (Paper IV).[131]

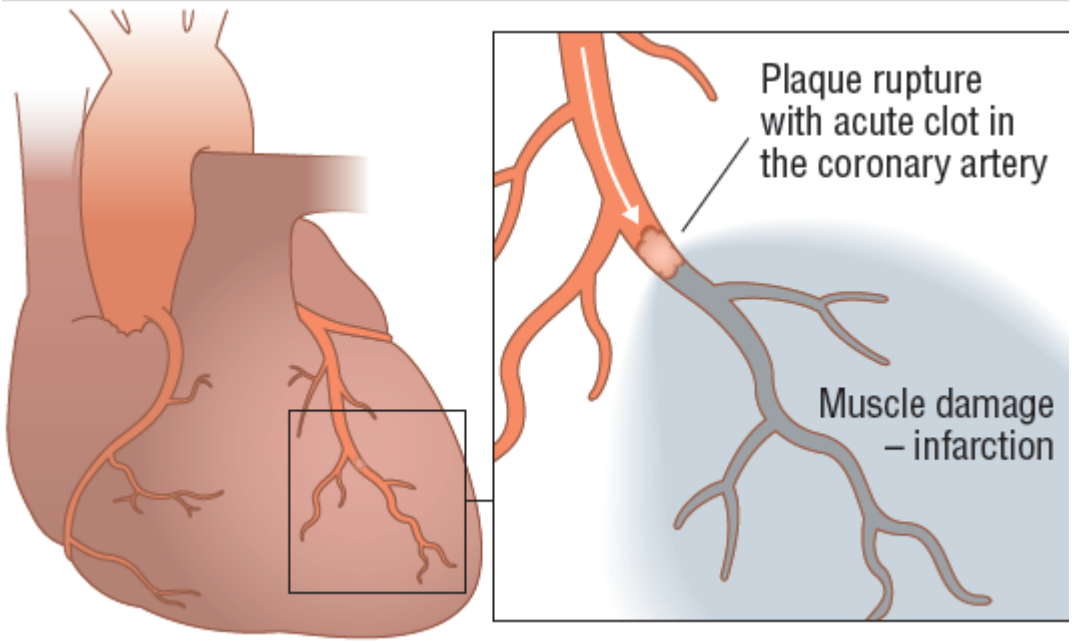

Figure 6. Association between plaque rupture, clot, muscle damage, and development of myocardial infarction.

Little is known about the association between superficial venous thrombosis and risk of arterial events. In a subanalysis of CALISTO trial data for 737 patients, Prandoni *et al.* examined whether superficial venous

thrombosis is associated with increased risk of subsequent arterial events. They reported a relative risk of 0.97 for arterial events in patients with superficial venous thrombosis compared to controls.[223]

Our group also examined the risk of subsequent deep venous thrombosis and arterial thrombotic events in 10,973 patients with a first-time diagnosis of superficial venous thrombosis and 515,067 general population comparison cohort members during 1980-2012. During median follow-up of seven years, the incidence rate of venous thromboembolism was 18 per 1,000 person-years (95% confidence interval: 17.2-18.9). The highest risk occurred during the first three months of follow-up (3%). Compared to the general population, the relative risk was 71.4 (95% confidence interval: 60.2-84.7) during this three-month period, decreasing to 5.1 (95% confidence interval: 4.6-5.5) five years after the superficial venous thrombotic event (Paper X).[133] The relative risk of acute myocardial infarction, stroke, and death was 1.2 (95% confidence interval: 1.2-1.3), 1.3 (95% confidence interval: 1.2-1.4), and 1.3 (95% confidence interval: 1.2-1.3), respectively. We concluded that a strong association exists between superficial venous thrombosis and subsequent deep venous thrombosis and pulmonary embolism, particularly during the first months of follow-up. The risk of subsequent acute myocardial infarction, stroke or mortality was likely higher in the superficial venous thrombosis patients than in the general population cohort.

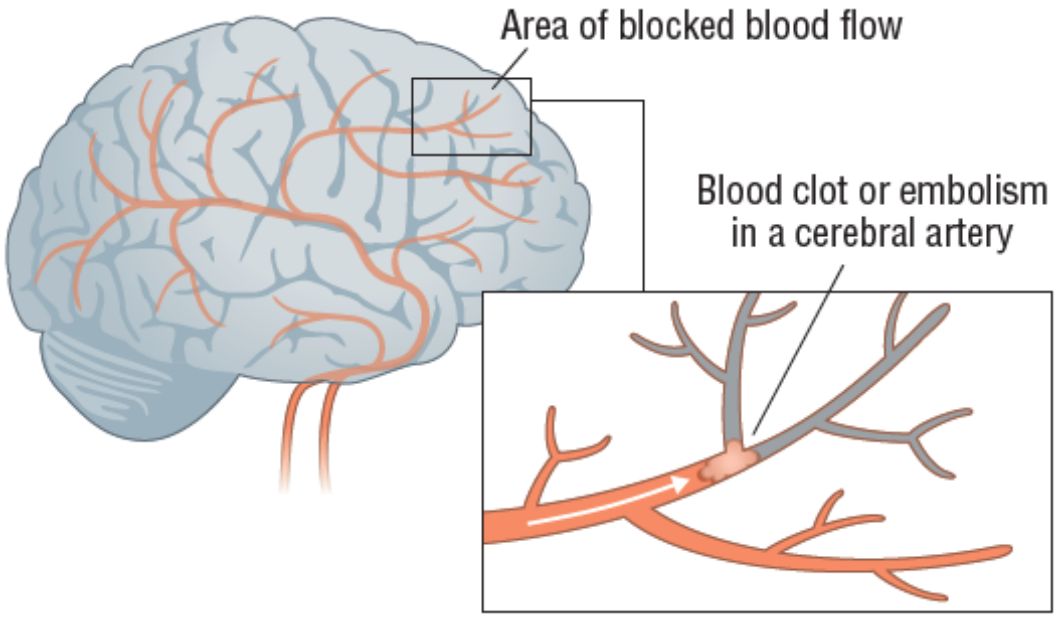

Figure 7. Ischemic stroke.

As little is known about arterial events following splanchnic venous thrombosis, we conducted a cohort study (Paper XII)[134] including 1,915 patients with splanchnic venous thrombosis, 18,373 patients with deep

venous thrombosis and pulmonary embolism, and 19,150 persons from the general population. The risk of arterial cardiovascular events in patients with splanchnic venous thrombosis was high during the year after the thrombosis diagnosis (absolute risk 3.3% [95% confidence interval: 2.6-4.2] for the first month, 7% from 1 month to 1 year). In an adjusted Cox regression analysis, we found that the risk of arterial cardiovascular events was higher in patients with splanchnic venous thrombosis than in patients with venous thromboembolism (hazard ratio 7.05 [95% confidence interval: 4.74-10.48] up to one month and 2.10 [95% confidence interval: 1.62-2.72] from one month to one year). Compared to the general population cohort, the hazard ratios were 15.95 (95% confidence interval: 9.26-26.19) and 3.17 (95% 2.34-4.27), respectively.

Atherosclerosis, arterial cardiovascular events, and subsequent risk of venous thromboembolism

Several large studies have examined whether atherosclerosis is associated with a subsequent increased risk of venous thromboembolism. In the Atherosclerosis Risk in Communities Study with 13,081 patients aged 45-64 years, no association was found between subclinical atherosclerosis measured by carotid ultrasound and venous thromboembolism risk (hazard ratio 0.97 [95% confidence interval: 0.72-1.29]).[291] A subsequent study of 4,108 persons over 65 years old in the Cardiovascular Health Study who underwent carotid ultrasound and ankle brachial blood pressure measures were followed for a median of 11.7 years. That study unexpectedly found an inverse association between atherosclerosis and venous thromboembolism.[292] The authors concluded that asymptomatic atherosclerosis probably does not play an important role in venous thromboembolism development. Based on the Tromsø study, Brækkan *et al*. examined roughly 21,000 persons aged 25-96 years and found that a family history of acute myocardial infarction increased the risk of overall venous thromboembolism and unprovoked venous thromboembolism, but observed no association between atherosclerosis and venous thrombosis.[293]

In our group's large population-based case-control study, arterial thrombotic events were associated with an increased risk of venous thromboembolism for three months after a myocardial infarction, with relative risks of 4.2 (95% confidence interval: 2.3-7.6) after acute myocardial infarction and 4.4 (95% confidence interval: 2.9-6.7) after stroke. The increase in risk was not long-term for acute myocardial infarction. Stroke patients had a 1 to 2-fold increased venous thromboembolism risk, probably due to the associated immobilization (Paper V).[132] Recently, Sejrup *et al.* published a case-crossover study, in which they concluded that 60% of the association between acute myocardial infarction and venous thromboembolism was mediated through immobilization and infections.[294]

We also recently conducted a study of venous thromboembolism risk after acute myocardial infarction. It included 160,338 patients with acute myocardial infarction and 792,384 members of a comparison cohort drawn from the general population. We examined the impact of comorbidities on venous thromboembolism risk after myocardial infarction. The 30-day and 1-12-month venous thromboembolism risks were 0.6% and 0.5%, respectively, in the myocardial infarction cohort, and 0.03% and 0.3%, respectively, in the comparison cohort. The relative risk of venous thromboembolism in the myocardial infarction cohort was 23 after one month and decreased during the one-year follow-up. Thirty days after myocardial infarction, the additive interaction between myocardial infarction and comorbidity accounted for 16.4% of venous thromboembolism rates in myocardial infarction patients with low to moderate and high comorbidity. These interactions were mainly driven by hemiplegia and cancer as underlying comorbidities in persons experiencing myocardial infarction.[295]

In 2016 our group conducted a similar cohort study encompassing 201,025 patients diagnosed with ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage or unspecified stroke and a comparison cohort of 983,222 members from of the general population. The cohorts were followed up to five years following their stroke date/index date. Five-year risks of venous thromboembolism were 2.1% and 1.9% in the stroke and comparison cohorts, respectively. Venous thromboembolism rates peaked at a 5-fold increase three months following stroke and remained 13% to 43% increased relative to the general population during subsequent follow-up. During the first three months after stroke, 15% to 33% of the venous thromboembolism rates were attributable to the additive interaction between stroke and moderate to high comorbidity. We also found that non-metastatic solid tumors and metastatic disease accounted for most of the observed interaction with stroke, representing 41% and 56%, respectively, of attributable three-month venous thromboembolism rates. We found no such interaction between comorbidity and stroke during subsequent follow-up. Comorbidity, particularly cancer, increased risk of venous thromboembolism within three months following stroke.[146]

In summary, the literature shows that venous thromboembolism and arterial events share a number of pathogenic mechanisms, including inflammation and high levels of coagulation factors. Moreover, the diseases share several common risk factors. The increased risk of venous thromboembolism immediately after stroke and acute myocardial infarction can be explained at least in part by immobilization and complications. After recovery from stroke and acute myocardial infarction, the risk of venous thromboembolism is relatively modest. In contrast, the risk of subsequent arterial events remains elevated in patients with venous thromboembolism, with the mechanism still largely unexplained.

Several hypotheses for the association between heart disease and pulmonary embolism have been proposed. Among patients with pulmonary embolism, 40% have no preceding or concurrent diagnosis of peripheral venous thrombosis, even after a detailed clinical examination.[29,296] In fact, a cross-sectional hospital database study reported a higher prevalence of heart disease in patients with pulmonary embolism without deep venous thrombosis than in patients who had pulmonary embolism and deep venous thrombosis.[297] This led our group to conduct a nationwide population-based case-control study (Paper VII)[298] including 45,282 patients with pulmonary embolism alone, 4,680 patients with pulmonary embolism and deep venous thrombosis, and 59,790 patients with deep venous thrombosis alone. We selected 541,561 population controls through risk set sampling. Our analysis showed that a high risk of apparently isolated pulmonary embolism was associated with a history of acute myocardial infarction and heart failure in the preceding three months (odds ratio 43.5 [95% confidence interval: 39.6-47.8] and odds ratio 32.4 [95% confidence interval: 29.8-35.2], respectively). With a history of acute myocardial infarction and heart failure in the preceding three months, the risk of a subsequent pulmonary embolism combined with deep venous thrombosis was lower (odds ratio 19.7 [95% confidence interval: 16.2-24.2] and odds ratio 22.1 [95% confidence interval: 18.7-26.0], respectively). For subsequent deep venous thrombosis alone, the odds ratios were 9.6 [95% confidence interval: 8.6-10.7] and 12.7 [95% confidence interval: 11.6-13.9]), respectively. The odds ratio for right-sided valvular heart disease was 74.6 (95% confidence interval: 28.4-195.8), much higher than that for left-sided valvular heart disease (odds ratio 13.5 [95% confidence interval: 11.3-16.1]). We concluded after careful consideration of potential biases that heart diseases may be associated with a near term risk of pulmonary embolism but not with peripheral deep venous thrombosis.

Chapter 5. Prognosis

The course of a disease is its natural history or its clinical course.[299] As many patients with venous thromboembolism have asymptomatic or undiagnosed disease, there is substantial uncertainty about its natural history, and whether most of the patients with a diagnosis of venous thromboembolism will be treated. Symptoms vary based on the anatomic location of the thrombus and its extent; therefore, the clinical spectrum of venous thromboembolism varies from asymptomatic disease to circulatory collapse. In general, major predictors of the clinical outcome of a disease are the underlying biology and severity of the index disease, comorbidities, diagnostic activity and quality, treatment, clinical performance, and adherence to therapy.[300]

The prognostic literature has focused mainly on the following main outcomes after venous thromboembolism: recurrence of venous thromboembolism, post-thrombotic syndrome, risk of chronic thromboembolic pulmonary hypertension, and mortality (Figure 8). Below we review some of the most important studies related to these outcomes. The associations between venous thromboembolism and subsequent risk of cancer risk and arterial cardiovascular events have been covered in the previous chapters.

Recurrence of venous thromboembolism

Patients with an incident venous thromboembolism have a 50% higher risk of a first recurrence of venous thromboembolism than individuals in the general population. Several factors, such as male gender, cancer, high body mass index, and neurological disease, are risk factors for recurrent venous thromboembolism.[71,72,260,301-304]

Barco *et al*. studied the risk of recurrent venous thromboembolism and death after distal deep venous thrombosis in 831 patients; 202 were diagnosed with isolated distal deep venous thrombosis and 629 had proximal deep venous thrombosis. A total of 125 patients developed recurrent proximal venous thrombosis or pulmonary embolism during 3,175 person-years of follow-up. The annual incidence rate was 4.8%, and the annual recurrence rate was between 2.0% and 4.2%; 263 patients died (31.6%) during follow-up.[305] Patients with a first isolated distal venous thrombosis had a lower risk of recurrence and death than patients with proximal deep venous thrombosis.

Galanaud *et al*. studied a cohort of patients with superficial venous thrombosis and proximal deep venous thrombosis without a diagnosis of cancer.[306] They used data from a prospective cohort study and followed patients for three years. Patients without superficial venous thrombosis had a lower risk of deep venous thrombosis recurrence compared to proximal deep venous thrombosis patients. The study was relatively small and the risk estimates were imprecise.[306] Galanaud *et al*. also compared the long-term outcome of cancer-related isolated deep vein thrombosis with the outcome of similar non-cancer patients with the same condition, in a small cohort study.[307] They found that cancer was a strong predictor of deep vein thrombosis recurrence and death. In a cohort study of 477 patients from Minnesota, Chee *et al*. demonstrated that active cancer is a strong predictor of both venous thromboembolism recurrence and bleeding.[308] In their study, 139 patients developed recurrent venous thromboembolism and the 10-year cumulative rate was 28.6%. Similar findings were reported in two cohorts from the Netherlands.[309]

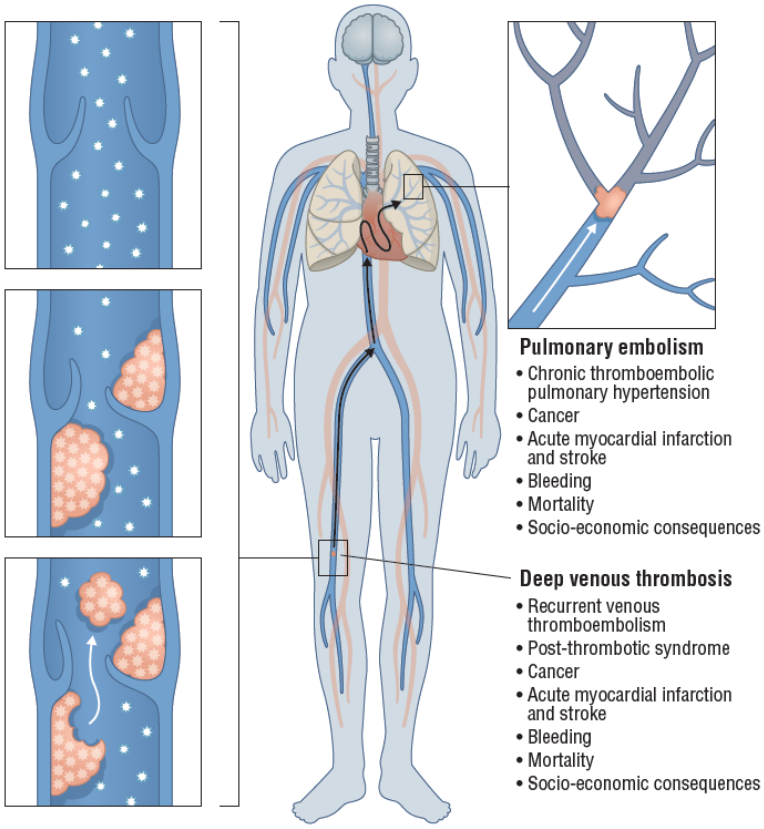

Figure 8. Medical and treatment complications of deep venous thrombosis and pulmonary embolism.

Albertsen et al examined recurrence risk after incident venous thromboembolism, stratified according to unprovoked, provoked, and cancer-related venous thromboembolism in Danish patients with incident venous thromboembolism. The study included 73,993 patients with venous thromboembolism and found

that patients with cancer-related venous thromboembolism had the highest risk of recurrence. At six-month follow-up, there were similar risks of recurrence for patients with unprovoked and provoked venous thromboembolism. At 10-year follow-up, recurrence risks were similar for patients with unprovoked venous thromboembolism and patients with cancer-related venous thromboembolism.[310]

Khan *et al.* examined the risk of a first recurrent venous thromboembolism after discontinuation of anticoagulation treatment in patients with a first episode of unprovoked venous thromboembolism in a meta-analysis. It included 18 randomized trials and cohort studies with 7,515 patients followed for recurrent venous thromboembolism up to 10 years. In patients with a first episode of unprovoked venous thromboembolism who had at least three months of anticoagulation therapy, the risk of recurrent venous thromboembolism was 10% in the first year after treatment, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent venous thromboembolism cases resulting in death.[311]

Iorio *et al*. conducted a systematic review of 11 studies to examine the risk of recurrent venous thromboembolism provoked by various transient risk factors.[312] The analysis included both randomized trials and observational studies. After 25 months of follow-up, the rate of recurrence was 3.3% per person-year. The authors concluded that risk of recurrence was low if the venous thromboembolism was associated with surgery, intermediate if provoked by non-surgical risk factors, and high if non-provoked factors played a role.

Our group examined the effectiveness of statins on venous thromboembolism recurrence in a cohort of 27,862 venous thromboembolism patients.[143] The accuracy of the venous thromboembolism discharge diagnoses was validated in a subsample. In the analysis we controlled for age, sex, year of diagnosis, provoking factors, comorbidities, and comedications, including time-varying use of aspirin and anticoagulant drugs. The adjusted hazard ratio for recurrence was 0.72 (95% confidence interval: 0.59-0.88) when comparing current use with no use. High potency statins had a an even stronger effect (0.40, 95% confidence interval: 0.21-0.78) than low potency statins (0.77, 95% confidence interval: 0.63-0.94).

Post-thrombotic syndrome

Post-thrombotic syndrome, occurring in 25%-50% of patients, is the most common complication of deep venous thrombosis.[313] The syndrome develops within the first few years after a thrombotic event, with symptoms such as pain, swelling, and leg heaviness. Among cases, 10% develop chronic venous leg ulcers.

Obesity, female gender, proximal location of the venous thrombosis, and varicose veins are risk factors for post-thrombotic syndrome.[313-315]

Chronic thromboembolic pulmonary hypertension

Approximately 2%-4% of patients develop pulmonary vascular disease in the lungs following a pulmonary embolism due to incomplete resolution of the pulmonary circulation.[316] Progressive pulmonary hypertension leads to right ventricular failure.[317,318] Splenectomy, infected ventricular atrial shunts, venous catheters, cancer, and chronic inflammation have been identified as risk factors for chronic thromboembolic pulmonary hypertension.[313,318,319] Although chronic thromboembolic pulmonary hypertension is a severe long-term complication of acute pulmonary embolism, it also occurs in patients with no history of venous thromboembolism.[318,320] It has been reported that 19-63% of patients with confirmed chronic thromboembolic pulmonary hypertension lack a history of symptomatic venous thromboembolism or pulmonary embolism.[319]

Mortality

Spencer et al. examined clinical characteristics and selected outcomes in 1,691 patients with confirmed symptomatic pulmonary embolism and isolated deep venous thrombosis in New England.[321] During three years of follow-up, the risk of subsequent pulmonary embolism, overall venous thrombosis, and major bleeding was 5.9%, 5.1%, and 15.0%, respectively, in patients with symptomatic pulmonary embolism, versus 17.9%, 15.6%, and 12.9%, respectively, among patients with isolated deep venous thrombosis. The authors also reported that one-month mortality for patients with pulmonary embolism was 13.2%, compared to 5.9% for patients with isolated venous thrombosis.[321]

Several other studies have reported survival after venous thromboembolism, with estimates ranging from 77% to 97% after one week and from 61% to 75% after 8-10 years.[37,322-324] Recently, a Norwegian study of 710 patients diagnosed from 1994 to 2012 reported 29.9% one-year overall mortality.[325] Similar mortality rates were reported in another Norwegian study.[66]

Several predictors of mortality following venous thromboembolism have been identified: age, male gender, low body mass index, in-hospital treatment, heart failure, chronic obstructive lung disease, neurological disease, and active cancer have been associated with reduced survival after venous thromboembolism.[260,326,327] A quarter of patients with pulmonary embolism face sudden death. Pulmonary

embolism is associated with a 3-fold increase in one-month mortality compared to isolated deep venous thrombosis.[61,69,321,326]

Few other studies have examined long-term mortality from venous thromboembolism. Flinterman *et al*. followed 4,947 patients with a first non-fatal venous thrombosis or pulmonary embolism enrolled in the Multiple Environmental and Genetic Assessment study of risk factors for venous thromboembolism and 6154 control individuals without venous thromboembolism for eight years.[328] They found that the overall mortality rate was 22.7 per 1,000 person-years for patients and 4.7 per 1,000 person years for controls. Patients with venous thromboembolism had a 4-fold increased risk of death compared to controls. The risk remained increased for up to eight years after the thrombotic event. The highest risk of death was found for patients who also had cancer, with a standardized mortality ratio of 5.5. The most common causes of death were diseases of the circulatory system, venous thromboembolism, and cancer. In another study, including 355 patients with first-time deep venous thrombosis, thrombosis-related mortality after eight years was 29.8%.

Presence of cancer at the time venous thromboembolism is diagnosed is a strong predictor of death.[260] There is strong evidence that cancer may explain a part of the high one-year case fatality from venous thromboembolism, as the mortality rate among cancer patients with venous thromboembolism is 60%-80% (Paper II).[66,98,325] Our group's 2000 study (Paper II) showed that venous thromboembolism is a strong prognostic factor for cancer patients.[98] Based on our earlier 1998 study, we hypothesized that venous thromboembolism in combination with cancer has a poor prognosis because of the association with metastases. We compared survival among cancer patients with and without venous thromboembolism, matching for type of cancer, age, gender, and year of diagnosis. Among the 668 cancer patients with a venous thromboembolism episode, 44% had distant metastases, compared to 35.1% in the comparison cancer cohort (prevalence rate ratio 1.26 [95% confidence interval: 1.13-1.14]). In the cohort of cancer patients with a venous thromboembolic episode, one-year survival was as low as 12%, compared to 36% in the comparison cohort without venous thromboembolism. The mortality ratio during the entire follow-up period was 2.20 (95% confidence interval: 2.05-2.40). Patients diagnosed with cancer within one year after the venous thromboembolic episode also had a high prevalence of distant metastases and a low rate of survival at one year (38% versus 47% in the comparison cohort).[98] In the case of a cancer diagnosis received one to seven years after a venous thromboembolism event, the prevalence of distant metastases and survival was similar for the venous thromboembolism cancer cohort and the venous thromboembolism-free cancer comparison cohort (Paper II).[98] The finding that cancer is a predictor of poor survival after

venous thromboembolism was confirmed in a study from California. This study was based on 235,149 cancer cases, 3,775 (1.6%) of which were diagnosed with venous thromboembolism within two years of their cancer diagnosis, 463 at the time of their cancer diagnosis (12%), and 3,312 before their cancer diagnosis (88 subsequently with venous thromboembolism). For most cancer types and stages, a venous thromboembolism diagnosis of venous thromboembolism during the first year of follow-up was a strong predictor of death.[233]

Only a few earlier cohort studies compared long-term mortality between venous thromboembolism patients and general population comparison cohorts. Because the existing studies provided inconsistent results, [66,328-330] our group conducted a thirty-year population-based cohort study during the 1980-2011 period (Paper IX).[331] We included 128,233 patients with venous thromboembolism and a general population comparison cohort of 640,760 persons. The mortality risk among patients with deep venous thrombosis or pulmonary embolism was markedly higher than for the general population during the first year of follow-up. We found a particularly elevated mortality risk during the first few months following venous thromboembolism. (In the three cohorts short-term mortality was 3%, 31%, and 0.4%, respectively). The overall 30-year mortality rate ratio was 1.95 (95% confidence interval: 1.53-1.57) for deep venous thrombosis patients and 2.77 (95% confidence interval: 2.74-2.81) for pulmonary embolism patients. The one-month mortality rate ratio was 5.38 for deep venous thrombosis and 80.9 for pulmonary embolism. During one to 10 years and 11 to 30 years of follow-up, the mortality rate ratios were increased 25% deep venous thrombosis patients and 40% for pulmonary embolism patients (Paper IX).[331] We also observed that 30-day mortality after deep venous thrombosis remained nearly constant over the last three decades, but improved markedly for pulmonary embolism. Furthermore, while patients with venous thromboembolism had an increased risk of mortality during the first year of follow-up, their elevated risk persisted during the entire 30 years of follow-up, with venous thromboembolism representing a major cause of death (Paper IX).[331]

In a prognostic analysis presented in Paper XI we examined survival among 1,191 patients with splanchnic venous thrombosis who were later diagnosed with liver cancer, pancreatic cancer, or myeloproliferative neoplasm, and compared their survival to that of a matched cancer patient cohort without splanchnic venous thrombosis.[102] We included up to five cancer comparisons for each splanchnic venous thrombosis cancer patient matched by gender, age, year of diagnosis, cancer type and stage, except for myeloproliferative neoplasms, for which there was no staging system. We showed that splanchnic thrombosis was associated with a poor prognosis for patients with liver and pancreatic cancer.

Schulman *et al.* investigated the long-term outcomes of venous thromboembolism within the framework of a randomized trial in which patients were randomized to different durations of tertiary prophylaxis. Among the 897 randomized patients, 545 patients could be followed for 10 years.[330] Death occurred in 28.5% of the patients--higher than that expected in the general population. The incidence ratio was 1.43 (95% confidence interval: 1.28-1.58). High mortality was seen especially in patients with cancer, acute myocardial infarction, and stroke. The standardized incidence ratios were 1.83 for the randomized patients versus 1.28 in the general population. The analysis also showed that extension of tertiary prophylaxis from six weeks to six months had no impact on mortality.[330] Among several other endpoints also examined, severe post-thrombotic syndrome developed in 6% of the patients, and a sign of post-thrombotic syndrome was seen in 56.3% of the patients evaluated. Predictors of post-thrombotic syndrome were old age and signs of impaired circulation at discharge from the hospital. Recurrent thromboembolism occurred in 29% of patients. Predictors were male gender, older age, permanent triggering risk factors, and venous insufficiency.

We recently examined receipt of work-related disability pensions and general socioeconomic status in a cohort of 41,928 Danish patients <65 years old with venous thromboembolism and in a cohort of 209,640 age-, gender-, and calendar-year matched persons from the general population without venous thromboembolism. We found that venous thromboembolism was a strong predictor for a work-related disability pension independent of comorbidities such as cancer and cardiovascular disease. Patients with low socioeconomic status and venous thromboembolism had the highest risk of receiving a work-related disability.[332] (Paper submitted)

In summary, venous thromboembolism is a serious and often chronic disease with high short-term and long-term mortality and substantial risk of recurrent venous thrombosis, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Moreover, mortality is elevated compared to that of the general population for decades following the thrombotic event. Common causes of death are venous thromboembolism, arterial disease, and cancer. Sporadic evidence also suggests that venous thromboembolism and its consequences is associated with reduced quality of life, social isolation, stress, and decreased physical functionality.[333-335] Venous thromboembolism is thus a chronic disease with frequent recurrence and complications.

Chapter 6. Methodological issues in using routine clinical data for studying the epidemiology of venous thromboembolism

The 12 studies from our group on which this dissertation is based utilized data from Danish health and administrative registries and databases.[22] Several limitations associated with these data sources must be considered. All registry data are essentially abstracts of the underlying clinical process in that they include only basic demographic information and selected data on conditions, events, and other outcomes. The Danish Cancer Registry, the Danish National Registry of Patients, and the Danish prescription databases all contain relatively few detailed clinical data. They do not record data on lifestyle habits and personal characteristics, such as cigarette smoking, alcohol use, and body mass index. In analyses requiring information on lifestyle factors, this may lead to unmeasured or residual confounding. Another concern relates to coding. Diagnoses in Danish registries are based on the *International Classification of Diseases, Eighth and Tenth Revisions*. As a result, laterality in paired organs, such as the legs, is not recorded. Changes in coding systems also create problems with comparability and detail. For example, venous thrombosis in the upper extremities had a separate code in the *International Classification of Diseases, Eighth Revision,* but not in the *Tenth Revision.* Another issue is that the Danish prescription databases currently do not include drugs administered during hospitalizations or any over-the-counter medications.[336] However, most drugs are dispensed in community pharmacies and captured in the databases. In the near future, data on in-hospital use of medications also will be included in the prescription databases.

Several classes of coding problems may limit the usefulness of diagnoses recorded in the registries: variation among coders; errors in coding; lack of codes for certain data points, especially lifestyle factors; limitations in the specificity of available codes; and errors and variation in the clinical diagnoses on which the coding is based.[337,338]

Modifications in diagnostic criteria, classifications, and methods may limit comparisons of data over long periods.[339,340] Furthermore, diagnostic criteria for some diseases have been changing and may be revised in the future. For example, the incidence of acute myocardial infarction started increasing in 2000 due to a change in diagnostic criteria, although its incidence had been declining steadily for the past 25 years.[341] Concurrently, the increasing incidence of pulmonary embolism may reflect better diagnostic methods.[76] Despite these limitations, research based on databases has many advantages. Because the data already have been collected, time requirements are likely to be considerably lower than for studies requiring primary data collection. This greatly increases efficiency and decreases costs. As well, the large size of many

databases offers the potential for precise effect estimates and the possibility of studying rare exposures or outcomes. Large population database studies are often the only option for obtaining sufficient sample sizes to perform meaningful subgroup analyses.[338,342]

Another advantage of Danish population-based registries is their complete population coverage and follow-up, greatly reducing the risks of referral and selection biases.[22,343,344] As well, collection of registry data independent of research projects reduces the risks of recall and non-response biases, as well as the impact on the diagnostic process of attention associated with the research.[342] In addition, databases allowing extensive follow-up can provide information on long-term prognoses or effects with a long induction period. In general, diagnoses of stroke and acute myocardial infarction have high data quality, measured as high positive predictive values, in the Danish National Registry of Patients. The data quality of venous thromboembolism diagnoses is somewhat lower, but still has high predictive value.[345,346] The positive predictive value of venous thromboembolism seems to have increased over recent decades.[347] When combined with a coded ultrasound diagnostic test, the positive predictive values increases.[346]

Diagnoses included in the Charlson Comorbidity Index also have high predictive value,[348] and the Danish Cancer Registry data[349] have similarly high data quality and completeness. If the misclassification of diagnoses is non-differential and unrelated to the occurrence of other errors, it will most likely produce bias towards the null in measures of association or effect.

Chapter 7. Conclusion

Based on available literature and a careful evaluation of potential biases and possible unmeasured and residual confounding, the following conclusions can be drawn from the 12 studies that form the basis of this dissertation.

Venous thromboembolism and cancer

Venous thromboembolism may be a marker of occult cancer. The risk of a cancer diagnosis following venous thromboembolism is elevated after the first year of follow-up. The reasons for the long-term elevated risk are largely unknown, but risk factors shared between venous thromboembolism and cancer may explain part of the association. Venous thromboembolism in patients with known cancer also may be a marker of a new cancer. In cancer patients, venous thromboembolism also is associated with an advanced cancer stage. Cancer diagnosed at the same time as or within one year after a venous thromboembolism episode is more frequently at an advanced stage with a poor prognosis. Risk of venous thromboembolism is substantially higher among cancer patients than in the general population. Predictors of venous thromboembolism include a recent cancer diagnosis, cancer site, stage, and types of cancer-directed treatment. Superficial venous thrombosis in the lower limbs also is a marker of occult cancer. As well, splanchnic venous thrombosis is a marker of occult cancer and a poor prognostic factor for cancer survival.

Venous thromboembolism and arterial cardiovascular events

Patients with venous thromboembolism have a substantially increased long-term risk of subsequent arterial cardiovascular events. Shared risk factors such as smoking and obesity likely play an important role. Patients with acute myocardial infarction and stroke are at short-term increased risk of venous thromboembolism, most likely due to immobilization, comorbidities, and complications. Stroke patients may have an excess long-term elevated risk of venous thromboembolism.

Patients with splanchnic venous thrombosis are at increased risk of arterial cardiovascular events compared to patients with venous thromboembolism and the general population. Superficial venous thrombosis is associated with an increased risk of acute myocardial infarction, ischemic stroke, and death. Conversely, heart disease may increase the near-term risk of pulmonary embolism not associated with peripheral venous thrombosis.

Venous thromboembolism and mortality

Patients with venous thromboembolism are at increased risk of mortality, especially during the first year after their diagnosis, but also during the subsequent 30 years. The presence of an underlying malignancy (diagnosed either before or after the venous thrombosis) is a strong prognostic factor. Thirty-day mortality after deep venous thrombosis has remained fairly constant over the last three decades but has improved markedly after pulmonary embolism. Overall, venous thromboembolism is an important cause of death.

In conclusion, venous thromboembolism is a chronic disease with frequent recurrences and complications, which reduce quality of life.

Chapter 8. Perspectives

Venous thromboembolism is a serious global health problem annually affecting more than 1 in 1,000 adults worldwide. More than 10% of in-hospital deaths are related to pulmonary embolism, and autopsy studies indicate that many cases are missed.[4] Hospitalization is an important risk factor for venous thromboembolism, as many patients do not receive appropriate prevention. The research presented in this dissertation shows that clinical care and research will remain suboptimal if they continue to focus only on individual diseases or episodes of illness, individual treatments, or mortality without attention to long-term morbidity and comorbidity.[17]

Acute myocardial infarction and stroke are well-established as leading causes of death. In contrast, venous thromboembolism is a major but underappreciated contributor to morbidity and mortality. Recognition of the signs and symptoms of venous thromboembolism is important to prevent a fatal outcome, but public and clinical recognition of venous thromboembolism remains low.[350] Raising awareness among clinicians is important, as 55%-60% of all venous thromboembolism events are related to hospital admission and occur either during hospitalization or within three months after discharge.[351]

Several options are available for thromboprophylaxis. Data from the National Health Service in England show that the systematic approach to preventing hospital-associated venous thromboembolism introduced in 2010 led to a 15.4% reduction in deaths within three months after discharge.[24] The rate of venous thromboembolism after surgery has decreased over the past 15 years in high-income countries, due to thromboprophylaxis, improved surgery and anesthesia, earlier mobilization, and shorter hospital stays.[23] Thus we already have the tools to prevent many cases of venous thromboembolism, *e.g.,* improving risk stratification, thromboprophylaxis, use of elastic stockings, and follow-up of patients after discharge.

This dissertation has shown that venous thromboembolism is associated with occurrence of other chronic diseases. It also points to the great need for more detailed observational epidemiological studies to identify groups at risk of venous thromboembolism. We need better information, for instance, about the patients who develop venous thromboembolism after hospitalization. This dissertation provides strong evidence that venous thromboembolism is a chronic disease with elevated mortality compared to the general population, persisting for decades after the venous thromboembolic event.

We need more data on the long-term clinical course of venous thromboembolism including preventive and diagnostic pathways. The key issue for thromboprophylaxis, in terms of drugs and treatment duration, is to clarify when the risk of thromboembolic events is surpassed by the risk of bleeding. Thus the need is great for improved epidemiological, health care, and clinical knowledge on the causation of venous thromboembolism and effective prevention and treatment. Existing Danish databases and biobanks represent a valuable tool to create new knowledge, provided that the strengths and limitations of these databases are understood.

Appendix I.

Wells clinical probability scores for deep venous thrombosis.

Variable	Points
Active cancer (treatment ongoing or within the previous 6 mo or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 d or major surgery, within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by >3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
History of deep venous thrombosis	1
Alternative diagnosis as likely as or more likely than deep venous thrombosis	-2

Using the original score, 2 points indicates high probability. Using the dichotomized score, ≤1 point indicates that DVT is unlikely and ≥2 points indicates that DVT is likely. ≤3 points indicates that that the patient should not be referred for compression ultrasonography and ≥4 points indicates that the patient should be directly referred for compression ultrasonography.[352,353]

Wells clinical probability scores for pulmonary embolism.

Variable	Points
Signs and symptoms of deep venous thrombosis	3
Alternative diagnosis is less likely than pulmonary embolism	3
Heart rate > 100 beats/minute	1.5
Immobilization/surgery in previous 4 weeks	1.5
History of deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1
Active cancer	1

Using the traditional score, >6.0 points indicates high probability, 2.0 – 6.0 points indicates moderate probability, and < 2.0 points indicates low probability. Using the simplified score, < 4 indicates that pulmonary embolism is likely and ≤4 points indicates that pulmonary embolism is unlikely.[352,353]

Appendix II.

Original Geneva score for assessing the probability of pulmonary embolism.

Variable		Points
Age		
	60-79 years	1
	≥ 80 years	2
Previous deep venous thrombosis or pulmonary embolism		2
Recent surgery within 4 weeks		3
Heart rate > 100 beats/min		1
$Paco_2$		
	< 35 mm Hg	2
	35-39 mm Hg	1
	40-48 mm Hg	4
	49-59 mm Hg	3
	60-71 mm Hg	2
	72-82 mm Hg	1
Band atelectatis on radiography		1
Elevation of hemidiaphragm on radiography		1

< 5 points indicate low probability, 5-8 points indicates intermediate probability, and > 8 points indicates high probability.[354]

Modified Geneva score for assessing the probability of pulmonary embolism.

Variable		Points
Age ≥ 65 years		1
Previous deep venous thrombosis or pulmonary embolism		3
Surgery or fracture within 1 month		2
Active cancer		2
Unilateral lower limb pain		3
Pain on deep palpation of lower limb and unilateral edema		4
Hemoptysis		2
Heart rate		
	75-94 beats/min	3
	≥ 95 beats/min	5

Using the modified score, < 3 points indicates low probability, 4-10 points indicated intermediate probability, and > 10 points indicates high probability. Using the simplified score, ≤2 points indicates that pulmonary embolism is unlikely.[354]

Appendix III.

Khorana Score for predicting venous thromboembolism in ambulatory cancer patients.

Variable		Points
Site of cancer		
	Very high risk (stomach, pancreas)	2
	High risk (lung, lymphoma, gynecological, bladder, or testicular)	1
Prechemotheraphy platelet count ≥350 x 109/L		1
Prechemotherapy hemoglobin level <100 g/L 1 or use of red cell growth factors		1
Prechemotherapy leukocyte count >11 x 109/L		1
Body Mass Index ≥35 kg/m2		1

A sum score of 0 points classifies patients as being of low risk of venous thromboembolism, 1 or 2 points at intermediate risk, and those with 3 points or more at high risk.[56,57]

Appendix IV.

Pulmonary Embolism Severity Index for predicting 30-day outcome of patients with pulmonary embolism using 11 clinical criteria.

Variable	
Age	Age in years
Sex	+ 10
History of cancer	+ 30
History of heart failure	+ 10
History of chronic lung disease	+ 10
Heart rate ≥110	+ 20
Systolic BP <100 mmHg	+ 30
Respiratory rate ≥30	+ 20
Temperature <36°C/96.8°F	+ 20
Altered mental status (disorientation, lethargy, stupor, or coma)	+ 60
O2 saturation <90%	+ 20

≤ 65 point: very low risk; 66–85 points: low risk; 86–105 points: intermediate risk; 106–125 points: high risk; > 125 points: very high risk.[355]

English summary

Venous thromboembolism occurs frequently and has a severe prognosis. Deep venous thrombosis and pulmonary embolism occur in one out of a thousand persons in the population each year and 6%-12% die within a month. This doctoral dissertation is based on a review of our 12 published papers on the associations among venous thromboembolism, cancer, arterial cardiovascular events, and mortality.

The studies were made possible through the Danish health and administrative registries, a unique international resource for clinical and epidemiological research. Cancer cases and causes of death have been recorded comprehensively in Denmark since 1943. All admissions to Danish hospitals have been registered since 1977 and prescriptions since 1989 in North Jutland County/North Denmark Region and on a nationwide basis since 1995. The establishment of the Danish Civil Registration System in 1968 allowed for individual-level identification of remarkably high quality, making it possible to gather information about a given person from multiple registries.

Study I showed that deep venous thrombosis and pulmonary embolism may be a marker of undiagnosed cancer. The risk of a cancer diagnosis was increased threefold within the first six months following venous thromboembolism, compared to the general population. Of patients with venous thromboembolism, 40% had distant metastases at the time of their cancer diagnosis. We found an association between venous thromboembolism and several types of cancer, including pancreatic, ovarian, liver, and brain cancer.

In Study II, we examined the prognosis of patients who received a cancer diagnosis at the same time as a venous thromboembolism diagnosis. We compared them with patients with the same type of cancer but without venous thromboembolism. One-year survival was 12% among cancer patients with venous thromboembolism compared with 36% in the control group. Patients receiving a cancer diagnosis within a year of hospitalization for venous thromboembolism had a one-year survival rate of 38%, compared to 27% in the control group.

Persons with a cancer diagnosis are at increased risk of a new primary cancer. In Study III, we examined whether 6,885 patients with cancer and a previous venous thromboembolism were at even higher risk of a secondary primary cancer. We compared them to 30,713 cancer patients with no history of venous thromboembolism, matched by age, gender, cancer type, and year of diagnosis. The study showed a 40% excess risk of a new primary cancer diagnosis among patients with a venous thromboembolism occurring

more than a year after their first cancer diagnosis. We concluded that the association between venous thromboembolism and subsequent cancer also applied to patients with an earlier cancer diagnosis.

In Study IV, we examined the risk of acute myocardial infarction and stroke in a 20-year follow-up study of 25,199 patients with deep venous thrombosis, 16,925 patients with pulmonary embolism, and 163,556 controls from the general population matched by age and gender. In patients with deep venous thrombosis, the relative risk was 1.60 for acute myocardial infarction and 2.19 for stroke in the first year after their venous thrombosis. In patients with pulmonary embolism, the relative risk was 2.60 for acute myocardial infarction and 2.93 for stroke. After the first year, a 20%-40% increased risk of myocardial infarction and stroke remained throughout the 20-year follow-up period.

In Study V, we conducted a nested case-control study of 5,824 patients with venous thromboembolism and 58,240 controls drawn from the general population. We found that patients with acute myocardial infarction or stroke had an increased relative risk of venous thromboembolism 3-4 months after their cardiovascular event. Thereafter, the risk decreased in patients with acute myocardial infarction but persisted in patients with stroke. Patients treated with statins, but not with a low dose of acetylsalicylic acid, had a reduced risk of developing venous thromboembolism.

In Study VI, we examined venous thromboembolism risk in 57,591 cancer patients and 287,476 persons from the general population. Patients with cancer were at increased risk of venous thromboembolism during the first year after cancer diagnosis, with strong associations with pancreatic, brain, and liver cancers, as well as multiple myeloma. Patients with an advanced stage of cancer and those receiving chemotherapy had a particularly high risk. We concluded that patients with cancer have a strongly increased risk of venous thromboembolism compared to persons in the general population. Cancer type, cancer stage, and treatment were important predictors.

Study VII, a nested case-control study conducted between 1980 and 2007, examined the hypothesis that heart disease increased the risk of pulmonary embolism in the absence of peripheral deep venous thrombosis. The study included 45,282 patients with pulmonary embolism, 4,680 patients with pulmonary embolism and deep venous thrombosis, 59,790 patients with deep venous thrombosis alone, and 541,561 persons from the general population based on risk set sampling. Acute myocardial infarction and heart failure were associated with a substantially increased risk of isolated pulmonary embolism, while the risk was lower for persons with a pulmonary embolism that appeared together with deep venous thrombosis

and for persons with deep venous thrombosis alone. Compared to patients with left-sided heart valve disease, those with right-sided disease had a lower risk of developing an isolated pulmonary embolism. We concluded that heart disease increased the risk of isolated pulmonary embolism in the absence of peripheral venous thrombosis.

Study VIII, an extension of Study I, was carried out between 1994 and 2009. Unlike Study 1, it included superficial venous thrombosis. We found that this condition also was a marker of occult cancer but carried a slightly lower risk than deep venous thrombosis and pulmonary embolism. The standardized incidence rate ratios were 2.46 for superficial venous thrombosis, 2.75 for deep venous thrombosis, and 3.27 for pulmonary embolism. After one year, the standardized incidence rate ratios fell to 1.05, 1.1, and 1.15, respectively. The study confirmed that deep venous thrombosis and pulmonary embolism were markers of occult cancer, and was one of the first to show that superficial venous thrombosis could also be a marker.

Few studies have examined long-term mortality in patients with venous thromboembolism. In Study IX, we conducted a 30-year (1980-2011) follow-up study of 128,213 patients with venous thromboembolism and a comparison cohort of 640,760 persons from the general population without venous thromboembolism, matched by age, gender, and calendar year. Patients with venous thrombosis and pulmonary embolism had 30-day mortality rates of 3% and 31%, respectively, compared with 0.4% in the general population. Over the 30-year period, the mortality rate ratio was 1.55 (95% confidence interval: 1.53-1.57) among patients with deep venous thrombosis and 2.77 (95% confidence interval: a 2.74-2.81) among those with pulmonary embolism. We concluded that patients with venous thromboembolism had a high risk of mortality, especially the first year after diagnosis, and retained a higher mortality rate than the general population during ensuing decades.

In Study X, we examined the association between venous and arterial thrombosis in 10,977 patients diagnosed with superficial venous thrombosis between 1980 and 2012. We compared their risk with that of a comparison cohort of 515,067 persons from the general population matched by age, gender, and calendar year. The relative risk of acute myocardial infarction, stroke, or death was 1.2 (95% confidence interval: 1.1-1.3), 1.3 (95% confidence interval: 1.2-1.4), and 1.3 (95% confidence interval: 1.2-1.3), respectively. The highest risk occurred shortly after occurrence of the superficial venous thrombosis. Similarly, risk of deep venous thrombosis was highest in the first three months after the superficial venous thrombosis, with a relative risk of 71.4 (95% confidence interval: 60.2-84.7) decreasing to 5.1 (95%

confidence interval: 4.6-5.5) after five years. We concluded that there was a strong association between superficial venous thrombosis and subsequent risk of deep venous thrombosis.

In Study XI, we examined whether splanchnic venous thrombosis was a marker of occult cancer with prognostic impact. The study included 1,191 patients diagnosed with splanchnic venous thrombosis between 1994 and 2011. We calculated standardized incidence rate ratios of cancer based on general population rates. Furthermore, a comparison cohort was selected from the Danish Cancer Registry for a prognostic analysis. The three-month cancer risk was 8%, corresponding to a standardized incidence rate ratio of 33. We found a strong association for liver and pancreatic cancers as well as for myeloproliferative syndrome. Similar to Study II, we also found that splanchnic venous thrombosis was associated with a poor prognosis in patients with liver and pancreatic cancers.

In Study XII, we examined the association between splanchnic venous thrombosis and risk of arterial vascular events and bleeding in 1,915 patients with splanchnic venous thrombosis, 18,373 patients with deep venous thrombosis or pulmonary embolism, and 19,150 persons from the general population. The patients with splanchnic venous thrombosis were at increased risk of bleeding 30 days after diagnosis, measured both as absolute risk (4.3%) and relative risk (9.64), compared to patients with deep venous thrombosis and pulmonary embolism. Their relative risk was 39.79 compared with the general population. The relative risk of bleeding among patients with splanchnic venous thrombosis within a year was 3.0 compared to patients with deep venous thrombosis and pulmonary embolism and 6.8 compared to the risk in the general population. Furthermore, the risk remained increased up to 10 years. We concluded that splanchnic venous thrombosis was associated with both arterial cardiovascular events and bleeding.

The main conclusions of this doctoral dissertation are that deep venous thrombosis and pulmonary embolism may be markers of occult cancer. Such cancers are often at an advanced stage at time of diagnosis and have a poor prognosis. Superficial venous thrombosis is also a marker of occult cancer. Venous thromboembolism occurring in cancer patients a year or more after their initial cancer diagnosis may be a marker of a new primary cancer diagnosis. We also concluded that patients with cancer have a substantially increased risk of venous thromboembolism compared to the general population.

In addition, we found that venous thromboembolism is associated with an increased risk of acute myocardial infarction and stroke up to 20 years after the venous thromboembolic event. Furthermore, both acute myocardial infarction and stroke may be associated with an increased risk of venous thrombosis and

pulmonary embolism. The risk of acute myocardial infarction is transient but the risk persists for stroke. Heart disease also may be a risk factor for pulmonary embolism without concomitant venous thrombosis, especially pronounced for right-sided heart disease. Finally, our research showed that both superficial venous thrombosis and splanchnic venous thrombosis are associated with an increased risk of both arterial events and cancer. In the case of cancer, the prognosis is serious.

Dansk resumé

Denne doktorafhandling omfatter en sammenfattende redegørelse baseret på 12 publicerede artikler.

Venøs tromboembolisme er en hyppig sygdom med en alvorlig prognose. Dyb venøs trombose og lungeemboli forekommer hos en ud af tusinde personer i befolkningen hvert år og 6-12 % dør inden for en måned.

Vi gennemførte 12 studier om sammenhængen mellem venøs tromboembolisme, cancer, akut myokardieinfarkt og apopleksi samt dødelighed.

Studierne er baseret på danske sundhedsregistre og administrative registre, som udgør en international unik ressource for klinisk og epidemiologisk forskning. Alle cancertilfælde og dødsårsager har været registreret i Danmark siden 1943. Alle indlæggelser på danske hospitaler har ligeledes været registreret siden 1977 og indløste recepter fra 1989 i Nordjyllands Amt/Region Nordjylland samt på landsdækkende basis fra 1995. Etableringen af Det Centrale Personregister i 1968 tillod personidentifikation af enestående høj kvalitet og gjorde det muligt at samle informationer om samme person i de forskellige registre.

På baggrund af disse datakilder undersøgte vi ovennævnte sammenhænge.

Det første studies hovedresultater var, at dyb venøs trombose og lungeemboli kan være en markør for en endnu ikke diagnosticeret cancer. Risikoen for en cancerdiagnose var inden for de første seks måneder efter venøs tromboembolisme forøget tre gange sammenlignet med baggrundsbefolkningen. 40 % af patienterne med venøs tromboembolisme havde fjernmetastaser på det tidspunkt de fik cancerdiagnosen. Vi fandt en sammenhæng mellem venøs tromboembolisme og adskillige cancerformer, såsom pancreas-, ovarie-, lever- og hjernecancer.

I studie II undersøgte vi prognosen for patienter, der fik en cancerdiagnose på samme tidspunkt, som de fik venøs tromboembolisme diagnosen. Vi sammenlignede disse patienter med patienter med samme type cancersygdom men uden venøs tromboembolisme. Et-års overlevelsen var 12 % sammenlignet med 36 % i kontrolgruppen. Patienter, hos hvem cancer blev diagnosticeret inden for et år efter indlæggelse for venøs tromboembolisme, havde en et-års overlevelse på 38 % sammenlignet med 27 % i kontrolgruppen.

Personer med en cancersygdom har en forøget risiko for at få en ny primær cancersygdom. I studie III undersøgte vi 6885 patienter med cancer om de havde en forøget risiko for en ny primær cancer, hvis de havde haft en episode med venøs tromboembolisme. Vi sammenlignede disse patienter med 30713 cancerpatienter, der ikke havde haft venøs tromboembolisme, matchet på alder, køn, cancertype og diagnoseår. Hos patienter med venøs tromboembolisme som optrådte mere end et år efter den første cancerdiagnose, fandt vi en overrisiko på 40 % for en ny primær cancerdiagnose, og vi konkluderede, at sammenhængen mellem venøs tromboembolisme og efterfølgende cancer også gælder patienter som allerede havde en cancerdiagnose.

I studie IV undersøgte vi risikoen for akut myokardieinfarkt og apopleksi i et 20-års opfølgningsstudie hos 25199 patienter med dyb venøs trombose, 16925 med lungeemboli og 163556 kontrolpersoner fra den generelle befolkning matched på alder og køn. Hos patienter med dyb venøs trombose var den relative risiko 1.60 for akut myokardieinfarkt og 2.19 for apopleksi i det første år efter venøs tromboembolisme. Den relative risiko for lungeemboli var 2.60 for akut myokardieinfarkt og 2.93 for apopleksi. Efter et års opfølgning fandtes en 20 %-40 % risiko gennem en 20 års opfølgningsperiode.

I studie V gennemførte vi et case-control studie baseret på 5824 patienter med venøs tromboembolisme og 58240 kontrolpersoner fra den generelle befolkning. Vi fandt, at patienter med akut myokardieinfarkt eller apopleksi havde en klart forøget relativ risiko for venøs tromboembolisme 3-4 måneder efter deres event. Derefter faldt risikoen for patienter med akut myokardieinfarkt, mens den persisterede for patienter med apopleksi. Patienter, der blev behandlet med statiner, havde en reduceret risiko for at udvikle venøs tromboembolisme, mens dette ikke var tilfældet for patienter behandlet med lav dosis acetylsalicylsyre.

I studie VI undersøgte vi risikoen for venøs tromboembolisme hos 57591 cancerpatienter og hos 287476 personer udtrukket fra baggrundsbefolkningen. Patienter med cancer havde en kraftig forøget risiko for venøs tromboembolisme sammenlignet med baggrundsbefolkningen i det første år efter cancerdiagnosen med stærke sammenhænge for pancreas, hjerne- og levercancer, samt myelomatose. Patienter med avanceret cancerstadie og dem som modtog kemoterapi, havde en særlig forøget risiko. Vi konkluderede, at patienter med cancer har en stærk forøget risiko for venøs tromboembolisme end personer i den generelle befolkning. Vigtige prædiktorer var cancertype, cancerstadie og behandling.

Studie VII er et case-control studie gennemført i perioden 1980 til 2007. Formålet var at undersøge hypotesen om hjertesygdom øgede risikoen for lungeemboli uden at den perifere venøse trombose var til

stede. I case-control undersøgelsen indgik 45282 patienter med lungeemboli, 4680 patienter med lungeemboli og dyb venøs trombose, 59790 patienter med venøs tromboembolisme og 541561 personer fra den generelle befolkning udtrukket ved såkaldt risk set sampling. Akut myokardieinfarkt og hjertesvigt var associeret med en stærkt forøget risiko for isoleret lungeemboli, mens risikoen var lavere for lungeemboli, som optrådte sammen med dyb venøs trombose og hos personer, som havde dyb venøs trombose alene. Patienter med venstresidig hjerteklapsygdom havde en lavere risiko for udvikling af isoleret lungeemboli end højresidig klapsygdom. Vi konkluderede, at hjertesygdom øgede risikoen for isoleret lungeemboli uden at perifer dyb venøs trombose var til stede.

Studie VIII var en udvidelse af studie I og blev gennemført i perioden 1994 til 2009. I modsætning til det tidligere studie indgik også superficiel venøs trombose i denne undersøgelse. Vi fandt, at superficiel venøs trombose også var en markør for okkult cancer men med en lidt lavere risiko end for patienter med dyb venøs trombose og lungeemboli. De standardiserede incidens rate ratioer var henholdsvis 2.46, 2.75 og 3.27. Efter et år faldt de standardiserede incidens rate ratioer til 1.05, 1.1 og 1.15. Undersøgelsen bekræftede således, at dyb venøs trombose og lungeemboli fortsat var en markør for okkult cancer. Undersøgelsen var også en af de første undersøgelser, der påviste, at superficiel venøs trombose også kunne være en markør for okkult cancer.

Der findes kun få studier omkring langtidsdødeligheden hos patienter med venøs tromboembolisme. I studie IX gennemførte vi et 30-års follow-up studie baseret på 128213 patienter med venøs tromboembolisme i perioden 1980 til 2011 og en sammenligningskohorte på 640,760 personer fra den generelle befolkning uden venøs tromboembolisme matchet på alder, køn og kalenderår. Patienter med venøs trombose og lungeemboli havde en 30-dages dødelighed på hhv. 3 % og 31 % mod 0.4 % i den generelle befolkning. Over hele 30-års perioden var mortalitets rate ratioen 1.55 (95% sikkerhedsinterval: 1.53-1.57) for dyb venøs trombose og 2.77 (95% sikkerhedsinterval: 2.74-2.81) for lungeemboli. Vi konkluderede, at patienter med venøs tromboembolisme havde en høj risiko for at dø, specielt det første år efter diagnosen, og at patienterne havde en generel forøget dødelighed sammenlignet med baggrundsbefolkningen gennem hele 30 års opfølgningsperioden.

I studie X undersøgte vi sammenhængen mellem venøs og arteriel trombose hos 10977 patienter med superficiel venøs trombose, der var blevet diagnosticeret mellem 1980 og 2012. Vi sammenlignede risikoen med en sammenligningskohorte fra den generelle befolkning på 515067 personer matchet på alder, køn og kalenderår. Den relative risiko for akut myokardieinfarkt, apopleksi og død var hhv. 1.2 (95%

sikkerhedsinterval: 1.1-1.3), 1.3 (95% sikkerhedsinterval: 1.2-1.4) og 1.3 (95% sikkerhedsinterval: 1.2-1.3). Vi fandt den højeste risiko kort efter den superficielle venøse trombose var diagnosticeret.

Risikoen for dyb venøs trombose var højest i de første tre måneder efter den superficielle venøse trombose med en relativ risiko på 71.4 (95% sikkerhedsinterval: 60.2-84.7), der faldt til 5.1 (95% sikkerhedsinterval: 4.6-5.5) fem år efter den superficielle venøse trombose. Vi konkluderede, at der var en stærk association mellem superficiel venøs trombose og efterfølgende risiko for dyb venøs trombose.

I studie XI undersøgte vi om splanknisk venøs trombose var en markør for okkult cancer og havde prognostisk betydning. I studiet indgik 1191 patienter med splanknisk venøs trombose i perioden fra 1994 til 2011. Standardiserede incidens rate ratioer for cancer blev beregnede baseret på baggrundsbefolkningens rater. Desuden blev en kontrolkohorte udvalgt fra Cancerregisteret til en prognoseanalyse. Tre måneders cancerrisiko var på 8 % svarende til en standardiseret incidens rate ratio på 33. Vi fandt stærke associationer for lever- og pancreas cancer samt myeloproliferativ syndrom. Undersøgelsen viste også i lighed med studie II, at splanknisk venøs trombose var associeret med en dårlig prognose hos patienter med lever- og pancreas cancer.

I studie XII undersøgte vi sammenhængen mellem splanknisk venøs trombose og risikoen for arterielle vaskulære events og blødning hos 1915 patienter med splanknisk venøs trombose, 18373 med dyb venøs trombose eller lungeemboli og 19150 personer fra den generelle befolkning. Patienterne havde en forøget risiko for blødning 30 dage efter diagnosen målt både som absolut risiko (4.3 %) og relativ risiko (9.64) sammenlignet med patienter med dyb venøs trombose og lungeemboli og en relativ risiko på 39.79 i den generelle befolkning. Den relative risiko for blødning inden for et år var 3.0 sammenlignet med venøs tromboembolisme og lungeemboli og 6.8 sammenlignet med den generelle befolkning. Den forblev forøget i op til 10 år. Vi konkluderede, at splanknisk venøs trombose var associeret med såvel arterielle kardiovaskulære events som blødning.

Doktorafhandlingens hovedkonklusioner er, at dyb venøs trombose og lungeemboli kan være en markør for okkult cancer, der ofte er i et avanceret cancerstadie på diagnosetidspunktet og behæftet med en dårlig prognose. Superficiel venøs trombose kan også være en markør for okkult cancer. Venøs tromboembolisme hos patienter med cancer et år efter den initiale cancerdiagnose kan være en markør for en sekundær primær cancerdiagnose. Vi fandt også, at patienter med cancer har en stærk forøget risiko for venøs tromboembolisme sammenlignet med den generelle befolkning.

Derudover fandt vi, at venøs tromboembolisme er associeret med en forøget risiko for akut myokardieinfarkt og apopleksi op til 20 år efter den venøs tromboembolske episode. Såvel akut myokardieinfarkt som apopleksi kan herudover være associeret med en forøget risiko for ny venøs trombose og lungeemboli. Risikoen for akut myokardieinfarkt er forbigående, men persisterer for apopleksi. Hjertesygdom kan ligeledes være en risikofaktor for lungeemboli uden samtidig venøs trombose, særlig udtalt for højresidig hjertesygdom. Slutteligt viste doktorafhandlingen, at såvel superficiel venøs trombose som splanknisk venøs trombose er associeret med en forøget risiko for både arterielle events og cancer. For cancersygdommenes vedkommende har disse en alvorlig prognose.

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Paper I

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THE RISK OF A DIAGNOSIS OF CANCER AFTER PRIMARY DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM

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ABSTRACT

Background Several small studies have indicated an association between deep venous thrombosis or pulmonary embolism and a subsequent diagnosis of cancer, but the subject is controversial.

Methods We conducted a nationwide study of a cohort of patients with deep venous thrombosis or pulmonary embolism that was drawn from the Danish National Registry of Patients for the years 1977 through 1992. The occurrence of cancer in the cohort was determined by linkage to the Danish Cancer Registry. The expected number of cancer cases was estimated on the basis of national age-, sex-, and site-specific incidence rates.

Results A total of 15,348 patients with deep venous thrombosis and 11,305 patients with pulmonary embolism were identified. We observed 1737 cases of cancer in the cohort with deep venous thrombosis, as compared with 1372 expected cases (standardized incidence ratio, 1.3; 95 percent confidence interval, 1.21 to 1.33). Among the patients with pulmonary embolism, the standardized incidence ratio was 1.3, with a 95 percent confidence interval of 1.22 to 1.41. The risk was substantially elevated only during the first six months of follow-up and declined rapidly thereafter to a constant level slightly above 1.0 one year after the thrombotic event. Forty percent of the patients given a diagnosis of cancer within one year after hospitalization for thromboembolism had distant metastases at the time of the diagnosis of cancer. There were strong associations with several cancers, most pronounced for those of the pancreas, ovary, liver (primary hepatic cancer), and brain.

Conclusions An aggressive search for a hidden cancer in a patient with a primary deep venous thrombosis or pulmonary embolism is not warranted. (N Engl J Med 1998;338:1169-73.)

THE association between cancer and venous thromboembolism is well known.[1] Over 100 years ago, Trousseau reported cases of episodic migratory thrombophlebitis in patients with cancer.[2] The pathogenic mechanisms for the association include hypercoagulability due to activation of clotting by tumor cells, vessel-wall injury, and stasis.[1] Occasionally, the thromboembolic event occurs before the diagnosis of cancer, and it has been suggested that deep venous thrombosis may be a predictor of the subsequent diagnosis of cancer; this idea is controversial, however. Several studies have indicated an association,[3-7] but others have not.[8,9]

Two recent studies have shown a significant association between primary venous thrombosis and a subsequent diagnosis of cancer. This link seems particularly strong in patients with recurrent deep venous thrombosis. Prandoni et al. followed 145 patients over a period of two years and found 11 cases of cancer, as compared with 2 cases among 105 patients with secondary venous thrombosis, representing an odds ratio of 2.3.[6] They also found that the incidence of cancer in patients with recurrent idiopathic venous thrombosis was higher than in patients without this condition, with an odds ratio of 4.3.[6] In a hospital-based study of 1183 patients with deep venous thrombosis,[5] Nordström and coworkers found five times the risk of cancer in these patients as compared with the general population during the first six months of follow-up but no increased risk during later follow-up.

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The existing studies are thus limited in size, and few are population-based, which limits the general applicability of the results. To assess whether this association has important clinical implications, we determined the risk of cancer after the diagnosis of primary deep venous thrombosis and pulmonary embolism, using population-based data from the Danish National Registry of Patients and the Danish Cancer Registry.

METHODS

The Danish National Registry of Patients was established in 1977, and 99.4 percent of all discharges from Danish medical hospitals are recorded there.[10] Recorded information includes the civil registration number, which is unique to every Danish citizen, the dates of admission and discharge, the surgical procedures performed, and up to 20 discharge diagnoses, classified according to the Danish version of the *International Classification of Diseases, 8th Revision* (ICD-8).[11] It is possible to obtain the full discharge history of a patient by linking discharge records to the civil registration number. All persons listed in the National Registry of Patients from January 1, 1977, to December 31, 1992, were included in the study if they had a diagnosis of deep venous thrombosis in the lower limb or pulmonary embolism (ICD-8 codes 451.00 and 450.99) during at least one hospitalization. Deep venous thrombosis and pulmonary embolism were defined as primary in the absence of the following: surgery during the six months before the diagnosis of thromboembolism (determined on the basis of surgical-procedure codes), a diagnosis of venous thrombosis or pulmonary embolism that was not the primary diagnosis in the discharge record, preexisting cancer, or pregnancy (ICD-8 codes 630.00 to 678.00). All cases of venous thrombosis and pulmonary embolism involving any of these circumstances were excluded from the analyses because they were thought to be secondary. Subcohorts were defined according to age at the time of entry (<60, 60 to 74, and >74 years of age) and according to whether there was recurrence of the thromboembolic event. A recurrent episode was defined as two or more diagnoses of deep venous thrombosis or pulmonary embolism separated by at least three months.

All members of the study cohort were linked through their civil registration numbers to the nationwide Cause of Death Registry and the Cancer Registry, which have kept records of all incident cases of cancer in Denmark since 1943, including benign brain tumors and papillomas of the urinary tract. Cancers are classified according to the modified Danish version of the *International Classification of Diseases, 7th Revision*.[12] The registration is based on notification forms that are filled in by hospital departments (including departments of pathology and forensic medicine) and practicing physicians whenever a case of cancer is diagnosed or found at autopsy and whenever there are changes in an initial diagnosis. The cases recorded manually are supplemented by unreported cases revealed by the computerized linkages to the death-certificate file and the National Registry of Patients. The entire process is supervised by medical doctors. Ambiguous or contradictory information, either within a notification form or between forms, leads to queries in approximately 10 percent of the notifications received. Comprehensive evaluation has shown that the Registry is 95 to 98 percent complete and valid.[13]

Each patient was followed for the occurrence of cancer from the date of the first hospitalization with deep venous thrombosis or pulmonary embolism until the date of death or December 31, 1993, whichever came first.

Statistical Analysis

The expected number of cases of cancer was calculated on the basis of national incidence rates obtained from the Cancer Registry according to sex, age, and calendar period in five-year intervals. Multiplying the number of person-years of observation by the incidence rates yielded the number of cancer cases that would be expected if patients with deep venous thrombosis and pulmonary embolism had the same risk of cancer as the general population. Confidence intervals for the standardized incidence ratio — i.e., the ratio of observed to expected cancers — were computed on the basis of the assumption that the observed number of cases in a specific category follows a Poisson distribution. Exact limits were used when the observed number was less than 10; otherwise, Byar's approximation was used.[14]

RESULTS

We identified 15,348 patients with deep venous thrombosis and 11,305 patients with pulmonary embolism, each cohort consisting of approximately similar proportions of men and women. In the two cohorts combined, 33 percent were below the age of 60 years at the time of the thromboembolic episode, 37 percent were 60 to 74 years old, and 30 percent were 75 or older. On average, the patients with deep venous thrombosis were followed for longer periods than the patients with pulmonary embolism (6.1 vs. 3.6 years).

Standardized incidence ratios of 1.3 for all types of cancer were observed in both the cohort with deep venous thrombosis and the cohort with pulmonary embolism, based on 1737 observed and 1372 expected cases among the patients with deep venous thrombosis (95 percent confidence interval for the standardized incidence ratio, 1.21 to 1.33) and 730 observed and 556 expected cases among those with pulmonary embolism (95 percent confidence interval for the standardized incidence ratio, 1.22 to 1.41). There were no particular differences in risks between men and women.

The risk for both cohorts was three times the expected level during the first six months of follow-up, after which the risk declined to a constant level of slightly more than 1.0 one year after the thrombotic event and throughout the study period (Fig. 1).

Table 1 shows the risks of various types of cancer in the two cohorts during the first year of follow-up. The overall risk of the subsequent diagnosis of the neoplasms listed in Table 1 was 2.2 for the group with deep venous thrombosis and 2.3 for the group with pulmonary embolism. For both cohorts there were strong associations with certain types of cancer — in particular, cancer of the pancreas, ovary, liver (primary hepatic cancer), and brain. We found no association in either cohort with a few types — namely, cancer of the breast, urinary bladder, and rectum, and malignant melanoma. Of the 560 cases of cancer that were diagnosed during the first year of follow-up, we had no information about the extent of the disease at the time of diagnosis in 95 cases (17 percent). Of the remaining 465 cases, 184 (40 percent) had distant metastases, 115 (25 percent) had regional spread of the disease, and 166 (36 percent) had no spread.

During the period of follow-up beyond one year, the overall occurrence of cancer was slightly though significantly increased in both cohorts (Table 2). However, this moderate overall excess was evenly distributed among various cancer sites, and no significant excess persisted for the sites (pancreas, ovary, liver, and brain) that showed the strongest association with both types of venous thromboembolism during the first year of follow-up. After one year of follow-up, only for leukemia was the lower confidence limit of the standardized incidence ratio above 1.0 among the patients with deep venous thrombosis. We did not find any substantial differences between smoking-related cancers and those without a known relation to smoking.

In the subcohort of 3762 patients with recurrent episodes of deep venous thrombosis or pulmonary embolism, the risk of all types of cancer combined was 3.2 (95 percent confidence interval, 2.0 to 4.8) during the first year of follow-up and 1.3 (95 percent confidence interval, 1.2 to 1.5) thereafter. Among the remaining 22,891 patients with only one episode

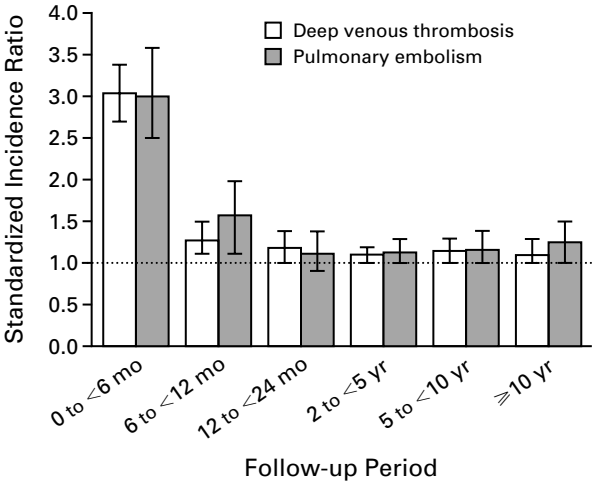

Figure 1. Risk of Cancer in Relation to the Length of the Follow-up Period in 26,653 Patients with Primary Deep Venous Thrombosis or Pulmonary Embolism.

The I bars represent 95 percent confidence intervals.

TABLE 1. STANDARDIZED INCIDENCE RATIOS (SIRS) FOR SELECTED CANCERS AMONG PATIENTS FOLLOWED FOR ONE YEAR AFTER HOSPITALIZATION FOR PRIMARY DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM.

SITE OR TYPE OF CANCER (ICD-7 CODE)*	DEEP VENOUS THROMBOSIS			PULMONARY EMBOLISM		
	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†
All malignant neoplasms (140–205)‡	390	181.5	2.1 (1.9–2.4)	170	74.1	2.3 (2.0–2.7)
Cancers with strong association in both cohorts						
Pancreas (157)	35	5.8	6.0 (4.2–8.4)	9	2.4	3.8 (1.7–7.2)
Ovary (175)	16	3.1	5.2 (2.9–8.3)	11	1.4	7.9 (4.0–14.4)
Liver, primary (155.0)	6	1.9	3.2 (1.2–6.9)	5	0.8	6.3 (2.1–15.3)
Brain (193)	10	3.3	3.0 (1.5–5.6)	7	1.4	5.0 (2.0–10.5)
Non-Hodgkin's lymphoma (200, 202)	10	3.5	2.9 (1.4–5.2)	4	1.4	2.9 (0.8–7.2)
Esophagus (150)	5	1.8	2.8 (0.9–6.6)	2	0.7	2.9 (0.3–10.4)
Kidney (180)	12	5.0	2.4 (1.2–4.1)	5	2.1	2.4 (0.8–5.6)
Leukemia (204)	11	4.4	2.5 (1.2–4.4)	3	1.8	1.7 (0.3–4.9)
Cancers with strong association in one cohort						
Prostate (177)	58	13.7	4.2 (3.2–5.5)	6	5.5	1.1 (0.4–2.4)
Corpus uteri (172)	10	3.4	2.9 (1.4–5.4)	1	1.5	0.7 (0.0–3.6)
Lung (162)	43	24.4	1.8 (1.3–2.4)	41	10.3	4.0 (2.9–5.4)
Cancers with weak or no association						
Stomach (151)	14	7.0	2.0 (0.7–3.3)	6	2.8	2.1 (0.8–4.6)
Colon (153)	26	16.3	1.6 (1.0–2.3)	13	6.5	2.0 (1.1–3.4)
Breast (170)	18	14.3	1.3 (0.7–2.0)	6	6.1	1.0 (0.4–2.2)
Urinary bladder (181)	12	11.9	1.0 (0.5–1.8)	7	4.8	1.5 (0.6–3.0)
Rectum (154)	6	9.1	0.7 (0.2–1.4)	6	3.7	1.6 (0.6–3.5)
Malignant melanoma (190)	1	3.0	0.3 (0.0–1.9)	0	1.2	0.0 (0.0–3.1)

*The sites and types of cancer are from the modified version of the *International Classification of Diseases, 7th Revision* (ICD-7) found in Storm et al.[12]

†$P<0.001$ by the test for homogeneity of the standardized incidence ratios for the sites and types of cancer listed. CI denotes confidence interval.

‡Because all cancer sites and types are not shown, the numbers of observed and expected cases for the individual sites and types do not add up to the total numbers.

TABLE 2. STANDARDIZED INCIDENCE RATIOS (SIRs) FOR SELECTED CANCERS AMONG PATIENTS FOLLOWED FOR 2 TO 17 YEARS AFTER HOSPITALIZATION FOR PRIMARY DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM.

SITE OR TYPE OF CANCER (ICD-7 CODE)*	DEEP VENOUS THROMBOSIS			PULMONARY EMBOLISM		
	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)‡
All malignant neoplasms (140–205)§	1347	1190.4	1.1 (1.1–1.2)	560	482.4	1.2 (1.1–1.3)
Pancreas (157)	50	36.1	1.4 (1.0–1.8)	18	14.7	1.2 (0.7–1.9)
Ovary (175)	21	18.6	1.1 (0.7–1.7)	7	7.8	0.9 (0.4–1.8)
Liver, primary (155.0)	11	12.1	0.9 (0.5–1.6)	4	4.9	0.8 (0.2–2.1)
Brain (193)	26	21.6	1.2 (0.8–1.8)	10	8.7	1.1 (0.6–2.1)
Non-Hodgkin's lymphoma (200, 202)	22	24.4	0.9 (0.6–1.4)	12	9.8	1.2 (0.6–2.1)
Esophagus (150)	20	12.4	1.6 (1.0–2.5)	9	4.9	1.8 (0.8–3.5)
Kidney (180)	25	32.5	0.8 (0.5–1.1)	22	13.2	1.7 (1.0–2.5)
Leukemia (204)	45	28.7	1.6 (1.1–2.1)	13	11.6	1.1 (0.6–1.9)
Prostate (177)	102	95.2	1.1 (0.9–1.3)	42	39.0	1.1 (0.8–1.5)
Corpus uteri (172)	26	21.0	1.2 (0.8–1.8)	7	8.9	0.8 (0.3–1.6)
Lung (162)	184	157.5	1.2 (1.0–1.4)	74	64.4	1.1 (0.9–1.4)
Stomach (151)	45	40.3	1.1 (0.8–1.5)	26	16.3	1.6 (1.0–2.3)
Colon (153)	114	106.5	1.1 (0.9–1.3)	44	43.0	1.0 (0.7–1.4)
Breast (170)	105	90.8	1.2 (0.9–1.4)	45	37.6	1.2 (0.9–1.6)
Urinary bladder (181)	82	80.3	1.0 (0.8–1.3)	42	32.4	1.3 (0.9–1.8)
Rectum (154)	53	57.6	0.9 (0.7–1.2)	25	23.3	1.1 (0.7–1.6)
Malignant melanoma (190)	27	20.3	1.3 (0.9–1.9)	8	8.1	1.0 (0.4–2.0)

*The sites and types of cancer are from the modified version of the *International Classification of Diseases, 7th Revision* (ICD-7) found in Storm et al.[12]

†P=0.22 by the test for homogeneity of the standardized incidence ratios of the sites and types of cancer listed. CI denotes confidence interval.

‡P=0.79 by the test for homogeneity of the standardized incidence ratios of the sites and types of cancer listed. CI denotes confidence interval.

§Because all sites and types of cancer are not shown, the numbers of observed and expected cases for the individual sites and types do not add up to the total numbers.

of deep venous thrombosis or pulmonary embolism, the overall risk of cancer was 2.2 (95 percent confidence interval, 2.0 to 2.4) during the first year and 1.1 (95 percent confidence interval, 1.1 to 1.2) during the subsequent years. The estimated risk of all types of cancer during the first year of follow-up decreased with increasing age at first discharge with venous thromboembolism (<60 years: standardized incidence ratio, 3.6; 95 percent confidence interval, 2.9 to 4.2; 60 to 74 years: standardized incidence ratio, 2.2; 95 percent confidence interval, 1.9 to 2.5; >74 years: standardized incidence ratio, 1.8; 95 percent confidence interval, 1.6 to 2.1).

DISCUSSION

We evaluated the association between deep venous thrombosis or pulmonary embolism and a subsequent diagnosis of cancer in a large cohort and found an increased risk of several types of cancer, almost entirely during the first year of follow-up. In particular, there was a strong association between thrombosis and cancer of the pancreas, ovary, liver, and brain during the first year. The magnitude of risk was similar to that observed in previous studies.[5,6] However, the rapid fall in the standardized incidence ratio after six months of follow-up strongly suggests that a thromboembolic event in patients later given a diagnosis of cancer is the result rather than the cause of the cancer. If the thromboembolic event had contributed to causing the cancer, we would have expected an increasing risk with length of follow-up, because of the long latency period for most cancers. If, alternatively, common risk factors for thromboembolism and cancer had been present, we would have expected a constant excess risk over time.

The higher risk of cancer among patients less than 60 years of age and among patients with recurrent episodes of deep venous thrombosis or pulmonary embolism accords with the results of a recent study.[6] These findings indicate that preclinical cancer has a larger role in thromboembolism among middle-aged patients than among older ones.

The large population we studied was well defined, and the follow-up almost complete, because the design relied on computerized registries with almost complete nationwide coverage. This gave us considerably more statistical precision than previous studies.[5-7] It is well known that discharge diagnoses vary in quality,[15] and some registered patients with deep venous thrombosis in their discharge records would not fulfill the criteria for thromboembolism. This would cause bias toward the null hypothesis. Our use of routine data might actually be a strength, since the study itself did not affect the diagnostic process and thus did not introduce bias due to surveillance in follow-up studies.[15]

The benefit of searching for cancer in a patient with a primary thrombotic event is difficult to assess.[16] In our cohort, most of the cancers that were found during the first year of follow-up were probably present at the time of the diagnosis of thromboembolism. The detection of some of these cancers would have required an extensive workup, and it is unclear whether early diagnosis would have changed the outcome. For several of the types of cancer, such as pancreas and liver cancers, early detection does not change the prognosis. Other cancers might be detected by simple methods.[17] In the group we studied, 26,600 persons would have had to be screened for the 304 excess cancers to be found during the first year of follow-up, and at least 40 percent of these patients would probably have had metastases at the time of diagnosis, as compared with 29 percent in a sex- and age-matched population of patients with the same types of cancer. Therefore, extensive cancer screening of patients with thromboembolism does not seem to be cost effective.[5] Extensive screening may cause several other problems, including discomfort and psychological stress.[16] Our results strongly support the pragmatic recommendation to use only simple methods of screening and to look for cancer in patients with signs and symptoms of cancer.[7,18]

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Paper II

PROGNOSIS OF CANCERS ASSOCIATED WITH VENOUS THROMBOEMBOLISM

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ABSTRACT

Background Little is known about the prognosis of cancer discovered during or after an episode of venous thromboembolism.

Methods We linked the Danish National Registry of Patients, the Danish Cancer Registry, and the Danish Mortality Files to obtain data on the survival of patients who received a diagnosis of cancer at the same time as or after an episode of venous thromboembolism. Their survival was compared with that of patients with cancer who did not have venous thromboembolism (control patients), who were matched in terms of type of cancer, age, sex, and year of diagnosis.

Results Of 668 patients who had cancer at the time of an episode of deep venous thromboembolism, 44.0 percent of those with data on the spread of disease (563 patients) had distant metastasis, as compared with 35.1 percent of 5371 control patients with data on spread (prevalence ratio, 1.26; 95 percent confidence interval, 1.13 to 1.40). In the group with cancer at the time of venous thromboembolism, the one-year survival rate was 12 percent, as compared with 36 percent in the control group ($P<0.001$), and the mortality ratio for the entire follow-up period was 2.20 (95 percent confidence interval, 2.05 to 2.40). Patients in whom cancer was diagnosed within one year after an episode of venous thromboembolism had a slightly increased risk of distant metastasis at the time of the diagnosis (prevalence ratio, 1.23 [95 percent confidence interval, 1.08 to 1.40]) and a relatively low rate of survival at one year (38 percent, vs. 47 percent in the control group; $P<0.001$).

Conclusions Cancer diagnosed at the same time as or within one year after an episode of venous thromboembolism is associated with an advanced stage of cancer and a poor prognosis. (N Engl J Med 2000;343: 1846-50.)

THE association between cancer and venous thrombosis was first recognized more than 100 years ago[1] by Trousseau.[2] Modern studies have consistently found a significantly increased risk of a diagnosis of cancer after an episode of venous thromboembolism, particularly within the first six months after the episode.[3-11] However, it is not clear whether this relation has implications for the clinical course of cancer in patients with venous thromboembolism. In addition, except for a case series of 84 patients and a secondary analysis of one diagnostic trial,[12,13] little is known about the prognosis of patients with cancer discovered at the time of or after a thromboembolic event.

To investigate this question, we conducted a follow-up study, using population-based data from the Danish National Registry of Patients, the Danish Cancer Registry, and the Danish Mortality Files. We examined the association between a history of venous thromboembolism and the extent of disease at the time of the diagnosis of cancer. We also compared the survival of patients with cancer and venous thromboembolism with the survival of patients with cancer who did not have venous thromboembolism.

METHODS

Study Design

The study was approved by the Danish data-protection board. The Danish National Registry of Patients[14] includes information about all patients admitted to nonpsychiatric hospitals in Denmark. We searched this registry for the period from January 1, 1977, to December 31, 1992, for patients who had either deep venous thrombosis in the leg or pulmonary embolism (codes 451.00 and 450.99, respectively, in the *International Classification of Diseases, 8th revision*)[15] during at least one hospitalization (63,196 patients). By linking this information with data from the Danish Cancer Registry, we excluded patients thought not to have primary (idiopathic) thrombosis or pulmonary embolism[10] — namely, those who had received a diagnosis of cancer (other than nonmelanoma skin cancer) before the thromboembolic event (11,313 patients), had undergone surgery within six months before the thromboembolic event (13,735), had been pregnant or had given birth within nine months before or three months after the thromboembolic event (242), or had received a secondary diagnosis of venous thromboembolism in the discharge record (10,585). After these exclusions, 27,321 patients with a record of primary venous thromboembolism (43.2 percent of the initial 63,196) remained in the study.

Since 1943 the Danish Cancer Registry[16] has kept records of all patients in Denmark with malignant neoplasms, as well as benign tumors of the central nervous system and papillomas of the urinary system. In this registry, the extent of spread of the tumor at the time of diagnosis is classified as localized, regional, metastatic to distant sites, or unknown. All the records of the 27,321 patients identified as having primary venous thromboembolism were linked to the Danish Cancer Registry to identify those who, before December 31, 1993, had received a diagnosis of cancer at the time of or after the thromboembolic event (3135 patients). Three cohorts were established according to the interval between the diagnosis of venous thromboembolism and the diagnosis of cancer: patients in whom cancer was diagnosed while they were hospitalized for primary venous thromboembolism (668), patients in whom cancer was diagnosed within the first year after hospitalization for venous thromboembolism (560), and patients in whom cancer was diagnosed 1 to 17 years after hospitalization for venous thrombo-

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embolism (1907). The patients in the second and third groups were described in an earlier report on the risk of cancer after venous thromboembolism.[10]

For each of the three cohorts of patients with venous thromboembolism, a group of patients who had not been hospitalized for venous thromboembolism was randomly selected from the Danish Cancer Registry and served as a control group. For each patient with cancer and venous thromboembolism, 10 control patients were matched according to the type of cancer (at the three-digit coding level of the *International Classification of Diseases, 7th revision*),[17] sex, age at the time of the diagnosis of cancer (in 10-year age groups), and the year of the diagnosis of cancer (5-year calendar periods). One patient in the cohort with a diagnosis of cancer 1 to 17 years after venous thromboembolism was excluded because it was not possible to find any matched control subjects. For 9 other patients, fewer than 10 controls were found. Thus, for the patients with a diagnosis of cancer at the time of a thromboembolic event, 6668 controls were found; for those with a diagnosis of cancer within 1 year after a thromboembolic event, 5586 controls were found; and for those with a diagnosis of cancer 1 to 17 years after a thromboembolic event, 19,042 controls were found. All the patients, both those with venous thromboembolism and those without it, were linked through the patient's civil registration number (which is unique to each resident of Denmark) to the Danish Mortality Files, which have been in operation since 1943.

Statistical Analysis

The proportion of patients with cancer and venous thromboembolism who had distant metastasis was compared with the proportion of the controls who had distant metastasis by calculating the prevalence ratio (the proportion of patients with distant metastasis and venous thromboembolism divided by the proportion of patients with distant metastasis but without venous thromboembolism) and associated 95 percent confidence interval. All the patients, both those with and those without venous thromboembolism, were followed from the date of the diagnosis of cancer until death or December 31, 1995, whichever came first. To summarize the survival of the patients with cancer over time, we used Kaplan–Meier analysis to construct survival curves, which were then compared with the results of log-rank tests. We used standard chi-square tests to assess the probability of survival at one year among the patients with venous thromboembolism as compared with the control patients. Finally, proportional-hazards regression analyses were used to compare the risk of death among the patients with venous thromboembolism with that among the controls, with calculation of the hazard ratios (mortality ratios) and associated 95 percent confidence intervals. Statistical tests were performed with use of SAS software (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Table 1 summarizes the demographic characteristics and types of cancer in the three cohorts of patients with cancer and venous thromboembolism. Overall, the most common sites of cancer were the lung, the prostate, the colon and rectum, the breast, and the pancreas. The proportion of patients with cancer and venous thromboembolism for whom information on the spread of tumor was available was similar to that of the control patients (Table 2). Among the patients in whom cancer was diagnosed at the time of an episode of venous thromboembolism, 44.0 percent had distant metastases, as compared with 35.1 percent of the matched control patients (prevalence ratio, 1.26; 95 percent confidence interval, 1.13 to 1.40) (Table 2). Among the patients in whom cancer was diagnosed within the first year after a thromboembolic event, 39.6 percent had distant metastases, as compared with 32.1 percent of the matched controls (prevalence ratio, 1.23; 95 percent confidence interval, 1.08 to 1.40). In contrast, the proportion of patients with distant metastasis among those in whom cancer was diagnosed more than one year after a thromboembolic event was similar to that of the controls (prevalence ratio, 1.04; 95 percent confidence interval, 0.94 to 1.14).

TABLE 1. CHARACTERISTICS AND CANCER SITES AMONG THE PATIENTS IN WHOM CANCER WAS DIAGNOSED AT THE TIME OF OR AFTER AN EPISODE OF VENOUS THROMBOEMBOLISM.*

CHARACTERISTIC	TIME OF DIAGNOSIS OF CANCER		
	AT THE TIME OF VENOUS THROMBOEMBOLISM	<1 YR AFTER VENOUS THROMBOEMBOLISM	1–17 YR AFTER VENOUS THROMBOEMBOLISM
No. of patients	668	560	1906†
Sex — M/F	305/363	317/243	1109/797
Age at cancer diagnosis — yr			
Mean	72	69	72
Range	15–100	19–94	22–97
Cancer type — no. (%)			
Lung	114 (17.1)	84 (15.0)	258 (13.5)
Prostate	46 (6.9)	64 (11.4)	144 (7.6)
Colon and rectum	54 (8.1)	39 (7.0)	158 (8.3)
Breast	24 (3.6)	24 (4.3)	150 (7.9)
Pancreas	64 (9.6)	44 (7.9)	68 (3.6)
Bladder	14 (2.1)	19 (3.4)	120 (6.3)
Stomach	35 (5.2)	20 (3.6)	71 (3.7)
Kidney	53 (7.9)	17 (3.0)	47 (2.5)
Leukemia	22 (3.3)	14 (2.5)	58 (3.0)
Ovary	35 (5.2)	27 (4.8)	28 (1.5)
Brain	30 (4.5)	17 (3.0)	36 (1.9)
Non-Hodgkin's lymphoma	14 (2.1)	14 (2.5)	34 (1.8)
Uterus	13 (1.9)	11 (2.0)	33 (1.7)
Liver	19 (2.8)	11 (2.0)	15 (0.8)
Cervix	13 (1.9)	10 (1.8)	18 (0.9)
Multiple myeloma	11 (1.6)	3 (0.5)	26 (1.4)
Esophagus	2 (0.3)	7 (1.2)	29 (1.5)
Other	105 (15.7)	135 (24.1)	613 (32.2)

*Because of rounding, not all percentages total 100.

†One patient in this group was excluded because no matched controls could be found.

Figure 1 shows the survival curves for patients in whom cancer was diagnosed at the time of an episode of primary venous thromboembolism and the matched control patients. Of the former, only 12 percent were alive at one year, in contrast to 36 percent of the control group ($P<0.001$). The mortality ratio was 2.46 (95 percent confidence interval, 2.25 to 2.68) for the first year of follow-up and 2.20 (95 percent confidence interval, 2.05 to 2.40) for the entire follow-up period.

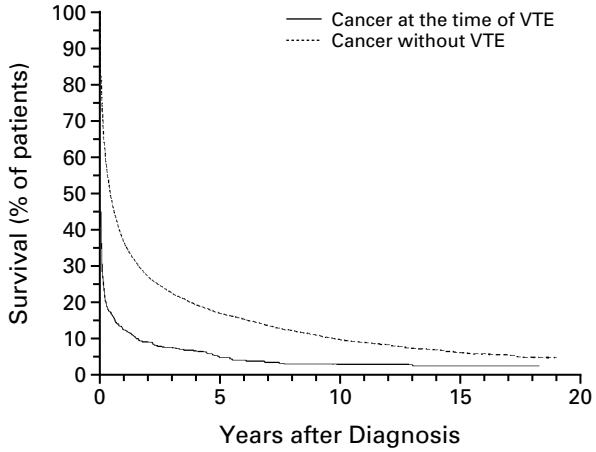
Patients in whom cancer was diagnosed within one year after an episode of primary venous thromboembolism also had a relatively poor prognosis (Fig. 2); 38 percent of them were alive at one year, as compared with 47 percent of the controls ($P<0.001$). The mortality ratio was 1.35 (95 percent confidence interval, 1.20 to 1.50) for the first year of follow-up and 1.30 (95 percent confidence interval, 1.18 to 1.42) for the entire follow-up period.

TABLE 2. EXTENT OF THE SPREAD OF CANCER, ACCORDING TO THE PRESENCE OR ABSENCE OF VENOUS THROMBOEMBOLISM.*

EXTENT OF SPREAD	CANCER AT SAME TIME AS VENOUS THROMBOEMBOLISM			CANCER <1 YR AFTER VENOUS THROMBOEMBOLISM			CANCER 1–17 YR AFTER VENOUS THROMBOEMBOLISM		
	PATIENTS (N=668)	CONTROLS (N=6668)	PREVALENCE RATIO (95% CI)	PATIENTS (N=560)	CONTROLS (N=5586)	PREVALENCE RATIO (95% CI)	PATIENTS (N=1906)†	CONTROLS (N=19,042)	PREVALENCE RATIO (95% CI)
	no. (%)			no. (%)			no. (%)		
Patients with data on spread	563 (84.3)	5371 (80.5)		465 (83.0)	4681 (83.8)		1516 (79.5)	15,712 (82.5)	
No spread	183 (32.5)	1835 (34.2)		166 (35.7)	2008 (42.9)		785 (51.8)	8,130 (51.7)	
Regional spread	132 (23.4)	1652 (30.8)		115 (24.7)	1171 (25.0)		371 (24.5)	3,982 (25.3)	
Distant metastasis	248 (44.0)	1884 (35.1)	1.26 (1.13–1.40)	184 (39.6)	1502 (32.1)	1.23 (1.08–1.40)	360 (23.7)	3,600 (22.9)	1.04 (0.94–1.14)

*The prevalence ratio is the proportion of patients with distant metastasis and venous thromboembolism divided by the proportion of patients with distant metastasis and no venous thromboembolism (i.e., control patients with distant metastasis). Because of rounding, not all percentages total 100. CI denotes confidence interval. Percentages for patients with data are of the entire group of patients. Percentages for patients in the extent-of-spread categories are of patients with data.

†One patient in this group was excluded because no matched controls could be found.



NO. AT RISK

Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

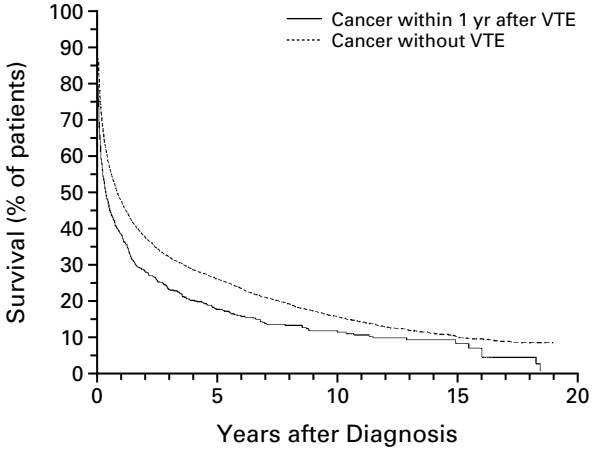
Figure 1. Survival Curves for Patients with a Diagnosis of Cancer at the Time of Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.

The control patients, who did not have venous thromboembolism, were matched with the patients who had venous thromboembolism according to cancer type, sex, age, and year of diagnosis. $P<0.001$ for the overall curves, by the log-rank test.

The survival curves for the entire follow-up period for the patients in whom cancer was diagnosed more than one year after an episode of venous thromboembolism were only slightly (though significantly) different from those of the matched control patients (data not shown). In the former group, the rate of survival at one year was 53 percent, as compared with 55 percent in the control group ($P=0.10$), and the mortality ratio was 1.08 (95 percent confidence interval, 1.00 to 1.15) for the first year. The mortality ratio for the entire follow-up period was 1.10 (95 percent confidence interval, 1.04 to 1.16).

DISCUSSION

In this analysis of more than 34,000 patients with cancer, those in whom cancer was diagnosed within one year after an episode of venous thromboembolism were more likely to have advanced disease and a



NO. AT RISK				
Cancer within 1 yr after VTE	560	72	37	7
Cancer without VTE	5586	1181	419	106

Figure 2. Survival Curves for Patients with a Diagnosis of Cancer within One Year after Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.

The control patients, who did not have venous thromboembolism, were matched with the patients who had venous thromboembolism according to cancer type, sex, age, and year of diagnosis. $P<0.001$ for the overall curves, by the log-rank test.

poor prognosis than patients with cancer who did not have venous thromboembolism. Survival was particularly poor when the diagnosis of cancer was concurrent with the thromboembolic event. These findings, which could not be explained by the type or extent of cancer or by age or sex, indicate that venous thromboembolism in a patient with cancer suggests the presence of advanced and aggressive disease.

Our findings agree with the very limited data available on the prognosis of patients who have both cancer and venous thromboembolism. In a case series without controls, Prandoni et al. found that 54 of 84 patients in whom cancer was diagnosed at the time of or after an episode of venous thromboembolism died within an eight-year follow-up period.[12] In a secondary analysis of a diagnostic trial involving 399 patients with pulmonary embolism (73 of whom had cancer), the most frequent cause of death in the year after the embolic event was cancer (35 percent).[13]

It seems unlikely that complications of venous thromboembolism can account entirely for the increased mortality among the patients in our study who had thromboembolic events. There are indications that the pathways of coagulation and fibrinolysis intersect with those of tumor growth.[18,19] There is also evidence that anticoagulant therapy can reduce the incidence of cancer and the rate of death due to cancer. In a recent trial in patients with recurrent venous thromboembolism, the incidence of cancer, over a mean follow-up period of 8.1 years, was lower among subjects randomly assigned to 6 months of anticoagulation with warfarin than among those randomly assigned to only 6 weeks of anticoagulation.[11] An earlier trial found that anticoagulant therapy may delay the progression of disease and improve survival in patients with small-cell lung cancer,[20] and another found that the rate of death due to cancer among patients with cancer who received low-molecular-weight heparin was 65 percent lower than among patients given standard heparin treatment.[21] However, another trial failed to show a similar effect.[22]

These findings raise the question of whether patients with venous thromboembolism and cancer should receive more aggressive anticoagulation than other patients with thrombosis. Our data do not answer this question but may provide an impetus for further study. The relatively poor prognosis of cancer diagnosed soon after venous thromboembolism also suggests that more aggressive therapy would be appropriate in such patients.

Our study has both strengths and limitations. We used nationwide, population-based registries with complete follow-up data. Clinicians caring for patients with venous thromboembolism could have increased their surveillance for cancer in these patients because of the known association with cancer. However, if anything, this should have resulted in earlier diagnosis in the patients with venous thromboembolism

and hence better survival. The survival curve for the patients in whom cancer was diagnosed more than one year after venous thromboembolism was similar to that for the matched patients without venous thromboembolism; this finding speaks against such a bias, which would have resulted in lower mortality in the former group.

A limitation of our data is the lack of clinical detail other than the relatively broad classification according to the extent of spread of disease, which was missing in 15 to 20 percent of the patients. In addition, it is well known that diagnoses at discharge are not entirely accurate; venous thromboembolism may have been misclassified in 10 to 20 percent of the cases listed in Scandinavian hospital discharge registries.[11] This lack of specificity may have led us to underestimate the differences between the patients with venous thromboembolism and those without it.

In conclusion, our data show that cancer discovered at the same time as or shortly after venous thromboembolism tends to be advanced, and the prognosis tends to be poor. These findings may have implications for the clinical care of patients with cancer.

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Paper III

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The risk of a second cancer after hospitalisation for venous thromboembolism

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Although venous thromboembolism (VTE) is common in patients with cancer, it is not known if it is associated with risk of a second malignancy. Using the Danish Cancer Registry and National Registry of Patients, we studied a population-based cohort of 6285 patients with cancer who had an episode of VTE. The risk of a second cancer was compared with that among 30 713 cancer patients without VTE, matched for age, sex, cancer site and year of diagnosis. Overall, the relative risk for a second cancer diagnosis was 1.3 (95% confidence interval (CI) 1.1–1.4). However, the excess risk varied with the time from the initial cancer diagnosis to the thrombotic event. If the thrombotic episode occurred within the first year, the relative risk for a second cancer was 1.0 (95% CI 0.9–1.3), but if the VTE occurred more than 1 year after the initial cancer, the overall relative risk for a second cancer was 1.4 (95% CI 1.2–1.7), with strong associations for cancers of the digestive organs, ovary and prostate. The association between VTE and subsequent incident cancer extends to patients who already have had a cancer diagnosis.
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Keywords: venous thromboembolism; epidemiology; prognosis; risk

The association between cancer and venous thrombosis has been recognised for more than 100 years (Piccioli *et al*, 1996), since episodic migratory thrombophlebitis was first reported in patients with cancer by Trousseau (Sørensen and Baron, 2005). Patients with clinically overt cancer may develop venous thromboembolism (VTE) at any stage of the disease (Agnelli, 1997; Rickles and Levine, 2001), aggravated by surgery, chemotherapy and intravenous catheters (Rickles and Levine, 2001). Occasionally, the thromboembolic event may occur before the clinical presentation of the cancer, and it is well known that the risk of a first cancer diagnosis is greatly increased in the year immediately after VTE (Prandoni *et al*, 1992; Baron *et al*, 1998; Sørensen *et al*, 1998, 2000; Murchison *et al*, 2004).

The implications of cancer risk subsequent to venous thrombosis for patients with a previous cancer are less clear. An episode of VTE is a marker of a poor cancer prognosis (Sørensen *et al*, 2000), but it is not known if this is associated with an increased risk of a second malignancy, as in patients without prevalent cancer. Since this may have important clinical implications for the care of cancer patients, we investigated the risk of a second cancer in patients with a known malignancy who experienced an episode of deep venous thrombosis or pulmonary embolism, using population-based data from the Danish Cancer Registry and National Registry of Patients.

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MATERIALS AND METHODS

This population-based study was based on a cohort of 45 201 patients with VTE identified through the Danish National Registry of Patients. This registry, established in 1977, includes information on 99.4% of all admissions to Danish acute care nonpsychiatric hospitals (Andersen *et al*, 1999). Recorded information includes the civil registration number (unique to each Danish citizen), the dates of admission and discharge, the surgical procedures performed and up to 20 discharge diagnoses, classified according to the Danish version of the International Classification of Diseases, 8th edition (ICD-8) (Andersen *et al*, 1999) until the end of 1993, and ICD-10 thereafter. It is possible to obtain the full discharge history of a patient by linking discharge records with the civil registration number. Study subjects were identified by searching for patients who had a first time discharge diagnosis of either lower limb deep venous thrombosis or pulmonary embolism (ICD-8 codes 451.00 and 450.99; ICD-10 codes I26, I80.1, I80.2 and I80.3) during at least one hospitalisation between 1 January 1977 and 31 December 1999.

To identify members of the VTE cohort with prevalent cancers (other than nonmelanoma skin cancer), we used civil registration numbers to link them to the Danish Cancer Registry (Storm *et al*, 1997). Here, cancers are classified according to the modified Danish version of the ICD, 7th Revision. Registration is based on notification forms completed by hospital departments and practicing physicians whenever a case of cancer is diagnosed or found at autopsy and whenever there are changes in an initial diagnosis. The Registry has been in operation since 1943 and is

95–98% complete and valid (Storm *et al*, 1997). In the VTE cancer cohort, we identified 10 107 patients who had had a cancer diagnosis prior to the VTE hospitalisation (4711 with deep venous thrombosis, 5312 with pulmonary embolism and 84 with both diagnoses): 3822 patients died during the hospital admission for VTE, leaving 6285 patients for follow-up.

As a control cohort, we selected from the Cancer Registry patients with a primary cancer diagnosis but without evidence of VTE in the National Registry of Patients. For each VTE cancer case, five cancer controls were identified, matched on age (within 5 years), sex, primary cancer site and year of cancer diagnosis. We required each control to be alive on the discharge date of the corresponding case for VTE.

Statistical analysis

Members of both study cohorts were linked through their civil registration numbers to the nationwide Danish Civil Registration System (with electronic records on vital status, including dates of emigration and death for the entire Danish population), and to the Danish Cancer Registry to identify subsequent deaths and cancer diagnoses. Both cohorts were followed from the date of the case VTE hospitalisation until the date of a second cancer (other than nonmelanoma skin cancer), censoring from death or emigration, or end of follow-up (31 December 1999), whichever came first. We estimated the relative risk by comparing the incidence of a second primary cancer between the VTE cancer patients and the cancer controls, using rate ratios with 95% confidence intervals (CI) computed from proportional-hazard regression models. We also computed these rate ratios within two strata of time between the first primary cancer and the thrombosis hospitalisation (a year or less, *vs* more than 1 year). We estimated cumulative risks using life-table methods.

RESULTS

The mean age of the 6285 members of the VTE cancer cohort was 68.6 years (standard deviation 12.2); 46.1% were men. The cancer sites most heavily represented in the cohort were breast (13.8%), colon (10.0%), prostate (9.6%), lymphatic system (9.1%), urinary tract (7.7%), rectum (6.8%), lung (6.8%) and corpus uteri (5.6%). In 974 patients (15.5%), the first episode of VTE occurred within a month of the initial cancer diagnosis.

A total of 343 second cancers were diagnosed in the VTE cancer cohort compared with 1981 in the control cancer cohort, yielding a relative risk during the entire follow-up of 1.3 (95% CI 1.1–1.4). The relative risks were slightly lower for those over 70 years of age, 1.2 (95% CI 1.1–1.4) than for those younger, 1.4 (95% CI 1.2–1.7), but were almost identical for men and women (data not shown). For the various second malignancies, relative risks for cancers of the upper gastrointestinal tract, ovary and prostate were particularly increased (Table 1).

Figure 1 shows the evolution over time of the cumulative risk of a second cancer in the two cohorts. In the first year after the VTE, there was a second cancer diagnosis for 2.3% of the VTE cancer patients and for 1.4% of cancer controls (relative risk 1.6, 95% CI 1.3–2.0) (Table 1).

Of the 3339 VTE cancer cohort members alive 1 year after the thrombotic event and without a second cancer up to that time, 238 had a diagnosis of a malignancy at a later time (years 2–23 of follow-up) *vs* 1610 second cancers among 21 713 1-year survivors in the control cancer cohort (relative risk 1.1, 95% CI 1.0–1.3) (Table 2). There was little variation over time in the relative risks during this period (data not shown). Cancer of the prostate and colorectal cancer were the only cancer sites with significantly elevated thrombosis-associated risks that persisted beyond the first year of follow-up.

The risk of a second cancer varied with the interval between the first cancer and the VTE episode. Patients with a thromboembolic event more than a year after their cancer diagnosis had a 40% increase in risk for a second cancer (relative risk 1.4, 95% CI 1.2–1.7). The relative risk of a second cancer was slightly higher (relative risk 1.7, 95% CI 1.3–2.2) in the first year after the thrombotic event, but there was also a clear increase in cancer risk

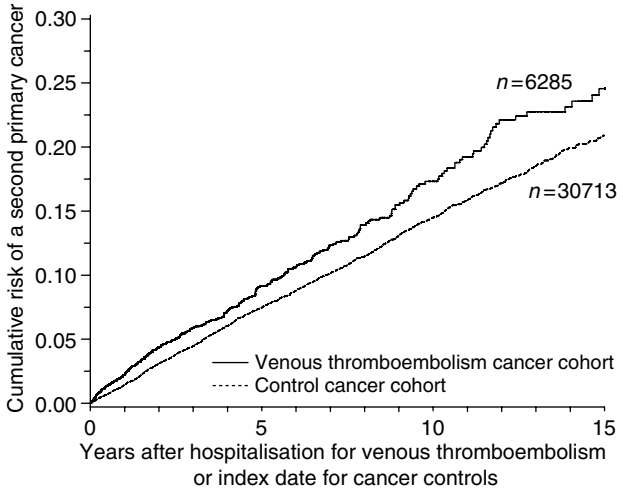

Figure 1 Cumulative risk of a second cancer among cancer cases with venous thromboembolism and cancer controls.

Table 1 Relative risk (rate ratio) of a second cancer among thrombosis cancer patients and control cancer patients in the first year of follow-up

	VTE cancer cohort, $N=6285$		Control cancer cohort, $N=30\,713$		
Sites of second cancer (ICD-7 code)[a]	**No. of events**	**No./1000 person-year**	**No. of events**	**No./1000 person-year**	**Relative risk (95% CI)**
All	105	24.3	371	14.5	1.6 (1.3–2.0)
Oesophagus (150)	3	0.7	8	0.3	2.2 (0.6–8.4)
Colon, rectum (153, 154)	13	3.0	55	2.2	1.4 (0.8–2.5)
Liver, primary, gall bladder, pancreas (155.0, 155.1, 157)	13	3.0	23	0.9	3.2 (1.6–6.4)
Lung, primary (162)	16	3.7	67	2.6	1.4 (0.8–2.4)
Breast (170)	7	2.2	181	1.8	1.3 (0.9–1.9)
Ovary (175)	5	1.2	6	0.2	5.0 (1.5–16.3)
Prostate (177)	11	2.5	29	1.1	2.2 (1.1–4.3)
Kidney, bladder (180, 181)	13	3.0	48	1.9	1.6 (0.9–2.9)
Lymphatic and haematological (200–205)	5	1.2	20	0.8	1.5 (0.6–4.0)

VTE = venous thromboembolism; CI = confidence interval. [a]Modified version of the 7th International Classification of Diseases.

Epidemiology

Table 2 Relative risk (rate ratio) of a second cancer of selected sites among thrombosis cancer patients and control cancer patients during 2–23 years of follow-up

	VTE cancer cohort, $N = 3339$		Control cancer cohort, $N = 21\,713$		
Sites of second cancer (ICD-7 code)[a]	**No. of events**	**No./1000 person-year**	**No. of events**	**No./1000 person-year**	**Relative risk (95% CI)**
All	238	18.2	1610	15.8	1.1 (1.0–1.3)
Oesophagus (150)	4	0.3	22	0.2	1.4 (0.5–4.0)
Colon, rectum (153, 154)	47	3.6	254	2.5	1.4 (1.1–2.0)
Liver, primary, gall bladder, pancreas (155.0, 155.1, 157)	11	0.8	89	0.9	0.9 (0.5–1.8)
Lung, primary (162)	30	2.3	276	2.7	0.8 (0.6–1.2)
Breast (170)	29	2.2	181	1.8	1.3 (0.9–1.9)
Ovary (175)	3	0.2	33	0.3	0.7 (0.2–2.3)
Prostate (177)	30	2.3	121	1.2	1.8 (1.2–2.7)
Kidney, bladder (180, 181)	22	1.7	194	1.9	0.9 (0.6–1.3)
Lymphatic and haematological (200–205)	18	1.4	129	1.3	1.1 (0.7–1.8)

VTE = venous thromboembolism; CI = confidence interval. [a]Modified version of the 7th International Classification of Diseases.

Table 3 Relative risk (rate ratio) of a second cancer diagnosis ($n = 343$) among cancer patients ($n = 6285$) with venous thromboembolism by time after first cancer diagnosis

		Follow-up interval		
Interval between first cancer and VTE	**Number of VTE cancer patients/controls**	**First year**	**1+ years**	**Overall**
Overall	6285/30 713	1.6 (1.3–2.0)	1.1 (1.0–1.3)	1.3 (1.1–1.4)
0–1 year	3081/14 896	1.6 (1.1–2.3)	0.9 (0.7–1.1)	1.0 (0.9–1.3)
>1 year	3204/15 817	1.7 (1.3–2.2)	1.4 (1.2–1.6)	1.4 (1.2–1.7)

VTE = venous thromboembolism.

Table 4 Cumulative 1-year risk of a second cancer in patients with an episode of VTE more than 1 year after the first cancer

Variable	**Number of subjects at risk**	**Cumulative absolute risk[a]**
All	3204	2.7 (2.1–3.3)
Women	1764	2.6 (1.7–3.4)
Men	1440	2.9 (1.9–3.8)
< 70 years	1386	2.9 (1.9–3.9)
⩾70 years	1818	2.7 (1.8–3.5)
Site of first cancer (ICD-7 code)		
Colon, rectum (153, 154)	489	2.9 (1.9–3.9)
Breast (170)	607	1.2 (0.2–2.2)
Prostate (177)	352	2.7 (0.7–4.7)
Kidney, bladder (180, 181)	423	4.5 (2.3–6.7)
Lymphatic and haematological (200–205)	261	2.4 (0.3–4.5)
Other	1072	3.3 (2.0–4.5)

VTE = venous thromboembolism; ICD-7 = 7th International Classification of Diseases. [a]Percentage.

even over more prolonged follow-up (relative risk 1.4, 95% CI 1.2–1.6) (Table 3). In contrast, cancer patients hospitalised with VTE within 1 year of the first cancer diagnosis had exactly the same overall risk of a subsequent second cancer as controls (relative risk 1.0, 95% CI 0.9–1.3). These patients with early thrombosis did have an increased cancer risk in the first year after the VTE (relative risk 1.6; 95% CI 1.1–2.3), but this was followed by a subsequent period of slightly lower cancer risk, which brought the overall relative risk to unity (Table 3).

Table 4 shows the cumulative 1-year risks of a second primary cancer in subgroups of patients with VTE more than 1 year after the first cancer. Particularly, high risks of a second cancer were seen for patients with kidney and bladder cancer (1 year cumulative risk 4.5%, 95% CI 2.3–6.7).

DISCUSSION

In this large nationwide follow-up study of cancer patients, we found an increased risk of second cancers associated with VTE, largely among patients whose thrombotic episode occurred 1 or more years after the first primary cancer. Risks of cancers of the ovary, prostate, hepatobiliary tract and pancreas were increased in the first year after the thrombosis diagnosis; there was a longer-term substantial increase in risk only for prostate and colorectal cancer.

The associations we observed with second cancers parallels that for a first malignancy, in which risk is also increased soon after a thrombotic episode (Baron *et al*, 1998; Sørensen *et al*, 1998; Prandoni, 2002). The spectrum of thrombosis-associated second cancers is very similar to that for first cancers (Baron *et al*, 1998; Sørensen *et al*, 1998), and thus similar aetiologic factors may be at play.

Among patients with early VTE – within a year of the first cancer diagnosis – increased surveillance is likely to be a factor in explaining the pattern of increased risks followed by decreased risks. The absence of such a pattern for patients with a later thrombotic episode suggests that diagnostic bias is probably not a factor, and implies that the association in this group has a biological basis. The variation over time in the relative risks provides some clues regarding this issue.

It is implausible that VTE or its treatment could cause a second solid tumour to develop within a year or two. Indeed, if the thrombotic event somehow contributed to the aetiology of the second cancer, we would have expected the relative risks to increase with follow-up, reflecting the long latency period of most epithelial cancers (Baron *et al*, 1998). If, on the other hand, shared risk factors were underlying the association, a more or less constant excess risk over time would be expected, as seen among patients with a thrombotic episode more than 1 year after the first cancer diagnosis. These risk factors could theoretically be smoking, obesity and hormone replacement therapy, since these factors are suggested or established risk factors for both VTE and cancer (Baron *et al*, 1998). However, the cancers with the increased relative risks in association with venous thrombosis – ovary,

prostate, liver, biliary and pancreas – do not prominently share these lifestyle risk factors. On balance, it is most likely that the second cancer was occult and caused the venous thrombosis, conceivably through changes in the clotting pathway (Silverstein and Nachman, 1992; Zacharski *et al*, 1992).

Our study has both strengths and limitations. The large population we studied was well defined and the long-term follow-up complete, because our design relied on computerised registries with complete nationwide coverage. This prevented selection bias and gave us a relatively high statistical precision. It is also well known that many cancers are associated with an increased risk of a second malignancy (Curtis *et al*, 1994; Leone *et al*, 1999; Levi *et al*, 1999; Brenner *et al*, 2000), and we therefore used other patients with incident cancers as controls. Our use of routine data underlies another strength: since the study itself did not affect the diagnostic process, it could not introduce surveillance bias in follow-up. On the other hand, we identified cases of VTE through an administrative database, the Danish National Registry of Patients, which may not be entirely accurate. This misclassification has been estimated to approximately 8–20% in Sweden and the US (Kniffin *et al*, 1994; Schulman and Lindmarker, 2000). Any misclassification of VTE in the hospital discharge records would cause bias towards the null hypothesis. As noted above, differential surveillance might also play a role.

The absolute risk of a second cancer after thromboembolism is relatively low (about 2% over the first year), and so the benefit of screening for a second cancer in cancer/thrombosis patients seems limited. Detection of a second malignancy would require an extensive work-up with high costs to detect a relatively small number of cancers. Moreover, the sites of the second malignancies are not those for which effective screening programmes have been devised and it is unclear if screening for a second cancer in this setting would change prognosis.

Over the past 20 years, there has been increasing clinical evidence that anticoagulants have antitumour effects reducing the risk of cancer in patients with VTE and improving survival in patients with advanced malignancy (Zacharski *et al*, 1981; Schulman and Lindmarker, 2000; Kakkar *et al*, 2004). Cancer patients with VTE are at increased risk of second malignancies, but further work is needed before specific guidelines for their management would be appropriate.

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Paper IV

Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study

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Summary

Background In some studies, venous thromboembolism has been associated with atherosclerosis and with the risk of arterial cardiovascular events such as myocardial infarction and stroke. Other studies, however, do not show this association. To help clarify these discrepant findings, we aimed to investigate the risk of arterial cardiovascular events in patients who were diagnosed with venous thromboembolism.

Methods We undertook a 20-year population-based cohort study using data from nationwide Danish medical databases. After excluding those with known cardiovascular disease, we assessed the risk of myocardial infarction and stroke in 25 199 patients with deep venous thrombosis, 16 925 patients with pulmonary embolism, and 163 566 population controls.

Findings For patients with deep venous thrombosis, the relative risks varied from 1·60 for myocardial infarction (95% CI 1·35–1·91) to 2·19 (1·85–2·60) for stroke in the first year after the thrombotic event. For patients with pulmonary embolism, the relative risks in that year were 2·60 (2·14–3·14) for myocardial infarction and 2·93 (2·34–3·66) for stroke. The relative risks were also raised, though less markedly, during the subsequent 20 years of follow-up, with 20–40% increases in risk for arterial cardiovascular events. Relative risks were similar for those with provoked and unprovoked deep venous thrombosis and pulmonary embolism.

Interpretation Patients with venous thromboembolism have a substantially increased long-term risk of subsequent arterial cardiovascular events.

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Introduction

Venous thromboembolism is a common and serious disorder in Western countries, with hospital admission rates that seem to be increasing.[1–4] Venous thromboembolic disorders are generally considered to be distinct from thrombotic atherosclerotic diseases, since arterial thrombi consist mainly of platelets, in contrast to venous thrombi, which mainly consist of red blood cells and fibrin.[5]

In 2003, an association between venous thromboembolism and markers of atherosclerosis was reported, suggesting that both conditions share activation of blood coagulation and platelets.[6] In this case-control study, patients with unprovoked venous thromboembolism had a higher prevalence of asymptomatic carotid atherosclerosis than did patients with secondary thrombosis and age-matched and sex-matched hospital controls without venous thrombosis.[6] Another case-control study, showing an increased prevalence of coronary calcification in patients with unprovoked venous thromboembolism, supported the observation.[7]

In contrast, two other studies failed to find a relation between atherosclerosis and venous thromboembolism.[8,9] These investigations looked at the risk of subsequent venous thromboembolism in patients with and without non-invasive markers of atherosclerosis.[8,9] A cross-sectional autopsy study provided inconclusive data.[10] In other reports, patients who had venous thrombosis or pulmonary embolism (especially those with an unprovoked event) had an increased risk of atherosclerotic cardiovascular events.[11–14] However, most of these investigations were clinic-based studies from referral centres with few outcomes, and so their interpretation is limited.[11–14] Thus whether venous thromboembolism is associated with arterial cardiovascular morbidity, and if so, to what extent, is not clear.

Data on this issue are important, as they could foster the understanding of both venous thrombosis and atherosclerotic disease, and provide further insight into the clinical course of patients with venous thromboembolism. We therefore undertook a large, population-based assessment of the risk of hospitalisation due to acute myocardial infarction and stroke after a diagnosis of venous thromboembolism, using data from Danish medical databases.[15,16]

Methods

Patients and procedures

With the approval of the Danish Registry Board we obtained data from the Danish National Registry of Patients, which since 1977 has recorded 99·4% of all discharges from Danish acute-care non-psychiatric hospitals.[15–17] The recorded information includes: dates of hospital admission and discharge, surgical procedures done, and up to 20 discharge diagnoses, classified according to the International Classification of Diseases,

8th revision (ICD-8) until Dec 31, 1993, and according to the 10th revision thereafter. In all Danish medical registries, patients are identified through the civil registration number. These are unique identifiers, assigned at birth, and stored in the Danish Civil Registration System along with date of birth, residency status, and dates of immigration, emigration, and death (if any).

To form a cohort of individuals with venous thromboembolism and no history of cardiovascular disease, we identified the first recorded inpatient hospital discharge diagnosis of lower limb deep venous thrombosis, or pulmonary embolism, or both, between Jan 1, 1980, and Dec 31, 2005, in all Danish residents aged at least 40 years. Using the civil registration number, we searched the National Registry of Patients to identify and exclude cases with any previous or concurrent discharge diagnosis of cardiovascular disease. We also excluded those with a venous thromboembolism diagnosis during the first three years of the registry's running (1977–79) to avoid including patients treated for complications or recurrence of previous thromboembolism.

We defined provoked venous thromboembolism cases as those with a diagnosed malignancy before or within 90 days after the thrombotic event in the hospital registry, and those with a discharge diagnosis of fracture, surgery, trauma, or pregnancy within 90 days before the hospitalisation for venous thromboembolism.[18] The remaining venous thromboembolism cohort members were classified as unprovoked.[18]

We formed a population-based control cohort using the Danish Civil Registration System.[19] For each patient in the venous thromboembolism cohort, five population controls were randomly chosen from the entire registry, matched for sex, age, and municipality of residence. Each control was required to be alive on the date the corresponding case person was first hospitalised with venous thromboembolism, the "index date" for the matched set. With the venous thromboembolism patients, we excluded comparison cohort members with a hospital discharge diagnosis of any cardiovascular disease before the index date. Starting in 1994, the hospital registry included hospital outpatient visits. In Denmark, these data include essentially all outpatient specialist encounters, including visits to cardiologists. This information enabled us to exclude people with venous thromboembolism (and population controls) who had been diagnosed with a prior cardiovascular disease but who had not been hospitalised.

By use of the civil registration number, all members of the two study cohorts were linked to the Civil Registration System and to the National Registry of Patients so as to identify all inpatient hospitalisations after the index dates for acute myocardial infarction or stroke. We did not undertake a separate analysis of haemorrhagic stroke and heart failure, since these can be complications of anticoagulation therapy and venous thromboembolism, respectively. However, we studied stroke (type unspecified) and not solely ischaemic stroke because of the clinical difficulty in separating ischaemic and non-ischaemic cerebrovascular events. We also considered the combined endpoint of acute myocardial infarction and stroke.

Statistical analysis

We assessed the association between venous thromboembolism and later arterial cardiovascular events both overall and separately for unprovoked and provoked thrombotic episodes. We followed the cohorts from the index dates to the occurrence of a hospitalisation for one of the outcome cardiovascular diseases, or to emigration, death, end of December, 2005, or 20 years of follow-up, whichever came first.

To summarise time-to-events, we used Kaplan-Meier analysis to construct survival curves and life table techniques to compute risks of the outcomes.

We used proportional hazards regression to compute hazard ratios and 95% CIs as measures of relative risk for the endpoint diagnoses. In all models, we adjusted for age, sex, and index calendar year. In the analyses of provoked venous thromboembolism we also adjusted for recent (within 90 days) pregnancy or surgery (including trauma and fractures), and main types of cancers (respiratory, gastrointestinal, urogenital, central nervous system, breast, haematological, and other cancers). We used the χ^2 test to compute p values for differences in proportions.

By 1994 the diagnostic approach to venous thromboembolism had become relatively homogeneous in Denmark.[20] When we restricted analysis to venous thromboembolism cases diagnosed after 1994 (and their corresponding unaffected population controls), the findings were essentially identical with those obtained with the complete cohorts, and are not presented here. Statistical analyses were done with SAS software (version 9.1).

Role of the funding source

The sponsor had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 90 384 individuals with a first discharge diagnosis of venous thromboembolism after age 40 years, and 451 920 population controls. 48 260 (53·4%) venous thromboembolism cases and 108 483 (24·0%) population control cohort members had a discharge diagnosis of cardiovascular disease before, or concurrent with, the index date and were excluded from further analysis. The most common diagnoses in those excluded from the

	Deep venous thrombosis cohort (n=25 199)	Deep venous thrombosis population control cohort (n=97 773)	p*	Pulmonary embolism cohort (n=16 925)	Pulmonary embolism population control cohort (n=65 793)	p*
Age (years)						
40–55	6750 (26·8%)	29 883 (30·6%)		3475 (20·5%)	15 448 (23·5%)	
56–70	8783 (34·9%)	35 245 (36·0%)		5651 (33·4%)	22 909 (34·8%)	
≥71	9666 (38·4%)	32 645 (33·4%)	<0·0001	7799 (46·1%)	27 436 (41·7%)	<0·0001
Sex						
Female	12 765 (50·7%)	49 885 (51·0%)	0·30	9289 (54·9%)	36 490 (55·5%)	0·17
Male	12 434 (49·3%)	47 888 (49·0%)		7636 (45·1%)	29 303 (44·5%)	
Recent malignancy (before, or up to 90 days after, venous thromboembolism or index date)						
Yes	4544 (18·0%)	4600 (4·7%)	<0·0001	3785 (22·4%)	3311 (5·0%)	<0·0001
No	20 655 (82·0%)	93 173 (95·3%)		13 140 (77·6%)	62 482 (95·0%)	
Recent pregnancy (up to 90 days before venous thromboembolism or index date)						
Yes	15 (0·1%)	15 (0%)	<0·0001	21 (0·1%)	10 (0%)	<0·0001
No	25 184 (99·9%)	97 758 (100%)		16 904 (99·9%)	65 783 (100%)	
Recent surgery (including trauma, fractures (up to 90 days before venous thromboembolism or index date)						
Yes	3427 (13·6%)	1595 (1·6%)	<0·0001	2678 (15·8%)	948 (1·4%)	<0·0001
No	21 772 (86·4%)	96 178 (98·4%)		14 247 (84·2%)	64 845 (98·6%)	

Data are number (%), unless otherwise specified. *p for differences in proportions for age and the indicated medical history.

Table 1: **Descriptive data for patients with venous thromboembolism and their population control cohorts**

	Deep venous thrombosis cohort (n=25 199)		Deep venous thrombosis population control cohort (n=97 773)		Adjusted relative risk (95% CI)*		Pulmonary embolism cohort (n=16 925)		Pulmonary embolism population control cohort (n=65 793)		Adjusted relative risk (95% CI)*	
	1-year follow-up	2–20 years' follow-up	1-year follow-up	2–20 years' follow-up	1-year follow-up	2–20 years' follow-up	1-year follow-up	2–20 years' follow-up	1-year follow-up	2–20 years' follow-up	1-year follow-up	2–20 years' follow-up
Acute myocardial infarction or stroke	380	2388	806	10 009	1·88 (1·66–2·12)	1·26 (1·20–1·31)	254	1133	611	7559	2·73 (2·36–3·16)	1·31 (1·23–1·39)
Acute myocardial infarction	176	1157	447	5107	1·60 (1·35–1·91)	1·18 (1·11–1·26)	144	597	383	3918	2·60 (2·14–3·14)	1·32 (1·21–1·43)
Stroke	209	1367	371	5504	2·19 (1·85–2·60)	1·31 (1·23–1·39)	113	608	237	4069	2·93 (2·34–3·66)	1·29 (1·18–1·40)
Ischaemic stroke	92	587	195	2267	1·85 (1·44–2·37)	1·36 (1·24–1·48)	45	272	118	1707	2·34 (1·66–3·31)	1·34 (1·18–1·52)

Data are number of events, unless otherwise specified. *Adjusted for sex, age, and year of venous thromboembolism diagnosis.

Table 2: **Relative risks of arterial cardiovascular disease during follow-up in patients with venous thrombosis or pulmonary embolism, and in population controls**

venous thrombosis and population cohorts were hypertension (29 580), chronic atherosclerotic heart diseases (25 008), acute myocardial infarction (19 380), stroke or transient ischaemic attack (19 378), heart failure (13 423), and angina pectoris (12 145).

Table 1 shows characteristics of the remaining 25 199 patients with deep venous thrombosis, and the 16 925 patients with pulmonary embolism and their population control cohorts. In both groups there were slightly more women than men. Between a third and a half of the two case cohorts were older than 70 years (table 1). As expected, in comparison to controls, more venous thromboembolism patients than population controls had a malignancy, or recent surgery or pregnancy.

Overall, venous thromboembolism was a clear marker of subsequent risk of each of the arterial cardiovascular endpoints (table 2). For patients with deep venous thrombosis, the relative risks during the first year after the thrombotic event were 1·60 (95% CI 1·35–1·91) for myocardial infarction and 2·19 for stroke (1·85–2·60); the relative risks were higher for pulmonary embolism (table 2).

Some venous thromboembolism patients had a high absolute risk of arterial cardiovascular events. In those with pulmonary embolism who were older than 70 years, the risk of myocardial infarction or stroke in the first year of follow-up was 3·96% versus 1·59% for the comparison cohort (relative risk 2·57; 95% CI 2·13–3·10). By contrast, in patients aged 40–55 years with pulmonary embolism, the relative risk over the first follow-up year was higher (3·68; 2·23–6·08), but the increase in risk was small: the absolute risks were 0·88% versus 0·24% in the control cohort.

	Deep venous thrombosis cohort (n=18 087)		Deep venous thrombosis population control cohort (n=66 657)		Adjusted relative risk (95% CI)*		Pulmonary embolism cohort (n=11 037)		Pulmonary embolism population control cohort (n=40 643)		Adjusted relative risk (95% CI)*	
	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2-20 years' follow-up
Acute myocardial infarction or stroke	273	1961	517	7051	1·87 (1·62–2·17)	1·25 (1·19–1·31)	191	911	362	4708	2·84 (2·38–3·38)	1·34 (1·25–1·44)
Acute myocardial infarction	138	961	289	3627	1·74 (1·42–2·13)	1·18 (1·10–1·27)	108	486	233	2454	2·62 (2·09–3·29)	1·36 (1·23–1·49)
Stroke	137	1118	234	3861	2·01 (1·63–2·48)	1·29 (1·21–1·38)	84	488	133	2521	3·17 (2·41–4·17)	1·32 (1·20–1·45)
Ischaemic stroke	59	489	127	1627	1·60 (1·18–2·18)	1·34 (1·21–1·48)	35	219	62	1073	2·82 (1·86–4·27)	1·36 (1·17–1·57)

Data are number of events, unless otherwise specified. *Adjusted for sex, age, and year of venous thromboembolism diagnosis.

Table 3: **Risks of arterial cardiovascular disease in patients with unprovoked venous thrombosis or pulmonary embolism, and in population controls**

	Deep venous thrombosis cohort (n=7112)		Deep venous thrombosis population control cohort (n=27 038)		Adjusted relative risk (95% CI)*		Pulmonary embolism cohort (n=5888)		Pulmonary embolism population control cohort (n=22 603)		Adjusted relative risk (95% CI)*	
	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up	1 year follow-up	2–20 years' follow-up
Acute myocardial infarction or stroke	107	427	240	2635	1·82 (1·38–2·38)	1·26 (1·06–1·51)	63	222	221	2662	2·28 (1·64–3·19)	1·17 (0·94–1·47)
Acute myocardial infarction	38	196	135	1322	1·22 (0·80–1·87)	1·17 (0·89–1·53)	36	111	134	1380	2·63 (1·67–4·14)	1·31 (0·94–1·81)
Stroke	72	249	111	1459	2·62 (1·84–3·73)	1·38 (1·10–1·73)	29	120	91	1436	2·16 (1·33–3·50)	1·07 (0·79–1·44)
Ischaemic stroke	33	98	55	578	2·59 (1·53–4·39)	1·45 (1·01–2·09)	10	53	50	591	1·48 (0·69–3·21)	1·22 (0·78–1·92)

Data are number of events, unless otherwise specified. *Adjusted for sex, age, and year of venous thromboembolism diagnosis, pregnancy, surgery up to 90 days before hospitalisation for venous thromboembolism, malignancy (respiratory, gastrointestinal, urogenital, central nervous system, breast, haematological and other cancers) before, or up to 90 days after, the venous thrombotic episode.

Table 4: **Relative risks of arterial cardiovascular disease in patients with provoked venous thrombosis or pulmonary embolism, and in population controls**

After the first year of follow-up, the excess relative risks persisted, but at a lower level, roughly 20–40% above risks in the control cohort (table 2). 1–5 years after deep venous thrombosis, the relative risk for myocardial infarction or stroke was 1·33 (95% CI 1·24–1·43); this fell to 1·14 (0·99–1·31) 16–20 years after the event. After pulmonary embolism, the relative risks were similar during these two periods (data not shown).

Tables 3 and 4 summarise the risk estimates for unprovoked and provoked venous thromboembolism, respectively. The relative risks for arterial cardiovascular events were similar in the two analyses. As in the overall analysis, the excess risks were lower for deep venous thrombosis than for pulmonary embolism, and the modest, longer term associations were also present. The relative risks for unprovoked deep venous thrombosis fell slowly over the long-term follow-up (figure), whereas for unprovoked pulmonary embolism the excess relative risk appeared more constant. For patients with a provoked presentation, there was no evidence of a substantial change over time after the first year (figure).

In general we did not identify any major differences in relative risks between females and males. However, the relative risk estimates for the first year of follow-up tended to be slightly higher for females than males for both unprovoked and provoked pulmonary embolism (data not shown).

Discussion

Our large nationwide population-based study provides strong evidence that patients with venous thromboembolism have an increased risk of subsequent arterial cardiovascular events, compared with population controls. The excess risk was most pronounced during the first year of follow-up, persisted for up to 20 years, and was noted after both deep venous thrombosis and pulmonary embolism. The relative risks were similarly high in patients with unprovoked venous thromboembolism and in those with provoked disease.

Our population-based data are largely consistent with the initial observations of higher prevalences of asymptomatic carotid plaques[6] or coronary calcifications[7] in patients with unprovoked deep venous thrombosis than in matched hospital controls. The cross-sectional

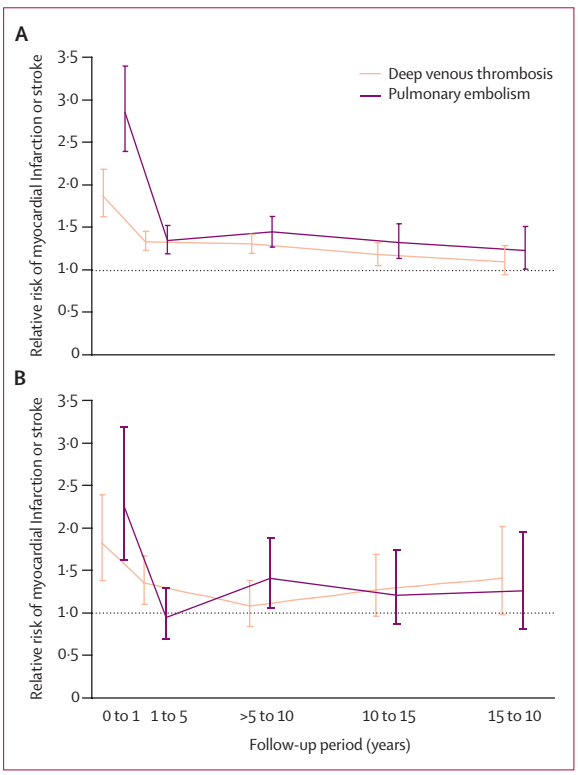

Figure: **Relative risk of acute myocardial infarction and stroke during follow-up in patients with provoked (A) and unprovoked (B) venous thromboembolism**

nature of these analyses and their reliance on preclinical markers of atherosclerosis necessarily limits their potential to clarify the time course and clinical impact of the association—important issues that we were able to address. Our findings are likewise consistent with a follow-up study of 151 venous thrombosis patients and 151 clinic controls that reported a relative risk of arterial cardiovascular events of 2·86 (95% CI 1·07–7·62).[14] In contrast, two cohort studies investigating the association between subclinical markers of atherosclerotic disease and subsequent development of venous thromboembolism failed to find such an association.[8,9] One of these[8] reported a direct association between arterial cardiovascular and venous thrombotic events during follow-up[8] while the other[9] identified an inverse relationship.

In contrast to some previous studies,[11,12] we found an increased risk of subsequent arterial cardiovascular events not only in patients with unprovoked venous thromboembolism, but also in those with thrombosis secondary to pregnancy, surgery, or other predisposing conditions. Unlike those previous studies, we did not include use of hormone-replacement therapy or oral contraceptives as predisposing factors in women. However, since the associations for venous thrombosis we noted were similar in men and women, differences in inclusion or exclusion criteria between studies could not explain the differences in findings. Our population-based analysis included all patients with a hospital diagnosis of venous thromboembolism and so was free from the potential distortions of selection and response factors, which can complicate clinic-based cohorts or use of hospital controls.[6,7,11,12]

The mechanism underlying the association between venous thromboembolism and atherosclerotic disease is not clear. It is not plausible that venous thromboembolism in itself causes myocardial infarction and stroke. Rather, the association we find must be due to shared risk factors or aetiologic pathways, or both.[21] With the exception of obesity, there is only weak and inconsistent evidence that venous and atherosclerotic diseases share common risk factors such as diabetes, hypertension, hyperlipidaemia, and cigarette smoking.[5,18,22–28]

Nonetheless, the increased risk of myocardial infarction and stroke for both provoked and unprovoked venous thromboembolism is consistent with underlying common prothrombotic mechanisms such as thrombogenesis, endothelial damage, or inflammation.[21] Acute arterial events such as these are associated with activation of platelets and blood coagulation, and a role of this prothrombotic state in the promotion of venous thrombosis is plausible.[5,6] Atherosclerosis itself seems also related to a hypercoaguable state, though perhaps to a lesser extent.[29] This weaker relationship could explain why the clinical arterial events have been more consistently associated with risk of venous thromboembolism than with (subclinical) markers of atherosclerosis. In any case, similar biological triggers could be responsible for activating coagulation and inflammatory pathways in both arterial disease and venous thromboembolism.[21]

However, differences in the aetiology of ischaemic stroke and myocardial infarction could complicate this inference. Ischaemic strokes are more often caused by emboli originating from the heart, the aorta or the carotid arteries than by local thrombi within the brain.[30] By contrast, rupture of coronary atherosclerotic plaques and local thrombi are the cause of most myocardial infarctions.[31] Therefore, the mechanism behind the association between venous thromboembolism and myocardial infarction could differ from that between deep venous thrombosis and pulmonary embolism, and stroke. Other examples of conditions associated with both arterial and venous thromboembolic disorders are hyperhomocysteinaemia, inherited thrombophilia, antiphospholipid antibodies, and various infections such as those due to *Chlamydia pneumoniae*.[5,28,32]

Our study has both strengths and limitations. We studied important clinical arterial cardiovascular events, and our risk estimates are derived from a population-based cohort study, in a setting with a national health service with free access to health care that largely removed referral and diagnostic biases. The large population we studied was well-defined, and the follow-up was complete

because our design relied on computerised registries with complete nationwide coverage. We had access to the entire hospital discharge registry history and, since 1994, outpatient clinic data as well. We did not include cardiovascular deaths in our analysis. The Danish National Registry of Patients records patients for whom cardiac arrest occurred outside hospital if there was an admission for a resuscitation attempt. However, patients with a myocardial infarction or stroke who died suddenly outside the hospital without a previous admission would not have been judged to have developed the study endpoints.

The validity of our findings depends ultimately on the accurate coding of venous thromboembolism and of cardiovascular endpoints. In administrative databases, the predictive value of a discharge diagnosis of pulmonary embolism and myocardial infarction has been reported to be 90%,[33,34] though slightly lower for stroke and venous thrombosis.[33,35–37] However, lack of specificity of the outcome diagnosis would bias our risk estimates towards the null, probably more for stroke than for myocardial infarction.

The cancer and procedure data we used to define provoked venous thromboembolism have high validity, making the specificity of this classification quite high.[38] Any misclassification between a provoked and unprovoked venous thromboembolism will attenuate the difference in the relative risk estimates between the two groups. Our use of routine data might actually be a strength. The study itself could not have affected the diagnostic process, although it is certainly possible that the clinicians making the cardiovascular diagnoses were affected by the previous medical history (including that of thromboembolism). We did not have data on use of oral anticoagulation therapy, widely used in patients with venous thromboembolism, which reduces the risk of myocardial infarction and stroke.[39] All these biases will tend to be conservative, and result in underestimation of the strength of the association between venous thromboembolism and arterial cardiovascular events.

Our findings could have clinical implications. Our data showed an increased relative risk of cardiovascular disease in patients with venous thromboembolism comparable to that of other conventional risk factors[18,40] for arterial cardiovascular events—at least during the first year of follow-up. However, the value of preventive measures against myocardial infarction and stroke in patients with venous thromboembolism is uncertain. Two ongoing studies are evaluating the effect of aspirin on the long-term treatment of venous thromboembolism.[5] A few observational studies have shown that statins might reduce the risk of venous thromboembolism,[41] but the role of these drugs specifically for the prevention of myocardial infarction and stroke in patients with venous thromboembolism has not yet been explored.[41]

Thus, we find strong evidence that venous thromboembolism is associated with an increased long-term risk of arterial cardiovascular events irrespective of the presence or absence of classic risk factors for venous thromboembolism. Common risk factors or pathways are most likely responsible for the association. Future studies are needed to further clarify the association, and to evaluate its implications for clinical practice.

Contributors

HTS was the principal investigator and lead author in the conception and design of the study, analysis of the data and drafting of the manuscript. EH-P and LP coordinated the data collection and did the statistical analysis. JAB participated in the study design, provided statistical suggestions, and participated in the interpretation of the results. PP participated in the conception and design of the study and the interpretation of the data. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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Paper V

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IN FOCUS

Arterial cardiovascular events, statins, low-dose aspirin and subsequent risk of venous thromboembolism: a population-based case-control study

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Summary. *Background:* Atherosclerotic disease has been associated with the risk of venous thromboembolism, but the available data are conflicting. There are similar confusions regarding the association of the use of aspirin and statins with venous thromboembolism. *Objectives:* To determine whether arterial cardiovascular events, use of statins and low-dose aspirin were associated with the risk of venous thromboembolism. *Patients and methods:* In this population-based case–control study, we identified 5824 patients with venous thromboembolism and 58 240 population controls with a complete hospital and prescription history. We used logistic regression to estimate the relative risk of venous thromboembolism, adjusted for potentially confounding factors. *Results:* Patients with a history of arterial cardiovascular events had a clearly increased relative risk. An event within 3 months before the index date conferred large increases in risk [relative risk 4.22 (95% confidence interval (CI), 2.33–7.64) after myocardial infarction, 4.41 (95% CI, 2.92–6.65) after stroke]. Myocardial infarction more than 3 months before the index date was not significantly associated with risk, although there was a relative risk of 1.29 (95% CI, 1.05–1.57) for myocardial infarction more than 60 months previously. A history of stroke was associated with small increases in risk after 3 months. Current use of statins was associated with a reduced risk of venous thromboembolism [relative risk = 0.74 (95% CI, 0.63–0.85)]. Aspirin use was not associated with risk. *Conclusions:* Patients with cardiovascular events are at a short-term increased risk of venous thromboembolism. Statins might prevent venous thromboembolism but aspirin does not. However, as the study is non-randomized residual confounding cannot be excluded.

Keywords: aspirin, myocardial infarction, statins, stroke, venous thromboembolism.

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Introduction

Venous thrombosis, with its complications such as pulmonary embolism and post-thrombotic syndrome, is a common and often serious disease process, affecting approximately two per 1000 persons per year in Western populations [1,2]. Thrombosis can occur in any venous system, but predominantly occurs in the vessels of the lower limbs. Well-established risk factors include recent surgery, cancer, fractures, immobilization, recent pregnancy and use of estrogens [3,4].

Atherosclerotic disease and venous thromboembolism have been considered two separate disease entities [5] with distinct pathologies, as arterial thromboses are mainly comprised of platelets, in contrast to venous thrombi which generally consist of red blood cells and fibrin [5]. Nonetheless, there is increasing epidemiological evidence that patients with either provoked or unprovoked venous thromboembolism have an increased risk of subsequent atherosclerotic disease [5–11]. Conversely, patients with atherosclerotic disease may also have an increased risk of venous thromboembolism, although data regarding this point are conflicting [12–15]. The relative immobility associated with acute myocardial infarction and stroke certainly has the potential to generate such an association, as does the slow blood

flow associated with congestive heart failure, but it is not clear whether there is an association in other circumstances [5,12,14].

Some of the drugs commonly used in patients with atherosclerosis may in themselves affect the risk of venous thromboembolism. There is some evidence that cardioprotective use of aspirin may be associated with a reduced risk of postoperative venous thromboembolism [16]. However, population-based data are limited [16], and it is not clear if the anti-platelet actions of the drug lead to decreased risks in other settings.

Statins are potent lipid-lowering drugs that are commonly used by patients with atherosclerosis to reduce cardiovascular risk. In addition to their antithrombotic effect, statins have anti-inflammatory and immunomodulatory influences and affect D-dimer levels [17–22]. The unexpected finding of a reduction in risk of venous thromboembolism with use of statins in the Heart and Estrogen/Progestin Replacement Study of postmenopausal women led to the working hypothesis that this class of drugs may reduce the risk of venous thromboembolism [23,24]. Findings from subsequent studies have generally supported such a protective effect [25–28], but one population-based study failed to find such an association [29] and another was inconclusive [15]. One study reported different associations for individual statin drugs [25].

To clarify these issues, we undertook a large population-based case–control study to investigate whether arterial cardiovascular events and use of statins and low-dose aspirin are associated with the risk of venous thromboembolism.

Material and methods

Study population and design

We conducted this population-based case–control study using medical databases from the counties of North Jutland and Aarhus, Denmark, which have a combined population of 1.1 million (approximately 20% of the total Danish population). We used the unique personal identifier assigned to each Danish citizen at birth to link records to individuals across the registries and databases [30]. Only cases and controls living in the study area continuously since 1977 were included to ensure a complete hospital history.

Cases with venous thromboembolism

To identify incident cases of venous thromboembolism for the years 1997–2005, we used computerized data from the county hospital registries since 1977, dates that correspond to the availability of complete computerized medication data in both counties (see below).

For each hospital admission since 1977 (and, since 1995, for all hospital specialist outpatient visits), the hospital registries have recorded the civil registration number of the patient, dates of admission and discharge, surgical procedure(s) performed and up to 20 diagnoses, classified according to the International Classification of Diseases (ICD), 8th revision until the end of 1993 and the 10th revision thereafter. We searched the hospital registries for codes for lower limb deep venous thrombosis and for pulmonary embolism (both primary and secondary diagnoses). We did not include patients with an out-patient diagnosis of pulmonary embolism without a subsequent inpatient diagnosis of venous thromboembolism, as a large proportion of these patients most likely had coding errors. In this way, we identified 5824 individuals with a first recorded diagnosis of venous thromboembolism (3823 deep venous thrombosis and 2001 pulmonary embolism); 5037 (86%) of these were inpatients.

In a second analysis, we focused on patients with primary (unprovoked) venous thromboembolism by excluding patients (n = 2458) with classic predisposing conditions: surgery, fractures, major trauma or pregnancy during the 3 months before the diagnosis of venous thromboembolism, as well as pre-existing cancer or a new cancer diagnosis within 3 months after venous thromboembolism [31]. These conditions were identified (and the corresponding patients excluded from analysis) through linkage to the hospital registries. For cases identified through inpatient records, we also excluded subjects whose venous thromboembolism was a secondary (i.e. not first listed) diagnosis for the venous thrombosis hospital encounter. This left 3366 adult patients (18–89 years) with residence in one of the two counties, diagnosed with primary incident venous thromboembolism, 2310 with venous thrombosis and 1056 with pulmonary embolism. 2811 (84%) of the primary venous thromboembolism patients were inpatients.

Population controls

We used the population registries of the two counties as a source of controls. These registries, updated daily, have maintained records on vital status (dead or alive), date of death and the residence of all Danish citizens since 1 April 1968 [30]. For each case with venous thromboembolism, we selected 10 population controls who were alive at the diagnosis date of the corresponding case (the index date) and without a hospital admission or outpatient visit with a venous thromboembolism diagnosis before that time. Controls were matched to cases using age (within 1 year), gender and county. The controls were thus selected using risk set sampling [each control is sampled for the risk set (the set of people in the source population who are at risk of venous thromboembolism at that time) for each case] [32] and assigned an index date identical to the venous thromboembolism admission date for the matched case. A total of 58 240 population controls were included in the study.

Data on cardiovascular disease, obesity and medication use

We scanned the hospital registries to ascertain whether the cases and controls had received a hospital diagnosis of myocardial infarction or stroke after 1 January 1977 and prior to the index date. In addition, we recorded information regarding prior hospital diagnoses of heart failure and obesity, which may be confounding factors as they are associated with atherosclerotic heart disease and also predispose to venous thromboembolism.

The two counties are served by pharmacies equipped with electronic accounting systems that are primarily used to secure reimbursement from the National Health Service [33,34]. The Health Service provides tax-supported health care for all inhabitants of Denmark, and refunds part of the cost of prescribed medications such as statins. In Denmark, cardioprotective aspirin (75 and 150 mg aspirin) is mainly provided on prescription, and so eligible for reimbursement. For each filled prescription, the patient's civil registration number, the type and amount of drug prescribed, according to the Anatomical Therapeutical Chemical classification system and the date of dispensing of the drug were transferred from the pharmacies to the prescription databases.

We used the population-based prescription databases of North Jutland (1989–2005) and Aarhus (1996–2005) counties to identify all prescriptions for statins and cardioprotective aspirin filled by cases and controls within 365 days before the date of hospital admission or outpatient visit with venous thromboembolism of the cases or the index date among controls. We defined 'current use' of statins as the filling of at least one prescription within 90 days before admission for venous thromboembolism or the corresponding date for controls, and 'former use' as the absence of recorded prescriptions within 90 days before admission/index date and the filling of at least one prescription within 91–365 days before.

From the prescription databases, we also ascertained current use of anti-psychotic medications and postmenopausal hormone replacement therapy as these drugs have been linked to an increased risk of venous thrombosis [3,4,15]. We also retrieved data regarding ever use of oral hypoglycaemic agents and insulin, as a marker of diabetes mellitus.

Statistical analysis

We assessed the association between prior diagnoses of atherosclerotic events and risk of venous thromboembolism using odds ratios (ORs) with 95% confidence intervals (CI) as a measure of relative risk computed by unconditional logistic regression with adjustment for the matching factors of age, gender and county.

We also fitted models with further adjustment for the potentially confounding factors listed in Tables 1–4. As we used risk set sampling of controls, these ORs are unbiased estimates of the corresponding rate ratios. We computed the ORs according to the time interval after the most recent cardiovascular event, and used polytomous logistic regression to determine if ORs differed for deep venous thrombosis and pulmonary embolism after adjustment for co-variates, age and gender. We used Wald statistics to compute *P*-values for the difference in risk between deep venous thrombosis and pulmonary embolism.

Results

Descriptive data are presented in Table 1 for the 5824 individuals with venous thromboembolism and 58 240 population controls. Slightly more than half of the cases and controls were female; less than half were older than 70 years (Table 1). Of the 5824 cases of venous thromboembolism, 3366 were unprovoked (Table 1). Their age and gender distribution was similar to that for the overall case group.

Relative risks associated with atherosclerotic cardiovascular events

Compared with controls, cases had a higher prevalence of previous hospitalizations for the atherosclerotic events studied. This was the case for both all venous thromboembolism and for those with an unprovoked presentation (Table 1). For all venous thromboembolism, the adjusted relative risk was 1.25 (95% CI: 1.10–1.42) for a history of myocardial infarction and 1.31 (95% CI: 1.17–1.48) for a history of stroke (Table 2). The corresponding risk estimates for unprovoked venous thromboembolism were similar. When we restricted the analysis to inpatients with venous thromboembolism and their controls, the risk estimates for the atherosclerotic events were slightly higher (data not shown). The adjusted relative risk for myocardial infarction (but not stroke) was slightly higher for pulmonary embolism than for deep venous thrombosis (Table 3).

The relative risk estimates for atherosclerotic disease differed according to the time before the venous thromboembolic events. Atherosclerotic events within 3 months before the index date conferred large increases in risk, with an adjusted relative risk of 4.22 (95% CI: 2.33–7.64) for myocardial infarction and 4.41 (95% CI: 2.92–6.65) for stroke. Myocardial infarction more than 3 months before the index date was not significantly associated with risk, although there was an adjusted relative risk of 1.29 (95% CI: 1.05–1.57) for myocardial infarction more than 60 months previously (Table 4). A history of stroke was associated with small increases in risk in each time interval after 3 months.

Relative risks associated with use of statins and aspirin

The prevalence of current use of statins was very similar among patients with venous thromboembolism (about 4%) and among population controls (about 4%) for both venous thrombosis case–control datasets. Likewise, approximately 7–8% of cases and controls were current users of low-dose aspirin. Without adjustment for previous cardiovascular events there was no association between statin use and venous thromboembolism (Table 2). However, a high proportion of statin users had a history of arterial cardiovascular events, which, as shown above, conferred an increased risk of venous thrombosis and pulmonary embolism.

Consequently, with adjustment for cardiovascular events, we found that current use of statins was inversely associated with a risk of both all venous thromboembolism [adjusted relative risk = 0.74 (95% CI: 0.63–0.85)] and unprovoked venous thromboembolism [adjusted relative risk = 0.79 (95% CI: 0.65–0.96)]. The risk for current use of statins was lower for patients with a recent myocardial infarction or stroke (within

Table 1 Characteristics of cases with venous thromboembolism and population controls

Variable	Characteristics of cases with venous thromboembolism and population controls		Characteristics of cases with unprovoked venous thromboembolism and population controls	
	Cases (%) n = 5824	Controls (%) n = 58 240	Cases (%) n = 3366	Controls (%) n = 33 560
Age				
≤ 54	1292 (22.2%)	12920 (22.2%)	846 (25.1%)	8460 (25.2%)
55–70	1747 (30.0%)	17470 (30.0%)	984 (29.2%)	9838 (29.3%)
71 +	2785 (47.8%)	27850 (47.8%)	1536 (45.6%)	15262 (45.5%)
Gender				
Females	3186 (54.7%)	31860 (54.7%)	1796 (53.4%)	17907 (53.4%)
Males	2638 (45.3%)	26380 (45.3%)	1570 (46.6%)	15653 (46.6%)
Current* use of statins	256 (4.4%)	2604 (4.5%)	130 (3.9%)	1352 (4.0%)
Former† use of statins	70 (1.2%)	685 (1.2%)	40 (1.2%)	335 (1.0%)
Current* use of low-dose aspirin	494 (8.5%)	4557 (7.8%)	276 (8.2%)	2413 (7.2%)
Former† use of low-dose aspirin	258 (4.4%)	1954 (3.4%)	129 (3.8%)	1070 (3.2%)
Previous hospital diagnosis of myocardial infarction	393 (6.8%)	2806 (4.8%)	217 (6.5%)	1556 (4.6%)
Previous hospital diagnosis of stroke	423 (7.3%)	2890 (5.0%)	221 (6.6%)	1494 (4.5%)
Previous hospital diagnosis of heart failure	398 (6.8%)	2179 (3.7%)	209 (6.2%)	1133 (3.4%)
Previous cancer‡	1161 (19.9%)	4814 (8.3)	-	-
Hospitalization or hospital clinic visit for surgery§	1662 (28.5%)	2171 (3.7%)	-	-
Hospitalization or hospital clinic visit for trauma or fracture§	461 (7.9%)	1058 (1.8%)	-	-
Pregnancy§	41 (0.7%)	116 (0.2%)	-	-
Current use of hormone replacement therapy	181 (3.1%)	1847 (3.2%)	85 (2.5%)	931 (2.8%)
Current use of anti-psychotics	281 (4.8%)	1496 (2.6%)	164 (4.9%)	864 (2.6%)
Current use of K-vitamin antagonists	147 (2.5%)	1068 (1.8%)	73 (2.2%)	552 (1.6%)
Hospitalization or hospital clinic visit for diabetes mellitus or use of antidiabetic medicine	452 (7.8%)	3191 (5.5%)	268 (7.7%)	1700 (4.9%)
Obesity	223 (3.8%)	853 (1.5%)	125 (3.7%)	470 (1.4%)

*Within 90 days before admission or index date among controls.
†Within 91–365 days before admission or index date among controls.
‡Pre-existing cancer or a cancer diagnosis within 3 months after venous thrombosis/index date.
§Three months before admission/index date.

3 months) [adjusted relative risk 0.47 (95% CI: 0.24–0.89)] than for patients with an earlier arterial event [adjusted relative risk 0.73 (95 CI: 0.57–0.93, P = 0.14)].

When we restricted the analysis to inpatient venous thromboembolism cases and their controls, the adjusted risk estimates for current use of statins were virtually identical.

As myocardial infarction/stroke and use of statins are strongly related, we also conducted an analysis restricted to persons without a history of cardiovascular events. In this group of subjects, the adjusted relative risk estimate was 0.75 (95% CI: 0.61–0.91) for current use of statins.

The statin relative risks differed slightly for deep venous thrombosis and pulmonary embolism (Table 3). After adjustment for a previous diagnosis of atherosclerotic events and multiple covariates, use of statins was associated with a 19% reduced risk of deep venous thrombosis (adjusted relative risk 0.81, 95% CI: 0.68–0.97) and a 39% reduction in risk of pulmonary embolism (adjusted relative risk 0.61, 95% CI: 0.48–0.78) (P = 0.05) (Table 3). Current use of each of the three individual statin drugs available in Denmark (simvastatin, pravastatin and atorvastatin) with more than five exposed cases was similarly associated with a reduced risk of venous thromboembolism. Overall, we did not find any substantial differences in the relative risks for statins and low-dose aspirin, between females and males (data not shown).

Use of low-dose aspirin was also common among patients with cardiovascular disease, and in unadjusted analyses, low-dose aspirin use was correspondingly associated with an increased risk of venous thrombosis. This disappeared after adjustment for vascular history (Tables 2 and 3). In an analysis restricted to persons without former cardiovascular events the adjusted relative risk was 0.98 (95% CI, 0.86–1.12).

Discussion

In this population-based case–control study, we found strong evidence that a hospital diagnosis of cardiovascular events was associated with a markedly increased risk of venous

Table 2 Relative risk estimates for venous thromboembolism for all cases with venous thromboembolism and unprovoked venous thromboembolism and their controls

	Relative risks* and 95% confidence intervals (CI) for venous thromboembolism		Relative risks* and 95% confidence intervals (CI) for unprovoked venous thromboembolism	
Variable	Unadjusted relative risk (95% CI)	Adjusted relative risk† (95% CI)	Unadjusted relative risk (95% CI)	Adjusted relative risk† (95% CI)
Previous hospital diagnosis of myocardial infarction	1.45 (1.29–1.61)	1.25 (1.10–1.42)	1.43 (1.23–1.66)	1.25 (1.06–1.46)
Previous hospital diagnosis of stroke	1.52 (1.36–1.69)	1.31 (1.17–1.48)	1.52 (1.31–1.77)	1.39 (1.19–1.62)
Current‡ use of statins	0.98 (0.86–1.12)	0.74 (0.63–0.85)	0.96 (0.80–1.15)	0.79 (0.65–0.96)
Former§ use of statins	1.02 (0.80–1.31)	0.70 (0.53–0.92)	1.19 (0.86–1.66)	0.97 (0.69–1.36)
Current‡ use of low-dose aspirin	1.10 (0.99–1.21)	0.96 (0.86–1.08)	1.16 (1.01–1.32)	1.03 (0.90–1.18)
Former§ use of low-dose aspirin	1.34 (1.17–1.53)	1.09 (0.94–1.27)	1.21 (1.00–1.46)	1.08 (0.89–1.31)

*Computed with unconditional logistic regression.
†Adjusted for use of anti-psychotic medications, postmenopausal hormone replacement therapy, K-vitamin antagonists, heart failure, diabetes, obesity, cancer, surgery, fractures, trauma, pregnancy, age, gender and the other variables in the table. Only fractures, surgery, trauma, pregnancy or delivery were included only within 3 months before case status or index date. Those diagnoses and cancer were not included in the analysis of unprovoked venous thromboembolism, because they are included in the definition of unprovoked venous thromboembolism.
‡Within 90 days before admission or index date among controls.
§Within 91–365 days before admission or index date among controls.

Table 3 Relative risk estimates for all cases with venous thrombosis and pulmonary embolism and their controls

	Relative risks and 95% confidence intervals (CI) for deep venous thrombosis		Relative risks and 95% confidence intervals (CI) for pulmonary embolism		
Variable	Unadjusted relative risk (95% CI)	Adjusted relative risk* (95% CI)	Unadjusted relative risk (95% CI)	Adjusted relative risk* (95% CI)	*P*-value†
Previous hospital diagnosis of myocardial infarction	1.22 (1.06–1.41)	1.08 (0.92–1.27)	1.85 (1.57–2.17)	1.57 (1.30–1.88)	0.001
Previous hospital diagnosis of stroke	1.54 (1.35–1.76)	1.34 (1.16–1.54)	1.47 (1.24–1.74)	1.27 (1.06–1.52)	0.61
Current‡ use of statins	1.04 (0.89–1.22)	0.81 (0.68–0.97)	0.89 (0.71–1.11)	0.61 (0.48–0.78)	0.05
Former§ use of statins	1.13 (0.84–1.51)	0.81 (0.60–1.11)	0.84 (0.54–1.30)	0.52 (0.33–0.82)	0.09
Current‡ use of low-dose aspirin	1.14 (1.01–1.28)	1.02 (0.89–1.16)	1.02 (0.87–1.20)	0.87 (0.73–1.04)	0.14
Former§ use of low-dose aspirin	1.27 (1.07–1.50)	1.07 (0.89–1.28)	1.46 (1.19–1.79)	1.13 (0.91–1.41)	0.68

*Computed with polytomous logistic regression, with adjustment for use of anti-psychotic medications, postmenopausal hormone replacement therapy, K-vitamin antagonists, heart failure, diabetes, obesity, cancer, surgery, fractures, trauma, pregnancy, age, gender and the other variables in the table. (Fractures, surgery, trauma, pregnancy or delivery were included only if they were within 3 months before the case diagnosis or control index date.) Those diagnoses and cancer were not included in the regression models for unprovoked venous thromboembolism, because they are excluded by the definition of unprovoked venous thromboembolism.
†*P*-values for comparison of the adjusted relative risk between deep venous thrombosis and pulmonary embolism.
‡Within 90 days before admission or index date among controls.
§Within 91–365 days before admission or index date among controls.

Table 4 Adjusted relative risk estimates* for unprovoked venous thromboembolism cases and their controls in relation to time since cardiovascular events

	Time before venous thromboembolism event		
	0–3 months	4–60 months	> 60 months
Myocardial infarction			
Cases, n = 217	18 (8.3%)	74 (34.1%)	125 (57.6%)
Controls, n = 1556	34 (2.2%)	646 (41.5%)	876 (56.3%)
Relative risks (95% CI)	4.22 (2.33–7.64)	1.01 (0.78–1.31)	1.29 (1.05–1.57)
Stroke			
Cases, n = 221	36 (16.3%)	102 (46.1%)	83 (37.6%)
Controls, n = 1494	73 (4.9%)	821 (54.9%)	600 (40.2%)
Relative risks (95% CI)	4.41 (2.92–6.65)	1.18 (0.95–1.46)	1.28 (1.01–1.62)

*Computed with unconditional logistic regression with adjustment for use of statins, low-dose aspirin, anti-psychotic medications, postmenopausal hormone replacement therapy, K-vitamin antagonists, diabetes, obesity, heart failure, age, gender and the other variables in the table.

thromboembolism in the 3 months after the cardiovascular event. The increased risk seems to extend beyond that accompanying hospitalization with stroke and perhaps myocardial infarction, but the associations were much weaker over the long term. Use of statins was associated with a reduced risk of venous thromboembolism, but low-dose aspirin was not.

Risk of venous thromboembolism in patients with atherosclerotic events

There is evidence that patients with venous thrombosis have an increased risk of subsequent myocardial infarction and stroke [11]. Our data provide some evidence for the converse: that cardiovascular events are a predictor of subsequent risk of venous thromboembolism, at least in the months after the cardiovascular event. These findings contrast with studies that reported no association between non-invasive markers of atherosclerosis and subsequent risk of venous thromboembolism [12,14]. However, in a subanalysis, one of these studies found a direct association between arterial cardiovascular and venous thrombotic events during follow-up [14], whereas the other found an inverse relation [12]. A case–control study from Britain found relative risk estimates similar to ours for the association of cardiovascular events with subsequent venous thromboembolism, but the analysis did not take into consideration time intervals before venous thromboembolism, and only found an association for pulmonary embolism [15]. We did not have data on smoking and confounding from the potentially shared common risk factors may explain the long-term elevated risk [35,36].

Statins, low-dose aspirin and venous thromboembolism

Our findings provide further evidence that the use of statins is inversely associated with the risk of venous thromboembolism [25–28]. Unlike Doggen *et al.* [25], we did not find any substantial differences in effect between simvastatin and pravastatin, or between men and women. (Doggen *et al.* [25] found the reduced risk to be confined to women using simvastatin.)

It is certainly possible that differences in characteristics between statin users and non-users (i.e. unmeasured confounding) can explain our findings [37]. However, the clinical trigger for use of statins is quite clear: hypercholesterolemia or a clinical cardiovascular event, and there are no compelling clinical indications for one drug or another. Hyperlipidemia may be discovered in the context of clinical atherosclerotic disease. As vascular disease is positively associated with the risk of venous thromboembolism, the direction of confounding by atherosclerotic disease in our study would be to also make statins positively associated with venous thromboembolism. The fact that we saw the opposite pattern strengthens the argument for a truly causal association. The mechanisms that might underlie any preventive effect of statins on venous thrombosis are not clear. However, there are suggestions that these drugs have anti-thrombotic, anti-inflammatory and immune modulating effects [17–22]. As a cardiovascular event is both an indication for statin use and also a risk factor for venous thromboembolism, it is difficult from our non-randomized study to draw firm inferences regarding the effect of statins on venous thromboembolism risk in patients with a previous arterial event, but our data suggested that a protective effect was present in both patients with and without a former arterial event.

Our data do not suggest that low-dose aspirin prevents venous thromboembolism, and so contradict the 25% risk reduction of pulmonary embolism reported in a large meta-analysis of 32 trials on antiplatelet therapy in cardiovascular prevention and other evidence found in high-risk groups [38]. One possible reason for the differences in findings is that we specifically studied the long-term effect of aspirin in a population setting, rather the short-term effect after acute events. Our findings are consistent with a recent randomized trial of healthy women, who did not report any effect of low-dose aspirin on venous thromboembolism [39].

Strengths and limitations

Several issues should be taken into consideration in the interpretation of our data. The main strengths of our study are its large size, the well-defined population, the uniformly organized health care system with complete population coverage and the use of appropriate controls. Further, we were able to link different population-based registries with complete data on outpatient visits, hospitalization and drug use. The universal provision of health care (including reimbursement for prescription medications) considerably reduces the likelihood that our findings are as a result of substantial confounding by social characteristics of statin users [34]. A potential weakness is that our data on venous thromboembolism were derived from discharge and outpatient diagnoses, which may not be entirely accurate. About 10–20% of the patients listed in the discharge registries with venous thromboembolism might not fulfill strict criteria for the disease, and the misclassification is most likely higher for outpatients [40,41]. However, the accuracy of the venous thromboembolism diagnosis is unlikely to differ by previous medication exposure and so any misclassification should bias the observed relative risk towards unity. The specificity of the discharge diagnosis of myocardial infarction, heart failure and stroke is reported to be high [42–44]. The cancer and procedure data we used to define provoked venous thromboembolism have high validity, making the specificity of this classification high [11,33].

Statins are officially recommended for Danish patients with myocardial infarction and stroke [45]. Our drug exposure data are left truncated (i.e. we have no information prior to 1989 in North Jutland County, 1996 in Aarhus County), but the use of statins in the study population was very limited before 1998 [46]. As suggested previously, statin users may be 'healthy users' [47], which means that they should be healthier than non-users. However, another study in our region has shown

that statin users have much higher cardiovascular morbidity, chronic pulmonary diseases and diabetes than non-users [48]. A similar pattern between users and non-users is found in our study (data not shown). Moreover, high proportions of statin users have a medical indication for statin use [48]. Therefore, severe social confounding by socioeconomic differences is unlikely in Denmark's universal health care system [34]. However, unknown or unmeasured risk factors may cause some uncontrolled confounding. The definition of current use of statins based on a 3-month window is artificial, as statin treatment is a life-long therapy for patients with atherosclerosis and discontinuation typically occurs in Denmark only because of side effects or non-adherence. This might explain the similar risk estimates for current and former use we obtained in some of our analysis. However, the 3-month window ensures that current users are in fact recently exposed to statins.

In conclusion, we find that patients with arterial events are at increased short-term risk of venous thromboembolism. Use of statins is inversely associated with a risk of venous thromboembolism, and thus might be an attractive preventive intervention, whereas low-dose aspirin does not seem to prevent venous thromboembolism. However, the efficacy of statins in this regard can only be proven through a randomized controlled trial [19,37].

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

Deep vein thrombosis ICD-8 451.00, ICD-10 I80.1-3
Pulmonary embolism ICD-8 450.99, ICD-10 I26.0, I26.9
Cancer ICD-8 140–209, ICD-10 C00–C99
Pregnancy or delivery ICD-8 630–680, ICD-10 O00–O99
Fractures, trauma ICD-8 800–929, 950-959, ICD-10 S00–T14
Stroke ICD-8 431–435, ICD-10 I61, I63, I64, I65, I66
Myocardial infarction ICD-8 410, ICD-10 I21
Heart failure ICD-8 42709, 42710, 42711, ICD-10 I50
Diabetes ICD-8 249, 250, ICD-10 E10, E11
Obesity ICD-8 277, ICD-10 E66
Antidiabetics A10A, A10B
Statins C10AA
Simvastatin C10AA01
Pravastatin C10AA03
Atorvastatin C10AA05
Low dose aspirin B01AC06
Postmenopausal hormone replacement therapy G03C
Anti-psychotics N05A
K-vitamin antagonists B01AA03, B01AA04

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Paper VI

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Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006

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BACKGROUND: Venous thromboembolism (VTE) frequently complicates cancer. Data on tumour-specific VTE predictors are limited, but may inform strategies to prevent thrombosis.

METHODS: We computed incidence rates (IRs) with 95% confidence intervals (CIs) for VTE hospitalisation in a cohort of cancer patients ($n = 57\,591$) and in a comparison general-population cohort ($n = 287\,476$) in Denmark. The subjects entered the study in 1997–2005, and the follow-up continued through 2006. Using Cox proportional-hazards regression, we estimated relative risks (RRs) for VTE predictors, while adjusting for comorbidity.

RESULTS: Throughout the follow-up, VTE IR was higher among the cancer patients (IR = 8.0, 95% CI = 7.6–8.5) than the general population (IR = 4.7, 95% CI = 4.3–5.1), particularly in the first year after cancer diagnosis (IR = 15.0, 95% CI = 13.8–16.2, *vs* IR = 8.6, 95% CI = 7.6–9.9). Incidence rates of VTE were highest in patients with pancreas (IR = 40.9, 95% CI = 29.5–56.7), brain (IR = 17.7, 95% CI = 11.3–27.8) or liver (IR = 20.4, 95% CI = 9.2–45.3) tumours, multiple myeloma (IR = 22.6, 95% CI = 15.4–33.2) and among patients with advanced-stage cancers (IR = 27.7, 95% CI = 24.0–32.0) or those who received chemotherapy or no/symptomatic treatment. The adjusted RR (aRR) for VTE was highest among patients with pancreas (aRR = 16.3, 95% CI = 8.1–32.6) or brain cancer (aRR = 19.8 95% CI = 7.1–55.2), multiple myeloma (aRR = 46.1, 95% CI = 13.1–162.0) and among patients receiving chemotherapy, either alone (aRR = 18.5, 95% CI = 11.9–28.7) or in combination treatments (aRR = 16.2, 95% CI = 12.0–21.7).

CONCLUSIONS: Risk of VTE is higher among cancer patients than in the general population. Predictors of VTE include recency of cancer diagnosis, cancer site, stage and the type of cancer-directed treatment.

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Since Trousseau's observation in 1865 (Trousseau, 1865), venous thromboembolism (VTE) has been widely documented as a serious complication of malignancy (Rickles and Levine, 2001; Prandoni *et al*, 2005; Blom *et al*, 2006b). Factors implicated include tumour-induced hypercoagulability; vascular injury caused by tumour, treatment or surgery; and, among bed-ridden cancer patients, venous stasis due to immobilisation (Gouin-Thibault *et al*, 2001; Prandoni *et al*, 2005; Zwicker *et al*, 2009).

The identification of factors associated with the incidence and clinical time-course of VTE in cancer patients compared with the general population is fundamental for further understanding of the association between cancer and VTE, and potentially prevent the occurrence of VTE. Risk factors for VTE include cancer type (adenocarcinomas of the viscera, brain and urogenital cancers); advanced stage; and cancer therapies, such as chemotherapy and surgery (Otten *et al*, 2004; Chew *et al*, 2006; Ogren *et al*, 2006; Stein *et al*, 2006; Khorana *et al*, 2007; Rodriguez *et al*, 2007). Although there is evidence that cancer patients have twice the risk of VTE compared with non-cancer patients undergoing the same surgical procedures (Rickles and Levine, 2001), few investigations have directly compared VTE incidence in cancer patients with cancer-free members of the general-population (Blom *et al*, 2006b; Heit *et al*, 2001; White *et al*, 2007). None of the previous studies were able to implement matching, which, in cohort studies, enables control of potential confounding at the design stage.

We took advantage of Danish population-based registries to conduct a study of predictors of VTE, including cancer site, stage, treatment and time since diagnosis, in cancer patients using a matched cohort design with prospectively collected data, a task which is prohibitively expensive in conventional epidemiological settings.

MATERIALS AND METHODS

Study population

We conducted this cohort study among individuals aged ⩾15 years residing in northern Denmark (1.8 million inhabitants).

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In Denmark, all medical records are tracked for individual patients using their civil personal registration number—a unique identifier encoding sex and date of birth—assigned to all Danish residents since 1968. Using the civil personal registration number, we linked data from the Danish National Registry of Patients (DNRP), the Danish Cancer Registry (DCR) and the Danish Civil Registration System (Andersen *et al*, 1999; Frank, 2000; Pedersen *et al*, 2006).

The DNRP has tracked acute non-psychiatric hospitalisations since 1977 and outpatient and emergency-room visits since 1995; diagnoses have been coded using the eighth revision of the International Classification of Diseases (ICD-8 (Sundhedsstyrelsen, 1986)) through 1993 and the tenth revision (ICD-10 (Sundhedsstyrelsen, 1993)), thereafter. Information is recorded immediately after discharge or outpatient visit and includes admission and discharge dates, and up to 20 diagnoses (Andersen *et al*, 1999). We obtained complete hospital history (including VTE) for the cancer and general-population cohorts and linked the resulting data set to records in the Civil Registration System, which tracks vital status and migration nationwide.

Cancer cohort

From the DNRP, we identified individuals in the study area with a first cancer diagnosis, excluding non-melanoma skin cancer (ICD-10 codes: C00-C97.9) recorded between January 1, 1997 and December 31, 2005. We chose this period to ensure homogeneity of VTE diagnostic procedures (for example, ultrasound for deep vein thrombosis) for the included cancer patients (Lensing *et al*, 1989). The date of cancer diagnosis was that specified in the DNRP. We eliminated cases ($\sim$6%) for which a hospital diagnosis did not correspond to an incident cancer recorded at the same site in the DCR. All Danish cancer cases are reportable to the DCR and recorded using the ICD-7 (seventh revision) since 1943 and ICD-O (oncology revision) since 1977. The DCR is over 95% complete and has almost 100% validity (Storm *et al*, 1997). For cancers diagnosed in 2004–2005, we included patients with cancers recorded in the DNRP only because DCR records were not available for this period.

Because VTE can indicate undiagnosed cancer (Baron *et al*, 1998; Sorensen *et al*, 1998), we excluded cancer patients diagnosed with VTE in the year before their cancer diagnosis ($n = 124$) from all analyses.

General-population cohort

We used the Civil Registration System to assemble a general-population comparison cohort (Frank, 2000). For each patient with cancer, we randomly selected five general-population members from a pool of individuals who were alive and free of cancer on the date of the matched person's cancer diagnosis as recorded in the DNRP (the index date), matched on birth year, sex and county of residence.

To maintain comparability of the cohorts, we also excluded from the pool of the general-population members available for matching persons who had been diagnosed with VTE in the year before the index date.

Tumour predictors of VTE

In sub-analyses limited to cancer patients and their matched comparison group diagnosed while DCR records were available (<2004), we ascertained information on cancer site from the DCR. The DCR records data on cancer stage and treatment administered within 4 months of diagnosis (initial treatment). We classified cancer stage according to Tumour Node Metastasis stages I, II, III, IV and unknown. To examine VTE incidence by treatment and stage, we conducted a sub-analysis, including patients with records in the DCR and DNRP through 2003 and their matched members of the general-population, yielding a 6-year maximum follow-up.

Comorbidity data

We used the DNRP to retrieve information on history of inpatient diagnoses of potential confounding diseases. We ascertained the following diagnoses: myocardial infarction (ICD-8:410; ICD-10:I21), congestive heart failure (ICD-8:427; ICD-10:I50.0), atherosclerosis and peripheral vascular disease (ICD-8:440; ICD-10:I73), chronic obstructive pulmonary disease (ICD-8:491; ICD-10:J44), inflammatory bowel disease (ICD-8:563; ICD-10:K50–K52), peptic ulcer disease (ICD-8:531–533; ICD-10:K27), liver disease (ICD-8:570–573; ICD-10:K70–K77), renal disease (ICD-8:400–404; ICD-10:I10–I15), diabetes (ICD-8:249 and 250; ICD-10:E10–E14), obesity (ICD-8:277; ICD-10:E66), pancreatitis (ICD-8:577.00–577.09; ICD-10:K85), alcoholism and alcoholism-related conditions (ICD-8:291–303; ICD-10:F10) and hypertension (ICD-8:400–404; ICD-10:I10–I15).

VTE data

Individuals were followed-up from the cancer diagnosis/index date until an inpatient VTE diagnosis, death, emigration or 31 December 2006, whichever came first, or until cancer diagnosis for members of the general-population cohort, for 9 years maximum follow-up. We did not include individuals with an outpatient or emergency-room VTE diagnosis without a subsequent inpatient diagnosis, because such diagnoses were likely to represent coding errors (Severinsen *et al*, 2010). We used all diagnosis fields in the DNRP to identify VTE events that occurred after cancer diagnosis/index date and included pulmonary embolism (ICD-10: I26), phlebitis and thrombophlebitis (deep vein thrombosis or superficial thrombosis—ICD-10: I80) and other venous embolism and thrombosis (ICD-10: I81 and I82).

Statistical analyses

We computed crude incidence rates (IRs) of hospitalisation for VTE as the number of cases per 1000 person-years (p-y) and associated 95% confidence intervals (CI) for the cancer and general-population cohorts. Among the cancer patients, we estimated VTE incidence by patient, tumour and treatment characteristics and by time since cancer diagnosis. Incidence rates were compared using the Poisson distribution; two-sided *P*-values <0.05 were considered statistically significant. We compared IRs of VTE between men and women for cancers that affect both men and women. To describe time to and absolute risk of VTE, we constructed Nelson–Aalen plots using product-limit methods (Ludbrook and Royse, 2008) illustrating cumulative incidence for VTE in select cancers.

We used Cox proportional-hazards regression to estimate the hazard ratio as a measure of the relative risk (RR) of VTE among cancer patients compared with the general-population, adjusting for comorbidity. For the analysis of time since diagnosis, additional adjustment for age and sex was done in the regression model to account for any age and sex imbalances potentially produced by differences in the cohort composition after the diagnosis/index date. We examined the RR of 'provoked' and 'unprovoked' VTE by stratifying our analyses by the receipt of surgery within 90 days before the VTE diagnosis (Glynn and Rosner, 2005).

In an analysis restricted to the cancer patients, we also computed RRs to assess the association between VTE risk and cancer site, stage and initial treatment, adjusting for age, sex, county and comorbidity using colon cancer as a reference group. Cox proportional-hazards regression was also used to examine

whether any cancer site-related differences were explainable by stage and/or treatment.

RESULTS

Descriptive data

We identified 57 591 incident cancer cases diagnosed between 1997 and 2005 and matched 287 476 individuals without cancer from the general-population (Table 1). Follow-up spanned 127 492 p-y for the cancer cohort (median: 1.23 p-y) and 1 087 946 p-y for the general-population cohort (median: 3.46 p-y). The most common cancer sites were the colorectum, lung and breast, each representing approximately 14% of all cancers. There were slightly more women than men in the study sample (52 versus 48%) and 69% of the sample were aged at least 60 years at cancer diagnosis/ index date.

Incidence rate of hospitalisation for VTE

The overall IR of VTE in cancer patients was 8.0 cases per 1000 p-y (95% CI = 7.6–8.5, Table 2). Incidence was highest during the first year following cancer diagnosis (15.0 cases per 1000 p-y, 95% CI = 13.8–16.2), declining to 6.3 cases per 1000 p-y (95% CI = 5.4–7.3) during the second year following cancer diagnosis and to 4.2 cases per 1000 p-y (95% CI = 3.7–4.7) thereafter (Supplementary Table 2). For cancers that affect men and women, the rate of VTE in men (IR = 10.0 cases per 1000 p-y, 95% CI = 9.1–11.0) was very similar to that in women (IR = 10.1 cases per 1,000 p-y, 95% CI = 9.1–11.3), ($P = 0.99$).

The cumulative incidence of VTE after cancer diagnosis initially rose sharply, with a diminishing rate of increase over subsequent years (Figure 1). Overall, during the first year of follow-up, VTE was diagnosed in 1.4% of cancer patients and in 0.2% of the general-population cohort, and this difference varied by cancer site (e.g., 4.4% for pancreas and 0.7% for breast *vs* 0.3 and 0.1% in the general-population comparators for these cancers, respectively). VTE IRs were highest for patients with pancreas, liver, lung, ovary and brain cancers, and for multiple myeloma (Supplementary Table 2). Overall, the IRs of VTE were higher in the first year after the index date than in subsequent years. However, for some cancer sites (pancreas, liver and lung) the CIs associated with rates in the first year overlapped with those associated with rates in subsequent years.

RR of VTE among cancer patients compared with the general population

Overall, the risk of VTE was higher among cancer patients than in the general population, after adjustment for comorbid conditions

Table 1 Characteristics of the cancer and general-population cohorts and the distribution of incident hospitalisation for VTE (Danish National Registry of Patients, 1997–2005)

	Cancer patients			General-population cohort		
Characteristic	**Total number**	**VTE number (%)[a]**	**Observation time, person-years**	**Total number**	**VTE number (%)[a]**	**Observation time, person-years**
Overall	57 591	1023 (1.8%)	127 492	287 476	2204 (0.8%)	1 087 946
Sex						
Female	30 060	527 (1.8%)	74 825	150 078	1088 (0.7%)	592 092
Male	27 531	496(1.8%)	52 667	137 398	1116 (0.8%)	495 854
Age at diagnosis, years						
<50	7356	105 (1.4%)	24 427	36 792	82 (0.2%)	158 635
50–59	10 262	215 (2.1%)	27 337	51 231	204 (0.4%)	215 803
60–69	14 231	305 (2.1%)	31 885	71 143	502 (0.7%)	285 230
70–79	16 068	271 (1.7%)	30 405	80 181	882 (1.1%)	291 450
80–89	8702	119 (1.4%)	12 504	43 245	497 (1.1%)	126 419
90+	972	8 (0.8%)	935	4884	37 (0.8%)	10 409
Cancer site						
Oesophagus	938	14 (1.5%)	872	4682	29 (0.6%)	17 155
Stomach	1172	18 (1.5%)	1417	5851	61 (1.0%)	21 933
Colon	5595	126 (2.3%)	13 252	27 922	230 (0.8%)	100 694
Rectum	2778	55 (2.0%)	7361	13 866	113 (0.8%)	52 623
Liver	550	6 (1.1%)	295	2746	11 (0.4%)	10 216
Pancreas	1671	36 (2.2%)	881	8342	80 (1.0%)	30 467
Lung	7975	127 (1.6%)	7872	39 810	336 (0.8%)	151 350
Breast	8586	119 (1.4%)	30 391	42 869	234 (0.5%)	171 760
Cervix	1019	16 (1.6%)	3499	5090	24 (0.5%)	22 341
Endometrium	1453	22 (1.5%)	5049	7258	59 (0.8%)	28 604
Ovary	1534	49 (3.2%)	4066	7663	48 (0.6%)	31 828
Prostate	4457	98 (2.2%)	9757	22 230	219 (1.0%)	70 899
Kidney	1376	12 (0.9%)	2972	6864	37 (0.5%)	25 538
Urinary bladder	2445	62 (2.5%)	5980	12 205	116 (1.0%)	45 436
Brain	1133	19 (1.7%)	1071	5653	37 (0.7%)	21 685
Hodgkin lymphoma	336	6 (1.8%)	1143	1680	4 (0.2%)	6851
Non-Hodgkin lymphoma	2003	47 (2.3%)	4788	9999	79 (0.8%)	38 013
Leukaemia	1516	41 (2.7%)	2943	7567	66 (0.9%)	28 060
Multiple myeloma	643	26 (4.0%)	1149	3211	30 (0.9%)	11 972
Bone	229	4 (1.4%)	541	1143	7 (0.6%)	4709

Abbreviation: VTE = venous thromboembolism. [a]VTEs which occurred in the year before cancer diagnosis/ index date were excluded.

Table 2 IRs of hospitalisation for VTE per 1000 person-years in the cancer cohort

Characteristic	IR (95% CI)	aRR (95% CI)
Overall	8.0 (7.6–8.5)	4.7 (4.3–5.1)
Sex		
Female	7.0 (6.5–7.7)	4.8 (4.2–5.4)
Male	9.4 (8.6–10.3)	4.6 (4.1–5.3)
Age, years		
<50	4.3 (3.6–5.2)	8.7 (6.2–12.2)
50–59	7.9 (6.9–9.0)	9.6 (7.6–12.2)
60–69	9.6 (8.6–10.7)	5.6 (4.7–6.6)
70–79	8.9 (7.9–10.0)	3.1 (2.7–3.7)
80–89	9.5 (8.0–11.4)	2.9 (2.3–3.7)
90+	8.6 (4.2–17.1)	3.0 (1.1–8.7)
Cancer site		
Oesophagus	16.1 (9.5–27.1)	11.6 (3.8–35.0)
Stomach	12.7 (8.0–20.2)	8.9 (3.8–20.7)
Colon	9.5 (8.0–11.3)	4.8 (3.7–6.2)
Rectum	7.5 (5.7–9.7)	4.0 (2.8–5.9)
Liver	20.4 (9.2–45.3)	—[a]
Pancreas	40.9 (29.5–56.7)	16.3 (8.1–32.6)
Lung	16.1 (13.6–19.2)	8.0 (6.0–10.7)
Breast	3.9 (3.3–4.7)	3.3 (2.6–4.2)
Cervix	4.6 (2.8–7.5)	10.8 (4.2–28.1)
Endometrium	4.4 (2.9–6.6)	2.2 (1.1–3.9)
Ovary	12.1 (9.1–15.9)	10.1 (6.1–16.7)
Prostate	10.0 (8.2–12.2)	3.1 (2.4–4.1)
Kidney	4.0 (2.3–7.1)	2.7 (1.1–6.6)
Urinary bladder	10.4 (8.1–13.3)	4.5 (3.1–6.4)
Brain	17.7 (11.3–27.8)	19.8 (7.1–55.2)
Hodgkin Lymphoma	5.3 (2.4–11.7)	9.7 (2.3–41.3)
Non-Hodgkin Lymphoma	9.8 (7.4–13.1)	6.6 (4.2–10.5)
Leukaemia	13.9 (10.3–18.9)	9.1 (5.3–15.8)
Multiple Myeloma	22.6 (15.4–33.22)	46.1 (13.1–162.0)
Bone	7.4 (2.8–19.7)	9.7 (0.7–130.9)

Abbreviations: aRR = adjusted relative risk; CI = confidence interval; IR = incidence rate; VTE = venous thromboembolism. Cox proportional hazards regression models computing the adjusted relative risks (aRRs) (Adjusted for myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, peptic ulcer disease, liver disease, renal disease, diabetes, obesity, acute pancreatitis, alcoholism and hypertension when the number of VTE events for a given comorbidity was sufficient) of hospitalisation for VTE in the cancer cohort compared with the general-population (Danish National Registry of Patients, 1997–2005). *Please see Supplementary Information for IR and RR by time since diagnosis/index date.* [a]Too few VTE events to estimate incidence.

(adjusted RR (aRR) = 4.7, 95% CI = 4.3–5.1) (Table 2). The aRR of VTE declined with increasing age at diagnosis, particularly for events during the first year after cancer diagnosis (aRR = 21.0, 95% CI = 11.0–39.9 among those aged <50 years *vs* aRR = 7.0, 95% CI = 1.7–29.6 among those aged at least 90 years) ($P = 0.14$) (Supplementary Table 2). The aRR of VTE varied by cancer site, with higher RRs for oesophagus, pancreas and brain cancers or multiple myeloma and lower RRs for breast, endometrial and kidney cancer. For most cancer sites, the aRRs of VTE were higher during the first and second years of follow-up than in subsequent years. Surgery within 90 days of VTE conferred a significantly increased risk of VTE (see Supplementary Table 5). This was true for all years of follow-up.

Cancer stage, treatment, site and risk of VTE

Our sub-analysis of patients with cancer records in both the DCR and DNRP included 40 994 cancer patients diagnosed between 1997 and 2003 (comprising 91.3% of cases identified in the DNRP during this period) and their 204 970 matched cancer-free members of the general-population. The effect of cancer on VTE risk increased with advancing tumour stage (aRR (95% CI) = 2.9 (1.5–5.5); 2.9 (2.4–3.5); 7.5 (6.0–9.4); and 17.1 (12.6–23.3) among patients with stage I, II, III and IV disease, respectively, Table 3).

VTE IRs were highest among patients who received initial treatment of either chemotherapy alone or no/symptomatic treatment compared with patients treated with any other regimen or combination therapy (Table 3). After adjusting for comorbidity, age and sex, relative to the general-population cohort, VTE risk in cancer patients was strongest in those treated with any chemotherapy-containing regimen as part of initial cancer treatment (aRR = 18.5, 95% CI = 11.9–28.7 for chemotherapy alone and aRR = 16.2, 95% CI = 12.0–21.7 for chemotherapy combined with other treatments). VTE risk among patients who received chemotherapy within 4 months of cancer diagnosis remained substantially elevated during the first 2 years after cancer diagnosis, whereas it diminished substantially after the first year among patients treated with radiotherapy or surgery (Supplementary Table 3).

In the cancer cohort only, we examined the RR of VTE for tumour site, stage and treatment, while adjusting for sex, age, county and comorbid conditions. Compared with colon cancer, VTE risk was higher for brain, liver, ovary and pancreas cancers and lower for breast cancer and melanoma after controlling for stage and treatment (Supplementary Table 4). Likewise, chemotherapy was associated with a higher VTE risk compared with no/symptomatic treatment. VTE risk increased markedly with advancing stage.

DISCUSSION

We found that cancer patients had a greater risk for hospitalisation with VTE (1.8%) than cancer-free members of the general population (0.8%). The overall incidence of VTE in the cancer cohort is consistent with that reported in other studies (1.2% within the first 6 months; 1.6% within the first 2 years and 2.0% over all years of follow-up after cancer diagnosis (Blom *et al*, 2006a; Chew *et al*, 2006; Stein *et al*, 2006). VTE risk was increased over eight-fold during the first year following cancer diagnosis, over three-fold during the second year and over two-fold during subsequent years. In addition to survival time, strong predictors of VTE were cancer site, stage and type of initial cancer treatment.

The cancers we found associated with especially high rates of VTE (pancreas, liver, brain and multiple myeloma) are consistent with other research (Baron *et al*, 1998; Levitan *et al*, 1999; Blom *et al*, 2005; Blom *et al*, 2006b; Chew *et al*, 2006). Pancreas cancer has been associated with a high VTE risk (Chew *et al*, 2006; Ogren *et al*, 2006). Although it is frequently metastatic at diagnosis and may be associated with VTE on that basis alone, it has been suggested that an unknown VTE risk factor inherent to pancreas cancer may further increase risk (Ogren *et al*, 2006).

An important finding of our study is the high VTE risk associated with multiple myeloma, consistent with some published findings (Blom *et al*, 2006b; Khorana *et al*, 2007). New treatments for myeloma emerged during the period of our analysis, including the anti-angiogenic agents thalidomide and lenalidomide (Hales, 1999; Singhal *et al*, 1999). Recent reports suggest that thromboprophylaxis in myeloma patients may decrease the risk of VTE associated with these treatments (Knight *et al*, 2006; Falanga and Marchetti, 2009).

We confirmed the findings from Keenan and White, who concluded no evidence of a sex difference in VTE incidence either during hospitalisation or in the first year following cancer diagnosis (Keenan and White, 2007). Similar to our findings, studies show a decline in the overall IR of VTE in cancer patients with longer follow-up (Blom *et al*, 2005; Chew *et al*, 2006; White *et al*, 2007). Despite this, the excess risk of VTE in the cancer

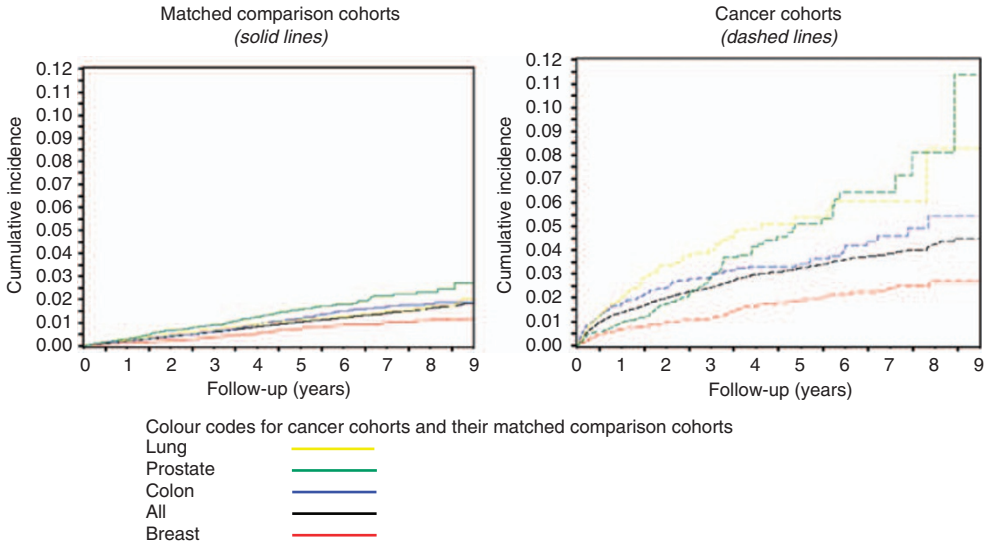

Figure 1 Cumulative incidence of hospitalisation for venous thromboembolism (VTE) in the cancer and general-population cohorts overall and for the four most common cancer types (Danish National Registry of Patients, 1997–2005).

Table 3 IRs of hospitalisation for VTE[a] per 1000 person-years in the cancer cohort ($n = 40\,994$) and aRRs[b] of hospitalisation for venous thromboembolism in the cancer cohort compared with the general-population ($n = 204\,970$) (DCR, 1997–2003)[c]

Characteristic	N	IR (95% CI)	aRR[b] (95% CI)
Cancer stage[c]			
Stage I	1240	44 (2.7–7.1)	2.9 (1.5–5.5)
Stage II	14520	44.9 (4.0–5.7)	2.9 (2.4–3.5)
Stage III	10499	11.1 (9.7–12.7)	7.5 (6.0–9.4)
Stage IV	9125	27.7 (243.0–32.0)	17.1 (12.6–23.3)
Unspecified	5610	12.2 (10.1–14.8)	5.6 (4.1–7.5)
Treatment[c,d]			
No/symptomatic	8565	20.8 (17.3–25.0)	8.4 (6.2–11.4)
Chemotherapy only	3026	23.1 (19.0–28.1)	18.5 (11.9–28.7)
Radiation only	2512	10.1 (7.2–14.1)	8.9 (5.0–16.0)
Surgery only	16564	6.5 (5.7–7.3)	3.2 (2.7- 3.8)
Other[e]	781	13.4 (7.6–23.7)	6.0 (2.3–15.6)
Combination therapy	8625	8.5 (7.3–9.9)	8.6 (6.7–11.1)
Unspecified	921	9.2 (4.8–17.6)	5.8 (2.1–16.6)
Treatment including[c]			
No/symptomatic	8565	20.8 (17.3–25.0)	8.4 (6.2–11.4)
Chemotherapy	7154	14.0 (12.2–16.2)	16.2 (12.0–21.7)
Radiation	6943	8.2 (6.8–9.9)	7.9 (5.8–10.7)
Surgery	24525	7.0 (6.3–7.7)	4.1 (3.6- 4.7)
Other[e]	781	13.4 (7.6–23.7)	6.0 (2.3–15.6)
Unspecified	921	9.2 (4.8–17.6)	5.8 (2.1–16.6)

Abbreviations: aRR = adjusted relative risk; CI = confidence interval; DCR = Danish Cancer Registry; IR = incidence rate; VTE = venous thromboembolism. Please see Supplementary Information for IR and RR by time since diagnosis/index date. [a]We excluded VTEs that occurred in the year before diagnosis/ index date. [b]Adjusted for age, sex, myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, peptic ulcer disease, liver disease, renal disease, diabetes, obesity, acute pancreatitis, alcoholism and hypertension when the number of VTE events for a given comorbidity was sufficient. [c]To obtain data on cancer stage and treatment, analyses are based on cancer patients in the DCR and their matched members of the general-population cohort. [d]Mutually–exclusive treatment categories [e]Others describe treatment other than chemotherapy, radiation and/or surgery. This includes cryocoagulation, anti-hormone therapy and other treatments not further specified.

cohort compared with the general population prevailed throughout follow-up possibly because of patient, cancer and treatment related factors. A study of ovarian cancer patients suggested that early thrombotic events were associated with cancer treatment, whereas later events correlated with older age, a history of thrombosis, advanced stage and residual disease (Rodriguez *et al*, 2007).

The greater overall excess risk of VTE among cancer patients with advanced stage in our study agrees with other studies (Blom *et al*, 2006b; Chew *et al*, 2006; Rodriguez *et al*, 2007), and was evident even after adjusting for cancer site. Furthermore, our findings clearly showed that chemotherapy is a predictor of VTE in cancer patients, as has been reported (Otten *et al*, 2004; Blom *et al*, 2006b; Khorana *et al*, 2007). This excess risk was evident even after adjusting for cancer site and stage.

Regarding surgery, White *et al.* (2007) reported that patients surgically treated for cancers of the colon, breast and ovary had the lowest VTE incidence within 3 months of diagnosis compared with patients with cancer at other sites, whereas those with gliomas had the highest incidence in that time period. Although elevated relative to the general population, in our study the IR associated with surgery was not as high as that for chemotherapy. However, surgery is not a treatment option for all cancers (e.g., haematological cancers or those metastatic at diagnosis). Surgical patients may also have received post-surgical thromboprophylaxis (White *et al*, 2007), may have been selected for better performance status and overall health status, and/or may have had non-advanced (thus operable) disease at diagnosis. If true, these factors would decrease the apparent VTE risk among surgical patients.

Recent surgery is a strong transient risk factor for VTE, denoted 'provoked VTE' (Glynn and Rosner, 2005; Huerta *et al*, 2007). Our findings regarding such 'provoked VTE' concur with those of Huerta and colleagues (Huerta *et al*, 2007), who reported a nine-fold excess risk of VTE among individuals who had surgery up to 6 months before VTE diagnosis.

Strengths of our study include prospectively collected data and complete follow-up, reducing selection bias. Cancer diagnoses recorded in the DCR and DNRP have a high validity (Storm, 1988). We had a large sample size, enabling the study of many cancers, including rare cancers, such as multiple myeloma. Inability to examine rare cancers has been a limitation of other, smaller, studies (Heit *et al*, 2001; Blom *et al*, 2005).

Limitations of our study include lack of clinical characteristics and personal detail regarding the subjects. In particular, our findings may have been affected by unmeasured confounding by VTE risk factors, such as post-menopausal hormone replacement therapy and thromboprophylaxis, which could contribute to or diminish the observed cancer effect on risk of VTE. We relied

on recorded registry diagnoses, which are not perfect. VTE diagnosis in the DNRP has an estimated positive predictive value of 75% (95% CI = 71.9–77.9%) (Severinsen *et al*, 2010). Our outcome variable, VTE, includes upper extremity VTE, which has no dedicated ICD code (Sundhedsstyrelsen, 1993) and can occur as a complication of indwelling catheters in cancer patients (Bernardi *et al*, 2001). However, most patients have VTE at sites other than the upper extremities (Arcelus *et al*, 2003). Our inclusion of superficial venous thrombosis may have contributed to the elevated IRs associated with cancer treatment and in the first year after cancer diagnosis because superficial venous thrombosis may result from venous catheters associated with chemotherapy or surgery. Cancer patients may have received heightened surveillance for VTE, leading to surveillance bias and inflating our VTE RR estimates. Such bias is unlikely to extend beyond 1 year of follow-up; when most cancer patients receive active treatment and close medical observation (Rodriguez *et al*, 2007).

The DCR records treatment administered within 4 months of diagnosis. Therefore, if a treatment increases VTE risk and is administered over 4 months after cancer diagnosis, we may have underestimated its impact. A 'watchful waiting' strategy (where treatment was administered on appearance of symptoms) may explain the consistently high excess risk of VTE among prostate cancer patients throughout follow-up, whereas VTE risk associated with many other cancers declined over time.

Our study furthers the understanding of the association between cancer and VTE. Within the cancer cohort, the elevated risk of VTE for some cancer sites, even after adjusting for cancer treatment, stage, age, sex and potential confounding diseases, suggests that increased VTE occurrence is an inherent biological property of some tumours (e.g., brain and pancreas cancers).

In cancers associated with a slightly elevated risk of VTE compared with the general population (e.g., breast cancer), VTE may be attributable to cancer-directed treatment or stage (Stein *et al*, 2006; Hernandez *et al*, 2009). VTE may also be related to the biological aggressiveness of the malignant process in general as suggested by the elevated risk of VTE in all patients with advanced stage. However, cancer patients are also likely to be burdened with increased medical intervention and forced sedentary lifestyle, factors that would increase the VTE risk. Nonetheless, in our study, even patients with early-stage cancer had increased VTE risk relative to the general population. The increased risk persisted among patients who received treatments other than chemotherapy or no/symptomatic treatment and remained elevated throughout follow-up. These findings suggest that some factors underlying the association between VTE and cancer are present even at the earliest stages of disease. The likely multi-factorial mechanism for increased VTE risk in cancer patients remains to be elucidated (Kakkar, 2010).

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Author contributions HTS and JA conceived the study idea and designed the study. HTS and LAP collected the data. LAP, DPCF, JAB and HTS planned and performed the analyses. DPCF reviewed the literature and drafted the paper. DPCF, JPF, KC, JA, JAB and HTS edited the paper.

Disclosures

DPCF, FS, LP, JPF and JAB have no conflicts of interest. KC and JA are employees of Amgen Incorporated. Dr HT Sørensen did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various other companies as research grants to (and administered by) Aarhus University. None of these other studies have relation with the present study.

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Paper VII

Heart Disease May Be a Risk Factor for Pulmonary Embolism Without Peripheral Deep Venous Thrombosis

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Background—Heart diseases increase the risk of arterial embolism; whether they increase the risk of pulmonary embolism without peripheral venous thrombosis is less certain.

Methods and Results—We conducted a nationwide, population-based case-control study in Denmark using patients diagnosed with pulmonary embolism and/or deep venous thrombosis between 1980 and 2007. We computed odds ratios to estimate relative risks associating preceding heart disease with pulmonary embolism, pulmonary embolism and deep venous thrombosis, or deep venous thrombosis alone. In this study, 45 282 patients had pulmonary embolism alone, 4680 had pulmonary embolism and deep venous thrombosis, and 59 790 had deep venous thrombosis alone; 541 561 were population controls. Myocardial infarction and heart failure in the preceding 3 months conferred high risks of apparently isolated pulmonary embolism (odds ratio, 43.5 [95% confidence interval (CI), 39.6–47.8] and 32.4 [95% CI, 29.8–35.2], respectively), whereas the risks of combined pulmonary embolism and deep venous thrombosis (19.7 [95% CI, 16.0–24.2] and 22.1 [95% CI, 18.7–26.0], respectively) and deep venous thrombosis alone (9.6 [95% CI, 8.6–10.7] and 12.7 [95% CI, 11.6–13.9], respectively) were lower. Left-sided valvular disease was associated with an odds ratio of 13.5 (95% CI, 11.3–16.1), whereas the odds ratio was 74.6 (95% CI, 28.4–195.8) for right-sided valvular disease. Restricting the analysis to cases diagnosed after 2000 led to lower risk estimates but the same overall pattern.

Conclusion—Heart diseases increase the near-term risk for pulmonary embolism not associated with diagnosed peripheral vein thrombosis. **(*Circulation*. 2011;124:1435-1441.)**

Key Words: case-control studies ■ epidemiology ■ heart diseases ■ pulmonary embolism ■ venous thrombosis

Venous thromboembolism (ie, pulmonary embolism and deep venous thrombosis) has an estimated overall incidence of 1 per 1000 persons per year and a 6% to 12% case fatality rate within 1 month.[1–3] Pulmonary embolism often develops as a complication of deep venous thrombosis, stemming from an underlying silent or overt thrombosis in the lower or upper extremities.[4] However, ≈40% of patients with pulmonary embolism have no preceding or concurrent diagnosis of peripheral thrombosis, even after careful venous examination.[5,6]

Clinical Perspective on p 1441

Several explanations for pulmonary embolism in the absence of peripheral deep venous thrombosis have been postulated. It is possible that the thrombus originated peripherally but became dislodged, so the remainder could not be detected even by sensitive methods.[7] Alternatively, there may be other sources of right-sided thrombi, including the heart itself, especially in the setting of cardiac diseases that are notoriously associated with an increased risk of left-side cardiac thromboses and subsequent embolic stroke.[8] Indeed, autopsy series have shown that right intracardiac thrombosis may be as common as thrombosis on the left,[9–11] and ultrasound surveys have reported a high prevalence of right-side thrombi in patients with acute pulmonary embolism.[12–14] A recent cross-sectional hospital database study reported a higher prevalence of heart disease in patients with pulmonary embolism and no accompanying peripheral venous thromboembolism compared with patients who had pulmonary embolism with peripheral venous thromboembolism.[7]

A longitudinal study of the association between heart disease and pulmonary embolism is needed to further elucidate the hypothesis that sources of thrombi other than those in the peripheral venous system increase the risk of pulmonary embolism. Evidence provided by such a study would improve our understanding of the clinical course of heart disease and may potentially lead to improved understanding and prevention of pulmonary embolism. We therefore undertook a

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nationwide population-based case-control study to evaluate whether common heart diseases that increase the risk of left-sided arterial embolism (such as heart failure, myocardial infarction, atrial fibrillation or flutter, and valvular heart disease) are also associated with increased risk of incident pulmonary embolism without apparent peripheral venous thrombosis.

Methods

Design and Rationale

We chose to study the relation between incident heart disease and pulmonary embolism both with and without preceding deep venous thrombosis, as well as the relation with deep venous thrombosis without pulmonary embolism. Examination of the relation between incident heart disease and these 3 outcomes using the same study design allows comparisons of the strengths of association, which can further elucidate possible mechanisms.

Source Population

Our case-control study was nested in the entire population of Denmark (population, 5.4 million) during the years 1980 to 2007. We obtained data from the Danish National Patient Registry, which contains records of all acute care hospital discharges since January 1, 1977, and outpatient specialist clinics and emergency room visits since January 1, 1995,[15] and from the Danish Civil Registration System. The civil registration number, a personal identifier assigned to all Danes at birth and residents at immigration, was used to link records across registries.

Identification of Cases With Venous Thromboembolism

Our approach to ascertaining the outcomes of pulmonary embolism and deep venous thrombosis has been described previously.[16,17] The Danish National Patient Registry records civil registration numbers, dates of hospital admission and discharge, and surgical procedures performed. For each discharge, the registry includes up to 20 discharge diagnoses assigned by the discharging physician and classified according to the *International Classification of Diseases* (ICD), 8th revision until December 31, 1993, and 10th revision thereafter. Among the discharge diagnoses in the Danish National Patient Registry, one is registered as primary and the others as secondary. According to Danish guidelines, the primary diagnosis (called the action diagnosis in the registry) is the main reason for the admission. We obtained from the Danish National Patient Registry all initial discharge diagnoses of venous thromboembolism (see the Appendix for the ICD codes) between January 1, 1980, and December 31, 2007.[18–20] The start date of the study was set 3 years after the establishment of the Danish National Patient Registry to enable us to exclude prevalent venous thromboembolism cases. We identified 109 752 inpatients with a first recorded hospitalization for pulmonary embolism (primary and secondary discharge diagnoses) and/or of deep venous thrombosis in a lower limb.

Population Controls

The Danish Civil Registration System updates its records daily, including changes to vital status (dead or alive), date of death, and the home address of all Danish residents.[21] For each case, we used risk-set sampling to select 5 population controls from this registry matched to the case on age and sex. We assigned the date of the case's first hospital admission for venous thromboembolism (pulmonary embolism alone, pulmonary embolism and deep venous thrombosis, or deep venous thrombosis alone) as the index date both for the case and for the case's matched controls. Thus, in addition to fulfilling the matching criteria, the controls had to be alive on the index date and could not have had a study outcome before this date. A total of 541 561 population controls were included in the study.

Preceding Heart Disease

We used the Danish National Patient Registry to identify history of inpatient heart disease admissions between January 1, 1977, and the index date of cases and their matched controls. The ICD codes used in the study are provided in the Appendix. In accordance with an earlier design,[20] we examined the associations between incident, registry-recorded heart disease, and venous thromboembolism within 2 time periods, defined by whether the heart disease had been recorded first within 3 months before the index date or >3 months before.

Potential Confounders

To classify patients as having unprovoked versus provoked venous thromboembolism, we collected data on preceding inpatient cancer, fractures, trauma, surgery, and pregnancy diagnoses from the Danish National Patient Registry.[18–20] We also retrieved data on obesity and psychiatric diseases (as a marker of antipsychotic drug use), which have been reported as risk factors for venous thromboembolism.[20] Only diagnoses recorded on and before the index date were included. For cancer, we also included cancer diagnosis 3 months after the index date because occult cancer is a strong risk factor for venous thromboembolism.[19] The relevant ICD codes are provided in the Appendix.

Statistical Analysis

We tabulated the frequency and proportion of venous thromboembolism cases and population controls within categories of demographic variables, heart disease history, and candidate confounders. We assessed associations using odds ratios (ORs) with 95% confidence intervals (CIs). Given the risk-set sampling of controls, these ORs provide an unbiased estimate of the corresponding rate ratios.

Because we examined multiple outcomes combining pulmonary embolism and deep venous thrombosis, we estimated the ORs using unconditional polytomous logistic regression, with adjustment for the matching factors and covariates. We examined whether the adjusted ORs differed for pulmonary embolism with and without reported deep venous thrombosis. We used Wald statistics to compute *P* values testing the homogeneity of these adjusted ORs. We repeated all analyses using conditional logistic regression, and no result varied substantially from those presented here.

In a subanalysis, we restricted the analysis to cases of pulmonary embolism and deep venous thrombosis diagnosed after January 1, 2000, to reflect the improved diagnostic accuracy of these disorders with increased use of CT scan of the lungs and ultrasound of the legs. In the same time period, the treatment of acute myocardial infarction and heart failure also improved,[4,22–24] with less bed rest recommended.

Results

Descriptive data are presented in Table 1 for the 109 752 patients with venous thromboembolism and 541 561 population controls. Among the patients, 59 790 had a diagnosis of deep venous thrombosis only, 45 282 had a diagnosis of pulmonary embolism only, and 4680 patients had both diagnoses. There were more women than men, and 40% to 50% were >70 years of age. Most cases were unprovoked. The age and sex distributions of patients with unprovoked deep venous thrombosis and/or pulmonary embolism were similar to those for the overall group (data not shown). Compared with controls, all 3 case groups had a higher prevalence of previous hospitalization for heart disease. This difference held true for all cases and for those with unprovoked presentation.

The OR estimates for heart disease differed according to the time before the venous thromboembolic event, with strong associations between heart disease hospitalizations in

Table 1. Characteristics of Cases Diagnosed With the 3 Venous Thromboembolism Outcomes (Pulmonary Embolism Alone, Pulmonary Embolism With Preceding Deep Vein Thrombosis, or Deep Vein Thrombosis Alone) and Their Matched Controls

	Cases (n=109 752), n (%)			
Variable	Pulmonary Embolism (n=45 282)	Pulmonary Embolism and Deep Venous Thrombosis (n=4680)	Deep Venous Thrombosis (n=59 790)	Controls (n=541 561), n (%)
Age, y				
≤55	7959 (18)	1391 (30)	18 011 (30)	136 633 (25)
56–70	12 634 (28)	1487 (32)	17 669 (30)	157 377 (29)
≥71	24 689 (54)	1802 (38)	24 110 (40)	247 551 (46)
Sex				
Female	24 638 (54)	2180 (47)	31 169 (52)	286 223 (53)
Male	20 644 (46)	2500 (53)	28 621 (48)	255 338 (47)
Previous cancer*	8330 (18)	646 (14)	9328 (16)	32 276 (6.0)
Hospitalization or hospital clinic visit for surgery†	13 817 (31)	1044 (22)	13 820 (23)	13 578 (2.5)
Hospitalization or hospital clinic visit for trauma or fracture†	3584 (7.9)	247 (5.3)	3654 (6.1)	3058 (0.6)
Pregnancy†	226 (0.5)	25 (0.5)	608 (1.0)	710 (0.1)
Obesity	1763 (3.9)	195 (4.2)	2551 (4.3)	5966 (1.1)
Psychiatric diseases	1924 (4.3)	177 (3.8)	3376 (5.7)	9966 (1.8)
Myocardial infarction				
≤3 mo before VTE‡	2538 (5.6)	113 (2.4)	648 (1.1)	633 (0.1)
>3 mo before VTE§	3598 (8.0)	211 (4.5)	2483 (4.2)	18 367 (3.4)
Heart failure				
≤3 mo before VTE	3299 (7.3)	198 (4.2)	1318 (2.2)	853 (0.2)
>3 mo before VTE	3559 (7.9)	167 (3.6)	2282 (3.8)	12 519 (2.3)
Atrial fibrillation/flutter				
≤3 mo before VTE	2122 (4.7)	199 (4.3)	1257 (2.1)	709 (0.1)
>3 mo before VTE	2367 (5.2)	114 (2.4)	1991 (3.3)	13 620 (2.5)
Valvular heart disease				
≤3 mo before VTE	365 (0.8)	17 (0.4)	145 (0.2)	166 (0.0)
>3 mo before VTE	534 (1.2)	21 (0.5)	329 (0.6)	2873 (0.5)

VTE indicates venous thromboembolism.
*Preexisting cancer or a cancer diagnosis within 3 months after VTE/index date.
†Three months before admission/index date.
‡Within 3 months before VTE but not more than 3 months before VTE.
§More than 3 months before VTE.

the 3 months before the index date and thromboembolism and nearly null associations for the time period >3 months before (Table 2). Isolated pulmonary embolism was strongly associated with both acute myocardial infarction (OR, 43.5; 95% CI, 39.6–47.8) and heart failure admission (OR, 32.4; 95% CI, 29.8–35.2) in the 3 months before the index date but much less strongly associated with valvular heart disease hospitalization during that time window (OR, 11.1; 95% CI, 8.9–13.8). However, the latter association differed substantially between left-sided (mitral or aortic) and right-sided (tricuspid or pulmonary) pathology. A diagnosis of left-sided valvular disease was associated with an OR of 13.5 (95% CI, 11.3–16.1), whereas for right-sided valve disease, the OR was 74.6 (95% CI, 28.4–195.8; *P* for test of homogeneity=0.0006).

The ORs associated with myocardial infarction and heart failure admissions in the 3 months before the index date were substantially lower for deep venous thrombosis and deep venous thrombosis with pulmonary embolism than for isolated pulmonary embolism. For incident atrial fibrillation/flutter and valvular disease, the ORs were similar (Table 2).

Much of the association was driven by coincident hospitalization for heart disease and venous thromboembolism. If there was a hospitalization for heart disease within 3 months before the index admission but not during that hospitalization, the relative risk estimates were lower. For acute myocardial infarction, the OR for isolated pulmonary embolism was 6.3 (95% CI, 5.5–7.2); for pulmonary embolism and deep venous thrombosis, 4.2 (95% CI, 2.9–6.0); and for deep venous thrombosis alone, 2.9 (95% CI, 2.4–3.3). The corresponding

Table 2. Relative Risk Estimates (Odds Ratios) For Pulmonary Embolism Alone, Pulmonary Embolism With Preceding Deep Vein Thrombosis, or Deep Vein Thrombosis Alone, Stratified by Whether Heart Disease Was First Recorded Within 3 Months Before the Outcome of Venous Thromboembolism (VTE) or >3 Months Before the Outcome

	Isolated Pulmonary Embolism		Pulmonary Embolism and Deep Venous Thrombosis		Isolated Deep Venous Thrombosis	
Variable	Adjusted Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI
Myocardial infarction						
≤3 mo before VTE†	43.5	39.6–47.8	19.7	16.0–24.2	9.6	8.6–10.7
>3 mo before VTE‡	1.8	1.7–1.9	1.2	1.0–1.4	1.11	1.06–1.17
Heart failure						
≤3 mo before VTE†	32.4	29.8–35.2	22.1	18.7–26.0	12.7	11.6–13.9
>3 mo before VTE‡	2.6	2.5–2.8	1.6	1.4–1.9	1.6	1.5–1.7
Atrial fibrillation/flutter						
≤3 mo before VTE†	23.5	21.4–25.8	28.4	24.1–33.6	15.2	13.8–16.8
>3 mo before VTE‡	1.24	1.18–1.31	0.9	0.7–1.1	1.18	1.12–1.25
Valvular heart disease						
≤3 mo before VTE†	11.1	8.9–13.8	6.8	4.1–11.3	5.5	4.3–7.0
>3 mo before VTE‡	1.1	0.9–1.2	0.7	0.4–1.0	0.8	0.7–0.9

CI indicates confidence interval; VTE, venous thromboembolism.

*Computed with polytomous logistic regression with adjustment for preceding cancer, surgery, fractures, trauma, pregnancy, age and sex, obesity, psychiatric diseases, and the other variables in Table 1.

†Within 3 months before VTE but not more than 3 months before VTE.

‡More than 3 months before VTE.

risk estimates for heart failure and valvular heart disease showed the same pattern, whereas the risk estimates for atrial fibrillation were almost the same with an OR of ≈3.5 for the 3 outcomes (data not shown). Even stronger associations were seen after the overall analysis was restricted to patients with venous thromboembolism as the second diagnosis in the discharge records, indicating that venous thromboembolism was a complication of the heart disease or another disease recorded in that hospitalization (Table 3).

A hospital encounter for myocardial infarction or heart failure >3 months before the pulmonary embolism and/or deep venous thrombosis was associated with only slightly elevated ORs. For atrial fibrillation, the ORs were ≈1, whereas for valvular heart disease, the ORs were <1 for pulmonary embolism with deep venous thrombosis and for deep venous thrombosis alone.

After restriction of the analysis to patients with unprovoked venous thromboembolism, the risk estimates showed the same relative pattern as for the overall venous thromboembolism outcomes (data not shown). Limiting the overall analysis to the time period after 2000 showed the same pattern, but with lower relative risks. Isolated pulmonary embolism was still associated with both acute myocardial infarction (OR, 10.1; 95% CI, 8.1–12.7) and heart failure (OR, 19.3; 95% CI, 16.5–22.6). The association with valvular disease still differed substantially between left- and right-sided pathology. A diagnosis of left valvular disease was associated with an OR of 5.7 (95% CI, 4.1–8.0) and right-sided valvular disease (OR, 37.5; 95% CI, 7.4–191.3; *P* for homogeneity=0.03).

Discussion

In this large population-based case-control study, inpatient diagnoses of heart disease were associated with a markedly increased risk of venous thromboembolism in the subsequent 3 months. The relative risk was particularly high for isolated pulmonary embolism without a concurrent diagnosis of primary deep venous thrombosis. The association was substantially higher for right-sided than for left-sided valvular disease. The increased relative risks associated with myocardial infarction and heart failure seem to extend beyond 3 months past the initial hospitalization for heart disease, but the associations were much weaker over the long term. The risk estimates were substantially more pronounced when episodes of venous thromboembolism were the second diagnoses in the record, indicating that venous thromboembolism was a complication of the heart disease and not vice versa. The risk estimates were lower but showed the same patterns for the period 2000 forward, a period of greater diagnostic accuracy for pulmonary embolism and deep venous thrombosis and shorter bed rest after myocardial infarction and chronic heart failure.

The increase in the risk of deep venous thrombosis, alone or associated with pulmonary embolism, after a cardiac diagnosis is consistent with the fact that several heart diseases induce venous stasis and elevated systemic venous pressure.[25] The remarkable increase in the risk of apparently isolated pulmonary embolism in the 3 months after incident heart disease suggests that several heart diseases may directly cause the development of symptomatic embolism without apparent peripheral thrombosis.

Table 3. Relative Risk Estimates (Odds Ratios) for Pulmonary Embolism Alone, Pulmonary Embolism With Preceding Deep Vein Thrombosis, or Deep Vein Thrombosis Alone (as the Second Diagnoses in the Discharge Records), Stratified by Whether Heart Disease Was First Recorded Within 3 Months Before the Outcome of Venous Thromboembolism or >3 Months Before the Outcome

	Isolated Pulmonary Embolism		Pulmonary Embolism and Deep Venous Thrombosis		Isolated Deep Venous Thrombosis	
Variable	Adjusted Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI
Myocardial infarction						
≤3 mo before VTE†	111.0	95.5–129.1	83.3	62.1–111.8	34.6	29.2–41.0
>3 mo before VTE‡	2.0	1.9–2.2	1.8	1.3–2.4	1.2	1.1–1.4
Heart failure						
≤3 mo before VTE†	54.1	47.2–62.0	59.7	46.0–77.4	32.3	28.0–37.4
>3 mo before VTE‡	3.6	3.3–3.9	2.8	2.0–3.7	2.4	2.2–2.6
Atrial fibrillation/flutter						
≤3 mo before VTE†	35.4	30.1–41.7	52.0	38.6–70.1	32.6	27.6–38.5
>3 mo before VTE‡	1.4	1.3–1.6	1.3	0.9–1.8	1.5	1.4–1.7
Valvular heart disease						
≤3 mo before VTE†	14.9	10.3–21.5	5.1	1.6–16.7	8.0	5.3–12.1
>3 mo before VTE‡	1.1	0.9–1.3	0.7	0.3–1.6	0.9	0.7–1.1

CI indicates confidence interval; VTE, venous thromboembolism.

*Computed with polytomous logistic regression, with adjustment for preceding cancer, surgery, fractures, trauma, pregnancy, age and sex, obesity, psychiatric diseases, and the other variables in Table 1.

†Within 3 months before VTE but not more than 3 months before VTE.

‡More than 3 months before VTE.

Previous studies of heart diseases as a risk factor for isolated pulmonary embolism with heart disease have not been conclusive. Using a study design based on the entire longitudinal hospital history of cases and controls, we found stronger associations than reported in a small hospital-based cross-sectional study from Italy.[7] Prandoni et al[7] conducted a cross-sectional study and reported ORs of 1.15 for the association of venous thromboembolism with valvular heart disease and 1.28 for the association with coronary heart disease. The study was based on 9019 patients with pulmonary embolism alone and 2157 patients with both pulmonary embolism and deep venous thrombosis who served as a control group. This difference in design partly explains the large difference between our OR estimates and those reported in the Italian study because this study did not have a control group unaffected by any venous thromboembolism. Other small clinical case series, cross-sectional autopsy studies, and an ultrasound study showed associations similar to those in the Italian study.[9–14]

Our data are thus largely consistent with the hypothesis that right intracardiac thrombosis is a risk factor for pulmonary embolism just as left-sided intracardiac thrombosis is a well-established risk factor for arterial embolism such as that which occurs, for example, in atrial fibrillation.[8] Our data furthermore confirm that cardiovascular events affect subsequent risk of venous thromboembolism, at least in the 3 months after the cardiovascular event or during the initial hospitalization for the event.[20] Earlier studies have reported no association between noninvasive markers of atherosclerosis in patients without symptoms and subsequent risk of venous thromboembolism.[26,27] Therefore, bed rest and the immobilization related to clinical heart disease likely partly explain the increased risk. A British case-control study reported relative risk estimates similar to ours for the association of cardiovascular events with subsequent venous thromboembolism after 3 months, but the analysis did not take into consideration the time intervals to venous thromboembolism.[28] The reduced risk associated with a diagnosis of atrial fibrillation and valvular disease >3 months before the index date might be explained by anticoagulation therapy.[29]

Several issues should be taken into consideration in the interpretation of our data. The main strengths of our study are its large size, its well-defined population, Denmark's uniformly organized healthcare system with complete population coverage, and the use of population-based controls.

The proportion of isolated pulmonary embolism was higher than expected,[7] and we lacked clinical data on how often the presence of peripheral deep venous thrombosis was assessed in patients with a diagnosis of pulmonary embolism. Asymptomatic deep venous thrombosis is common in this setting, occurring in 20% to 30% of patients with pulmonary embolism.[8] Based on data from general practitioners' records, a British study found that only 6% of its sample of venous thromboembolism patients had both deep venous thrombosis and pulmonary embolism recorded.[28] It is thus likely that in the presence of a pulmonary embolism, physicians do not pursue a separate deep venous thrombosis diagnosis because it would not change the recommended treatment.

Therefore, in our study, patients with pulmonary embolism may be less likely to also receive a deep venous thrombosis diagnosis. If the rate of such underdiagnosis is independent of preceding heart disease (ie, is nondifferential) and the heart

disease associations with pulmonary embolism and venous thromboembolism are lower than the heart disease associations with isolated pulmonary embolism, the underdiagnosis would bias our estimates of association for isolated pulmonary embolism toward the null. A similar phenomenon was found in the Italian study.[7] However, serious bias would have been introduced if there was a differential diagnostic approaches to heart disease and deep venous thrombosis among the 2 pulmonary embolism groups. Most likely, patients with pulmonary embolism with and without venous thrombosis had the same cardiac diagnostic approach during the venous thromboembolism hospitalization in the recent decades, in contrast to patients with isolated deep venous thrombosis, in whom the use of echocardiographic examinations would most likely be lower than in the presence of pulmonary embolism. At the time of the index hospitalization, we found elevated relative risk estimates for venous thromboembolism as secondary diagnoses as a marker for complications to already diagnosed heart disease. We also found that if the heart disease occurred within 3 months before the index hospitalization, but not during the same index hospitalization, the risk estimates showed the same relative pattern.

A weakness is that our data on diagnoses were obtained from a medical database, which may not be entirely accurate. Of patients listed in discharge registries with a diagnosis of venous thromboembolism, 15% to 20% might not fulfill strict clinical criteria for the disease.[30–32]

The specificity of discharge diagnoses of acute myocardial infarction, heart failure, and atrial fibrillation is high,[33–35] and the procedure data we used to define provoked venous thromboembolism have high validity, which leads to high specificity of this classification.[36] Therefore, the exposure and covariate data should have little nondifferential misclassification, resulting in little bias.

Overall, 2 issues speak for a causal association between right-sided heart disease and the risk of isolated pulmonary embolism. First, diagnoses of isolated pulmonary embolism were substantially more frequent for right-sided valvular heart disease compared with left-sided valvular heart disease. Second, the estimates for acute myocardial infarction and heart failure were higher for isolated pulmonary embolism as a primary diagnosis than for pulmonary embolism and deep venous thrombosis. These distinct patterns would be expected to arise from a causal association but are unlikely to arise from an underlying bias.

Conclusions

We found that patients with heart disease are at increased short-term risk of venous thromboembolism. This result seemed most apparent for isolated pulmonary embolism and suggests that common heart diseases may directly account for the development of pulmonary embolism. In patients with pulmonary embolism and no apparent deep venous thrombosis, sources of emboli should be sought and appropriate targeted treatment instituted.

Appendix

International Classification of Diseases Codes Defining Venous Thromboembolism

Deep venous thrombosis: ICD-8: 451.00; ICD-10: I80.1 to I80.3. Pulmonary embolism: ICD-8: 450.99; ICD-10: I26.

International Classification of Diseases Codes Defining Heart Diseases

Myocardial infarction: ICD-8: 410; ICD-10: I21 to I23. Heart failure: ICD-8: 427.09 to 427.19; ICD-10: I50. Atrial fibrillation/flutter: ICD-8: 427.93 and 427.94; ICD-10: I48.9. Valvular heart disease: ICD-8: 394 to 398; ICD-10: I34 to I37. Left-sided valvular disease: ICD-8: 394, 395, 396, 424.00–424.19, 746.60, and 746.62; ICD-10: I05, I06, I08.0, I34, I35, I39.0, I51.1A, and Q23. Right-sided valvular disease: ICD-8: 397.00, 397.01, 424.90 to 424.92, 746.61, and 746.63; ICD-10: I07, I36, I37, I09.8, I39.3, and Q22.

International Classification of Diseases Codes Defining Comorbidities

Cancer: ICD-8: 140 to 209; ICD-10: C00 to C99. Trauma or fracture: ICD-8: 800 to 929 and 950 to 959; ICD-10: S00 to T14. Pregnancy: ICD-8: 630 to 680; ICD-10: O00 to O99. Obesity: ICD-8: 277; ICD-10: E65 to E66. Psychiatric diseases: ICD-8: 291 to 301 and 304; ICD-10: F10.4-F10.9, and F11 to F69.

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Disclosures

None.

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CLINICAL PERSPECTIVE

It is well established that heart diseases such as atrial fibrillation increase the risk of arterial embolism. However, whether heart diseases similarly increase the risk of pulmonary embolism without peripheral venous thrombosis is less certain. Using Danish medical databases, we conducted a nationwide population-based case-control study of 45 282 patients with embolism alone, 4680 patients with pulmonary embolism and lower-limb deep venous thrombosis, 59 790 with deep venous thrombosis alone, and 541 561 population controls. Myocardial infarction and heart failure in the preceding 3 months conferred remarkably high risks of apparently isolated pulmonary embolism, with odds ratios of 43.5 (95% confidence interval, 39.6–47.8) and 32.4 (95% confidence interval, 29.8–35.2), respectively. There was a particularly strong association of right-sided valvular disease with isolated pulmonary embolism (odds ratio, 74.6; 95% confidence interval, 28.4–195.8). We conclude that heart disease is associated with an increased short-term risk of venous thromboembolism, including isolated pulmonary embolism. Because common heart diseases may directly account for the development of pulmonary embolism, in patients with pulmonary embolism and no apparent deep venous thrombosis, cardiac sources of emboli should be considered and appropriate treatment instituted.

Paper VIII

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Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer

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ABSTRACT

Background: In contrast to deep venous thrombosis and pulmonary embolism, superficial venous thrombosis has not been considered to be a marker of occult cancer. However, actual data regarding the association are very limited.

Methods: We identified all patients in Denmark from 1994 to 2009 with a diagnosis of superficial venous thrombosis, deep venous thrombosis in the legs or pulmonary embolism using population-based health registries. The occurrence of cancer in the three venous thromboembolism cohorts was compared with the expected numbers of cases estimated using national incidence rates to compute standardised incidence ratios (SIRs).

Findings: We identified a total of 7663 patients with superficial venous thrombosis, 45,252 with deep venous thrombosis and 24,332 with pulmonary embolism. In the first year of follow-up, very similar proportions of patients in the three cohorts were diagnosed with cancer. The SIR was 2.46 (95% CI, 2.10–2.86) for superficial venous thrombosis, 2.75 (95% CI, 2.60–2.90) for deep venous thrombosis, and 3.27 (95% CI, 3.03–3.52) for pulmonary embolism. After one year, the SIRs declined to 1.05 (95% CI, 0.96–1.16), 1.11 (95% CI 1.07–1.16) and 1.15 (95% CI, 1.09–1.22), respectively. For all three patient cohorts, particularly strong associations were found for cancers of the liver, lung, ovaries and pancreas as well as for non-Hodgkin's lymphoma.

Interpretation: Venous thrombosis, whenever it is seen in the lower limbs, is a preclinical marker of prevalent cancer, particularly during the first year after diagnosis.

1. Introduction

The association between cancer and venous thromboembolism has been recognised since Trousseau reported more than 100 years ago that cancer patients often also had episodic migratory thrombophlebitis.[1] Since then a large body of literature has provided strong evidence that deep venous thrombosis and pulmonary embolism not only are complications of cancer,[2–5] but also may be harbingers of a new cancer diagnosis. Indeed, patients with deep venous thrombosis or pulmonary embolism have a 2–4-fold increased risk of cancer in the first year after the venous thromboembolic event.[6–9]

In contrast, superficial venous thrombosis is generally understood to be a relatively benign condition[10,11] without significant implications for cancer risk, though with substantial uncertainty about the clinical course. However, investigation of the relationship between superficial thrombophlebitis and cancer risk is limited to one study of only

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250 patients diagnosed in five primary health care centres in Amsterdam.[12]

To understand better the cancer risks associated with all types of venous thrombosis, we determined the risk of cancer after a diagnosis of superficial venous thrombosis in the legs, deep venous thrombosis and pulmonary embolism using population-based registries in Denmark.

2. Methods

This registry based cohort study was based on the entire Danish population of 5·4 million people.[13] The Danish National Registry of Patients was established in 1977 and 99.4% of all discharges from acute care Danish non-psychiatric hospitals are recorded in it. Since 1995, the Registry has also included all outpatient hospital and emergency room visits, encompassing virtually all specialist care in the country.[14]

Recorded information includes the civil registration number, which is unique to every Danish citizen, dates of admission and discharge, surgical procedures performed, and up to twenty discharge diagnoses, classified according to the International Classification of Diseases, 8th edition until 1994 and the International Classification of Diseases, 10th edition thereafter.

It is possible to obtain the hospital history of a patient back to 1977 by linking records in the registry to the civil registration number. All persons listed in the National Registry of Patients with an inpatient or outpatient diagnosis of superficial venous thrombosis in the lower limb (see Appendix for the ICD codes), deep venous thrombosis in the lower limb or pulmonary embolism between 1st January 1994 and 31st December 2009 were identified.

All cases with a (inpatient) diagnosis of venous thrombosis between 1977 and 1994 were excluded from the study cohort. All members of the study cohort were linked through the civil registration number to the nationwide Danish Cancer Registry[15] and the Danish Civil Registration System.[13] The Cancer Registry has kept records of all reported incident cancer cases in Denmark since 1943, with compulsory registration beginning in 1987. Cancers are reclassified according to the International Classification of Diseases, 10th Revision.

2.1. *Statistical analysis*

Standardised incidence ratios (SIRs) were used as a measure of relative risk, comparing the observed cancer incidence among patients with venous thrombosis or pulmonary embolism with that expected in the entire Danish population. Expected numbers of cancer cases were estimated based on national cancer incidence rates by age (5 year groups), sex, and individual calendar year. Confidence intervals (CI) for the standardised incidence ratio were computed based on the assumption that the observed number of cases in a specific category follows a Poisson distribution. Exact limits were used when the observed number was less than 10; otherwise Byar's approximation was used.

Each patient was followed for the occurrence of cancer from the date of the first record with a diagnosis of venous thrombosis or pulmonary embolism until the date of death or 31st December 2009, whichever came first.

3. Role of funding source

The sponsor had no role in the study design; in the collection, analysis and interpretation of the data, in the writing of this report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. No ethics approval was required because no primary data collection was done.

4. Results

We identified 77,247 patients with lower limb superficial or deep venous thrombosis and/or pulmonary embolism (Table 1). The largest group of patients consisted of those with deep venous thrombosis (45,252), followed by pulmonary embolism (24,332) and 7663 patients with superficial venous thrombosis. 168 patients had diagnoses of both superficial and deep venous thrombosis and 97 patients had both superficial venous thrombosis and pulmonary embolism. These patients were classified as deep venous thrombosis and pulmonary embolism, respectively. Thus, 2.1% of patients with superficial venous thrombosis (168/7831) had a concurrent deep venous thrombosis.

36,620 patients (47%) were more than 65 years old. There were slightly more women (41,507, 54%) than men (35,740, 46%). On average the patients were followed for 5.0 years. During follow-up of patients with superficial thrombosis, 869 (11%) developed deep venous thrombosis, 114 (1.5%) had pulmonary embolism and 97 (1.3%) had both. Within 3 months after superficial venous thrombosis, 382 (5.0%) had a deep venous thrombosis, 26 (0.3%) had a pulmonary embolism, while 18 (0.2%) had both.

2124 patients (2.7%) had a cancer diagnosis within the first year of follow-up, and 4205 (7.0%) during the subsequent follow-up of up to 15 years. All forms of venous thrombosis and embolism were clearly associated with cancer risk. The risk of cancer during the first year of follow-up was 2.2% for superficial venous thrombosis, 2.7% for deep venous thrombosis and 2.9% for pulmonary embolism. The corresponding SIRs were 2.46 (95% CI, 2.10–2.86) for superficial venous thrombosis, 2.75 (95% CI, 2.60–2.90) for deep venous thrombosis and 3.27 (95% CI, 3.03–3.52) for pulmonary embolism. The relative risk was slightly lower for patients older than 65 years than for those younger (Table 1).

For 6507 (14%) patients with lower limb deep venous thrombosis there was information in the hospital registry regarding the exact location of the thrombosis. The SIR for cancer was similar for distal (SIR = 2.87, 95% CI 2.38–3.42) and femoral venous thrombosis (SIR = 3.10, 95% CI 2.39–3.95)(Tables 2–4).

For superficial thrombophlebitis, lower limb deep venous thrombosis and pulmonary embolism, particularly strong associations were found for cancers of the liver, lung, pancreas and ovaries, as well as for non-Hodgkin's lymphoma.

Table 1 – Standardised cancer incidence ratios (SIRs) for all cancers for patients with venous thromboembolism during the first year of follow-up.

	Superficial thrombosis			Deep venous thrombosis			Pulmonary embolism			All venous thromboembolism		
	N	Observed no. of cancers	SIR (95%CI)	*N*	Observed no. of cancers	SIR (95%CI)	*N*	Observed no. of cancers	SIR (95% CI)	*N*	Observed no. of cancers	SIR (95% CI)
Total	7663	171	2.5 (2.1–2.9)	45,252	1236	2.7 (2.6–2.9)	24,332	717	3.3 (3.0–3.5)	77,247	2124	2.9 (2.8–3.0)
Female	4404	87	2.3 (1.8–2.8)	23,647	581	2.7 (2.5–2.9)	13,456	382	3.5 (3.1–3.8)	41,507	1050	2.9 (2.7–3.0)
Male	3259	84	2.7 (2.2–3.3)	21,605	655	2.8 (2.6–3.0)	10,876	335	3.1 (2.8–3.4)	35,740	1074	2.9 (2.7–3.1)
Age at thrombosis: <65	4905	66	3.0 (2.3–3.8)	25,322	399	3.5 (3.2–3.9)	10,400	258	5.5 (4.8–6.2)	40,627	704	3.9 (3.7–4.3)
Age at thrombosis: 65+	2758	105	2.2 (1.8–2.7)	19,930	837	2.5 (2.3–2.7)	13,932	459	2.7 (2.5–3.0)	36,620	1420	2.5 (2.4–2.7)
1994–1999	2414	47	2.2 (1.6–2.9)	13,709	373	2.8 (2.5–3.1)	7541	189	3.3 (2.8–3.8)	23,664	609	2.9 (2.7–3.1)
2000–2004	2649	68	2.7 (2.1–3.5)	14,496	408	2.8 (2.5–3.0)	7706	227	3.1 (2.7–3.5)	24,851	703	2.8 (2.6–3.1)
2005–2009	2600	56	2.4 (1.8–3.1)	17,047	455	2.7 (2.5–2.9)	9085	301	3.4 (3.0–3.8)	28,732	812	2.9 (2.7–3.1)
Unprovoked venous thromboembolism	6199	129	2.3 (1.9–2.7)	34,152	959	2.8– (2.6–3.0)	18,215	559	3.3 (3.0–3.6)	58,568	1647	2.9 (2.7–3.0)
Provoked venous thromboembolism	7116	42	3.4 (2.5–4.6)	40,176	277	2.6 (2.3–3.0)	21,950	158	3.1 (2.6–3.6)	69,241	477	2.8 (2.6–3.1)
No fractures in previous 3 months	6509	164	2.5 (2.1–2.9)	37,025	1169	2.9 (2.7–3.0)	19,376	685	3.4 (3.1–3.6)	62,913	2018	3.0 (2.9–3.1)
Fractures in previous 3 months	1464	7	1.6 (0.6–3.2)	11,100	67	1.6 (1.2–2.0)	6117	32	1.9 (1.3–2.7)	18,679	106	1.7 (1.4–2.0)
No surgical procedure in past 3 months	547	132	2.2 (1.9–2.6)	5,076	1000	2.7 (2.5–2.9)	2382	574	3.2 (3.0–3.5)	8006	1706	2.8 (2.7–3.0)
Surgical procedure within 3 months	1154	39	3.9 (2.8–5.3)	8227	236	2.9 (2.5–3.3)	4956	143	3.4 (2.9–4.0)	14,334	418	3.1 (2.8–3.4)

Table 2 – Standardised cancer incidence ratios (SIRs) for patients with venous thromboembolism during the second and subsequent years of follow-up.

	Superficial thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolism	
	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)
Total	457	1.1 (1.0–1.2)	2605	1.1 (1.1–1.2)	1143	1.2 (1.1–1.2)	4205	1.1 (1.1–1.2)
Female	253	1.1 (0.9–1.2)	1212	1.1 (1.1–1.2)	601	1.2 (1.1–1.3)	2066	1.1 (1.1–1.2)
Male	204	1.1 (0.9–1.2)	1393	1.1 (1.0–1.2)	542	1.1 (1.0–1.2)	2139	1.1 (1.0–1.1)
Age at thrombosis: 0–65	222	1.1 (1.0–1.3)	1120	1.2 (1.1–1.3)	445	1.3 (1.2–1.4)	1787	1.2 (1.2–1.3)
Age at thrombosis: 65+	235	1.0 (0.9–1.1)	1485	1.1 (1.0–1.1)	698	1.1 (1.0–1.2)	2418	1.0 (1.0–1.1)
1994–1999	250	1.1 (0.9–1.2)	1347	1.1 (1.0–1.1)	572	1.1 (1.1–1.2)	2169	1.1 (1.0–1.1)
2000–2004	169	1.1 (0.9–1.3)	936	1.1 (1.1–1.2)	424	1.2 (1.1–1.3)	1529	1.1 (1.1–1.2)
2005–2009	38	0.9 (0.7–1.3)	322	1.2 (1.0–1.3)	147	1.1 (1.0–1.3)	507	1.1 (1.0–1.2)
Unprovoked venous thromboembolism	379	1.0 (0.9–1.2)	1994	1.1 (1.0–1.1)	887	1.2 (1.1–1.2)	3260	1.1 (1.1–1.1)
Provoked venous thromboembolism	78	1.1 (0.9–1.4)	611	1.2 (1.1–1.3)	256	1.1 (1.0–1.3)	945	1.2 (1.1–2.0)
No fractures in previous 3 months	431	1.1 (1.0–1.2)	2364	1.1 (1.1–1.2)	1076	1.2 (1.1–1.2)	3871	1.1 (1.1–1.2)
Fractures within 3 month	26	1.0 (0.7–1.5)	241	1.1 (1.0–1.3)	67	0.9 (0.7–1.2)	334	1.1 (1.0–1.2)
No surgical procedure	396	1.1 (1.0–1.2)	2134	1.1 (1.0–1.1)	922	1.2 (1.1–1.2)	3452	1.1 (1.1–1.1)
Surgical procedure within 3 months	61	1.0 (0.8–1.3)	471	1.2 (1.1–1.3)	221	1.1 (1.0–1.3)	753	1.2 (1.1–1.2)

From the second through the 15th year of follow-up, the relative risks for most cancers were only slightly increased, and to a similar extent for all three patient cohorts. For all invasive cancers, the SIR during the later follow-up for superficial venous thrombosis was 1.05 (95% CI, 0.96–1.16), 1.11 (95% CI 1.07–1.16) for deep venous thrombosis and 1.15 (95% CI, 1.09–1.22) for pulmonary embolism (Fig. 1). In general the cancer site specific risk estimates were broadly similar. The risk was similar for men and women but slightly higher for persons younger than 65 years of age compared with older patients.

In an additional analysis, patients with superficial thrombophlebitis were censored at the time of other venous thromboembolism. This left the standardised incidence rate (SIR) for the first year of follow-up virtually unchanged (SIR = 2.31, 95% CI, 1.95–2.71).

5. Discussion

We found that patients with a diagnosis of superficial venous thrombosis—like those with deep venous thrombosis and pulmonary embolism[6–9]—had a clearly higher occurrence of cancer than expected, particularly during the first year after diagnosis. The excess occurrence subsequently decreased markedly, though venous thrombosis or embolism, wherever its location, remained a marker of slightly increased long-term cancer risk.[6,7] The increased risks of cancer diagnosis were similar in magnitude for each of the thrombotic manifestations, and each showed particularly strong associations with cancers of the liver, lung, ovaries and pancreas, as well as non-Hodgkin's lymphoma. We also found that distal deep venous thrombosis was associated with cancer relative risks similar to those for femoral thrombosis and pulmonary embolism.

Several clinical studies have reported cancer associations similar to ours for the first year of follow-up after deep venous thrombosis,[9] and our findings were also broadly similar to former reports associated with specific types of cancer.[6–8] However, our results for superficial thrombosis differ from the one previous report on the topic. In this small study from Holland, five out of 25 (2%) patients developed cancer within two years compared with 2% in the control group.[12] The study was only able to control for family physician, but did not exclude persons with a cancer diagnosis before their superficial venous thrombosis diagnosis and had incomplete follow-up. The standardised mortality ratio was 1.1 (95% CI, 0.5–2.7) after 2 years of follow-up based on five cases of cancer.

Our study has limitations. No acute private care exists in Denmark and so our study is virtually population based. Nonetheless, we likely included only a sub-group of patients with superficial venous thromboembolism, namely those diagnosed in the hospital service rather than in the general practitioners' clinics. Data on the incidence of this disorder are very limited, but it seems to be fairly common in the general population,[16,17] and selection factors might partly explain the different results from the previous study.[12] Also, the recorded diagnosis in the Patient Registry may have been erroneous. However, such potential misclassification would tend to result in underestimation of the overall associations.[17]

Table 3 – Standardised cancer incidence ratios (SIRs) for major cancer sites in patients with venous thromboembolism during the first year of follow-up.

Cancer site	Superficial venous thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolism	
	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR(95% CI)	Observed no. of cancers	SIR(95% CI)	Observed no. of cancers	SIR(95% CI)
All	171	2.5 (2.1–2.9)	1236	2.7 (2.6–2.9)	717	3.3 (3.0–3.5)	2124	2.9 (2.8–3.0)
Oesophagus	4	4.2 (1.1–10.7)	13	1.9 (1.0–3.3)	14	4.4 (2.4–7.3)	31	2.8 (1.9–4.0)
Stomach	5	3.5 (1.1–8.2)	28	2.9 (1.9–4.2)	19	4.1 (2.5–6.4)	52	3.3 (2.5–4.3)
Large intestine incl. Colon rectosigmoid	9	1.3 (0.6–2.4)	102	2.1 (1.7–2.6)	65	2.7 (2.1–3.5)	176	2.2 (1.9–2.6)
Rectum	6	1.8 (0.7–3.9)	41	1.8 (1.3–2.4)	14	1.3 (0.7–2.1)	61	1.6 (1.3–2.1)
Liver	6	8.2 (3.0–17.9)	14	2.8 (1.5–4.8)	10	4.2 (2.0–7.7)	30	3.7 (2.5–5.3)
Gallbladder and biliary tract4	0	–	13	3.8 (2.0–6.5)	10	5.9 (2.8–10.8)	23	4.1 (2.6–6.1)
Pancreas	10	4.6 (2.2–8.5)	79	5.4 (4.3–6.8)	50	6.9 (5.2–9.2)	139	5.8 (4.9–6.9)
Larynx	0	–	2	0.5 (0.1–1.8)	1	0.6 (0.0–3.1)	3	0.5 (0.1–1.4)
Lung, bronchi and trachea	31	3.1 (2.1–4.4)	194	3.0 (2.6–3.4)	183	5.7 (4.9–6.6)	408	3.8 (3.4–4.2)
Malignant melanoma	4	1.6 (0.4–4.0)	22	1.4 (0.9–2.2)	8	1.1 (0.5–2.2)	34	1.4 (0.9–1.9)
Breast	15	1.4 (0.8–2.4)	66	1.2 (0.9–1.5)	40	1.5 (1.0–2.0)	121	1.3 (1.1–1.5)
Cervix of uterus	1	1.2 (0.0–6.4)	15	3.4 (1.9–5.6)	6	2.9 (1.1–6.3)	22	3.0 (1.9–4.6)
Uterus	4	2.1 (0.6–5.4)	30	2.9 (1.9–4.1)	16	3.0 (1.7–4.9)	50	2.8 (2.1–3.7)
Ovary	4	2.6 (0.7–6.6)	43	5.2 (3.8–7.0)	44	10.5 (7.6–14.1)	91	6.5 (5.2–8.0)
Prostate	14	2.1 (1.1–3.5)	164	3.1 (2.7–3.7)	57	2.2 (1.7–2.9)	235	2.8 (2.4–3.2)
Testicle	0	–	9	5.5 (2.5–10.4)	0	–	9	3.6 (1.6–6.8)
Kidney	0	–	15	1.7 (0.9–2.8)	21	4.9 (3.0–7.5)	36	2.5 (1.7–3.4)
Urinary bladder	8	3.6 (1.5–7.0)	38	2.3 (1.7–3.2)	17	2.1 (1.2–3.4)	63	2.4 (1.8–3.1)
Brain	6	3.5 (1.3–7.7)	20	1.9 (1.2–3.0)	8	1.7 (0.7–3.3)	34	2.0 (1.4–2.8)
Hodgkin lymphoma	1	5.4 (0.1–30.3)	2	1.8 (0.2–6.6)	3	6.3 (1.3–18.4)	6	3.4 (1.3–7.5)
Non-Hodgkin lymphoma	7	3.4 (1.3–6.9)	57	4.2 (3.2–5.5)	19	2.9 (1.7–4.5)	83	3.7 (3.0–4.6)
Leukaemia	8	4.4 (1.9–8.6)	46	3.7 (2.7–4.9)	9	1.5 (0.7–2.8)	63	3.1 (2.4–4.0)
Metastases and non-specified cancer in lymph nodes	12	5.5 (2.8–9.6)	84	5.6 (4.5–6.9)	30	4.0 (2.7–5.7)	126	5.1 (4.3–6.1)
Multiple myeloma	4	5.1 (1.4–12.9)	16	3.0 (1.7–4.9)	11	4.2 (2.1–7.5)	31	3.5 (2.4–5.0)

Table 4 – Standardised cancer incidence ratios (SIRs) for major cancer sites in patients with venous thromboembolism during the second and subsequent years of follow-up.

Cancer site	Superficial venous thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolisms	
	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)
All	457	1.1 (1.0–1.2)	2605	1.1 (1.1–1.2)	1143	1.2 (1.1–1.2)	4205	1.1 (1.1–1.2)
Oesophagus	6	1.0 (0.4–2.2)	37	1.1 (0.7–1.5)	22	1.5 (1.0–2.3)	65	1.2 (0.9–1.5)
Stomach	10	1.2 (0.6–2.2)	51	1.1 (0.8–1.4)	17	0.8 (0.5–1.3)	78	1.0 (0.8–1.3)
Large intestine incl. colon rectosigmoid	46	1.1 (0.8–1.4)	272	1.1 (1.0–1.3)	145	1.4 (1.2–1.6)	463	1.2 (1.1–1.3)
Rectum	22	1.0 (0.7–1.6)	125	1.1 (0.9–1.3)	42	0.8 (0.6–1.1)	189	1.0 (0.9–1.2)
Liver	3	0.7 (1.1–2.0)	36	1.4 (1.0–2.0)	21	2.0 (1.2–3.1)	60	1.5 (1.1–1.9)
Gallbladder and biliary tract	3	1.0 (0.2–2.8)	25	1.5 (1.0–2.2)	6	0.8 (0.3–1.8)	34	1.3 (0.9–1.8)
Pancreas	25	1.8 (1.2–2.7)	94	1.3 (1.0–1.5)	40	1.2 (0.9–1.7)	159	1.3 (1.1–1.5)
Larynx	5	1.4 (0.5–3.3)	20	1.0 (0.6–1.5)	7	0.9 (0.4–1.8)	32	1.0 (0.7–1.4)
Lung, bronchi and trachea	53	0.9 (0.6–1.1)	359	1.1 (1.0–1.2)	163	1.1 (1.0–1.3)	575	1.1 (1.0–1.1)
Malignant melanoma	13	0.8 (0.4–1.4)	79	0.9 (0.7–1.2)	41	1.2 (0.8–1.6)	133	1.0 (0.8–1.2)
Breast	70	1.1 (0.8–1.3)	320	1.1 (1.0–1.2)	170	1.3 (1.1–1.5)	560	1.2 (1.1–1.3)
Cervix of uterus	2	0.4 (0.1–1.5)	30	1.5 (1.0–2.1)	12	1.4 (0.7–2.4)	44	1.3 (0.9–1.7)
Uterus	19	1.6 (1.0–2.6)	53	1.1 (0.8–1.4)	15	0.6 (0.4–1.1)	87	1.0 (0.8–1.3)
Ovary	6	0.7 (0.2–1.4)	39	1.0 (0.7–1.4)	18	1.0 (0.6–1.6)	63	0.9 (0.7–1.2)
Prostate	37	0.8 (0.6–1.1)	333	1.1 (1.0–1.2)	97	0.8 (0.6–1.0)	467	1.0 (0.9–1.1)
Testicle	3	2.1 (0.4–6.1)	9	1.1 (0.5–2.1)	6	2.1 (0.8–4.7)	18	1.5 (0.9–2.3)
Kidney	11	1.3 (0.7–2.4)	55	1.2 (0.9–1.6)	26	1.4 (0.9–2.0)	92	1.3 (1.0–1.5)
Urinary bladder	17	1.2 (0.7–2.0)	75	0.9 (0.7–1.1)	44	1.3 (0.9–1.7)	136	1.0 (0.9–1.2)
Brain	9	0.9 (0.4–1.7)	65	1.2 (0.9–1.6)	24	1.1 (0.7–1.6)	98	1.1 (0.9–1.4)
Hodgkin lymphoma	2	2.0 (0.2–7.1)	6	1.1 (0.4–2.4)	0	–	8	0.9 (0.4–1.8)
Non-Hodgkin lymphoma	15	1.1 (0.6–1.9)	70	1.0 (0.8–1.2)	32	1.1 (0.7–1.5)	117	1.0 (0.8–1.2)
Leukaemia	16	1.4 (0.8–2.3)	89	1.4 (1.1–1.7)	43	1.6 (1.2–2.2)	148	1.5 (1.2–1.7)
Metastases and non-specified cancer in lymph nodes	16	1.2 (0.7–2.0)	83	1.1 (0.9–1.4)	43	1.3 (1.0–1.8)	142	1.2 (1.0–1.4)
Multiple myeloma	9	1.8 (0.8–3.4)	37	1.3 (0.9–1.9)	16	1.4 (0.8–2.2)	62	1.4 (1.1–1.8)

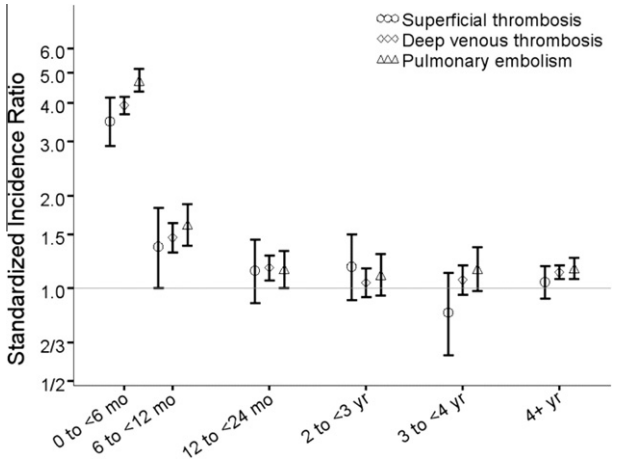

Fig. 1 – Relative risk (Standardised Incidence Ratio) of cancer in relation to length of the follow-up period in patients with superficial venous thrombosis, deep venous thrombosis or pulmonary embolism. The I bars represent 95% confidence intervals.

Our cancer data have high quality and completeness and comprehensive validation has shown that the Cancer Registry is 95–98% complete and valid.[15]

It is possible that unrecognised concomitant deep vein thrombosis, reported to occur in up to 25% of patients with superficial vein thrombosis,[18] might have contributed to the increased risk. Thus we cannot exclude the possibility that in patients with isolated superficial vein thrombosis the incidence of occult or subsequent cancer is lower than that observed in our population. Nonetheless, our findings remained unchanged after omission of patients who subsequently developed deep venous thrombosis or pulmonary embolism.

There may be several explanations for an association between venous thrombosis and cancer risk. Heightened diagnostic activities likely explain some of the associations during the first year of follow-up. Our finding of increased risk of virtually all cancers during that period is consistent with such diagnostic surveillance. However, the persistent increased risk after one year of venous thromboembolism speaks against the prominent diagnostic bias. Likewise, we did not see a compensatory deficit in the cancer risk in the data in the follow-up period more than 1 year later.

Our data are consistent with two other options: on the one hand, common factors may predispose individuals to both thrombosis and cancer[19–22]; on the other hand, occult malignant changes can promote venous thromboembolism. Smoking, obesity and use of oestrogens are indeed risk factors for both deep venous thrombosis and cancer, although obesity and oestrogen use each predisposes only to a limited range of cancers.[21,22] The increased risk of upper gastrointestinal neoplasm and lung cancer after venous thromboembolism is consistent with the smoking exposure.

The manner in which cancer can lead to thrombosis has been studied in detail over the last decades, but the mechanisms are complex and multifactorial.[2,3,23] Cancer growth is associated with the development of a hypercoagulable state. Malignant cells can activate blood coagulation in several ways: by producing fibrinolytic, and proaggregating activities though release of pro-inflammatory and proangiogenetic cytokines, and by interacting directly with host vascular and blood cells, such as endothelial cells, leucocytes and platelets, by means of adhesion molecules.[2]

The practical implications of our findings are unclear. In general a venous thrombotic event within a year of a diagnosis of cancer is a marker of an aggressive malignancy: only 12% of affected patients are alive after one year.[24] However, the implications for screening seem remote. In our study 45,981 persons with venous thrombosis/embolism would have to be investigated for the 304 excess cancers to be found during the first year of follow-up. One cohort study[25] of 830 patients and a clinical trial of 201 patients[26] investigated whether early detection of an occult cancer in patients with venous thromboembolism would yield a more favourable outcome.[25,26] Unfortunately the two studies were not definitive enough to establish whether an early cancer diagnosis ultimately prolongs life in venous thromboembolism patients.

6. Contributors

HTS was the principal investigator and lead author in the conception and design of the study, supervision of the analysis of the data and drafting of the manuscript. CS, DKF and LP coordinated the data collection and did the statistical analysis. JAB, TLL and CFC participated in the study design, provided statistical suggestions and participated in the interpretation of the results. PP participated in the conception and design of the study and the interpretation of the data. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement

None declared.

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Appendix

International Classification of Diseases (ICD) codes defining venous thromboembolism

Superficial thrombophlebitis: ICD-8: 451.01; ICD-10: I80.0
Deep venous thrombosis: ICD-8: 451.00; ICD-10: I80.1–3
Pulmonary embolism: ICD-8: 450.99; ICD-10: I26, I26.98

ICD codes defining cancer

Oesophagus ICD-10: C15
Stomach ICD-10: C16
Large intestine incl. colon rectosigmoid ICD-10: C18-C19

Rectum ICD-10: C20
Liver ICD-10: C22
Gallbladder and biliary tract ICD-10: C23–C24
Pancreas ICD-10: C25
Larynx ICD-10: C32
Lung, bronchi and trachea ICD-10: C33–C34
Malignant melanoma ICD-10: C43
Breast ICD-10: C50
Cervix of uterus ICD-10: C53
Uterus ICD-10: C54–C55
Ovary ICD-10: C56, C570–C574
Prostate ICD-10: C61
Testicle ICD-10: C62
Kidney ICD-10: C64
Urinary bladder ICD-10: C67, D303, D413
Brain ICD-10: C71, D33, D352–D354, D43, D443–D445
Hodgkin malignant lymphoma ICD-10: C81 or pathological morphology codes M965, M966
Non-Hodgkin malignant lymphoma ICD-10: C82–C85, C901–C902 or pathological morphology codes M967, M972
Leukaemia ICD-10: C91–C95
Metastases and non-specified cancer in lymph nodes ICD-10: C77–C79
Multiple myeloma ICD-10: C900

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Paper IX

30-Year Mortality After Venous Thromboembolism
A Population-Based Cohort Study

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Background—Studies on long-term mortality after venous thromboembolism (VTE) are sparse.

Methods and Results—Using Danish medical databases, we conducted a 30-year nationwide population-based cohort study of 128 223 patients with first-time VTE (1980–2011) and a comparison cohort of 640 760 people from the general population (without VTE) randomly matched by sex, year of birth, and calendar period. The mortality risks for patients with deep venous thrombosis (DVT) and pulmonary embolism (PE) were markedly higher than for the comparison cohort during the first year, especially within the first 30 days (3.0% and 31% versus 0.4%). Using Cox regression, we assessed mortality rate ratios (MRRs) with 95% confidence intervals (CIs). The overall 30-year MRR was 1.55 (95% CI, 1.53–1.57) for DVT and 2.77 (95% CI, 2.74–2.81) for PE. The 30-day MRR was 5.38 (95% CI, 5.00–5.80) for DVT and 80.87 (95% CI, 76.02–86.02) for PE. Over time, the 30-day MRR was consistently 5- to 6-fold increased for DVT, whereas it improved for PE from 138 (95% CI, 125–153) in 1980 to 1989 to 36.08 (95% CI, 32.65–39.87) in 2000 to 2011. The 1- to 10-year and 11- to 30-year MRRs remained 25% to 40% increased after both DVT and PE but were 3- to 5-fold increased after DVT and 6- to 11-fold increased after PE when VTE was considered the immediate cause of death.

Conclusions—Patients with VTE are at increased risk of dying, especially within the first year after diagnosis, but also during the entire 30 years of follow-up, with VTE as an important cause of death. Although 30-day mortality after DVT remained fairly constant over the last 3 decades, it improved markedly for PE. **(*Circulation*. 2014;130:829-836.)**

Key Words: epidemiology ■ mortality ■ prognosis ■ thromboembolism

Venous thromboembolism (VTE), encompassing deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common condition. In the existing literature, the magnitude of long-term mortality after VTE varies substantially.[1–9] A recent study reported an 8-year mortality risk of 12%,[1] whereas in an earlier study, mortality risk reached 50% after 8 years of follow-up.[5] Previous studies were limited by short follow-up time (maximum, 10 years),[1–4,6–11] age restrictions (<70 years of age[1] or between 65 and 89 years of age[7]), lack of adjustment for comorbidity[3,12] or calendar period,[3,5] and failure to examine mortality for DVT and PE separately.[1,8,12] Only a few studies have compared long-term mortality between VTE patients and a comparison cohort from the general population, with inconsistent results.[1,3,8,12] The reported risk varied between a null association,[3] a 40% higher mortality in VTE patients after 10 years compared with expected mortality in the general population,[8] a higher mortality only among patients with cancer,[12] and higher mortality for both cancer patients and noncancer patients.[1]

Clinical Perspective on p 836

Critical unanswered questions remain about long-term VTE mortality in unselected patients. It is not clear if 30-day survivors of VTE remain at increased risk of death compared with the general population and whether recurrent thromboembolic events are frequent causes death among VTE patients. Moreover, it is unclear if mortality differs according to VTE subtypes and underlying comorbidity burden and whether short- and long-term mortality has improved over the last 3 decades.

We therefore undertook this nationwide population-based cohort study to examine 30-year VTE mortality according to VTE subtypes, underlying comorbidity, and calendar periods of diagnosis.

Methods

Study Design and Setting

This cohort study drew on the entire Danish population, with 7 046 778 residents alive between 1980 and 2011. Data were obtained from the Danish National Registry of Patients, which

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contains records on >99% of all discharges from Danish hospitals since 1977[13] and on emergency room and outpatient clinic visits since 1994. Recorded information includes civil registration number (unique personal identifier assigned to all Danish residents), dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses classified according to the *International Classification of Diseases*, *8th Revision* (*ICD-8*) until the end of 1993 and 10th revision (*ICD-10*) thereafter. The main reason for diagnostic workup and treatment during hospitalization is labeled the primary (first-listed) diagnosis, whereas other important acute and chronic diseases or conditions are recorded as secondary diagnoses.[13]

We used the Danish Register of Causes of Death[14] to obtain information on causes of death for VTE patients and the comparison cohort. The register contains information from all Danish death certificates since 1943, coded according to the Danish version of the *International Classification of Diseases* (*ICD-8* from 1972–1993; *ICD-10* from 1994–2011).

We also used data from the Danish Civil Registration System, which has monitored changes in vital status and migration on a daily basis for the entire Danish population since 1968.[15]

Patients With VTE

We identified patients with a first-time hospital discharge diagnosis of DVT or PE from January 1980 through December 2011. Patients with diagnoses of both conditions were considered to have only PE. We included both primary and secondary diagnoses. Patients with only emergency room diagnoses of VTE (7.7%) and patients diagnosed only in the hospital outpatient setting (5.4%) were excluded from the analysis because of the expected low positive predictive value of working diagnoses in these settings.[16] Patients with a previous VTE diagnosis during the 3 years before our study period were excluded to avoid inclusion of patients with recurrent thrombosis or complications of previous VTE.

Population Comparison Cohort

We used the Danish Civil Registration System to generate a population-based comparison cohort. For each VTE patient, we randomly matched 5 individuals from the general population on sex, year of birth, and calendar period of VTE diagnosis. To be eligible for the study, persons in the comparison cohort could not have had a hospitalization for VTE before the admission date for the corresponding VTE patient. If a member of the comparison cohort subsequently experienced a VTE, he or she joined the VTE cohort.[17] The admission/matching date for VTE patients/comparison cohort members was defined as the index date.

Patient Characteristics

We obtained information on covariates from the Danish National Registry of Patients. First, we defined the classic risk factors for VTE, that is, cancer diagnosed previously or within 90 days after VTE, fracture/trauma, surgery, or pregnancy within 90 days before the VTE diagnosis.[18] We also included risk factors and potential prognostic factors for VTE[2,4,5,19–21]: myocardial infarction, heart failure, intermittent claudication, stroke, chronic pulmonary disease, diabetes mellitus, ulcer disease, chronic kidney disease, severe liver disease, obesity diagnosed any time before the VTE diagnosis, and pneumonia diagnosed simultaneously or within 90 days before the VTE diagnosis. We created a combined covariate covering echocardiography and imaging examinations of the lungs or lower limbs (ultrasonography, computed tomography scan, magnetic resonance venography, angiography, and ventilation-perfusion scan of the lungs).

Statistical Analysis

We followed up all patients until date of death; emigration; December 31, 2011; or 30 years of follow-up, whichever came first. We characterized VTE patients and comparison cohort members in terms of sex, age categories (<55, 55–64, 65–74, and ≥75 years), calendar period of diagnosis (1980–1989, 1990–1999, and 2000–2011), presence of classic VTE risk factors, and other covariates. We computed the median age with the interquartile range (IQR) at inclusion and median follow-up for all patients and for 30-day survivors. Using the Kaplan-Meier estimator, we computed the 30-day, 31- to 364-day, 1- to 10-year, 11- to 30-year, and 30-year mortality risk for VTE patients overall and for subgroups of patients with DVT, PE, cancer, fracture/trauma, and surgery.

We computed standardized mortality rates per 1000 person-years and illustrated graphically standardized mortality risks for DVT and PE patients (standardized to the age distribution of persons diagnosed with VTE in 2000) for the first 30 days, 31 to 364 days, 1 to 10 years, and 11 to 30 years of follow-up. For the same time periods, we used Cox proportional hazards regression to compute mortality rate ratios (MRRs; specifically, hazard ratios) as measures of relative mortality risk, comparing VTE patients with members of the comparison cohort. We used log-log plots to test the proportionality of hazards visually and found that the assumptions were fulfilled for each of the follow-up periods. In the regression analysis, we dissolved the matching and instead included the matching factors as covariates in the model. In addition to sex, age, and calendar period of diagnosis, we adjusted for the established VTE risk factors and the other covariates. We presented adjusted estimates stratified by age, sex, established VTE risk factors, and other covariates in a forest plot. We tested for secular trends using the Wald χ^2 test.

We computed standardized mortality rates for the most frequent causes of death and compared cause-specific mortality rates among VTE patients and the comparison cohort. To improve the specificity of the VTE diagnosis, we estimated MRRs comparing VTE patients who were diagnosed after 2000 and had a relevant imaging examination during their hospitalization with matched comparison cohort members.

All statistical analyses were carried out with SAS version 9.2 (SAS Institute Inc, Cary, NC). The study was approved by the Danish Data Protection Agency, record number 1-16-02-1-08. Data in the Danish registries are available to researchers, and their use does not require informed consent or ethics approval.

Results

Patient Characteristics

We identified 128 223 persons with a first-time diagnosis of VTE, among whom 74 157 had DVT and 54 066 had PE (10% registered with simultaneous DVT). The comparison cohort included 640 760 persons from the general population matched by year of birth and sex. There were slightly more women (53%) than men for both DVT and PE. The median age was 69 years (IQR, 55–78 years; Table 1) among all VTE patients, 66 years (IQR, 52–77 years) among DVT patients, and 72 years (IQR, 60–80 years) among PE patients. Median follow-up time was 3.8 years overall (IQR, 0.5–9.9 year): 5.6 years (IQR, 1.8–11.8 years) for DVT patients and 1.2 years (IQR, 0–6.6 years) for PE patients. For 30-day survivors, the median follow-up time for VTE patients was 5.3 years (IQR, 2.0–11.1 years). As expected, obesity and other established VTE risk factors were more common among VTE patients than among members of the comparison cohort. The prevalence of other comorbidities was also higher among VTE patients (Table 1).

Overall 30-Year Mortality

VTE patients had higher mortality risk than members of the comparison cohort, with the most pronounced difference in risk within the first year of follow-up (Table 2). We

Table 1. Descriptive Data for Patients With Venous Thromboembolism and for the General Population Comparison Cohort

Characteristics	Deep Venous Thrombosis Cohort (n=74 157), n (%)	Pulmonary Embolism Cohort (n=54 066), n (%)	Comparison Cohort (n=640 760), n (%)
Women	38 410 (52)	29 155 (54)	337 600 (53)
Median age, y	66 (52–77)	72 (60–80)	69 (55–78)
Age categories, y			
<55	21 635 (29)	9850 (18)	157 567 (25)
55–64	13 438 (18)	8451 (16)	109 388 (17)
65–74	17 387 (23)	14 409 (27)	159 161 (25)
≥75	21 697 (29)	21 356 (39)	214 644 (33)
Calendar periods			
1980–1989	22 719 (31)	18 898 (35)	207 670 (32)
1990–1999	19 957 (27)	12 131 (22)	160 455 (25)
2000–2011	31 481 (43)	23 037 (43)	272 635 (43)
Classic venous thromboembolism risk factors	12 798 (17)	11 707 (22)	47 677 (7.4)
Cancer	17 958 (24)	15 501 (29)	26 969 (4.2)
Surgery	6671 (9.0)	4948 (9.2)	9943 (1.6)
Fracture/trauma	764 (1.0)	261 (0.5)	1059 (0.2)
Pregnancy			
Comorbid conditions			
Myocardial infarction	3449 (4.7)	4460 (8.2)	24 445 (3.8)
Congestive heart failure	3576 (4.8)	5137 (9.5)	18 881 (2.9)
Intermittent claudication	819 (1.1)	696 (1.3)	3650 (0.6)
Stroke	3372 (4.5)	3160 (5.8)	20 560 (3.2)
Chronic pulmonary disease	5902 (8.0)	6339 (12)	29 372 (4.6)
Ulcer disease	3467 (4.7)	2678 (5.0)	19 547 (3.1)
Diabetes mellitus	4051 (5.5)	3651 (6.8)	22 993 (3.6)
Chronic kidney disease	1550 (2.1)	1307 (2.4)	5597 (0.9)
Severe liver disease	278 (0.4)	137 (0.3)	703 (0.1)
Obesity	3131 (4.2)	2182 (4.0)	10 423 (1.6)
Pneumonia	4222 (5.7)	5148 (9.5)	13 844 (2.2)

observed a 2-fold increased MRR for VTE overall throughout the follow-up period (DVT, 1.55 [95% confidence interval (CI), 1.53–1.57]; PE, 2.77 [95% CI, 2.74–2.81]; Table 3).

30-Day Mortality

The 30-day mortality risk for VTE patients was 3% for DVT and 31% for PE versus 0.4% for the comparison cohort. Patients with classic VTE risk factors had markedly elevated mortality risks (Table 2). The adjusted 30-day MRR, comparing VTE patients with the comparison cohort, varied according to VTE type (DVT, 5.38 [95% CI, 5.00–5.80]; PE, 80.87 [95% CI, 76.02–86.02]). The 30-day standardized mortality risk and MRR were fairly consistent across calendar periods for DVT (Table 4 and Figure A) but declined for PE (MRR from 138 [95% CI, 125–153] in 1980 to 1989 to 81.97 [95%

Table 2. Mortality Risk Among 128 223 Venous Thromboembolism Patients and 640 760 Members of the General Population Comparison Cohort by Follow-Up Period

	Mortality Risk, % (95% Confidence Interval)				
	30 d	31–364 d	1–10 y	11–30 y	0–30 y
Comparison cohort	0.4 (0.4–0.4)	4.0 (3.9–4.0)	36 (36–36)	68 (67–68)	80 (80–80)
Deep venous thrombosis*	0.4 (0.3–0.4)	3.5 (3.5–3.6)	33 (26–33)	64 (63–64)	85 (85–85)
Pulmonary embolism*	0.4 (0.4–0.4)	4.5 (4.4–4.6)	41 (40–41)	74 (73–74)	77 (76–77)
Venous thromboembolism cohort	15 (15–15)	15 (15–15)	43 (43–43)	68 (67–69)	87 (86–87)
Deep venous thrombosis	3.0 (2.9–3.1)	13 (12–13)	42 (42–43)	68 (67–69)	84 (84–85)
Pulmonary embolism	31 (31–32)	20 (19–20)	45 (44–46)	69 (67–71)	91 (90–91)
Venous thromboembolism subgroups	23 (23–24)	41 (41–42)	69 (68–70)	84 (81–88)	98 (97–98)
Cancer	19 (19–19)	19 (18–19)	42 (41–43)	64 (62–65)	86 (85–87)
Surgery	17 (17–18)	12 (12–13)	41 (39–42)	60 (56–63)	83 (81–84)
Fracture/trauma					

*Mortality risks are provided for each of the matched comparison cohorts.

Table 3. 30-Year Mortality After Venous Thromboembolism Compared With the General Population Comparison Cohort

	Persons, n/Deaths, n	Standardized Mortality Rate* (95% Confidence Interval)	Mortality Rate Ratio (95% Confidence Interval)	
			Crude†	Adjusted‡
Comparison cohort	640 760/297 407	64 (64–64)	1.00 (Referent)	1.00 (Referent)
Venous thromboembolism				
30 d	128 223/19 069	1978 (1950–2007)	44.28 (42.44–46.19)	32.97 (31.56–34.45)
31–364 d	108 732/16 028	188 (185–191)	4.54 (4.45–4.63)	3.28 (3.21–3.35)
1–10 y	88 784/ 31 863	81 (81–82)	1.57 (1.55–1.59)	1.37 (1.36–1.39)
11–30 y	31 778/ 13 198	127 (123–130)	1.31 (1.28–1.33)	1.29 (1.26–1.32)
0–30 y	128 223/80 158	136 (135–137)	2.26 (2.25–2.28)	1.93 (1.91–1.95)
Deep venous thrombosis				
30 d	74 157/2236	383 (367–399)	8.76 (8.18–9.38)	5.38 (5.00–5.80)
31–364 d	71 732/8904	157 (154–160)	3.90 (3.80–4.01)	2.88 (2.80–2.97)
1–10 y	60 756/21 679	80 (79–81)	1.55 (1.53–1.57)	1.36 (1.34–1.38)
11–30 y	22 746/9444	130 (126–134)	1.34 (1.31–1.37)	1.31 (1.28–1.34)
0–30 y	74 157/42 263	102 (101–103)	1.77 (1.75–1.79)	1.55 (1.53–1.57)
Pulmonary embolism				
30 d	54 066/16 833	4504 (4435–4573)	96.63 (90.96–103)	80.87 (76.02–86.02)
31–364 d	37 000/7124	248 (242–254)	5.95 (5.78–6.13)	4.20 (4.06–4.35)
1–10 y	28 028/10 184	84 (82–86)	1.63 (1.60–1.67)	1.41 (1.38–1.45)
11–30 y	9032/3754	119 (113–125)	1.25 (1.21–1.30)	1.24 (1.20–1.29)
0–30 y	54,066/37,895	211 (209–213)	3.29 (3.25–3.33)	2.77 (2.74–2.81)

*Rates per 1000 person-years.

†Adjusted for matching factors (age, sex, and calendar year).

‡Adjusted for matching factors, cancer, fracture/trauma, surgery, pregnancy, myocardial infarction, heart failure, intermittent claudication, stroke, chronic pulmonary disease, diabetes mellitus, ulcer disease, chronic kidney disease, severe liver disease, obesity, and pneumonia.

CI, 72.27–92.98] in 1990 to 1999 and to 36.08 [95% CI, 32.65–39.87] in 2000 to 2011) (Table 4 and Figure B).

31- to 364-Day Mortality

Risk of death remained high among patients who survived the first 30 days after VTE. The mortality risk during 31 to 364 days of follow-up was 13% for DVT patients, 20% for PE patients, and 4% for comparison cohort members (Table 2). The adjusted MRRs were 2.88 (95% CI, 2.80–2.97) for DVT and 4.20 (95% CI, 4.06–4.35) for PE (Table 3). Although less pronounced than for 30-day mortality, 31- to 364-day mortality after PE declined over time (Table 4 and Figure [B]).

Mortality Beyond 1 Year

MRRs for VTE patients surviving >1 year remained elevated for both DVT and PE, but the differences between the 2 groups were reduced. Compared with the population comparison cohort, the MRRs within 1 to 10 years and 11 to 30 years after diagnosis were 36% and 31% higher for DVT and 41% and 24% higher for PE. The 1- to 10-year and 11- to 30-year DVT- and PE-specific MRRs were similar during all calendar periods of diagnosis (Table 4).

Cause of Death

Compared with the general population, patients with VTE had markedly higher death rates for VTE and other cardiovascular diseases, cancer, and respiratory system diseases (Table 5). The adjusted MRR was overall 25-fold increased for VTE. The MRRs for death from PE and DVT were, as expected, substantially increased within the first 30 days but remained 3- to 5-fold increased after DVT and 6- to 10-fold increased after PE within both 1 to 10 years and 11 to 30 years of follow-up (Table 6).

Sensitivity Analyses

Thirty-year mortality remained consistently elevated among all subgroups of VTE patients, regardless of demographics and underlying comorbidity (Figures I and II in the online-only Data Supplement). Of note, patients with cancer had even higher MRRs after DVT and PE than patients without cancer, and patients with diabetes mellitus and liver disease had higher MRRs after PE than patients without these conditions (Figures I and II in the online-only Data Supplement). MRRs were higher for younger than older patients (Figures I and II in the online-only Data Supplement), independently of length of follow-up (Table I in the online-only Data Supplement).

For patients diagnosed between 2000 and 2011, 69% were registered as having had a relevant imaging procedure performed during their hospitalization. The 30-day adjusted MRR for PE was markedly lower for this group compared with all PE patients diagnosed in the same period (20.73; 95% CI, 18.16–23.65) versus 36.08 (95% CI, 32.65–39.87). For patients with DVT who had imaging examinations, the 30-day adjusted MRR was 5.83 (95% CI, 5.09–6.68) compared with 6.36 (95% CI, 5.68–7.13) for all DVT patients. MRRs for other follow-up periods were similar to those for the overall analysis.

Discussion

In this population-based 30-year cohort study, we found that patients with a first-time hospitalization for VTE compared with members of a population comparison cohort had a markedly increased risk of dying within the first year after the event, driven mainly by mortality associated with PE. However, an

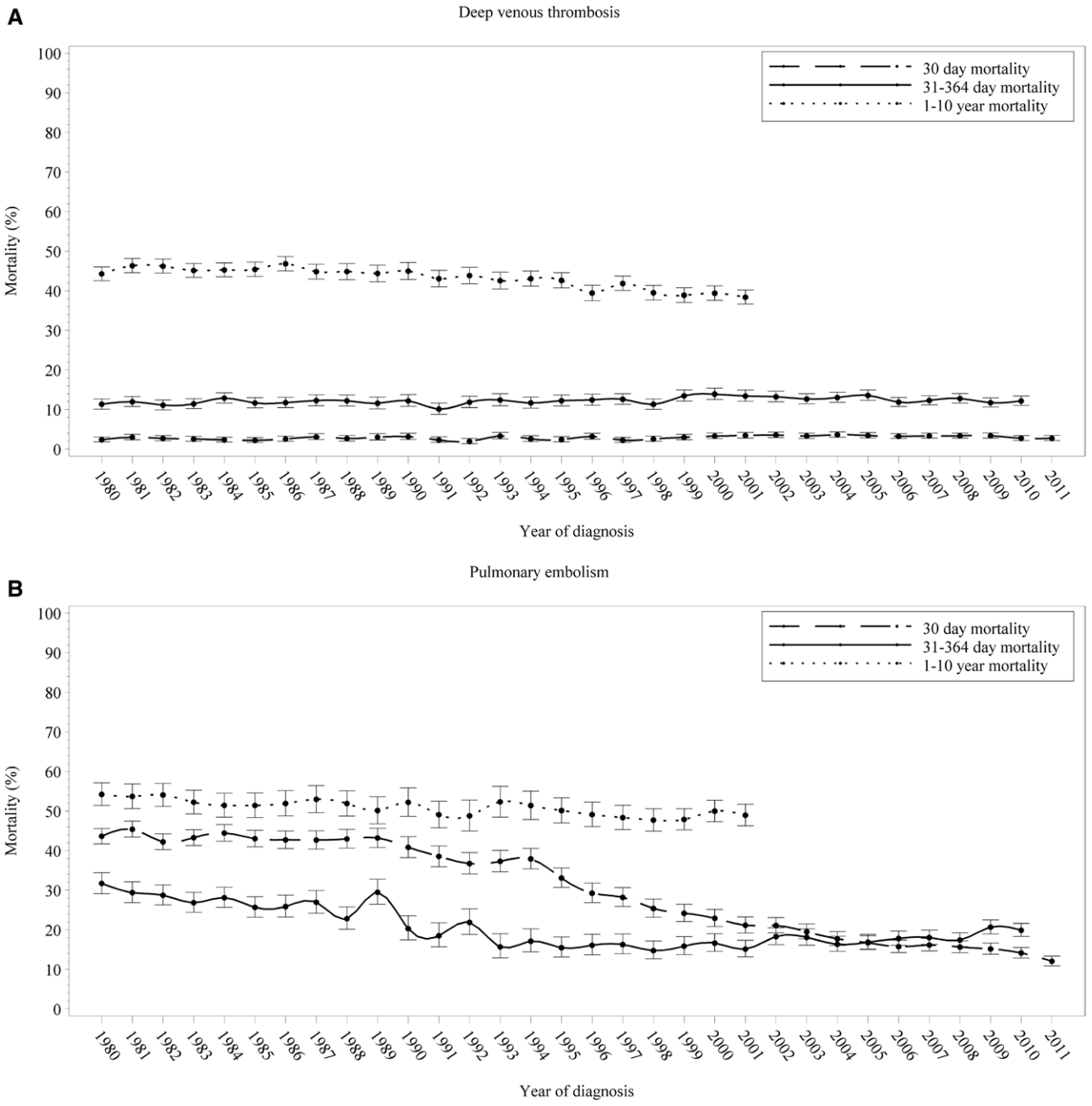

Figure. **A** and **B**, Standardized 30-day, 31- to 364-day, and 1- to 10-year mortality risk (%) after first-time hospitalization for venous thromboembolism between 1980 and 2011.

excess mortality risk persisted throughout the 30-year follow-up period, with similar risks for DVT and PE patients after the first year. We demonstrated a consistently increased mortality regardless of underlying comorbidities. Although DVT and PE were likely to be the cause of death in the short term, this finding persisted even 11 to 30 years after diagnosis. We observed no mortality improvement for patients with DVT, whereas 1-year mortality among patients with PE was markedly reduced over the last 3 decades.

The reported long-term mortality after VTE varies widely (between 12% and 50%) in the existing literature,[1–7,9] with advanced age,[7] cardiovascular disease,[2] underlying cancer,[2–4,12] recurrent VTE, or other medical conditions[4,5] representing important predictors of mortality. Only a few previous studies compared mortality among VTE patients and a population comparison cohort.[1,3,12,22] A recent cohort study from the Netherlands including 5000 adults (age, 18–70 years) diagnosed with a first-time VTE between 1999 and 2004 and with median follow-up of 5.5 years (maximum, 8 years) reported an almost 5-fold overall increased relative risk of mortality among 30-day survivors compared with the general population.[1] Mortality was markedly higher among patients with underlying cancer but was still twice as high in noncancer patients compared with control subjects after adjustment for several comorbidities.[1] Our study confirmed this finding by showing consistently

Table 4. Mortality Rate Ratio for Venous Thromboembolism Patients Compared With the General Population Comparison Cohort (Reference=1.00) by Calendar Period

	Adjusted Mortality Rate Ratio (95% Confidence Interval)*		
Calendar Period	Venous Thromboembolism	Deep Venous Thrombosis	Pulmonary Embolism
1980–1989			
30 d	52.99 (49.23–57.04)	4.79 (4.17–5.50)	138 (125–153)
31–364 d	3.49 (3.36–3.63)	2.64 (2.50–2.78)	5.90 (5.57–6.24)
1–10 y	1.38 (1.35–1.41)	1.39 (1.35–1.42)	1.40 (1.35–1.46)
11–30 y	1.28 (1.25–1.31)	1.31 (1.27–1.35)	1.22 (1.16–1.28)
1990–1999			
30 d	30.12 (27.66–32.80)	4.67 (4.05–5.38)	81.97 (72.27–92.98)
31–364 d	2.89 (2.77–3.02)	2.72 (2.58–2.88)	3.33 (3.09–3.59)
1–10 y	1.31 (1.28–1.34)	1.30 (1.26–1.34)	1.35 (1.29–1.40)
11–20 y	1.32 (1.27–1.37)	1.32 (1.26–1.37)	1.31 (1.23–1.41)
2000–2011			
30 d	18.81 (17.50–20.22)	6.36 (5.68–7.13)	36.08 (32.65–39.87)
31–364 d	3.34 (3.23–3.46)	3.19 (3.05–3.34)	3.57 (3.40–3.75)
1–10 y	1.43 (1.40–1.47)	1.40 (1.36–1.44)	1.49 (1.44–1.55)

We tested for secular trends using the Wald χ^2 test and found that the 30-day, 31- to 364-day, and 1- to 10-year mortality rate ratios were statistically different across the 3 decades for venous thromboembolism and subtypes.

*See the description of the adjusted model in Table 3 or the text.

increased relative mortality estimates for all comorbidities, with only a slight decline in the relative mortality rate after comprehensive adjustment. The Dutch study[1] found similar standardized mortality rates for cancer-free patients with DVT versus PE for the complete follow-up period. We found a substantial difference in standardized mortality rates for DVT versus PE within the first year after diagnosis. Thereafter, the difference in standardized mortality rates leveled out and remained consistently increased in subsequent years.

A Norwegian population-based study of 740 patients with a first-time VTE diagnosed between 1995 and 2001 compared mortality risk after 8 years of follow-up with that in a population comparison cohort.[12] Patients with underlying cancer had 13-fold age- and sex-adjusted increased mortality risk compared with the comparison cohort. This risk remained 2.5-fold increased for cancer patients who survived 3 years. For idiopathic VTE, the MRR was 2.6-fold higher than in the comparison cohort, but among 3-year survivors, the relative risk after 8 years was near unity.[12] The latter finding of unaltered long-term survival was supported by a recent cohort study comparing mortality among patients with VTE and population control subjects.[3] The follow-up period started 3 months after a first or subsequent VTE, and cancer patients were excluded from the study.[3] Similarly, a cohort study of VTE patients did not find an elevated standardized mortality rate among patients surviving cessation of oral anticoagulant treatment.[22] Finally, a population-based cohort study of 1567 patients with first-time VTE indicated a 10% decline in 3-year mortality in patients diagnosed in 2003 compared with 1999 (mortality risk, 0.90; 95% CI, 0.74–1.10).[23]

The mechanism behind the increased long-term mortality risk remains to be further investigated, but it likely reflects both the severity of underlying disease and a VTE-associated excess mortality rate. The high 30-day mortality risk for PE patients is likely directly caused by the thromboembolic event and subsequent complications. In addition to recurrent

Table 5. Cause of Death Among 37 895 Patients With Venous Thromboembolism

		Standardized Mortality Rate (95% Confidence Interval)*		Mortality Rate Ratio (95% Confidence Interval)	
Cause of Death (Immediate)	n (%)	Venous Thromboembolism Cohort	Comparison Cohort	Crude†	Adjusted†
Diseases of the circulatory system	27 989 (36)	34.0 (33.6–34.4)	12.5 (12.4–12.6)	3.16 (3.11–3.20)	2.67 (2.63–2.71)
Venous thromboembolism	9602 (12)	11.7 (11.4–11.9)	0.3 (0.3–0.3)	32.32 (30.77–33.95)	25.52 (24.24–26.87)
Myocardial infarction	1702 (2)	2.1 (2.0–2.2)	1.2 (1.2–1.2)	2.01 (1.91–2.12)	1.73 (1.63–1.83)
Stroke	1952 (2)	2.4 (2.3–2.5)	1.6 (1.5–1.6)	1.81 (1.72–1.90)	1.63 (1.55–1.72)
Diseases of the respiratory system	11 645 (15)	14.2 (13.9–14.4)	8.0 (7.9–8.0)	2.10 (2.06–2.15)	1.69 (1.65–1.72)
Chronic pulmonary disease	2541 (3)	3.1 (3.0–3.2)	1.4 (1.4–1.4)	2.55 (2.44–2.66)	1.93 (1.83–2.02)
Pneumonia	6048 (8)	7.4 (7.2–7.5)	4.8 (4.8–4.9)	1.86 (1.81–1.91)	1.51 (1.46–1.56)
Neoplasm	5524 (7)	6.7 (6.5–6.9)	3.0 (3.0–3.0)	2.46 (2.39–2.53)	1.88 (1.82–1.94)

Cause of death was missing for 11 773 venous thromboembolism patients (15%).

*Per 1000 person-years.

†See description of the crude and adjusted model in Table 3 or in the text.

Table 6. Mortality Among 9602 Venous Thromboembolism Patients With Deep Venous Thrombosis and Pulmonary Embolism as Causes of Death

		Adjusted Mortality Rate Ratio (95% Confidence Interval)*				
Cause of Death (Immediate)	n (%)	0–30 y	30 d	31–364 d	1–10 y	11–30 y
Venous thromboembolism	9602 (100)	25.52 (24.24–26.87)	1345 (876–2065)	45.03 (38.68–52.43)	6.46 (5.89–7.08)	4.00 (3.33–4.80)
Deep venous thrombosis	1404 (15)	7.21 (6.62–7.86)	110 (59.94–201)	17.59 (14.13–21.90)	4.77 (4.21–5.40)	3.41 (2.70–4.30)
Pulmonary embolism	8198 (85)	61.61 (57.27–66.28)	3362 (1807–6254)	118 (94.84–147)	10.96 (9.56–12.57)	5.62 (4.18–7.55)

Cause of death was missing for 11 773 venous thromboembolism patients (15%).

*Mortality rate ratio for venous thromboembolism patients compared with the general population comparison cohort. See the description of the adjusted model in Table 3 or in the text.

episodes of thrombosis, patients with VTE are at higher risk of subsequent cancer and cardiovascular disease.[8,24–27] We confirmed that cancer and cardiovascular diseases were frequent causes of death,[2,3,8] but more important, we also found that VTE and pneumonia were important causes of death among the patients in the VTE cohort. This long-term increased VTE-related death rate among patients diagnosed with VTE has not been reported before. This is highly relevant clinically, pointing to the need for individual patient counseling with a focus on optimizing treatment of VTE and reducing risk factors for VTE recurrence to prevent VTE-related death.

Our study was conducted in a setting with a national health service providing unfettered access to health care, thereby allowing us to avoid referral and selection biases. We included the entire Danish population and achieved complete patient-level follow-up with access to patients' full hospital registry histories (since 1977) and outpatient clinic histories (since 1994).

The validity of our absolute mortality risk estimates depends on the accuracy of VTE diagnoses, whereas that of the relative estimates depends on the ability to adjust for comorbid conditions and other confounders. A validation study comparing VTE diagnoses in the Danish National Registry of Patients and chart review demonstrated that the positive predictive value of inpatient diagnoses of DVT and PE was ≈70% and 80%, respectively.[16] However, these data are >10 years old. With the current use of improved diagnostic imaging, less serious embolisms may be detected, improving the positive predictive value of VTE diagnoses. As a consequence of this enhanced diagnostic procedure (together with a possible improvement in the treatment of VTE), our 30-year risk estimates may not be applicable to VTE diagnosed in more recent years. Although the proportion of patients diagnosed only in the outpatient clinics was very low, exclusion of these patients could potentially have increased our mortality estimates for DVT slightly.

Our finding of increased long-term mortality risk after VTE is likely generalizable to most industrial Western societies with comparable lifestyle, risk factor prevalence, and treatment regimens, but it may not apply to all races, ethnic subgroups, or socioeconomic classes of patients. Importantly, the Danish population is homogeneous in respect to ethnicities, with a majority of Scandinavian and European citizens. The relative mortality estimates are likely generalizable to most industrial Western societies and may apply to other more diverse populations assuming no effect modification by ethnicity or environmental factors.[28]

The cancer and procedure data that we used for defining classic VTE risk factors have high validity.[29] We adjusted for comorbidity-related confounding using a comprehensive list of comorbidities. Overall, the positive predictive values of the diagnoses included in the study have been shown to be consistently high (overall 98%),[30] whereas the completeness of coding is probably lower. Any misclassification of covariates as a result of incomplete registration would most likely be independent of a subsequent diagnosis of VTE. Therefore, if misclassification had any effect on our estimates, it biased them toward the null.[31] Nevertheless, in case of misclassification occurring not at random, the impact on our effect estimates would be less predictable. The registration of all-cause death is accurate.[14] However, the specific cause of death is based on a subjective judgment and therefore is not always correct. Unfortunately, we had no information on the extent of differential misclassification of VTE as the cause of death among our patients.

Conclusions

We found that patients with VTE have a long-term increased risk of dying. The risk is substantially elevated in the first year after diagnosis but remained increased during the entire 30 years of follow-up with VTE as an important cause of death. Over the past 3 decades, 30-day mortality has remained fairly constant after DVT but has improved markedly for PE.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Venous thromboembolism (VTE), encompassing deep venous thrombosis and pulmonary embolism (PE), is a common condition. The existing literature has focused mainly on short-term outcomes after VTE, but critical unanswered questions remain about long-term mortality. What is the absolute long-term mortality risk after deep venous thrombosis and PE, and is recurrent VTE an important cause of death? How does underlying comorbidity affect mortality? Has mortality associated with VTE improved over the last 3 decades? We examined 30-year VTE mortality and compared it with that of the general population. We estimated mortality according to VTE subtypes, underlying comorbidity, and calendar periods of diagnosis. We demonstrated high 30-day mortality for patients with PE, caused directly by the thromboembolic event or immediate complications. Mortality risk remained increased up to 30 years after the initial diagnosis for both deep venous thrombosis and PE, with VTE an important cause of death. We confirmed an increased overall mortality among patients with underlying cancer, congestive heart failure, and several other chronic and acute conditions. We observed no mortality improvement for patients with deep venous thrombosis, whereas 1-year mortality among patients with PE was markedly reduced over the last 3 decades. Our finding of increased short-term and long-term mortality after VTE may apply to most industrial Western societies in which changes in lifestyle, risk factor modification, and treatment regimens followed international recommendations. The clinical implications of our study point to the need for individual patient counseling with a focus on optimizing treatment of VTE and reducing risk factors for VTE recurrence to prevent VTE-related death.

Paper X

CLINICAL TRIALS AND OBSERVATIONS

Risk of venous and arterial thrombotic events in patients diagnosed with superficial vein thrombosis: a nationwide cohort study

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Key Points

- In the 3 months after isolated SVT, the risk of a deep venous event or pulmonary embolism is 3.4%.
- This risk remains fivefold increased more than 5 years after the superficial event.

Recently, it has become apparent that superficial vein thrombosis (SVT) can have serious complications. However, the magnitude of the risk of subsequent deep venous and arterial thrombotic events remains unknown. We examined this in a nationwide population-based setting during a period when SVT was not treated routinely with anticoagulants. The Danish National Registry of Patients, covering all Danish hospitals, was used to identify 10 973 patients with a first-time diagnosis of SVT between 1980 and 2012. A comparison cohort of 515 067 subjects, matched by age, gender, and calendar year, was selected from the general Danish population. Outcomes were venous thromboembolism, acute myocardial infarction, ischemic stroke, and death. During median follow-up of 7 years, the incidence rate of venous thromboembolism was 18.0/1000 person-years (95% confidence interval [CI], 17.2-18.9). The highest risk occurred in the first 3 months (3.4%; 95% CI, 3.0-3.7). Compared with the general population, the hazard ratio was 71.4 (95% CI, 60.2-84.7) in this period, steadily decreasing to 5.1 (95% CI 4.6-5.5), 5 years after the SVT. The hazard ratios for acute myocardial infarction, stroke, and death were 1.2 (95% CI, 1.1-1.3), 1.3 (95% CI, 1.2-1.4), and 1.3 (95% CI, 1.2-1.3), respectively, with the highest risk also shortly after SVT. These data indicate the prognostic importance of SVT and may form the basis for clinical decision-making regarding anticoagulation. (*Blood*. 2015;125(2):229-235)

Introduction

Superficial vein thrombosis (SVT) is a relatively common condition of which the incidence was recently established to be about 0.6 per 1000 person-years (py).[1] In the past, SVT has been considered a benign, self-limiting disorder, requiring only symptomatic treatment.[2,3] However, recent evidence showing that SVT is closely linked to occurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE) indicates the relevance of this condition.[4] Three possible types of associations between SVT and DVT/PE can be distinguished.[5] First, DVT or PE can be present concomitantly with the superficial event; this has been found in up to 29% of patients presenting with acute SVT.[4,6] Second, DVT or PE can develop shortly after a patient initially presents with an isolated superficial event. In a study of 600 patients with symptomatic SVT, but no other thromboembolic events, 18 patients (3%) developed DVT or PE within 3 months, despite most having received anticoagulants.[4] Third, patients with a history of SVT may have a four- to sixfold increased lifetime risk of DVT or PE.[7,8]

This close association between SVT and DVT/PE prompted the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial, which showed that a 45-day anticoagulant treatment regimen after SVT is effective and safe in preventing serious thrombotic events in the 3 months after diagnosis.[9] Two other trials have confirmed these findings.[10,11] As a result, current guidelines now recommend this treatment regimen for patients with SVT of at least 5 cm in length on a lower limb.[12]

Recently, Prandoni and colleagues performed a subanalysis of CALISTO trial data to examine whether SVT is associated with increased risk of subsequent arterial cardiovascular events.[13] The impetus for their research arose from the recently described association between venous and arterial thrombotic events.[14] However, such a relation could not be demonstrated, with a relative risk of 0.97 for arterial cardiovascular events in SVT patients compared with controls.[13]

Although the studies described here offer some insight into the risk of DVT, PE, or arterial events after a SVT diagnosis, they have limitations, such as inclusion of patients with concurrent DVT or small or selected populations (trial or specialist referral settings). We therefore set out to study the association in a large, unselected population (ie, the entire population of Denmark). The size of the study population allowed accurate estimation of absolute and relative risks as well as several subgroup analyses. Our study focused on patients with a first-time diagnosis of SVT without concurrent DVT or PE. We examined risks of subsequent DVT, PE, acute myocardial infarction (AMI), stroke, and death over different periods.

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The online version of this article contains a data supplement.

There is an Inside *Blood* Commentary on this article in this issue.

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Methods

Setting

We obtained data from the Danish National Registry of Patients, which has recorded virtually all acute care hospital discharges since 1977 and visits to outpatient specialist clinics and emergency rooms since 1995.[15] Our source population consisted of the entire cumulative population of Denmark between 1980 and 2012 (7.1 million inhabitants). In all Danish medical registries, patients are identified through their civil registration number. These unique identifiers are assigned at birth and stored in the Danish Civil Registration System (DCRS) along with date of birth, residency status, and dates of immigration, emigration, and death. Their use allows unambiguous linkage among registries. The data in the DCRS are virtually complete and highly accurate.[16]

Study population

Cohort of patients with SVT. We identified all individuals with a first recorded diagnosis of SVT (inpatients and patients treated in hospital outpatient clinics) between 1980 and 2012. We used International Classification of Diseases, 8th revision (ICD-8), codes until December 31, 1993, and ICD-10 codes thereafter (see the ICD Appendix for codes). Patients diagnosed during an emergency room visit were excluded from the cohort because of the low positive predictive value (PPV) of an SVT diagnosis in this setting.[17] We also excluded patients who were diagnosed with a DVT within 1 week of their SVT diagnosis date to avoid misclassification of SVTs that were actually DVTs.

Population comparison cohort. A comparison cohort was sampled from the DCRS. For each patient in the SVT cohort, 50 SVT-free general population cohort members were selected from persons alive on the date of the SVT diagnosis (index date) and matched by age and gender. Follow-up of persons in the comparison cohort was terminated if they developed SVT, in which case they started contributing person-time to the SVT cohort.

Sensitivity analyses. To further maximize the likelihood of restricting the cohort to patients with isolated SVT, we performed a sensitivity analysis focusing on the period between 2004-2012 for which information on anticoagulation therapy was available from the Danish National Database of Reimbursed Prescriptions.[18] Because patients with SVT were generally not treated with anticoagulant therapy during this time, we aimed to exclude possibly misclassified or concomitant DVT by excluding patients from both cohorts who had a redeemed prescription for an anticoagulant within 1 month before or 1 week after their SVT diagnosis date or the index date. In another sensitivity analysis focusing on the period between 2002-2012, we included only patients with a deep vein ultrasound scan within 1 week before or after their SVT diagnosis date or the index date in the comparison cohort.

Exclusions. Subjects from the SVT and general population comparison cohorts who had a prior diagnosis of venous thromboembolism (VTE), AMI, or stroke (on or before the SVT diagnosis date) were excluded.

Study outcomes

Members of the 2 cohorts were linked to the DCRS and the Danish National Registry of Patients to identify all inpatient and outpatient diagnoses of DVT, PE, AMI, and ischemic stroke as well as death (see the ICD Appendix for codes). All diagnoses from emergency room visits were excluded because of their low PPV.[17] Both primary and secondary diagnoses were included.

Confounders

Clinical variables that were related to occurrence of SVT and that were risk factors for any of the study outcomes were considered possible confounding factors. These variables included cancer, pregnancy, fracture, surgery, Charlson Comorbidity Index (CCI) score, and autoimmune disease (see the ICD Appendix for a list of diagnoses). Transient confounders, such as pregnancy, fracture, or surgery, were only considered as such when they occurred around the time of the SVT. When such an event arose later during follow-up and shortly before an outcome arose, it was used to classify the outcome (provoked vs unprovoked event) and not treated as a possible confounder.

Statistical analysis

We followed both cohorts from SVT diagnosis/index date until emigration, death, end of follow-up (December 31, 2012), or the occurrence of a study outcome, whichever occurred first. We calculated the rate of DVT, PE, AMI, stroke, and mortality for the SVT patients and members of the population comparison cohort. Rates were expressed as number of events per 1000 py. We used Kaplan-Meier analysis to construct survival curves, treating death as competing risk, and to estimate risks of each outcome. We used Cox regression to compute the hazard ratio (HR) with accompanying 95% confidence intervals (CI) as measures of relative risk for the endpoint analyses. The VTE outcome was disaggregated into provoked and unprovoked VTE and into DVT and PE. Provoked VTE was defined as all venous thrombotic events occurring within 3 months after surgery, pregnancy, or fracture or when a cancer diagnosis was present in the period of 1 year before and 3 months after the VTE diagnosis date. All other venous thrombotic events were considered unprovoked. All analyses were adjusted for age, gender, and calendar time by study design. We also adjusted for the possible confounders described previously. We stratified by time between index date and study outcome date as follows: 3 months, >3 months to 1 year, >1 year to 5 years, and more than 5 years. Finally, we conducted subgroup analyses for men and women separately as well as for patients without a cancer diagnosis 1 year before and 1 year after the SVT/index date. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Board (record number 1-16-02-1-08) and was conducted in accordance with the Declaration of Helsinki.

Results

Patient characteristics

We identified 10 973 subjects with a diagnosis of SVT, whereas the population comparison cohort (matched by gender, age, and index date) consisted of 515 067 subjects. The proportion of women was ~60% in both cohorts. The median age was 61.7 years (interquartile range 47.5-73.3 years) in the SVT cohort and nearly the same in the general population cohort. In the SVT cohort, 20 patients emigrated during the study period (0.18%); in the comparison cohort, 2505 subjects (0.49%) emigrated during this period. Compared with the population cohort, SVT patients had more cancer diagnoses in the period 1 year before to 1 year after the index date (9.2% vs 2.8%), had been pregnant more often within 3 months before the index date (4.5% vs 0.6% of all women), had more recent fractures (5.6% vs 1.6%) and surgery (19.2% vs 3.9%), had more comorbidity (CCI score >2: 7% vs 3.7%) and were more likely to have autoimmune disease (8.2% vs 4.9%). Patient characteristics are shown in Table 1.

DVT

Of the patients with SVT, 1170 developed DVT during a median follow-up of 6.4 years, leading to an incidence rate of 12.8 per 1000 py (95% CI 12.1-13.6). In the comparison cohort, 6096 developed DVT during a median follow-up of 8.4 years, with a corresponding incidence rate of 1.2 per 1000 py (95% CI 1.1-1.2). This yielded an age- and gender-adjusted HR of 11.8 (95% CI 11.1-12.6), with little change after adjustment for cancer, pregnancy, fracture, surgery, CCI score, and autoimmune disease (HR 11.3; 95% CI 10.5-12.1) (Table 2). Table 3 provides cumulative incidences; Table 4 shows HRs stratified by follow-up time. The risk of DVT after SVT was highest during the first 3 months of follow-up (incidence: 2.5%, 95% CI 2.2-2.8;

Table 1. Characteristics of the SVT cohort and general population comparison cohort, Denmark, 1980-2012

	SVT cohort (N = 10 973)		Comparison cohort (N = 515 067)	
	N	%	N	%
Gender				
Female	6504	59.3	308 895	60.0
Age groups				
0-49 y	3173	28.9	157 700	30.6
50-69 y	4266	38.9	201 883	39.2
>70 y	3534	32.2	155 484	30.2
Year of SVT diagnosis				
1980-1989	2661	24.3	128 139	24.9
1990-1999	2546	23.2	120 927	23.5
2000-2012	5766	52.5	266 001	51.6
Cancer diagnosis in the period 1 y before and 1 y after SVT/index date				
Yes	1010	9.2	14 519	2.8
Pregnancy 3 mo before SVT/index date				
Yes (% of all women)	294	4.5	1 811	0.6
Yes (% of all women <50 y)		16.0		2.0
Fracture 3 mo before SVT/index date				
Yes	619	5.6	8 142	1.6
Surgery 3 mo before SVT/index date				
Yes	2111	19.2	20 034	3.9
CCI score				
0	8692	79.2	449 028	87.2
1	1514	13.8	47 182	9.2
2-3	658	6.0	17 017	3.3
4+	109	1.0	1 840	0.4
Autoimmune disease				
Yes	900	8.2	25 087	4.9

Members of the comparison cohort were selected from persons alive on the date of the patients' SVT diagnosis (index date), matched by age and gender. For both cohorts, all characteristics were determined on or around this date.

adjusted HR: 87.7, 95% CI 70.8-108.6), decreasing steadily to a still considerably increased risk after 5 years of follow-up (adjusted HR: 6.3, 95% CI 5.6-7.0) (Figure 1A).

Two sensitivity analyses were performed to prevent misclassification of DVT as SVT. The first sensitivity analysis, excluding patients who had been using anticoagulants between 1 month before and 1 week after the date of SVT diagnosis or the index date, yielded a slightly higher adjusted risk estimate overall (HR: 15.8, 95% CI 13.6-18.5) as well as for the separate periods: HR for the first 3 months: 97.7 (95% CI 65.6-145.4), declining steadily to an HR for >5 years of 6.6 (95% CI 4.1-10.7) (see supplemental Table 1 on the *Blood* Web site). The second sensitivity analysis, restricted to patients who had an ultrasound scan within 1 week before or after their SVT admission date or the index date, also showed higher risk estimates, with an overall adjusted HR of 17.8 (95% CI 15.6-20.3) and HRs for the first and last periods of 111.5 (95% CI 78.5-158.5) and 7.7 (95% CI 5.6-10.7), respectively (supplemental Table 2).

To study the effect of cancer on our risk estimates, we excluded all patients diagnosed with any form of cancer within 1 year before or 1 year after the SVT or index date. This did not change the effect estimate, with the HR remaining at 11.4 (95% CI 10.6-12.3), again with highest risk occurring in the period shortly after the SVT (supplemental Table 3). In a subgroup analysis stratified by gender, we found that the association between SVT and subsequent DVT was stronger in men than in women (overall HR for men: 14.3 [95% CI 13.0-15.9] vs 9.3 [95% CI 8.4-10.2] for women) (Table 5).

PE

The incidence rate of PE was clearly lower than that of DVT. In patients with SVT, the incidence rate of PE was 4.5 per 1000 py (95% CI 4.1-4.9) compared with 0.9 (95% CI 0.9-1.0) in the general population cohort (Table 2). This yielded an age- and gender-adjusted HR of 4.9 (95% CI 4.4-5.4), which was affected little by adjustment for possible confounders (HR 4.5; 95% CI 4.1-5.0) (Table 2). As in the case of DVT, the risk was highest during the first 3 months of follow-up (0.9% [95% CI 0.7-1.1]; adjusted HR: 45.4 [95% CI 33.9-60.9]). This risk steadily decreased to an HR of 2.9 (95% CI 2.5-3.5) after 5 years of follow-up (Figure 1B). The relationship was stronger in the sensitivity analyses excluding patients who received anticoagulation therapy (overall HR: 6.4; 95% CI 5.1-8.0) and restricted to patients who had received an ultrasound scan (overall HR: 5.5; 95% CI 4.5-6.7) (supplemental Tables 1 and 2). Excluding patients with cancer had little effect (supplemental Table 3). Finally, as for DVT, the association between SVT and subsequent PE was stronger in men than in women (HR: 5.8 [95% CI 5.0-6.8] in men overall vs 3.8 [95% CI 3.3-4.4] in women overall) (Table 5).

Table 2. Incidence rates and hazard ratios by outcome in the SVT and general population cohorts

Outcome	Cohort	No. of events	Incidence rate (95% CI)	HR (95% CI)*	Adjusted HR (95% CI)†
VTE	SVT	1608	18.0 (17.2-18.9)	9.09 (8.60-9.60)	8.55 (8.07-9.05)
	Comparison	11 085	2.1 (2.1-2.2)	Reference	Reference
Unprovoked VTE	SVT	1145	12.8 (12.1-13.6)	9.84 (9.21-10.51)	9.98 (9.33-10.68)
	Comparison	7290	1.4 (1.4-1.4)	Reference	Reference
Provoked VTE	SVT	463	5.2 (4.7-5.7)	7.65 (6.92-8.46)	6.13 (5.51-6.82)
	Comparison	3795	0.7 (0.7-0.7)	Reference	Reference
DVT	SVT	1170	12.8 (12.1 – 13.6)	11.82 (11.07-12.63)	11.28 (10.53-12.08)
	Comparison	6096	1.2 (1.1-1.2)	Reference	Reference
PE	SVT	438	4.5 (4.1-4.9)	4.90 (4.43-5.42)	4.53 (4.09-5.03)
	Comparison	4989	0.9 (0.9-1.0)	Reference	Reference
AMI	SVT	562	5.8 (5.3-6.3)	1.23 (1.13-1.34)	1.17 (1.08-1.28)
	Comparison	24 971	4.8 (4.8-4.9)	Reference	Reference
Ischemic stroke	SVT	700	7.2 (6.7-7.8)	1.36 (1.26-1.47)	1.28 (1.18-1.38)
	Comparison	28 541	5.5 (5.5-5.6)	Reference	Reference
Death	SVT	4475	45.1 (43.8-46.4)	1.44 (1.40-1.49)	1.27 (1.23-1.31)
	Comparison	176 183	33.4 (33.3-33.6)	Reference	Reference

*Adjusted for age and gender by study design.

†Adjusted for age and gender by study design and additionally for cancer, pregnancy, fracture, surgery, CCI score, and autoimmune disease.

Table 3. Risks by outcome in different follow-up time frames after SVT

Outcome	Risks, % (95% CI)*				
	0-10 y	0-3 mo	>3 mo-1 y	>1-5 y	5-10 y
VTE	13.82 (13.12-14.53)	3.35 (3.02-3.70)	2.35 (2.07-2.66)	5.18 (4.72-5.66)	5.09 (4.52-5.70)
Unprovoked VTE	10.03 (9.42-10.66)	2.02 (1.76-2.29)	1.55 (1.33-1.81)	3.93 (3.53-4.36)	4.14 (3.63-4.70)
Provoked VTE	4.00 (3.61-4.41)	1.34 (1.14-1.57)	0.80 (0.64-0.99)	1.27 (1.05-1.53)	0.97 (0.74-1.26)
DVT	10.26 (9.65-10.89)	2.47 (2.19-2.77)	1.82 (1.58-2.10)	3.74 (3.35-4.15)	3.68 (3.20-4.20)
PE	3.58 (3.21-3.97)	0.88 (0.72-1.07)	0.50 (0.38-0.65)	1.35 (1.13-1.61)	1.24 (0.98-1.56)
AMI	4.49 (4.06-4.94)	0.19 (0.12-0.29)	0.55(0.42-0.71)	1.96 (1.69-2.27)	2.48 (2.10-2.91)
Ischemic stroke	5.21 (4.74-5.70)	0.28 (0.20-0.40)	0.46 (0.35-0.61)	2.09 (1.81-2.41)	3.24 (2.80-3.73)
Death	35.00 (33.97-36.04)	2.65 (2.36-2.96)	4.75 (4.35-5.17)	13.56 (12.85-14.28)	18.91 (17.91-19.94)

*Cumulative incidences estimated treating death as a competing risk.

Provoked vs unprovoked VTE

We examined differences between provoked and unprovoked venous thrombotic events, aggregating DVT and PE as VTE. The risk was 2.0% for unprovoked events vs 1.3% for provoked events in the first 3 months following SVT, with adjusted HRs of 69.9 and 59.2 in this follow-up period, respectively (Tables 3 and 4). Adjustment for possible confounders substantially attenuated the HRs only for provoked events (Tables 2 and 4, with crude HRs for the periods for provoked VTE of: 95.4 for 0 to 3 months, 17.8 for 3 months to 1 year, 5.5 for 1 to 5 years, and 3.6 for >5 years; crude HRs for the other outcomes not shown because they barely differed from the adjusted).

AMI and stroke

Over a median follow-up of 7.0 years, 562 patients in the SVT cohort developed an AMI, yielding an incidence rate of 5.8 per 1000 py (95% CI: 5.3-6.3). The corresponding rate in the general population cohort was 4.8 (95% CI: 4.8-4.9). This led to an age- and gender-adjusted HR of 1.2 (95% CI 1.1-1.3), which did not change after adjustment for possible confounders. For ischemic stroke, the rates were slightly higher in both cohorts, but the HRs were similar to those for AMI. The incidence rate was 7.2 (95% CI: 6.7-7.8) per 1000 py in the SVT group and 5.5 (95% CI: 5.5-5.6) in the general population cohort, yielding an unadjusted HR of 1.4 (95% CI 1.3-1.5) and an adjusted HR of 1.3 (95% CI 1.2-1.4) (Table 2). For both AMI and ischemic stroke, the HR was highest in the first 3 months after the SVT diagnosis (1.6 [95% CI 1.0-2.5] for AMI and 2.6 [95% CI 1.8-3.8] for ischemic stroke, decreasing over time to 1.2 [95% CI 1.0-1.3] for AMI and 1.3 [95% CI 1.1-1.4] for ischemic stroke 5 or more years after the SVT). The HRs were similar in the sensitivity analyses (supplemental Tables 1 and 2) and in the analysis excluding cancer patients (supplemental Table 3). A slightly higher risk was observed in men than in women (Table 5).

Mortality

During a median follow-up period of 7.2 years, 4475 SVT patients died, yielding a mortality rate of 45.1 (95% CI: 43.8-46.4) per 1000 py. During a median follow-up period of 8.4 years for the general population cohort, the mortality rate was slightly lower, at 33.4 (95% CI: 33.3-33.6). The unadjusted HR was 1.4 (95% CI 1.4-1.5) and the adjusted HR was 1.3 (95% CI 1.2-1.3). We found a gradient in risk over time, with an adjusted HR of 3.5 (95% CI 3.1-4.0) in the first 3 months after SVT and of 2.2 (95% CI 2.0-2.4) in the 3-month to 1-year period. Subsequently, risks were only minimally increased (Tables 3 and 4). The HR was somewhat lower after excluding cancer patients (supplemental Table 3), but were essentially unchanged in the 2 sensitivity analyses (supplemental Tables 1 and 2). We found no clear difference in mortality between men and women (Table 5).

Discussion

In this nationwide population-based study, we found a risk of 2.5% for subsequent DVT and of 0.9% for PE in patients who presented with an isolated SVT in the first 3 months after the SVT. The risk of subsequent AMI or ischemic stroke was slightly higher in SVT patients, as was their risk of death. The relation between SVT and risk of VTE was time-dependent, with a 70-fold increased risk of VTE in the first 3 months after SVT, declining gradually to a long-term fivefold increased risk after 5 years. These results remained robust in several sensitivity analyses. All HRs for VTE were about 1.5-fold higher in men than in women.

In recent years, data have accumulated on the seriousness of SVT. Having been considered a benign and self-limiting disease, not normally needing treatment, several large studies have shown that the risk of concomitant or subsequent DVT or PE is substantial,

Table 4. HRs by outcome in different follow-up time frames after SVT

Outcome	Adjusted HR (95% CI)*				
	Overall	0-3 mo	>3 mo-1 y	>1 y-5 y	>5 y
VTE	8.55 (8.07-9.05)	71.40 (60.16-84.74)	16.21 (13.92-18.87)	7.32 (6.59-8.12)	5.05 (4.61-5.54)
Unprovoked VTE	9.98 (9.33-10.68)	69.91 (56.56-86.41)	17.59 (14.60-21.20)	9.01 (7.98-10.16)	6.32 (5.69-7.02)
Provoked VTE	6.13 (5.51-6.82)	59.21 (43.75-80.12)	13.56 (10.33-17.78)	4.55 (3.69-5.62)	3.10 (2.57-3.74)
DVT	11.28 (10.53-12.08)	87.69 (70.84-108.55)	23.84 (19.88-28.60)	10.07 (8.89-11.41)	6.26 (5.60-7.00)
PE	4.53 (4.09-5.03)	45.44 (33.91-60.89)	7.23 (5.36-9.75)	3.85 (3.18-4.66)	2.94 (2.50-3.46)
AMI	1.17 (1.08-1.28)	1.62 (1.04-2.51)	1.60 (1.23-2.09)	1.08 (0.93-1.25)	1.15 (1.02-1.29)
Ischemic stroke	1.28 (1.18-1.38)	2.62 (1.82-3.78)	1.45 (1.09-1.94)	1.17 (1.01-1.35)	1.26 (1.14-1.39)
Death	1.27 (1.23-1.31)	3.50 (3.09-3.96)	2.15 (1.96-2.36)	1.12 (1.06-1.19)	1.16 (1.11-1.21)

*Adjusted for cancer, pregnancy, fracture, surgery, CCI score, and autoimmune disease. All hazard ratios compare the SVT cohort with the population cohort as the reference group.

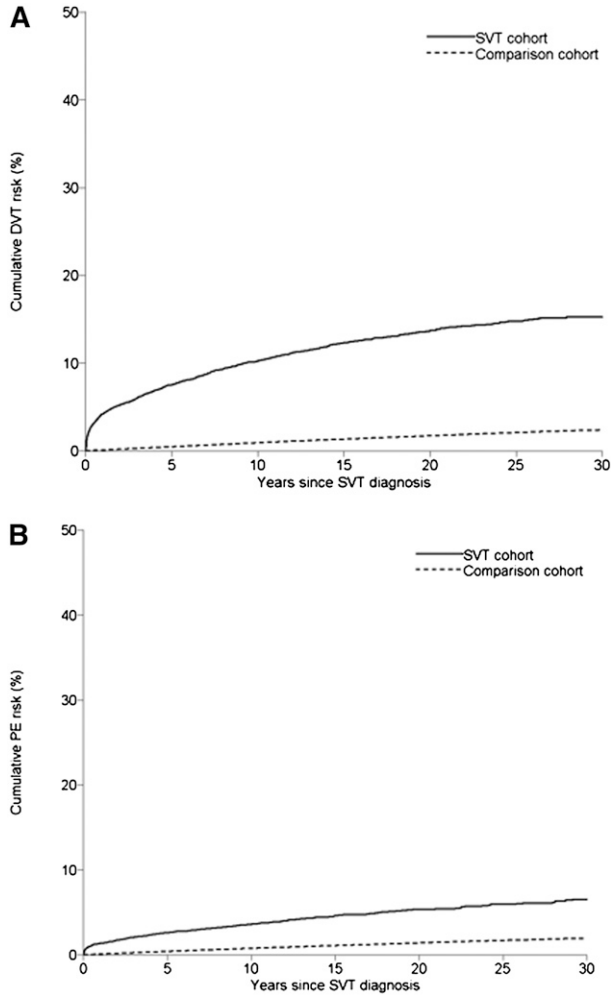

Figure 1. Cumulative incidence of DVT and PE in patients with SVT and in members of the general population comparison cohort. (A) DVT. (B) PE.

and that anticoagulant treatment is beneficial in preventing progression to a more serious thromboembolic event.[4,6,9] In our study, we focused on isolated SVT, excluding concomitant DVT or PE, and examined immediate and longer-term VTE risk during a period when SVT was not treated with anticoagulant therapy. Our findings suggest 2 conclusions about the relation between superficial and deep venous events. First, the immediate risk (within 3 months) of DVT is high (ie, 2.5% and almost 90 times increased). The immediate risk of PE is also elevated, although to a lesser extent (0.9% and 45-fold increased). Apparently, a superficial thrombus easily extends into a clot in the deep veins, which may subsequently embolize. Second, although these risks attenuate over time, they remain 3- to sixfold increased even after 5 years. Our findings are in accord with earlier studies showing VTE risks of 3% to 4% in the first 3 months after SVT[4,19] as well as a four- to sixfold increased long-term risk for deep venous events in patients with a history of SVT[7,8] and suggests that superficial and deep venous events result from a common hypercoagulable state. This thesis is supported by the finding that a DVT occurs in the contralateral leg in up to 10% of cases. The expected percentage would be 0% under the assumption that a DVT occurs only as an extension of the superficial event.[20] Furthermore, risk factors for SVT largely overlap with those for DVT, including high body mass index, immobility, and cancer, which also suggests that SVT and DVT have a similar etiology. Some investigators argue that SVT should not be categorized separately from DVT and PE, but rather be considered as part of the venous thrombotic spectrum.[21] Results from recent studies, including ours, support this view.

We found a clearly higher prevalence of several classical risk factors for DVT and PE in the SVT cohort compared with the general population cohort, such as cancer, surgery, pregnancy, and fracture. Adjustment for these factors led to attenuation of the HR in the provoked VTE group. This suggests that part of the risk in patients with provoked VTE is explained by these factors, which appear to affect the occurrence of both SVT and DVT/PE. The still considerable HR remaining after adjustment could result from other mutual risk factors for which we did not adjust. An alternative explanation is a direct relation in which DVT/PE results from SVT. Considering that we adjusted for the most common and strongest risk factors for VTE, and in light of the clinical course of SVT,[22] the latter mechanism is likely largely responsible for our findings.

In their study of the risk of arterial events in 737 patients with an isolated SVT not involving the saphenofemoral junction,[13] Prandoni and colleagues found no increased risk compared with controls. In our study, we found a slightly higher risk of AMI and stroke subsequent to SVT (HR of 1.2 and 1.3, respectively). As in the case of VTE, these risks were highest in the first 3 months after SVT (HR of 1.6 and 2.6, respectively). However, as described previously, the results of our sensitivity analyses suggest that these relative risks may be somewhat lower, with possibly no effect on AMI. In Prandoni et al's study, a slightly higher risk was also found for stroke compared with AMI among patients with SVT (1.6% vs 1.3%), so a weak association is more likely between SVT and stroke than between SVT and AMI.

Our study showed that risk of death in SVT patients was increased to a similar extent as for AMI and stroke, again with the highest risk close in time to the SVT event. When we excluded cancer patients, the HR was slightly reduced during the first year after SVT.

Table 5. Subgroup analysis with stratification by gender

	Men			Women		
	Adjusted HR (95% CI)*			Adjusted HR (95% CI)*		
Outcome	Overall	0-365 d of follow-up	>365 d of follow-up	Overall	0-365 d of follow-up	>365 d of follow-up
VTE	11.28 (10.37-12.27)	36.57 (31.23-42.81)	7.70 (6.95-8.53)	6.92 (6.40-7.48)	26.16 (22.57-30.31)	4.81 (4.37-5.28)
Unprovoked VTE	13.19 (11.93-14.57)	37.96 (31.26-46.10)	9.60 (8.53-10.81)	8.05 (7.33-8.84)	26.71 (22.22-32.10)	5.98 (5.36-6.67)
Provoked VTE	7.90 (6.75-9.25)	29.67 (22.42-39.25)	4.64 (3.77-5.72)	5.07 (4.38-5.87)	22.51 (17.40-29.13)	3.01 (2.48-3.64)
DVT	14.34 (12.98-15.85)	46.31 (38.38-55.88)	9.55 (8.45-10.80)	9.26 (8.41-10.19)	37.44 (31.05-45.14)	6.33 (5.64-7.11)
PE	5.81 (4.97-6.80)	19.63 (14.49-26.60)	4.27 (3.54-5.14)	3.83 (3.34-4.40)	14.07 (10.92-18.14)	2.73 (2.31-3.23)
AMI	1.25 (1.11-1.40)	1.51 (1.09-2.09)	1.22 (1.07-1.38)	1.09 (0.96-1.24)	1.72 (1.25-2.36)	1.02 (0.89-1.17)
Ischemic stroke	1.36 (1.21-1.53)	1.72 (1.21-2.45)	1.32 (1.17-1.50)	1.22 (1.10-1.35)	1.79 (1.33-2.41)	1.17 (1.05-1.31)
Death	1.34 (1.28-1.41)	2.82 (2.53-3.15)	1.19 (1.13-1.25)	1.22 (1.18-1.27)	2.29 (2.08-2.53)	1.12 (1.07-1.17)

*Adjusted for cancer, pregnancy, fracture, surgery, CCI score, and autoimmune diseases.

We lacked information on causes of death, so can only speculate that PE, AMI, and stroke all may have contributed to the slightly increased mortality.

We found that the relative risks of all thromboembolic outcomes were higher in men. This is remarkable considering that about 60% of SVT patients are female.[4,9] An increased risk of DVT/PE in men with SVT has been described in the POST study[4] and in the Superficial Thrombophlebitis Treated by Enoxaparin Study Group trial.[23] The higher risk in men than in women of recurrent VTE has been recognized for some time,[24] but only recently has it become clear that this disparity in risk also exists for first events.[25] Although the cause of the risk difference between the genders is not yet known, our results are in line with these findings.

While our study sheds light on the pathophysiology and natural course of SVT, it also underscores the clinical importance of anticoagulant treatment to prevent further extension of the superficial thrombus and development of a subsequent DVT or PE. Two recent trials that demonstrated clear beneficial effects of anticoagulant treatment showed that treatment of at least 30 days was necessary.[9,10] The long-term increased risk should be considered particularly in patients with a history of SVT when they are exposed to risk factors for VTE, such as use of oral contraception or a need to undergo surgery. Recently, relative risks of 9 to 50 for occurrence of VTE have been described in patients who had previous SVT and were exposed to such acquired risk factors.[26]

Strengths of our study were its large sample size and its unselected population, leading to precise estimates overall and in the many subgroups examined. Use of computerized registries with nationwide coverage assured virtually complete collection of clinical data.[16] Sufficient additional information was available to allow adjustment for several strong confounders as well as 2 sensitivity analyses.

A study limitation is the lack of detailed information on the extent of the superficial thrombus or the site of the affected leg. We therefore could not study a possible temporal relation between size and location of the superficial event and subsequent occurrence of DVT. Another concern is that we may have missed other confounding factors, such as oral contraceptive use, in the relation between superficial and deep venous events. However, because the relation remained strong after we adjusted for the primary VTE risk factors, it is unlikely that it can be fully explained by confounding. Another possible limitation is exclusion of SVT diagnoses made in the emergency room, which could have led to loss of information. However, emergency room diagnoses generally represent temporary "working diagnoses," which are not updated with final diagnoses (often determined much later). Because the inaccuracy of emergency room diagnoses would have led to misclassification and dilution of the true risks, we decided to exclude them. Furthermore, because our study was based on registry data, we cannot exclude misclassification of SVT or the outcome diagnoses. Although the latter diagnoses have been validated several times, with a PPV of about 75%,[17,27] SVT has been validated once in a study of pregnant and postpartum women.[28] In that study, a high PPV of 89.6% (95% CI 84.3-95.0) was found for SVT. The study's reported PPVs for DVT (74.5 [95% CI 66.8-81.2]) and PE (63.6 [95% CI 40.7-82.8]) did not differ greatly from other validation studies not restricted to pregnant/postpartum women (DVT: 71.3 [95% CI 67.4-75.0]; PE: 82.1 [95% CI 77.2-86.4]).[17] This suggests that the PPV for SVT was also quite accurate. We took several further precautions in our study to ensure that events classified as SVTs were not in fact DVTs. We excluded all DVTs occurring within a week of an SVT and performed 2 sensitivity analyses, which yielded slightly higher HRs than in the main analysis. If some SVTs in fact had been DVTs, we would have overestimated the risk of DVT, and it would be expected that in the more strictly construed sensitivity analyses, the HRs would decrease. Because the opposite occurred, we are quite confident that misclassification of DVTs as SVTs was minimal. Finally, we excluded patients with a history of VTE, AMI, or stroke, but because this history was only available from the start of the study, we may have included a few recurrences (rather than first events only) during the first years of cohort formation.

In conclusion, we found a strong relation between the presence of a superficial thrombosis and subsequent occurrence of a deep venous event in a large, unselected population during a period when SVT was not yet routinely treated with anticoagulants. This relation was strongest in the first months, but remained increased over time. These findings reflect the natural course and the prognostic significance of SVT and emphasize its clinical importance.

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Authorship

Contribution: H.T.S. conceived the study idea and developed it in collaboration with the other coauthors; all authors contributed to the design of the study; E.H.-P. and H.T.S. collected the data; S.C.C. and H.T.S. reviewed the literature; all authors directed the analyses,which were carried out by E.H.-P.; all authors participated in the discussion and interpretation of the results; S.C.C. organized the writing and wrote the initial draft; all authors critically revised the manuscript for intellectual content and approved the final version before submission; H.T.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Paper XI

CLINICAL TRIALS AND OBSERVATIONS

Splanchnic venous thrombosis is a marker of cancer and a prognostic factor for cancer survival

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Key Points

- SVT is a marker of occult cancer, in particular myeloproliferative neoplasms, liver cancer, and pancreatic cancer.
- SVT is a prognostic factor for short-term survival in patients diagnosed with liver or pancreatic cancer.

It is unknown if splanchnic venous thrombosis (SVT) is a marker of occult cancer and a prognostic factor for cancer survival. Using Danish medical registries, we conducted a nationwide cohort study including all patients with first-time SVT (n = 1191) between 1994 and 2011. We followed the patients for subsequent cancer diagnoses and calculated absolute risks and standardized incidence ratios (SIRs). We formed a matched comparison cohort of cancer patients without SVT, and assessed the prognostic impact of SVT on cancer survival by applying the Kaplan–Meier method and Cox regression. We followed the patients for a median of 1.6 years, and found that SVT was a marker of occult cancer. The 3-month cancer risk was 8.0% and the SIR was 33 (95% confidence interval, 27-40), compared with the general population. Increased risk was mainly found for liver cancer (risk = 3.5%; SIR = 1805), pancreatic cancer (risk = 1.5%; SIR = 256), and myeloproliferative neoplasms (risk = 0.7%; SIR = 764). The overall SIR remained increased twofold after 1 or more years of follow-up. SVT was also a prognostic factor for survival in patients with liver and pancreatic cancer. The clinical impact may be a more thorough diagnostic work-up in patients presenting with SVT. (*Blood*. 2015;126(8):957-963)

Introduction

Venous thromboembolism may be a marker of occult cancer. Patients with a lower-limb deep venous thrombosis (DVT) or pulmonary embolism (PE) have a two- to fourfold increased risk of a cancer diagnosis in the first year after the thromboembolic event, compared with the general population.[1-3] Recently, a similar association was demonstrated for superficial venous thrombosis.[4] Patients, in whom thrombosis occurs before cancer diagnosis, are more likely to have advanced disease and higher mortality than cancer patients without venous thromboembolism at time of diagnosis.[5] Splanchnic venous thrombosis (SVT) (ie, thrombosis of portal veins, hepatic veins [Budd-Chiari syndrome], mesenteric veins, and/or splenic veins)[6] also may precede diagnosis of a malignant neoplasm. A few case reports have described SVT as the first sign of liver and pancreatic malignancies.[7-9] A meta-analysis of 32 studies, each including between 10 and 237 patients with portal or hepatic vein thrombosis (HVT), showed that thrombosis often occurred prior to diagnosis of myeloproliferative neoplasms.[10]

The association between SVT and subsequent cancer risk has never been studied in a population-based setting using a comparison cohort. Moreover, the prognostic impact of SVT on cancer survival remains unknown.[11] We therefore examined cancer risk after a first-time SVT diagnosis, compared with cancer risk in the general Danish population. In addition, we compared survival among cancer patients with and without SVT. The present study may extend our understanding of the development of SVT and may have implications for diagnostic work-up for cancer among patients presenting with this indication.

Methods

Data sources and study population

The Danish National Health Service provides tax-funded medical care to all Danish residents and guarantees free access to hospitals and outpatient clinics.[12] We used data from the Danish National Patient Registry,[13] recorded according to International Classification of Diseases (ICD) codes (8th and 10th revision). We identified all hospital inpatients and outpatients with a first-time ICD-10 code of SVT from 1994 through 2011. We retrieved information on comorbidities characterizing the patients from 1977 onwards, using ICD-8 and ICD-10 codes. We categorized the patients according to overall comorbidity level, using diseases included in the Charlson Comorbidity Index.[14,15] We obtained information on diagnoses of liver disease (including varices and ascites), pancreatitis, diabetes, chronic obstructive pulmonary disease (as a proxy for smoking), venous thromboembolism (ie, DVT and PE), congestive heart failure, and myocardial infarction (MI) diagnosed at any time before SVT, and information on surgical procedures performed within 90 days before the thrombosis. We also retrieved registered abdominal ultrasound and computerized tomography (CT) scans performed within 30 days before or during the hospital contact with SVT. Registration of these diagnostic tests is complete since 2002.

Cancer outcomes

To identify patients with cancer, we linked the study cohort (using the patients' unique personal identification number)[16] to the Danish Cancer Registry,[17] which contains data on prospectively recorded incident cancers diagnosed in Denmark since 1943, including month and year of diagnosis, and information on cancer stage at diagnosis. We searched for all cancer diagnoses, myeloproliferative

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neoplasms (including polycythemia vera, primary myelofibrosis, and essential thrombocytemia), and myelodysplastic syndromes (MDS).[18] We excluded patients diagnosed with cancer (except for nonmelanoma skin cancer), myeloproliferative neoplasm, or MDS before the diagnosis date of SVT.

In the prognostic analysis, we examined survival among patients in our cohort who were later diagnosed with liver cancer, pancreatic cancer, or myeloproliferative neoplasm, and compared this with survival among matched cancer patients without SVT. We used the Danish Cancer Registry to identify up to five comparisons for each patient, matched by cancer type and stage (except for myeloproliferative neoplasm as there is no standard staging system), sex, age (5-year intervals), and year of diagnosis (5-year intervals).

All diagnosis codes and variable categorizations used are provided in the supplemental Appendix, available on the *Blood* Web site.

Statistical analysis

Descriptive data are presented as frequencies or as median values with interquartile ranges (IQRs). We followed each patient from date of first diagnosis of SVT until date of cancer diagnosis, emigration, death, or December 31, 2011, whichever came first.

We computed the absolute risk (cumulative incidence) of cancer in patients with a SVT diagnosis, treating death as a competing risk. Standardized incidence ratios (SIRs) (with 95% confidence intervals [CIs]) were used as a measure of relative risk, comparing cancer incidence observed among patients with SVT with that expected based on national cancer incidence rates by age, sex, and calendar year. SIRs were stratified by: patient characteristics, type of thrombosis, primary and secondary diagnoses, covariates, and cancer stage. We repeated the analyses for the subgroup of patients who had an ultrasound or CT scan within 30 days before or during their hospital contact with SVT.

The survival analysis was restricted to the most frequent cancers in the study cohort. We characterized the patients according to diseases occurring before their cancer diagnosis.

We summarized survival of cancer patients, by constructing Kaplan–Meier survival curves. We used Cox proportional hazard regression to compare risk of death among cancer patients with and without SVT, by computing mortality rate ratios and associated 95% CIs (adjusting for cancer type and stage, sex, age, and year of diagnosis).

All statistical analyses were conducted using the SAS statistical software package, version 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency, record #1-16-02-1-08. Danish registry data are generally available to researchers. According to Danish law, the use of registry data for research purposes does not require informed consent.

Table 1. Characteristics and SIRs for cancer in 1191 patients diagnosed with SVT from 1994 to 2011 in Denmark

	Patients, N (%)	Observed cancers, N	SIR (95% CI)
i. All patients	1191(100)	183	4.2 (3.6-4.9)
Women	567 (48)	77	4.1 (3.2-5.1)
Men	624 (52)	106	4.3 (3.5-5.2)
Age group (y)			
<40	213 (18)	22	9.5 (5.9-14)
41-64	479 (40)	86	4.5 (3.6-5.6)
65+	499 (42)	75	3.4 (2.7-4.3)
Calendar period			
1994-1999	216 (18)	40	3.0 (2.2-4.1)
2000-2005	364 (31)	62	3.7 (2.8-4.7)
2006-2011	611 (51)	81	6.0 (4.8-7.5)
SVT as primary diagnosis	674 (57)	104	3.8 (3.1-4.6)
SVT as secondary diagnosis	517 (43)	79	4.9 (3.9-6.1)
SVT confirmed by ultrasound and/or CT scan*	624 (71)	107	7.7 (6.3-9.4)
ii. Comorbidity level			
Low	512 (43)	88	4.7 (3.8-5.8)
Moderate	401 (34)	63	3.8 (2.9-4.8)
Severe	278 (23)	32	4.0 (2.7-5.6)
Liver disease			
Yes	234 (20)	37	6.8 (4.8-9.3)
No	957 (80)	146	3.9 (3.3-4.5)
Pancreatitis			
Yes	137 (12)	16	3.2 (1.8-5.2)
No	1054 (88)	167	4.4 (3.7-5.1)
Diabetes			
Yes	178 (15)	36	6.1 (4.3-8.5)
No	1013 (85)	147	3.9 (3.3-4.6)
Chronic obstructive pulmonary disease			
Yes	102 (9)	15	6.0 (3.4-9.9)
No	1089 (91)	168	4.1 (3.5-4.8)
Venous thromboembolism			
Yes	98 (8)	11	3.2 (1.6-5.8)
No	1093 (92)	172	4.3 (3.7-5.0)
Heart failure or previous MI			
Yes	178 (15)	27	4.4 (2.9-6.3)
No	1013 (85)	156	4.2 (3.6-4.9)
Surgical procedure within previous 90 d			
Yes	399 (33)	61	4.9 (3.7-6.3)
No	792 (67)	122	4.0 (3.3-4.7)

*Examination performed 30 days before or during the hospital contact, among a subgroup of 881 patients diagnosed between 2002 and 2011.

Results

Risk analysis

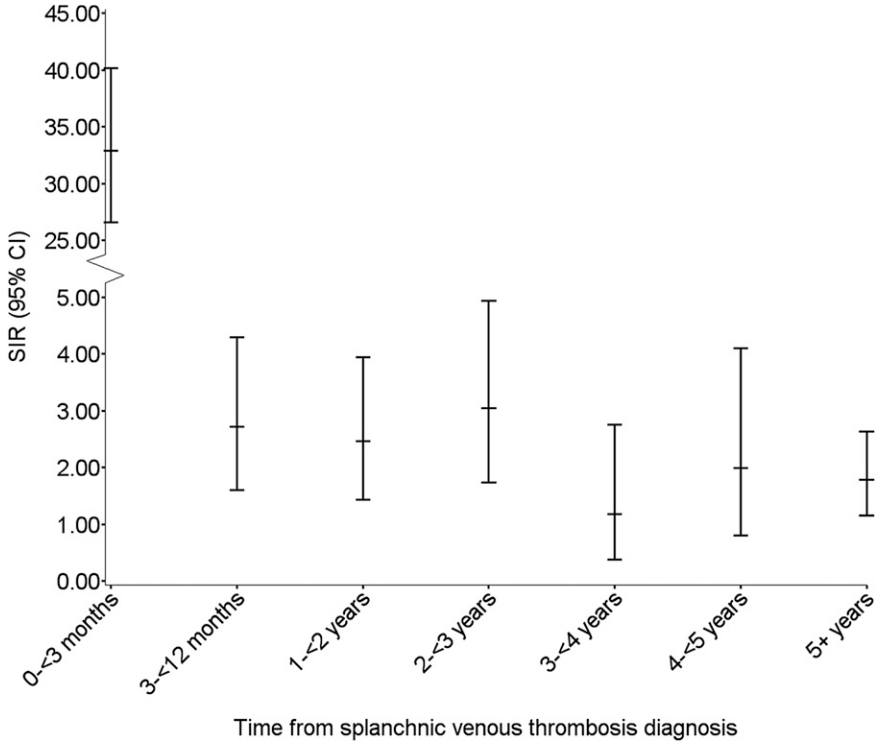
Patient characteristics. We identified 1191 patients with SVT; 924 (78%) had portal vein thrombosis (PVT), 141 (12%) had HVT, and 126 (10%) had mesenteric thrombosis. Median age was 61 years (46-74 years) and 52% were men. Nearly all patients, 1026 (86%) received their thrombosis diagnosis during a hospital admission, whereas only 165 (14%) were diagnosed in an outpatient clinic.

The majority of patients in our cohort had a moderate (34%) or severe (23%) level of comorbidity. In particular, we found a high prevalence of liver disease (20%), diabetes (15%), heart disease (15%), and previous pancreatitis (12%). In addition, 33% of the patients had undergone a surgical procedure less than 90 days prior to their thrombotic event (Table 1). Information on cancer stage was available for 111 (74%) of the 150 patients with nonhematologic cancers. Of these, 52 (47%) had localized cancer and 59 (53%) had regional spread or distant metastasis.

Overall cancer risk. During median follow-up of 1.6 years (IQR, 0-5 years), we identified 183 incident cancers, corresponding to an overall SIR of cancer of 4.2 (95% CI, 3.6-4.9). The majority of cancers were diagnosed among patients with PVT (n = 161, 88%), with an overall SIR of 4.7 (95% CI, 4.0-5.5) (Table 2). In total, 21 cancers (11%) were diagnosed among patients with HVT, corresponding to an overall SIR of 2.9 (95% CI, 1.8-4.4) (Table 2). One cancer was diagnosed in a patient with mesenteric vein thrombosis. During the first 3 months of follow-up, 95 cancers were diagnosed and among these, 53 were diagnosed within the first month. Three-month and 5-year absolute risks of cancer among SVT patients were 8.0% and 14.8%, respectively. During the first 3 months of follow-up, the SIR was 33 (95% CI, 27-40); between 3 and 12 months the ratio was 2.7 (95% CI, 1.6–4.3); and beyond 1 year of follow-up it remained increased twofold, compared with the risk in the general population (Table 1; Figure 1).

We observed no difference in cancer risk between men and women. Although the majority of cancers were diagnosed in patients older than 40 years, the excess risk was more pronounced in patients younger than

Figure 1. SIRs for cancer overall.



age 40. The risk of cancer subsequent to SVT increased during the study period, which likely reflected improved diagnostics with a higher accuracy of diagnoses. Between 1994 and 1999, the SIR was 3.0 (95% CI, 2.2-4.1) and between 2006 and 2011 it was 6.0 (95% CI, 4.8-7.5).

SVT was the primary reason for the hospital contact for 674 patients (57%). Stratification by thrombosis as the primary vs secondary reason for admission yielded SIRs of 3.8 (95% CI, 3.1-4.6) and 4.9 (95% CI, 3.9-6.1), respectively. Patients with liver disease, diabetes, or recent surgery were at higher risk of cancer than patients without these diseases or recent surgery (Table 1). In sub-analyses based on patient characteristics, only chronic obstructive pulmonary disease modified the SIRs after more than 1 year of follow-up (data not presented).

Liver and pancreatic cancer. The increased cancer risk during the first 3 months following an SVT diagnosis stemmed mainly from excess risk of liver cancer (absolute risk = 3.5%; SIR = 1805 [95% CI, 1295-2448]) and pancreatic cancer (absolute risk = 1.5%; SIR = 256 [95% CI, 149-409]), and occurred in patients with PVT. Although the prevalence of liver disease in the overall cohort was 20%, it was present in 50% of the patients diagnosed with liver cancer. Only 4 (20%) of the

Table 2. SIRs for cancer in 1191 patients with SVT, stratified by type of thrombosis

	Overall observed cancers and SIRs (95% CI)							
	Portal vein thrombosis		Hepatic vein thrombosis		Mesenteric vein thrombosis		Overall	
Cancer site								
Any	161	4.7 (4.0-5.5)	21	2.9 (1.8-4.4)	1	0.5 (0.0-2.5)	183	4.2 (3.6-4.9)
Liver	48	175 (129-232)	0	—	0	—	48	138 (101-182)
Myeloproliferative neoplasms	15	111 (62-184)	8	289 (125-570)	0	—	23	133 (85-200)
Pancreas	19	25 (15-40)	1	6.3 (0.2-35)	0	—	20	21 (13-32)
Hodgkin malignant lymphoma	1	13 (0.3-71)	0	—	0	—	1	9.7 (0.3-54)
Gallbladder or biliary tract	3	18 (3.8-53)	0	—	0	—	3	14 (2.9-41)
Metastases and nonspecified cancer in lymph nodes	4	6.5 (1.8-17)	1	7.1 (0.2-40)	0	—	5	6.3 (2.0-15)
MDS	2	14 (1.7-51)	0	—	0	—	2	11 (1.3-38)
Kidney	1	1.9 (0.1-10.5)	1	10 (0.3-55)	0	—	2	3.0 (0.4-11)
Leukemia	3	5.0 (1.0-15)	0	—	0	—	3	3.9 (0.8-11)
Non-Hodgkin malignant lymphoma	3	2.8 (0.6-8.2)	1	4.4 (0.1-25)	0	—	4	3.0 (0.8-7.5)
Lung, bronchi, or trachea	11	3.1 (1.5-5.5)	1	1.5 (0.0-8.3)	0	—	12	2.7 (1.4-4.7)
Colon	5	2.2 (0.7-5.1)	1	2.0 (0.1-11)	0	—	6	2.0 (0.7-4.4)
Breast	4	1.3 (0.4-3.3)	0	—	1	3.8 (0.1-21)	5	1.2 (0.4-2.8)
Bladder	8	4.9 (2.2-9.7)	0	—	0	—	8	3.9 (1.7-7.7)
Stomach	3	6.0 (1.2-17.5)	1	9.2 (0.2-52)	0	—	4	6.3 (1.7-16)
Rectum	0	—	2	7.7 (0.9-28)	0	—	2	1.3 (0.2-4.5)
Uterus	1	2.0 (0.1-11)	0	—	0	—	1	1.5 (0.0-8.4)
Prostate	6	1.6 (0.6-3.5)	0	—	0	—	6	1.3 (0.5-2.9)

Table 3. SIRs for cancer in 1191 patients with SVT

Cancer site	Observed cancers and SIRs (95% CI)							
	0 to <3 months		3 to <12 months		12+ months		Overall	
Any	95	33 (27-40)	18	2.7 (1.6-4.3)	70	2.1 (1.6-2.6)	183	4.2 (3.6-4.9)
Liver	41	1805 (1295-2449)	5	92 (30-215)	2	7.4 (0.9-27)	48	138 (101-182)
Myeloproliferative neoplasms	8	764 (329-1505)	3	119 (25-348)	12	88 (45-153)	23	133 (85-200)
Pancreas	17	256 (149-409)	0	—	3	4.0 (0.8-12)	20	21 (13-32)
Hodgkin malignant lymphoma	1	172 (4.3-956)	0	—	0	—	1	9.7 (0.3-54)
Gallbladder or biliary tract	2	132 (16-476)	1	28 (0.7-155)	0	—	3	14 (2.9-41)
Metastases and nonspecified cancer in lymph nodes	5	86 (28-201)	0	—	0	—	5	6.3 (2.0-15)
MDS	1	75 (1.9-415)	0	—	1	6.8 (0.2-38)	2	11 (1.3-38)
Kidney	2	47 (5.6-168)	0	—	0	—	2	3.0 (0.4-11)
Leukemia	2	38 (4.6-138)	0	—	1	1.7 (0.0-9.3)	3	3.9 (0.8-11)
Non-Hodgkin malignant lymphoma	3	34 (7.0-99)	0	—	1	0.9 (0.0-5.3)	4	3.0 (0.8-7.5)
Lung, bronchi, or trachea	4	13 (3.6-34)	1	1.4 (0.0-8.0)	7	2.0 (0.8-4.2)	12	2.7 (1.4-4.7)
Colon	2	9.5 (1.1-34)	1	2.1 (0.1-12)	3	1.3 (0.3-3.8)	6	2.0 (0.7-4.4)
Breast	1	3.6 (0.1-20)	0	—	4	1.2 (0.3-3.2)	5	1.2 (0.4-2.8)
Bladder	0	—	2	6.1 (0.7-22)	6	3.8 (1.4-8.3)	8	3.9 (1.7-7.7)
Stomach	0	—	1	9.8 (0.3-55)	3	6.1 (1.3-18)	4	6.3 (1.7-16)
Rectum	0	—	0	—	2	1.6 (0.2-5.8)	2	1.3 (0.2-4.5)
Uterus	0	—	1	8.9 (0.2-50)	0	0	1	1.5 (0.0-8.4)
Prostate	0	—	1	1.6 (0.0-8.7)	5	1.4 (0.4-3.2)	6	1.3 (0.5-2.9)

20 patients with pancreatic cancer had previous pancreatitis. Of note, among patients diagnosed with liver cancer with known stage during the first 3 months following the thrombotic event, 16 had localized cancer (SIR = 2451 [95% CI, 1400-3981]) and 9 had advanced cancer (SIR = 1191 [95% CI, 546-2263]). Among patients diagnosed with pancreatic cancer, 2 had localized cancer (SIR = 227 [95% CI, 27-820]) and 11 had advanced cancer (SIR = 263 [95% CI, 131-470]). We found a persistent increased cancer risk beyond 3 months of follow-up, but the estimates were imprecise (Table 3).

Hematologic cancer. The majority of hematologic cancers diagnosed in our cohort was myeloproliferative neoplasms, and were diagnosed among patients with HVT. The absolute risk of a myeloproliferative neoplasm diagnosis during the first 3 months was 0.7% and the SIR was 764 (95% CI, 329-1505) (Table 3). Beyond 1 year of follow-up, the patients still had a pronounced excess risk of myeloproliferative neoplasms (SIR = 88 [95% CI, 45-153]). After 5 years of follow-up, the absolute risk of myeloproliferative neoplasms was 2.2%, and at end of follow-up it was 3.5%. We also observed an excess risk of lymphoma,

Table 4. Characteristics of 91 patients with SVT before cancer diagnosis and 391 cancer patients without a prior SVT

	Cancer type, n (%)					
	Liver cancer		Pancreatic cancer		Myeloproliferative neoplasm	
	Prior SVT (n = 48)	No prior SVT (n = 211)	Prior SVT (n = 20)	No prior SVT (n = 96)	Prior SVT (n = 23)	No prior SVT (n = 84)
Female	11 (23)	36 (17)	9 (45)	45 (47)	17 (74)	54 (64)
Male	37 (77)	175 (83)	11 (55)	51 (53)	6 (26)	30 (36)
Median follow-up (IQR), d	76 (38-182)	115 (35-496)	31 (8-63)	97 (39-259)	2196 (1161-3133)	2499 (1699-3026)
Age at cancer diagnosis, y						
<40	2 (4)	0	0	0	10 (43)	19 (23)
40-64	23 (48)	96 (45)	12 (60)	56 (58)	11 (48)	55 (65)
65+	23 (48)	115 (55)	8 (40)	40 (42)	2 (9)	10 (12)
Median age (IQR), y	65 (58-72)	66 (60-73)	61 (57-70)	63 (57-72)	42 (34-53)	47 (41-55)
Year of cancer diagnosis						
1994-1999	3 (6)	10 (5)	0	0	1 (4)	1 (1)
2000-2005	16 (33)	67 (32)	3 (15)	25 (26)	10 (44)	41 (49)
2006-2011	29 (61)	134 (63)	17 (85)	71 (74)	12 (52)	42 (50)
Comorbidity level						
Low	8 (17)	62 (29)	6 (30)	54 (56)	10 (44)	56 (67)
Moderate	22 (46)	76 (36)	6 (30)	33 (35)	4 (17)	27 (32)
Severe	18 (37)	73 (35)	8 (40)	9 (9)	9 (39)	1 (1)
Liver disease	32 (67)	81 (38)	4 (20)	1 (1)	7 (30)	2 (2)
Pancreatitis	2 (4)	7 (3)	5 (25)	6 (6)	1 (4)	0
Diabetes	18 (38)	56 (27)	8 (40)	20 (21)	2 (9)	2 (2)
Chronic obstructive pulmonary disease	4 (8)	25 (12)	4 (20)	12 (13)	0	4 (5)
Heart failure or previous MI	10 (21)	24 (11)	3 (15)	6 (6)	1 (4)	1 (1)
Ascites	14 (29)	29 (14)	4 (20)	4 (4)	5 (22)	0
Varices	14 (29)	30 (14)	4 (20)	0	7 (30)	0
Surgical procedure within previous 90 d	35 (73)	100 (47)	15 (75)	50 (52)	15 (65)	13 (15)

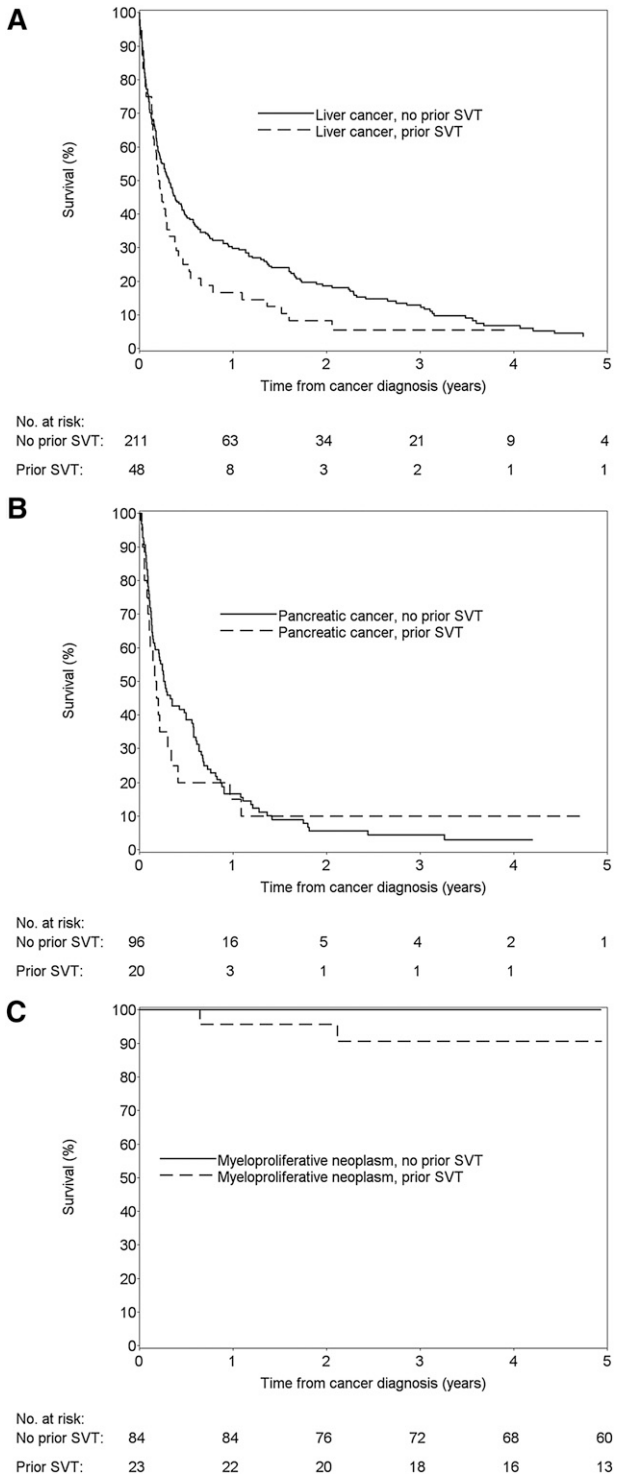


Figure 2. Survival curves for cancer patients with and without SVT. (A-C) Survival curves for patients with a diagnosis of liver cancer (A), pancreatic cancer (B), or myeloproliferative neoplasm (C) and SVT, and for a matched comparison cohort of cancer patients without SVT (matched by cancer type and stage, sex, age [5-year intervals], and year of diagnosis [5-year intervals]).

leukemia, and MDS during the first 3 months of follow-up. Thereafter, the risk did not differ from the expected risk (Table 3).

Other cancers. The number of lung, stomach, gallbladder/biliary tract, and urinary tract cancers observed during follow-up in patients diagnosed with SVT was higher than expected. The overall risk of being diagnosed with these smoking-related cancers was increased threefold to 14-fold compared with the expected (Table 3). Cancers of the colon, rectum, breast, uterus, and prostate were only weakly or not associated with SVT (Table 3).

Patients with ultrasound and/or CT scan-confirmed diagnosis of SVT. Among the 881 patients diagnosed with SVT after 2002, 624 events (71%) were confirmed by abdominal ultrasound and/or CT scan. In this subgroup, the overall cancer risk was even higher (7.7 [95% CI, 6.3-9.4]) than for the entire SVT cohort (Table 1). During the first 3 months of follow-up, the SIR for cancer was 52 (95% CI, 41-66); between 3 and 12 months of follow-up, the ratio was 4.3 (95% CI, 2.2-7.5); and beyond 1 year of follow-up it remained increased twofold. The proportion of SVT confirmed by ultrasound or CT scan increased from 66% in 2002 to 85% in 2011. For patients with a confirmed diagnosis between 2002 and 2006, the overall cancer SIR was 4.7 (95% CI, 3.4-6.5), and between 2007 and 2011 it was 12 (95% CI, 9.4-15).

Survival analysis

Characteristics. The survival analyses included 259 patients with liver cancer, 116 patients with pancreatic cancer, and 107 patients with myeloproliferative neoplasms. Among these patients, SVT preceded the cancer diagnosis in 48 (all with PVT), 20 (19 with PVT and 1 with HVT), and 23 (15 with PVT and 8 with HVT) patients, respectively. Compared with matched cancer patients without SVT, more patients diagnosed with SVT before their cancer diagnosis had a high comorbidity level, including liver disease and associated complications, diabetes, and more had undergone surgical procedures within 90 days (Table 4).

Survival. Patients with liver or pancreatic cancer had a poor outcome, regardless of presence of SVT before cancer diagnosis (Figure 2A-B).

The 3-month survival after liver cancer diagnosis was 44% for patients with and 55% for patients without SVT, corresponding to a mortality rate ratio of 1.5 (95% CI, 0.9-2.3). After 1 year of follow-up, thrombosis was still a prognostic factor for liver cancer patients; survival was 17% among patients with thrombosis and 30% among patients without thrombosis. At the end of follow-up, the mortality rate ratio for liver cancer was 1.6 (95% CI, 1.1-2.3).

SVT was also a prognostic factor for patients with pancreatic cancer. The 3-month survival after pancreatic cancer diagnosis was 35% for patients with and 53% for patients without SVT, yielding a 3-month mortality rate ratio for pancreatic cancer of 1.5 (95% CI, 0.8-2.9). Among patients with pancreatic cancer, SVT was not a prognostic factor for 1-year survival (15% for patients with and 17% for patients without thrombosis). The overall mortality rate ratio for pancreatic cancer was 1.4 (95% CI, 0.8-2.5).

In contrast, patients with myeloproliferative neoplasms had a much better prognosis (Figure 2C), regardless of the presence of an SVT. Due to the few deaths among these patients, we did not analyze the impact of SVT on relative mortality.

Discussion

In this cohort study, we found SVT to be a strong marker of occult cancer. In particular, we observed a higher incidence of liver cancer, pancreatic cancer, and myeloproliferative neoplasms than expected during the first 3 months after a PVT or HVT diagnosis. Although excess cancer occurrence decreased after 3 months, SVT remained a marker of slightly increased cancer risk during subsequent follow-up, especially for myeloproliferative neoplasms. SVT was a prognostic factor for short-term

survival in patients with liver and pancreatic cancer, but did not impact survival in patients with myeloproliferative neoplasms.

The pathogenesis of cancer-related SVT includes cancer-associated hypercoagulability, vessel-wall injury (tumor invasion), and stasis (splanchnic vein compression).[19] Our finding of a greatly increased short-term risk of cancer in patients with SVT may have several explanations. The substantial fall in risk after 3 months of follow-up implies that cancer preceded the thrombosis. An unrecognized malignancy likely triggered thrombus formation, and in some patients it may have been the first sign of cancer. Supporting this assumption, we found that more patients had SVT registered as the primary, rather than secondary, reason for their hospital contact. In other patients, the thrombosis may have been coincidentally detected in the diagnostic work-up for cancer,[11] which could be the case for patients diagnosed with both diseases during the first month of follow-up. The persistent increased risk of liver cancer is likely related to underlying diseases such as liver cirrhosis,[20] whereas the increased risk of myeloproliferative neoplasms beyond 1 year of follow-up may indicate that diagnosis of these neoplasms was delayed.[21] We had no information on test results for the JAK2V617F mutation, but it is possible that the finding of this mutation was related to diagnosis of myeloproliferative neoplasms in some patients.[10] Alcohol abuse is a risk factor for SVT, but is also associated with smoking.[22] Because smoking is a strong risk factor for cancer,[23] a combination of alcohol abuse and smoking may be the link behind the increased risk observed for lung, stomach, and bladder cancers. The increased risk of cancer during the study period likely reflects improved diagnostics, with more frequent use of CT scans.

Our study was conducted in a setting in which a national health service provides unfettered access to health care, allowing us largely to avoid referral and selection biases.[24] Other strengths were our inclusion of the entire Danish population and complete individual-level follow-up through access to patients' full hospital histories, as well as to outpatient clinic histories since 1994. Whereas diagnoses in the Danish Cancer Registry generally have high validity, with up to 95% to 98% completeness and accuracy of recorded diagnoses,[13,17] the registration of SVT in the Danish National Patient Registry has not been validated previously. We sought to strengthen the validity of SVT diagnoses by including only those registered with a specific anatomic location (excluding unspecified abdominal venous thrombosis). Moreover, we found that the majority (71%) of SVT diagnoses in our cohort were based on ultrasound examinations or CT scans, and hence were confirmed diagnoses. Finally, the use of registry data precluded detailed information on clinical care of patients.

Screening with abdomino-pelvic ultrasound, CT, or fluoro-2-deoxy-D-glucose–positron emission tomography combined with CT increases the chance of detecting an occult cancer in patients with venous thromboembolism.[25,26] The most recent guideline by the United Kingdom National Institute for Health and Clinical Excellence (NICE CG144; 2012), recommends considering an abdomino-pelvic CT scan in patients aged over 40 years presenting with venous thromboembolism.[27] We speculate if abdominal CT or PET/CT scans should be mandatory in the diagnostic work-up in patients with SVT. Nevertheless, proposals for implementing new diagnostic work-up procedures for occult cancer are only reasonable if they improve cancer-associated survival and are cost-effective. Based on the existing literature, screening for occult cancers in patients with lower-limb DVT and PE may help identify cancers at an early stage, but does not necessarily improve cancer-related survival.[28] However, the detection of underlying cancer potentially influences the management of venous thromboembolism,[29] as recurrence and complications are more frequent among cancer patients.[30,31]

In conclusion, we found evidence that SVT is a strong marker of occult cancer and a predictor of poor prognosis for patients with liver and pancreatic cancer.

Authorship

Contribution: K.K.S. and H.T.S. conceived the study idea, designed the study, and directed the analyses, which were carried out by D.K.F. and L.P.; K.K.S. reviewed the literature, organized the writing, and wrote the initial drafts; and all authors participated in the interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version.

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Paper XII

Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: a population-based cohort study

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Summary

Background Little is known about adverse events following splanchnic vein thrombosis. Venous thromboembolism has been associated with increased risks of bleeding and arterial cardiovascular events. To learn more about the clinical course of splanchnic vein thrombosis, we examined the risks of bleeding and arterial cardiovascular events in patients with the disease, and compared them with the risks in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) and individuals from the general population.

Methods In this population-based cohort study, we used data for all patients with a diagnosis of splanchnic vein thrombosis recorded in the Danish National Patient Registry (DNPR) between Jan 1, 1994, and Nov 30, 2013 (cumulative source population 7 310 450 individuals). We created two comparison cohorts using data from the DNPR and the Civil Registration System for the same period: one of patients with DVT or PE and another of individuals from the general population. Comparison cohorts (ten comparators per patient with splanchnic vein thrombosis) were matched on sex, age, and calendar year of diagnosis. We calculated absolute risks and used proportional hazard regression to calculate adjusted hazard ratios (HRs) for the primary outcomes of bleeding and arterial cardiovascular events after splanchnic vein thrombosis diagnosis (or the index date for comparison cohorts).

Findings 1915 patients with splanchnic vein thrombosis, 18 373 patients with DVT or PE, and 19 150 individuals from the general population were included in the study. Patients with splanchnic vein thrombosis were followed up for a median of 1 year (IQR 0·1–3·9). These patients had a high risk of bleeding in the 30 days after diagnosis, both in absolute terms (4·3% [95% CI 3·5–5·3]) and in adjusted models (HR 9·64 [95% CI 6·46–14·40] *vs* DVT or PE; 39·79 [19·44–81·46] *vs* general population). Bleeding risk was still significantly increased in patients with splanchnic vein thrombosis up to 1 year after diagnosis (HR 3·01 [95% CI 2·28–3·97] *vs* DVT or PE; 6·83 [4·83–9·65] *vs* general population), and remained elevated for up to 10 years compared with patients with DVT or PE (1·93 [1·12–3·34]) and for up to 19 years compared with the general population (5·90 [2·22–15·64]). The risk of arterial cardiovascular events in patients with splanchnic vein thrombosis was high in the year after diagnosis (absolute risk 3·3% [95% CI 2·6–4·2] up to 30 days; 7·0% [5·8–8·4] up to 31–365 days), and in adjusted models was significantly higher than in patients with DVT or PE (HR 7·05 [95% CI 4·74–10·48] up to 30 days; 2·10 [1·62–2·72] up to 31–365 days) and individuals from the general population (15·75 [9·26–26·79] and 3·17 [2·34–4·27], respectively). However, this risk did not remain significantly elevated above that of patients with DVT or PE after 1 year or the general population after 5 years.

Interpretation Patients with splanchnic vein thrombosis are at increased risk of adverse outcomes, particularly bleeding but also arterial cardiovascular events, for years after diagnosis compared with patients with DVT or PE and the general population. Physicians should be cognisant of these risks in patients with splanchnic vein thrombosis.

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Introduction

Splanchnic vein thrombosis describes venous thrombosis occurring in the intra-abdominal veins, including the portal, hepatic (Budd-Chiari syndrome), mesenteric, and splenic veins. The estimated incidence of splanchnic vein thrombosis is between three and 21 per 100 000 population each year.[1] Risk factors are heterogeneous and include cirrhosis, hepatobiliary cancers, myeloproliferative neoplasms, surgery, abdominal inflammation, and infection.[2] The association between venous thromboembolism and increased risks of bleeding and arterial cardiovascular disease has been extensively studied.[3–5] However, knowledge of the association between splanchnic vein thrombosis and these risks is limited. In 2015, an international multicentre registry with data for 604 patients with splanchnic vein thrombosis provided evidence of a high risk of both bleeding and thrombotic events.[2] In another analysis based on data from the same registry,[6] the incidence of bleeding and thrombotic events was similar among patients with incidentally detected

Research in context

Evidence before this study

Several previous studies have found that venous thromboembolism is associated with an increased risk of bleeding and arterial cardiovascular disease. However, knowledge of the associations between splanchnic vein thrombosis and these outcomes is limited. To date, the largest study of splanchnic vein thrombosis was an international multicentre study in 604 patients, which provided evidence of high risks of both bleeding and thrombotic events in these patients. The nomenclature used for splanchnic vein thrombosis and its manifestations, outcomes, and treatment options is largely non-standardised.

Added value of this study

By use of large-scale, population-based data with long-term follow-up, we confirmed the established increased bleeding risk in patients with splanchnic vein thrombosis. Additionally, we showed for the first time that patients with splanchnic vein thrombosis are also at increased risk of arterial cardiovascular events for up to 1 year after diagnosis compared with patients with deep vein thrombosis or pulmonary embolism and for up to 5 years compared with individuals from the general population.

Implications of all the available evidence

Although risk assessment in patients with splanchnic vein thrombosis is driven by bleeding concerns, the benefit assessment should take a broader perspective, including the excess risk of arterial cardiovascular events, rather than focusing on only prevention of progression and recurrence. Owing to the high risk of arterial cardiovascular disease in patients with splanchnic vein thrombosis, antithrombotic therapy might also be warranted to prevent arterial events in these patients.

versus clinically suspected splanchnic vein thrombosis. Members of our research group previously reported that 30 day mortality for patients with splanchnic vein thrombosis was about 20% and varied by subtype.[1] Circulatory system disease was the most frequent cause of death registered among these patients, while bleeding was recorded as the immediate cause of death in some.[1] High mortality from splanchnic vein thrombosis is likely dependent on thrombosis location[1] and the presence of underlying comorbidities. Additionally, an increased risk of subsequent cardiovascular or bleeding events might affect mortality.[2]

Although treatment of splanchnic vein thrombosis includes anticoagulants, their use is often limited by underlying conditions (eg, cirrhosis) that increase bleeding risk.[7] However, there is some evidence that use of anticoagulants in patients with splanchnic vein thrombosis might reduce the risk of subsequent thrombotic events without increasing the risk of haemorrhagic events.[6]

We investigated the absolute and relative risks of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis compared with patients with venous thromboembolism (deep vein thrombosis [DVT] or pulmonary embolism [PE]) and individuals from the general population in Denmark. These groups allowed comparison with patients with an established increased risk of bleeding and cardiovascular thromboembolic events (those with previous venous thromboembolism), and comparison from a population perspective (ie, among people with an a-priori lower baseline risk of the outcome).

See Online for appendix

Methods

Study design and participants

In this population-based nationwide cohort study, we used data from the Danish National Patient Registry (DNPR),[8] the Danish National Health Service Prescription Database (DNHSPD),[9] and the Civil Registration System (CRS).[10] The study was based on a cumulative source population of 7 310 450 people in Denmark who were alive between Jan 1, 1994, and Nov 30, 2013 (the last date for which data were available). The health-care system in Denmark provides tax-funded medical care to all residents, guaranteeing free access to hospitals and outpatient clinics. Data in the DNPR are coded according to the International Classification of Diseases (ICD) eighth revision (1977–93) and tenth revision (since 1994). The main condition prompting hospital contact is recorded as the primary diagnosis and other accompanying diseases as secondary diagnoses.[8] The availability of DNPR data since 1977 permits characterisation of patients' medical histories at the individual level; data for outpatient clinic visits are available since 1994.[8]

Since 2004, the DNHSPD has captured data on all reimbursed prescriptions redeemed at pharmacies in Denmark through their electronic accounting systems. This data source provided information about use of anticoagulant drugs in our cohorts.[9] The CRS has monitored changes in vital status and migration for the Danish population since 1968.[10] ICD codes, surgery codes, and *Anatomical Therapeutic Chemical Classification System* codes are provided in the appendix (p 2).

Methods for cohort identification were described previously.[1] Briefly, for the cohort of patients with splanchnic vein thrombosis, we identified all individuals (without age restrictions) with a first-time inpatient or hospital outpatient diagnosis of splanchnic vein thrombosis (primary or secondary diagnoses) that was recorded in the DNPR between Jan 1, 1994, and Nov 30, 2013. We excluded patients if they had been diagnosed with splanchnic vein thrombosis before 1994 because these patients would not represent incident cases. Patients with splanchnic vein thrombosis and a previous DVT or PE were eligible for inclusion. Owing to the register-based design, we did not have information about methods of disease evaluation, performance status, or laboratory tests.

We used data from the DNPR and CRS to construct two population-based comparison cohorts. We matched each patient with splanchnic vein thrombosis to ten individuals at random from the patient population in the DNPR with a previous diagnosis of DVT or PE and to ten individuals from the general population in the CRS without a previous diagnosis of DVT or PE. Members of the comparison cohorts were matched to patients with splanchnic vein thrombosis on sex and age, and were assigned an index date corresponding to the date of diagnosis of splanchnic vein thrombosis. Individuals in the general population comparison cohort who were diagnosed with splanchnic vein thrombosis, DVT, or PE after the index date, and those in the DVT or PE comparison cohort who were diagnosed with splanchnic vein thrombosis after the index date, remained in the cohort to avoid informative censoring (ie, censoring conditioned on events occurring in the future). We selected ten matched members for each patient with splanchnic vein thrombosis because this approach was not associated with extra expense (because of the availability of data for the whole population cohort) and to ensure adequate precision of our estimates.

Danish registry data are generally available to researchers. According to Danish law, use of registry data for research purposes does not require informed consent. Aarhus University, on behalf of the Danish Data Protection Board, approved the study (record number 2016-051-000001).

Outcomes

The primary outcomes were all episodes of bleeding and arterial cardiovascular events (recorded as primary diagnoses) occurring after diagnosis of splanchnic vein thrombosis (or the index date for the comparison cohorts). Events occurring on the same date were not included because we could not ascertain the order of diagnoses. Bleeding events included all hospital-based diagnoses of intracranial, respiratory tract, gastrointestinal, and urinary tract bleeding, and bleeding-associated anaemia. The arterial cardiovascular event outcome was a composite of unstable angina pectoris, acute myocardial infarction, and ischaemic stroke. We excluded venous thromboembolism from the composite outcome to avoid potential misclassification bias (given that we used previous DVT or PE to characterise one comparator cohort) and because of the difficulty in differentiating, on the basis of ICD codes, between previous and recurrent DVTs and PEs.[8,11]

We retrieved information from the DNPR about comorbidities in the splanchnic vein thrombosis cohort (previous primary and secondary diagnoses since 1977). Comorbidities included related conditions such as solid cancer, haematological cancer, cirrhosis, gastro-oesophageal varices, other alcoholism-related diseases, pancreatitis, acute abdominal inflammation, and infection (within the past 30 days of diagnosis), and surgical procedures (within the past 90 days; appendix p 2). Comorbidities also included the following general risk factors: previous bleeding, previous arterial cardiovascular events, atrial fibrillation or flutter, congestive heart failure, hypertension, chronic kidney disease, diabetes, obesity, hypercholesterolaemia, chronic obstructive pulmonary disease (a proxy for heavy smoking), inflammatory bowel disease, and recent pregnancy or childbirth (within the past 90 days). The confounders were selected a priori on the basis of expert knowledge and available data.[2] We searched for previous diagnoses of paroxysmal nocturnal haematuria among patients with splanchnic vein thrombosis, but no patient had a record of this condition.

We obtained prescription data (2004–13) on recent use (90 days before or after splanchnic vein thrombosis diagnosis or the index date) of vitamin K antagonists, low-molecular-weight heparin, aspirin or other non-steroidal anti-inflammatory drugs, clopidogrel, and statins.

Statistical analysis

We followed up patients from the date of splanchnic vein thrombosis diagnosis (or the index date for members of the comparison cohorts) to the date of their first subsequent (post-index date) bleeding event or arterial cardiovascular event, death, emigration, Nov 30, 2013, or censoring, whichever came first. We censored patients who had bleeding events for subsequent bleeding events (of other types) but not for subsequent arterial cardiovascular events, and those who had arterial cardiovascular events for subsequent arterial cardiovascular events (of other types) but not for subsequent bleeding events, which enabled events to be captured in both categories.

We characterised patients with splanchnic vein thrombosis and members of the comparison cohorts by sex, age (≤40 years, 41–64 years, and ≥65 years), calendar period of diagnosis (1994–98, 1999–2003, 2004–08, and 2009–13), comorbidity, and use of anticoagulant. We calculated median age at inclusion and median follow-up. We also assessed the risks of bleeding and of arterial cardiovascular events at 30 days, 31–365 days, 1–5 years, and 5–10 years after diagnosis or the index date using the cumulative incidence function and accounting for death as a competing risk for all three cohorts. We repeated these analyses according to subtype of splanchnic vein thrombosis and underlying comorbidities.

In accordance with the matched design, we used stratified Cox proportional hazard regression to estimate hazard ratios (HRs) with 95% CIs that compared outcomes in the splanchnic vein thrombosis cohort with those in the two comparison cohorts. We accounted for competing risk of death in the regression analysis by censoring individuals who died during follow-up. The proportionality of hazards was tested visually with log–log plots and found to be valid after dividing follow-up into the initial 30 days, 31–365 days, 1–5 years, 5–10 years, and 10–19 years. The disaggregated follow-up periods were thus chosen to fulfil the assumptions of non-crossing hazards. Moreover, if we had used 0–1 year or 0–5 year follow-up, the first 30 days would

	SVT cohort (n=1915)	DVT and PE cohort (n=18 373)	General population cohort (n=19 150)
Sex			
Men	1018 (53%)	9662 (53%)	10 180 (53%)
Women	897 (47%)	8711 (47%)	8970 (47%)
Age (years)	63 (49–74)	64 (51–74)	63 (49–74)
Age categories			
≤40 years	271 (14%)	2077 (11%)	2712 (14%)
41–64 years	777 (41%)	7743 (42%)	7740 (40%)
≥65 years	867 (45%)	8553 (47%)	8698 (45%)
Calendar period			
1994–98	224 (12%)	2014 (11%)	2240 (12%)
1999–2003	318 (17%)	3078 (17%)	3180 (17%)
2004–08	521 (27%)	5027 (27%)	5210 (27%)
2009–13	852 (44%)	8254 (45%)	8520 (45%)
SVT-related conditions			
Any cancer	410 (21%)	3083 (17%)	1537 (8%)
Solid cancer*	346 (18%)	2709 (15%)	1413 (7%)
Gastrointestinal	97 (5%)	598 (3%)	252 (1%)
Hepatobiliary tract	65 (3%)	62 (<1%)	12 (<1%)
Urinary or genital tract	89 (5%)	1015 (6%)	531 (3%)
Lung	21 (1%)	269 (2%)	62 (<1%)
Breast	48 (3%)	470 (3%)	331 (2%)
Haematological cancer*	78 (4%)	471 (3%)	147 (1%)
Lymphoma	27 (1%)	213 (1%)	66 (<1%)
Multiple myeloma	6 (<1%)	83 (1%)	10 (<1%)
Leukaemia†	16 (1%)	110 (1%)	34 (<1%)
Myeloproliferative neoplasms‡	23 (1%)	75 (<1%)	26 (<1%)
Myelodysplastic syndromes	8 (<1%)	19 (<1%)	9 (<1%)
Cirrhosis	215 (11%)	124 (1%)	58 (<1%)
Gastro-oesophageal varices	175 (9%)	38 (<1%)	21 (<1%)
Other alcohol-related diseases	223 (12%)	904 (5%)	386 (2%)
Pancreatitis	206 (11%)	258 (1%)	137 (1%)
Acute abdominal inflammation or infection§	74 (4%)	99 (1%)	24 (<1%)
Surgical procedures within 90 days	763 (40%)	3032 (17%)	1063 (6%)
Abdominal surgery	279 (15%)	353 (2%)	109 (1%)
General risk factors			
Previous bleeding	372 (19%)	2203 (12%)	1338 (7%)
Previous arterial cardiovascular events	354 (19%)	3200 (17%)	2154 (11%)
Atrial fibrillation or flutter	173 (9%)	1550 (8%)	847 (4%)
Congestive heart failure	169 (9%)	1324 (7%)	558 (3%)
Hypertension	387 (20%)	3475 (19%)	2136 (11%)
Chronic kidney disease	74 (4%)	588 (3%)	221 (1%)
Diabetes	306 (16%)	1454 (8%)	849 (4%)
Obesity	118 (6%)	1221 (7%)	490 (3%)
Hypercholesterolaemia	89 (5%)	991 (5%)	627 (3%)
Chronic obstructive pulmonary disease	159 (8%)	1813 (10%)	747 (4%)
Inflammatory bowel disease	69 (4%)	298 (2%)	176 (1%)
Pregnancy or childbirth within 90 days	6 (<1%)	85 (1%)	31 (<1%)

Data are n (%) or median (IQR). SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism. *Only the most common types are listed separately. †Chronic myeloid leukaemia accounted for three cases in the SVT cohort, 11 in the DVT and PE cohort, and two in the general population cohort. ‡Included polycythaemia vera, essential thrombocythaemia, and myelofibrosis. §Within 30 days of the SVT diagnosis date (or index date for members of the comparison cohorts).

Table 1: **Characteristics of the study cohorts, 1994–2013**

have had a disproportionately large effect on the estimates. We calculated HRs for the different follow-up periods, adjusting for potential confounders, including conditions related to splanchnic vein thrombosis (eg, cancer, cirrhosis, gastro-oesophageal varices) and general risk factors (eg, previous bleeding, hypertension, diabetes). We did not adjust for anticoagulant treatment because we considered it a mediator rather than a confounder, and adjustment would thus be inappropriate. The regression analysis was performed for the entire splanchnic vein thrombosis cohort, as well as individually for portal, hepatic, and mesenteric vein thrombosis.

To enhance the positive predictive value of splanchnic vein thrombosis diagnosis in the DNPR, we did an analysis restricted to patients who underwent ultrasonography, CT, MRI, or angiography within 30 days of diagnosis (or the index date) during the period of 2002–13 (when these data were available in the DNPR).

All statistical analyses were done with SAS software version 9.4.

Role of the funding source

The funder of the study provided a research grant but had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. BD, EH-P, and HTS had access to the raw data. HTS takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Results

We included 1915 patients with a diagnosis of splanchnic vein thrombosis (1500 with portal vein thrombosis,

204 with Budd-Chiari syndrome, and 211 with mesenteric thrombosis) recorded in the DNPR between Jan 1, 1994, and Nov 30, 2013. We included 18 373 patients in the DVT or PE cohort and 19 150 individuals in the general population cohort. 309 (1·6%) individuals in the general population cohort had DVT or PE during follow-up, and ten were subsequently diagnosed with splanchnic vein thrombosis.

Patients with splanchnic vein thrombosis were followed up for a median of 1 year (IQR 0·1–3·9). Patient characteristics by subtype are shown in the appendix (p 4). During the study period, the incidence of portal vein thrombosis and mesenteric vein thrombosis increased, whereas the incidence of hepatic vein thrombosis was stable over time (appendix pp 3, 4). 852 (44%) of 1915 patients with splanchnic vein thrombosis were diagnosed during 2009–13.

Matching on sex and age was successful because the characteristics of the comparison cohorts were similar to those of the splanchnic vein thrombosis cohort (table 1). Roughly half of patients were women. Median age was similar in all three cohorts (table 1), but varied by subtype of splanchnic vein thrombosis (63 years [IQR 49–73] for portal, 54 years [37–73] for hepatic, and 73 years [62–82] for mesenteric). Patients with splanchnic vein thrombosis had high levels of comorbidities, most frequently cancer, hypertension, diabetes, cirrhosis, and pancreatitis; they had also frequently undergone surgical procedures within the past 90 days (table 1). Patients with DVT or PE also had substantial levels of comorbidities (particularly cancer and hypertension), but recent surgical procedures, gastro-oesophageal varices, cirrhosis, pancreatitis, and other alcohol-related conditions were less common than in patients with splanchnic vein thrombosis (table 1). Members of the general population had a lower comorbidity burden and fewer recent surgical procedures than did members of the other cohorts (table 1). Use of anticoagulants was far higher among patients with splanchnic vein thrombosis, DVT, or PE than among the general population. Vitamin K antagonist use was higher among patients with DVT or PE than among patients with splanchnic vein thrombosis, whereas low-molecular-weight heparin use was higher among patients with splanchnic vein thrombosis than among those with DVT or PE (table 2). Use of aspirin or other non-steroidal anti-inflammatory drugs, clopidogrel, and statins was similar across cohorts.

The risk of bleeding was highest for patients with splanchnic vein thrombosis (table 3). The gastrointestinal tract was the most common site of bleeding in these patients, whereas the urinary tract (DVT or PE cohort and general population cohort) and lower gastrointestinal tract (DVT or PE cohort) were the most common sites of bleeding in the comparison cohorts (table 3). The difference in risk of bleeding between cohorts was mainly dependent on events occurring during the first 5 years after diagnosis (figure). For patients with splanchnic vein thrombosis, the absolute risk of bleeding within 30 days after diagnosis was 4·3% (95% CI 3·5–5·3), peaking at 13·7% (11·3–16·3) 1–5 years after diagnosis (table 4).

Our crude Cox model (adjusted for sex and age) indicated that the risk of bleeding in patients with splanchnic vein thrombosis during the 30 days after diagnosis was almost 11 times higher than in patients with DVT or PE and nearly 41 times higher than in the general population (table 5). After multivariable adjustment, the HRs remained largely unchanged (table 5). Within 1 year after diagnosis, the adjusted HR for bleeding in patients with splanchnic vein thrombosis was 3·01 (95% CI 2·28–3·97) compared with patients with DVT or PE and 6·83 (4·83–9·65) compared with individuals from the general population. HRs for patients with splanchnic vein thrombosis remained elevated for up to 10 years compared with patients with DVT or PE and for up to 19 years compared with individuals from the general population (table 5).

Risks of bleeding in patients with splanchnic vein thrombosis by site of thrombosis and risk factors are shown in the appendix (p 5). Although the absolute bleeding risk was higher in patients with mesenteric than with hepatic or portal vein thrombosis during the first year after diagnosis, bleeding risk after that timepoint was similar across subtypes. Bleeding risks

	SVT cohort (n=1393)	DVT and PE cohort (n=13 471)	General population cohort (n=13 930)
Vitamin K antagonists	534 (38%)	6605 (49%)	421 (3%)
LMWH	155 (11%)	771 (6%)	5 (<1%)
Aspirin or other NSAIDs	461 (33%)	4229 (31%)	3539 (25%)
Clopidogrel	38 (3%)	345 (3%)	237 (2%)
Statins	231 (17%)	2533 (19%)	2338 (17%)

Data are n (%). Denominators are different from the primary analyses because information about medications was available only from 2004 onwards. SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism. LMWH=low-molecular-weight heparin. NSAIDs=non-steroidal anti-inflammatory drugs.

Table 2: **Use of medications associated with increased risk of bleeding and arterial cardiovascular events registered within 90 days of SVT diagnosis, 2004–13**

	SVT cohort (n=1915)	DVT and PE cohort (n=18 373)	General population cohort (n=19 150)
Bleeding	369 (19%)	2165 (12%)	1494 (8%)
Intracerebral	16 (1%)	183 (1%)	178 (1%)
Respiratory tract	19 (1%)	279 (2%)	151 (1%)
Upper gastrointestinal tract	143 (7%)	276 (2%)	185 (1%)
Lower gastrointestinal tract	118 (6%)	645 (4%)	398 (2%)
Urinary tract	44 (2%)	649 (4%)	506 (3%)
Anaemia from bleeding	29 (2%)	133 (1%)	76 (<1%)
Arterial cardiovascular events	273 (14%)	3196 (17%)	2521 (13%)
Myocardial infarction	196 (10%)	2270 (12%)	1756 (9%)
Intracerebral thrombosis	77 (4%)	926 (5%)	765 (4%)

Data are n (%). SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism.

Table 3: **Number of bleeding and arterial cardiovascular events during follow-up**

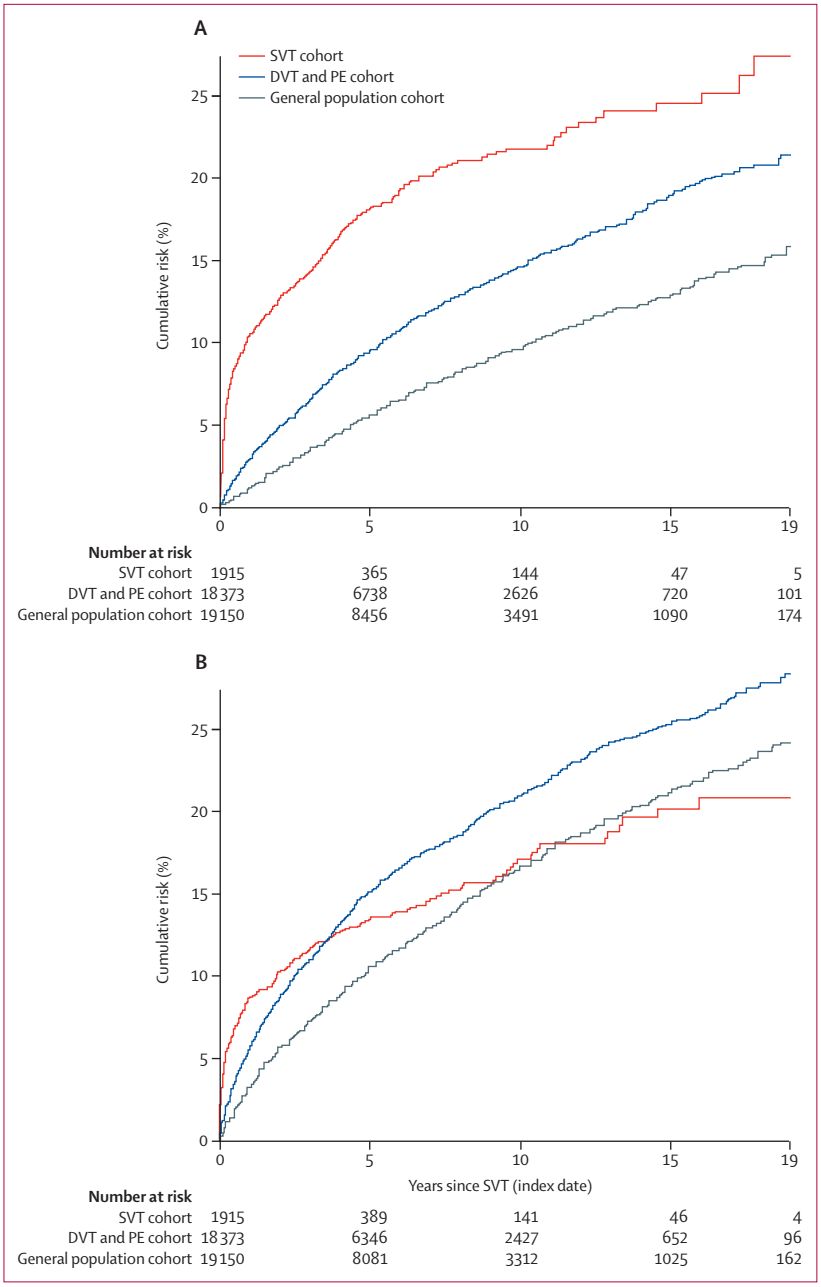

Figure: **Cumulative risk of bleeding (A) and arterial cardiovascular (B) events**
SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism.

within the first year were high among patients with cirrhosis, gastro-oesophageal varices, haematological cancer, atrial fibrillation, or diabetes (appendix p 5).

Most arterial cardiovascular events were myocardial infarction in all three cohorts (table 3). Compared with patients with DVT or PE and individuals from the general population, patients with splanchnic vein thrombosis had an elevated risk of arterial cardiovascular events during the first few years after diagnosis (figure). However, after about 3 years, patients with DVT or PE were at higher risk of arterial cardiovascular events than were patients with splanchnic vein thrombosis and individuals from the general population (figure). The absolute 30 day risk of arterial cardiovascular events among patients with splanchnic vein thrombosis was 3·3% (95% CI 2·6–4·2), and their 31–365 day risk was 7·0% (5·8–8·4; table 4). These observed risks were higher than in patients with DVT or PE and the general population. However, 1–5 years after diagnosis, the absolute risk of arterial cardiovascular events in patients with splanchnic vein thrombosis was lower than that of patients with DVT or PE, and was similar to the risk in the general population (table 4). For the period of 5–10 years after diagnosis, the risk was similar in all three cohorts (table 4).

After multivariable adjustment, the 30 day HR for arterial cardiovascular events in patients with splanchnic vein thrombosis was 7·05 (95% CI 4·74–10·48) compared with patients with DVT or PE and 15·75 (9·26–26·79) compared with individuals from the general population (table 5). During 31–365 days of follow-up, the risk of arterial cardiovascular events was twice as high in the splanchnic vein thrombosis cohort as in the DVT or PE cohort, but thereafter declined towards unity. The adjusted HR remained almost twice as high in patients with splanchnic vein thrombosis as in the general population for up to 5 years after the index date (table 5).

The risk of arterial cardiovascular events by subtype of splanchnic vein thrombosis and risk factors is shown in the appendix (p 6). Among anatomical sites, the risks of arterial cardiovascular events were similar during the first 30 days after diagnosis, but were particularly high for portal vein thrombosis after this period (appendix p 6). For comorbidities, we noted elevated risk among patients with heart disease and those with splanchnic vein thrombosis-related risk factors (appendix p 6).

The results of the sensitivity analysis confirmed the results of the main analysis and indicated an even higher relative risk of bleeding events among patients with splanchnic vein thrombosis who underwent ultrasonography, CT, MRI, or angiography within 30 days of diagnosis (appendix p 7). By contrast, the relative risks of arterial cardiovascular events in these patients were lower in the sensitivity analysis than in the main analysis (appendix p 7).

Discussion

In this nationwide, population-based study in Denmark, we found that patients with splanchnic vein thrombosis were at increased risk of bleeding and arterial cardiovascular events compared with patients with DVT or PE and individuals from the general population. Patients with splanchnic vein thrombosis had elevated risk of bleeding complications for more than 10 years compared with patients with DVT or PE and the general population. Similarly, risk of arterial cardiovascular events was elevated for 1 year compared with patients with DVT or

	30 days	31–365 days	1–5 years	5–10 years	10–19 years
Bleeding					
SVT cohort	4·3% (3·5–5·3)	8·4% (7·0–9·9)	13·7% (11·3–16·3)	9·7% (6·5–13·6)	20·0% (9·3–33·6)
DVT and PE cohort	0·5% (0·4–0·6)	2·7% (2·5–2·9)	7·3% (6·8–7·7)	7·5% (6·8–8·2)	13·0% (10·7–15·5)
General population cohort	0·1% (0·1–0·2)	1·1% (1·0–1·3)	4·6% (4·2–5·0)	5·0% (4·5–5·6)	9·2% (7·4–11·2)
Arterial cardiovascular events					
SVT cohort	3·3% (2·6–4·2)	7·0% (5·8–8·4)	8·3% (6·5–10·4)	9·2% (6·0–13·2)	12·5% (6·0–21·4)
DVT and PE cohort	0·9% (0·8–1·0)	4·8% (4·5–5·2)	11·0% (10·4–11·6)	9·1% (8·3–10·0)	15·2% (12·5–18·1)
General population cohort	0·4% (0·3–0·5)	2·8% (2·6–3·0)	7·6% (7·2–8·1)	7·9% (7·2–8·6)	12·1% (12·2–14·3)

Data in parentheses are 95% CIs. SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism.

Table 4: **Absolute risk of bleeding and arterial cardiovascular events during follow-up**

PE and for up to 5 years compared with the general population.

Short-term survival after splanchnic vein thrombosis depends on several factors, including extension of the thrombus, degree of tissue or organ damage due to compartment pressure, and underlying or coexisting morbidities.[12,13] In a previous study[1] in the same cohort, we reported a 30 day mortality risk of 20·6% in patients with splanchnic vein thrombosis. This risk was 15·6% for portal vein thrombosis, 13·2% for hepatic vein thrombosis, and 63·1% for mesenteric vein thrombosis.[1] Around 10% of recorded deaths were attributed to splanchnic vein thrombosis;[1] other causes included circulatory system disease (24%), respiratory system disease (15%), cancer (12%), liver disease (9%), and sepsis (8%).[1]

We observed a substantial increase in incidence of splanchnic vein thrombosis between 1994 and 2013, although only the incidence of portal vein and mesenteric vein thromboses increased during the study period; the incidence of hepatic vein thrombosis remained unchanged. Improved disease awareness, together with widespread availability of more advanced imaging technologies, could explain this increase, although further testing will be required to fully validate these results. Contradictory to our results, a cohort study[13] in Italy reported a stable incidence of both portal vein thrombosis and Budd-Chiari syndrome in 2002–13. The difference in trends in the incidence of portal vein thrombosis between the two studies might reflect differences in health-care systems or be due to consideration of patients with any hospital contact for splanchnic vein thrombosis in our study.

We found that, although patient characteristics were similar across cohorts, patients with splanchnic vein thrombosis were more likely than patients with DVT or PE to harbour disease-specific conditions such as cirrhosis, gastro-oesophageal varices, pancreatitis, and abdominal surgical procedures. The risk of major or fatal bleeding in patients with splanchnic vein thrombosis with chronic liver disease is much higher than in those without chronic liver disease,[2] especially if gastro-oesophageal varices are also present.[14,15] However, how liver-specific differences between patients might have afffected choice of treatment, and so the bleeding risk, was not examined in our study.

	SVT cohort *vs* DVT and PE cohort		SVT cohort *vs* general population cohort	
	Crude HR*	Adjusted HR	Crude HR†	Adjusted HR
Bleeding				
30 days	10·62 (7·71–14·62)	9·64 (6·46–14·40)	40·84 (25·05–66·58)	39·79 (19·44–81·46)
31–365 days	4·44 (3·56–5·54)	3·01 (2·28–3·97)	11·12 (8·53–14·50)	6·83 (4·83–9·65)
1–5 years	2·48 (1·98–3·11)	2·08 (1·60–2·70)	4·95 (3·89–6·31)	3·46 (2·57–4·68)
5–10 years	1·83 (1·16–2·88)	1·93 (1·12–3·34)	3·07 (1·97–4·78)	2·80 (1·57–4·98)
10–19 years	2·09 (1·05–4·18)	2·15 (0·98–4·71)	4·28 (2·05–8·95)	5·90 (2·22–15·64)
Arterial cardiovascular events				
30 days	4·85 (3·59–6·56)	7·05 (4·74–10·48)	12·82 (8·83–18·62)	15·75 (9·26–26·79)
31–365 days	2·15 (1·73–2·68)	2·10 (1·62–2·72)	4·06 (3·21–5·14)	3·17 (2·34–4·27)
1–5 years	1·04 (0·80–1·35)	0·99 (0·74–1·33)	1·87 (1·43–2·46)	1·70 (1·23–2·35)
5–10 years	1·50 (0·96–2·35)	1·32 (0·77–2·27)	2·16 (1·37–3·41)	1·53 (0·81–2·89)
10–19 years	1·68 (0·82–3·44)	1·33 (0·49–3·56)	2·09 (1·02–4·28)	1·02 (0·29–3·54)

SVT=splanchnic vein thrombosis. DVT=deep vein thrombosis. PE=pulmonary embolism. HR=hazard ratio. *Adjusted for age, sex, and calendar period. †Adjusted for age, sex, calendar period, solid cancer, haematological cancer, cirrhosis, gastro-oesophageal varices, other alcohol-related diseases, pancreatitis, acute abdominal inflammation or infection (within 30 days), surgical procedures (within 90 days), previous bleeding, previous arterial cardiovascular events, atrial fibrillation or flutter, congestive heart failure, hypertension, chronic kidney disease, diabetes, obesity, hypercholesterolaemia, chronic obstructive pulmonary disease, inflammatory bowel disease, and recent pregnancy or childbirth (registered 90 days before SVT).

Table 5: **Relative risk of bleeding and arterial cardiovascular events, by follow-up interval**

We found a higher prevalence of cancer among patients with splanchnic vein thrombosis than among individuals from the general population. Opportunistic screening focused on cancer-related symptoms and signs during diagnostic workup for splanchnic vein thrombosis might be prudent.[16] Although myeloproliferative neoplasms were more frequently recorded among patients with splanchnic vein thrombosis than among individuals in the comparison cohorts, data were too sparse to examine whether the arterial cardiovascular events were related to the presence of myeloproliferative neoplasms.

To our knowledge, no randomised trial has evaluated the risk–benefit ratio of anticoagulation for treatment or secondary prevention of venous thromboembolism or arterial thromboembolism in patients with splanchnic vein thrombosis. The most recent guidelines[17,18] recommend anticoagulation therapy for these patients, but

only after adequate prophylaxis for gastrointestinal bleeding in cases of cirrhosis and thrombosis.[19] These recommendations are based on observational studies that suggested improved survival, reduced recurrence, and improved recanalisation of thrombi with use of anticoagulation.[20–23] Nevertheless, the advantages of this treatment need to be weighed against the risk of gastrointestinal bleeding. The increased risk of bleeding during the first few weeks after any venous thrombosis (DVT, PE, or splanchnic vein thrombosis) is probably associated with the use of anticoagulant treatment. In patients with splanchnic vein thrombosis, this elevated risk might also be due to worsening portal hypertension caused by the thrombus, particularly in patients who are not given anticoagulants or who receive insufficient doses.[2,24] In these patients, the increased bleeding risk is often used as a reason to withhold antithrombotic therapies: a multicentre registry study[25] found that one in four patients with splanchnic vein were not receiving anticoagulant therapy.

Low-molecular-weight heparins are recommended over vitamin K antagonists for treatment of venous thromboembolism at unusual sites.[26] These short-acting drugs have a predictable dose response, have specific antidotes such as protamine, and are much less dependent on liver metabolism than are vitamin K antagonists.[27–29] In our study, patients with splanchnic vein thrombosis were more likely to receive low-molecular-weight heparin than vitamin K antagonist therapy, which is consistent with studies of patients with splanchnic vein thrombosis with comorbidities such as cirrhosis, cancer, and thrombocytopaenia.[26] A preference for low-molecular-weight heparin or fondaparinux (a synthetic pentasaccharide factor Xa inhibitor) over vitamin K antagonist was observed in a large multicentre registry of patients with splanchnic vein thrombosis.[25] Nevertheless, the safety and efficacy of using anticoagulants to treat splanchnic vein thrombosis are still highly debated.[24,30] Direct-acting oral anticoagulants have been shown to reduce the risk of major bleeding compared with vitamin K antagonist in patients with venous thromboembolism, and oral administration with its first-pass effect might produce high drug concentrations at the splanchnic vein thrombosis site.[31,32] Thus, direct-acting oral anticoagulants might also be useful in the treatment of splanchnic vein thrombosis, but more data to support this hypothesis are needed.

We showed that patients with splanchnic venous thrombosis were also at considerably higher risk of developing arterial cardiovascular events than were the two comparison cohorts during the first year of follow-up. This finding suggests that antithrombotic therapy might also be warranted to prevent arterial events in these patients.

Our study's methods were rigorous, based on nationwide health-care and administrative databases linked through unique personal identifiers. These databases contain information about diagnoses, hospital contacts, comorbidities, treatments, and mortality, and generally have a high validity.[9] However, this study has some limitations. As in any retrospective study relying on medical databases, potential misclassification of splanchnic vein thrombosis diagnoses cannot be ruled out. However, in a single-centre study[33] in patients with portal vein thrombosis in Denmark (1992–2005), the discharge diagnosis was confirmed in 67 of 70 patients, with medical record review used as the reference standard. Whereas the validity of the risk estimates depends mainly on adjustment for confounders, that of the absolute risk estimates relies on the accuracy of the diagnoses. Several diagnoses of cardiovascular disease and bleeding used in this study have also been validated and found to be sufficient for research purposes.[8,11] We did not have sufficient data to use the bleeding definition of the International Society of Thrombosis and Hemostasis (ISTH), which has become common practice in prospective research, so we used a modified definition of major bleeding events. However, the ISTH bleeding definition has limitations that can prevent its use in analyses of claims data or data in health-care databases, which often use standardised and validated algorithms. Our registry-based data did not permit identification of patients with recurrent venous thromboembolisms;[8,11] accordingly, these events were not included in the composite cardiovascular outcome.

Moreover, owing to the large scale of our data, we selected the first event for consistency, which meant that, for patients experiencing multiple events within the same category, we chose the first to define the outcome regardless of whether it was the most important or serious. We did not have clinical information to allow assessment of the degree and extension of thrombosis, severity of underlying diseases, presence of pro-thrombotic disorders, and medication administered during hospital stays. We also did not have valid information about the smoking status of patients and therefore used chronic obstructive pulmonary disease as a proxy for heavy smoking. Given that this condition is probably under-reported in our registries, imperfect confounder adjustment in the regression analysis might have led to residual confounding and overestimation of the associations. Finally, we had information about prescriptions for anticoagulant medication in the community but not about anticoagulants administered during hospital stays. The absence of this information prevented analysis of the data according to anticoagulant treatment. Although our study was limited to the population in Denmark, our results are probably generalisable to splanchnic vein thrombosis cohorts in most high-income countries.

In conclusion, we showed that the risks of bleeding and arterial cardiovascular events were increased in patients with splanchnic vein thrombosis compared

with patients with DVT or PE and individuals from the general population. We cannot make specific recommendations about treatment options for patients with splanchnic vein thrombosis. Every case is different and requires assessment of risks and benefits at the level of the individual. However, we suggest that, although risk assessments are driven by bleeding concerns, the assessment should take a broader perspective, including the excess risk of arterial cardiovascular events.

Contributors

KKS, KA, BD, WA, JB-W, and HTS designed the study. BD, EH-P, and HTS obtained and assembled the data. KKS, KA, BD, EH-P, WA, JB-W, and HTS analysed and interpreted the data. KKS, KA, and JB-W wrote the manuscript. All authors revised the manuscript and approved the final version.

Declaration of interests

HTS does not report receiving fees, honoraria, grants, or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. WA reports a research grant from Bayer to support a study of treatment of splanchnic vein thrombosis with rivaroxaban. All other authors declare no competing interests.

Data sharing

Data, analytical methods, and study materials will not be made available to other researchers.

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