The Epidemiology of Venous Thromboembolism in Alberta, Canada: A Population Based Cohort Study.

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

Background: Venous thromboembolism (VTE), comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common acute cardiovascular event associated with increased long-term morbidity, disability, all-cause mortality, and high rates of recurrence. Major advances in diagnosis, prophylaxis, and treatment over the past 3-decades have likely changed its clinical epidemiology. However, there are little published data describing contemporary, population-based, trends in VTE epidemiology.

Objectives: To examine recent trends in the epidemiology of clinically recognized VTE and assess the disease burden in the Canadian province of Alberta.

Methods: Initially, we developed and validated a VTE case identifying algorithm using a combination of International Classification of Diseases (ICD) diagnostic codes and a VTE related imaging procedure codes against patient charts. Then, two retrospective cohort studies based on linkage of administrative health databases in Alberta, Canada, provided estimates of VTE incidence and case fatality over the past decade. Also, we investigated the effect of cancer on overall, short- and long-term mortality in a cohort of consecutive incident PE patients. Poisson regression and Cox's proportional hazard models were used in the multivariate analysis.

Results: 1361 patients were used for the validation of the case-definition. The sensitivity and specificity of our algorithm for identifying patients with VTE using administrative data is 75% (95% CI: 69.18-80.22) and 93.78% (92.19-95.13), respectively. Subsequently, we identified 31,656 cases of acute symptomatic VTE between April 1, 2002, and March 31, 2012. The age and sex adjusted incidence rate of VTE was 1.38 (95% CI: 1.37, 1.40) per 1000 person-years. For pulmonary

embolism it was 0.38 (95% CI: 0.36, 0.40) per 1000 person-years and for deep vein thrombosis it was 1.0 (95% CI: 0.99, 1.1) per 1000 person-years. The adjusted model showed no significant change in the incidence of VTE during the study period. The 30-day case fatality rate of VTE was 2.0% (95% CI: 1.89, 2.21) and was almost doubled in patients with PE 3.9% (95% CI: 3.50-4.33). The 1-year case fatality was 9.2% (95% CI: 8.88-9.52) for VTE and 12.9% (95% CI: 12.2-13.6) for patients with PE. In patients with PE, The 1-year and 5-year survival probabilities were 61% (95% CI: 57-64) and 39% (95% CI: 36-43) in cancer-associated PE patients, 93% (95% CI: 92-94) and 80% (95% CI: 78-81) in provoked PE patients, and 94% (95% CI: 93-95) and 85% (95% CI: 83-87) in unprovoked PE patients, respectively. Compared to patients with unprovoked PE events both short-term and long-term survival in patients with cancer-associated PE have significantly higher observed risk of all-cause mortality in all age groups, P-value <0.001. In contrast, patients with provoked events had similar short- and long-term hazard of death.

Conclusion: Venous thromboembolism is a disease with significant morbidity and mortality. Despite advances in identification, prophylaxis, and treatment in the last decade, the disease burden remains high. While this may be partially due to increased sensitivity of diagnostic methods, especially for PE, it may also imply that current prevention and treatment strategies are less than optimal.

PREFACE

Some of the work referred to, and presented in this dissertation, has been published, will be published, or is currently under peer-review.

Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. Vascular medicine. 2015; 20:364-368

Chapter III and IV (submitted to peer-review journal)

The research project, of which this thesis is a part, received the following research ethics approvals from the University of Alberta Research Ethics Board:

Project Name "Validation of ICD codes for identification of patients with venous thromboembolism in a large health system." No. Pro00048871, May 30, 2014.

Project Name "Establishing a Provincial Venous Thromboembolism Database", No. Pro00044383, November 28, 2013.

DEDICATION

This PhD dissertation is dedicated first and foremost to the greatest women alive. My mother; thank you for teaching me how to hold a pencil.

To my father; thanks for always holding a special place in your heart for me.

I would like to extend this dedication with love to my wife, Bodour. Without your patience, love and encouragement, I wouldn't have accomplished this. I hope your first pregnancy goes well.

To the man, the role-model and the godfather of this work, Dr. Michael Sean McMurtry. This work wouldn't be possible without your constant attention, encouragement, and suggestions, thank you.

To the bionic woman, Dr. Cynthia Wu. Thank you for answering my first email and believing in me. You've been supportive all the way. Your accessibility and immediate responses to feedback as well as your sharing of expertise enabled me to complete all of our projects in a timely manner.

Finally, special thanks to Dr. Khalid Alsaleh and to Dr. Mnahi Bin Saeedan for being so inspirational to me.

ACKNOWLEDGMENT

I am completely grateful to Allah, who blessed me with health and wellbeing to complete this program. I also want to express my deepest gratitude and utmost appreciation to my life mentors: Prof. Ambikaipakan Senthilselvan, Prof. Donald Voaklander, and Dr. Marc Carrier (University of Ottawa) for their expertise and guidance during the different stages of my PhD research.

The staff at the John W. Scott Health Sciences Library have been efficient and helpful beyond expectations. I thank them for their prompt and courteous assistance.

Finally, I am gratefully indebted for the financial support that I received during the completion of my graduate studies by my sponsor (King Saud University-Saudi Arabia) that has provided me with the necessary funds to conduct my studies; this project could not have existed without its support.

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Chapter 1

Introduction

1.1. Introduction to venous thromboembolism

Pulmonary embolism (PE) and deep vein thrombosis (DVT), collectively referred to as venous thromboembolism (VTE), are major sources of morbidity and mortality. DVT is a blood clot that occurs in the venous system.[1] Venous thrombi are clinically significant as they obstruct the veins decreasing return of blood flow to the heart and lungs which results in symptoms such as leg swelling, pain and redness. More importantly, they are possible sources of emboli. Emboli are dislodged thrombi, which travel through the blood to a site distant from their points of origin. Generally, emboli travel through the venous system and the right side of the heart into the pulmonary arterial vasculature. Here the emboli, now considered a PE, obstruct pulmonary circulation and may cause shortness of breath, chest pain and even lead to death.

1.2. Natural history

Although venous thrombosis may occur in any vein, 90% occur in the lower extremities.[2] Superficial venous thrombi generally occur in varicosities, and though they may cause local swelling, pain, and tenderness, they rarely embolize.[1,2] DVT is more serious. Most DVT begin in the calf veins.[2-4] From the calf, the DVT may extend into the proximal veins, and eventually break free to cause PE. In most instances the symptoms of DVT, which include pain, tenderness, edema, and erythema,[5] are not present until the thrombus has extended into the proximal veins.[6]

Among patients presenting with VTE approximately one-third have symptomatic PE.[7] Notably, of patients with symptomatic proximal DVT without symptoms of PE, 40% to 50% have ventilation-perfusion lung scan findings which indicate a high probability of PE.[3] Given the low sensitivity of lung scans for PE,[8] it is believed that PE occurs in most instances of symptomatic proximal DVT.[3] Approximately 10% of individuals with symptomatic PE die within 1 hour of onset.[9] The signs and symptoms of PE are typically nonspecific, and include dyspnea, pleuritic chest pain, cough, leg swelling, hemoptysis, tachypnea, and tachycardia.[5] Given that these symptoms are non-specific, the diagnosis of PE is often delayed or missed. Thus, in many instances only an autopsy can identify PE as the cause of death.[9] Among patients diagnosed with PE prior to death, 5% to 10% are in cardiogenic shock; presenting with both PE and shock is associated with a mortality of 25% to 50%.[10,11] Patients with VTE are at risk of recurrence, chronic thromboembolic pulmonary hypertension (CTEPH) and also of developing post-thrombotic syndrome (PTS).

The risk of VTE recurrence after stopping anticoagulant therapy differs significantly depending on the initial identified provoking factor.[3,12] In patients with a first episode of provoked VTE (i.e., VTE associated with a major transient risk factor like surgery and hospitalization), the risk of recurrence after anticoagulants are stopped is approximately 3% per year.[13,14] In those with a continuing risk factor such as an underlying malignancy, or those with unprovoked thrombosis (i.e., idiopathic), this risk is at least 10% per year, and the risk is greatest shortly after stopping therapy.[15]

CTEPH has been reported as a long-term complication of pulmonary embolism with a cumulative incidence between 0.1% and 9.1% after symptomatic PE.[16,17]

CTEPH as a direct consequence of symptomatic PE is rare, and a significant number of CTEPH cases develop in the absence of previous recognized acute PE. The hallmark of CTEPH is fibrotic transformation of pulmonary arterial thrombus, leading to mechanical obstruction of pulmonary arteries.[18]

Post-thrombotic syndrome occurs as a consequence of venous reflux and residual venous obstruction at the site of a prior DVT.[19] Clinical characteristics can range from mild (e.g. light pain, occasional swelling, and venous ectasia) to severe (e.g. chronic pain, intractable edema, skin alterations, and venous ulcers).[19,20] Approximately 20-50% of patients with a first DVT will develop the syndrome within 1-2 years of symptomatic DVT, and among 5- 10% the symptoms are severe.[21] Therapeutic options for patients with post-thrombotic syndrome are limited. Fortunately, in over 50% of patients most acute DVT symptoms resolve over time.[22]

1.3. Burden of VTE

1.3.1. Incidence

A wide range of VTE incidence rates have been observed, ranging from 0.75 to 2.69 per 1000 individuals in the population, with the incidence in most of the studies ranging between 1.07 and 1.83 per 1000 individual. Numbers may vary depending on the case definition used and the population under study.[23] Also, there is consistent and strong evidence that the global incidence of VTE increases with increasing age.[23] The relative incidence of DVT versus PE is largely a function of whether autopsy data was used in case determination. In instances where autopsy data was not used in the diagnosis of VTE,[7] approximately 33% of VTE cases had PE, and 66% DVT alone. For example, in the Worcester DVT Study, Anderson reported that

32% of VTE cases had PE,[24] while Murin found 30%,[25] and LITE 37%.[26] Direct comparison of these estimates, however, is difficult as studies used different data sources and covered different periods of follow-up.

Although there are few studies designed to look at the trend of VTE incidence,[27-29] a significant increase in VTE incidence has been reported by comparing incidence rates between studies over the last two decades where efficacious and cost-effective DVT prophylaxis strategies were used for medical as well as surgical patients.[30-32] As a result, several evidence-based VTE prevention and treatment guidelines were developed[30,33] and related measures were adopted among quality of care indices for accreditation, quality improvement and benchmarking purposes.[34] In Canada, few studies have reported VTE incidence[35] but none looked at the trend of the disease burden over the recent years.

1.3.2. Mortality

Accurate estimates of VTE case-fatality rates are challenging, especially when autopsies are not performed on patients who die of unexplained causes.[7] Comparing case-fatality rates across studies is difficult due to the differences in follow-up lengths defining case-fatality.[26] Additionally, the distinction between case fatality rates after PE events and DVT events is crucial, as their case-fatality rates differ substantially. The overall 28-day case-fatality of VTE was 11% in the LITE study, while for DVT it was 9% and for PE 15%.[26] The case-fatality rates reported by LITE are generally similar to those of other studies with a comparable definition of case-fatality, however, it is unknown if the trend is changing over the years.[25,29,36] In patients with PE, there is a progressive decline in survival during a median follow-up of 2.1 years through non-PE related deaths.[37] In addition, studies recently reported a 30% all-cause

mortality rate after PE after a median follow-up of 3.3 years.[38] However, describing the long-term outcome of PE in relation to patient's age, baseline comorbidities, and cause- mortality is necessary.

About 70% of fatal PEs are first detected post-mortem,[39] between 60,000 and 300,000 deaths occur annually in the United States from PE, and as many as 200,000 of those deaths occur in hospitals. The in-hospital death rate from pulmonary embolism exceeds the death rate from myocardial infarction.[40-43] Furthermore, up to 2,000,000 new DVTs occur each year within the U.S.[40] Each year, the direct medical costs for the treatment of patients with nonfatal VTE are estimated to be between 5.8 to 7.8 billion US dollars.[44] Despite the large disease and economic burden of VTE, there is a lack of systematic surveillance system for VTE and, therefore, several public health agencies have recognized that the true burden of venous thrombosis is unknown and have highlighted the importance of obtaining contemporary population-based estimates of incidence and mortality.[44]

1.4. Risk factors for initial VTE

Understanding risk factors for VTE is imperative in order to maximize the prevention of this disease in high risk individuals. The major risk factors for thrombosis include intrinsic patient characteristics such as age, gender, obesity and genetic factors, and triggering factors such as malignancy, surgery, immobility or pregnancy. Some of the risk factors are modifiable, while others, like advancing age and genetic predispositions, are not. In the 1856, the pathophysiology of VTE was described by a German physician, Virchow, and this framework has become known as Virchow's triad.[45] The factors making up this triad are vascular endothelial damage, alteration in blood flow (particularly stasis/immobility for venous

thrombosis), and hypercoagulability. Patients who had a disease or condition that included one of these factors were considered to have a predisposing condition, whereas patients without any of these factors were categorized as having an idiopathic venous thrombosis. Back then, the main terms used to categorize acute venous thrombotic events were idiopathic and secondary venous thromboembolism. Subsequently, the term unprovoked, first coined by Kearon,[46] began to be used instead of idiopathic, and provoked was used in place of secondary. Accurate classification of an acute VTE as either provoked, unprovoked or cancer-associated is important because there is mounting evidence that the risk of recurrent venous thromboembolism and mortality is different among patients who have a provoking risk factor than among patients who have an unprovoked VTE.[47]

1.5. Diagnosis of VTE

The substantial mortality associated with PE and the understanding that PE is common in patients with proximal DVT underscores the importance of accurate diagnosis of patients with proximal DVT and PE with prompt initiation of treatment. The goal of diagnostic testing for VTE is to identify which patients should be treated and which should have anticoagulation withheld. When VTE is suspected, diagnostic testing is performed until the post-test probability is either high enough that there is consensus that patients should be treated, or low enough that there is consensus that patients should not be treated. There is consensus that a post-test probability of greater than 85% justifies treatment for VTE without further testing. For example, in patients with high clinical pre-test probability (CPTP) and a high probability ventilation perfusion lung scan, 85% have PE on pulmonary angiogram.[8] This study validated the use of the VQ scan for the diagnosis of PE. There is consensus that a post-test

probability of 2% or less for developing progressive or recurrent VTE in the next three months justifies not treating for VTE.[48] This criterion has been used in management studies that have evaluated the safety of various combinations of test results to rule out VTE. It is also supported by the finding that patients with a probability of PE of 2% or less are more likely to be harmed by further testing (i.e. from adverse effects of computed tomographic pulmonary angiography) than benefit from the information obtained from the test.[48] If the post-test probability of VTE is less than 85% but greater than 2%, additional diagnostic testing is required, with the goal of obtaining a post-test probability of greater than 85% or less than 2%. Most tests for DVT and PE are insufficiently powerful to rule in and rule out VTE on their own. Therefore, most patients require more than one diagnostic test to rule in, or rule out, VTE. The first step in diagnostic approach to VTE involves making a clinical assessment of the pre-test probability of VTE. What tests (typically imaging studies) if any follow after the clinical assessment depend on the estimated probability of disease, as well as the patient's comorbid conditions.[49]

1.5.1. Clinical pre-test probability

Several pre-test probability (PTP) scoring systems, such as the Wells clinical prediction rule,[50,51] the Hamilton score,[52] and the AMUSE (Amsterdam Maastricht Utrecht Study on thromboEmbolism) score,[53] are available for DVT assessment. Among them, the Wells rule is perhaps the best known. It divides patients into low-, intermediate-, and high-PTP categories.[50,52,54] The prevalence of DVT is 5, 17, and 53 percent for these groups, respectively.[55] Similarly, in cases of suspected PE, a pre-test probability should be assigned. The physician's clinical judgment, essentially estimation of the probability of PE in a given patient, has been evaluated and found to

be moderately accurate for classifying patients into three categories of clinical likelihood of PE: low, intermediate, and high.[56] Because this approach lacks standardization, implicit clinical judgment can be replaced with explicit clinical prediction rules. Several clinical prediction rules have been reported in the literature, including the Geneva rule, the PERC (pulmonary embolism rule-out criteria) rule, the PISA-PED (Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis) rule, and the Wells rule.[57-59] As with DVT, no single rule has been proven to be superior, however, the Wells prediction rule has been widely validated and commonly used for assigning a pre-test probability of PE.[59]

1.5.2. Imaging modalities

For suspected proximal DVT, compression ultrasonography should be the initial test when the pre-test probability of DVT is intermediate to high. Ultrasonography achieves its best sensitivity (89% to 96%) and specificity (94% to 99%) in symptomatic patients with proximal thrombosis of the lower extremities.[60] However, sensitivity decreases to as low as 47% for asymptomatic patients with proximal thrombosis, but the specificity is preserved.[61] In patients with intermediate to high pre-test probability of DVT, a negative ultrasonography result alone is insufficient to exclude the diagnosis of DVT. Further assessment is recommended, including checking D-dimer level and repeating ultrasonography in one week if D-dimer level is elevated.[62]

For suspected PE, multidetector CT angiography (CTPE) is the most commonly employed imaging modality for diagnosis. It is the diagnostic test of choice when the technology is available and appropriate. Its clinical validity for diagnosing PE is similar to that reported for conventional pulmonary angiography and

ventilation-perfusion (V/Q) scanning.[63,64] In patients at intermediate to high risk of PE, the positive predictive value of CT angiography is 92% to 96%.[65] However, it cannot reliably exclude PE when the clinical probability is high. In patients with a high clinical probability of PE, the negative predictive value is only 60%.[65] When results are discordant with the clinical suspicion, further evaluation is needed, including compression ultrasonography to look for concurrent DVT.

Although V/Q scans are widely used to assess for PE, the use of V/Q scanning has been in decline. Whereas CT angiography yields a dichotomous result, V/Q scan results are reported as a probability along a spectrum (i.e., normal; or low, intermediate, or high probability of pulmonary embolism).[8] A normal V/Q scan result excludes PE, and a high probability scan establishes the diagnosis. However, most V/Q scan results are non-diagnostic (low or intermediate probability). As with CTPE, a V/Q scan result that is discordant with the preassigned clinical probability requires further evaluation. For patients with contraindications to CT, including contrast allergy, significant renal disease, and to some extent pregnancy, V/Q scanning may be the preferred imaging modality for evaluation of possible pulmonary embolism.[66]

1.6. Objectives and scope of dissertation

1.6.1 Study rationale and significance

The evidence on the characteristics, epidemiology and risk factor for VTE in Canada is very limited and mainly derived from cross-sectional population surveys or longitudinal analyses of administrative health data. To our knowledge, only one longitudinal cohort study based on administrative health data has provided limited insight into the baseline characteristics, epidemiology of VTE in Quebec, Canada.

Additionally, the impact of VTE burden has not been fully assessed in the context of Alberta. There is a need for comprehensive epidemiological studies profiling the epidemiology and patterns of health services use among Albertans, and how these indicators compare to VTE literature. The paucity of this information hampers the ability of the health system to identify priority areas for prevention and treatment as they relate to VTE.

The goal of this research is to expand the current knowledge base of the burden of venous thromboembolic diseases affecting peoples in Canada. The research presented in this dissertation is the most comprehensive longitudinal analysis of ten years of administrative health data to characterize patients with VTE and examine the epidemiology and outcomes among residents of Alberta during the period 2002-2012.

1.6.2. Research objectives

The objectives of this research are:

1. To validate the case definition in the Alberta VTE (AB-VTE) database using selected International classification of disease (ICD) diagnosis codes with imaging procedure codes in the linked AB-VTE administrative data.

2. To describe characteristics, epidemiology and risk factor associated with VTE as well as the case fatality during the short- and long-term follow-up.

3. To evaluate the risk of mortality in patients with provoked and unprovoked pulmonary embolism before and after the initial 3 months form diagnosis.

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CHAPTER 2

The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism events using administrative data.

2.1. Abstract

Purpose: To evaluate the accuracy of using a combination of ICD diagnostic codes and imaging procedure codes for identifying deep vein thrombosis (DVT) and pulmonary embolism (PE) within administrative databases.

Methods: Information from the Alberta Health (AH) inpatients and ambulatory care administrative databases in Alberta, Canada was obtained for subjects with a documented imaging study result performed at a large teaching hospital in Alberta to exclude venous thromboembolism (VTE) between 2000 and 2010. In 1361 randomly selected patients, the proportion of patients correctly classified by AH administrative data, using both ICD diagnostic codes and procedure codes, was determined for DVT and PE using diagnoses documented in patient charts as the gold standard.

Results: Of the 1361 patients, 712 had suspected PE and 649 had suspected DVT. The sensitivities for identifying patients with a PE or DVT using administrative data were 74.83% (95% CI: 67.01-81.62) and 75.24% (95% CI: 65.86-83.14), respectively. The specificities for PE or DVT were 91.86% (95% CI: 89.29-93.98) and 95.77% (95% CI: 93.72-97.30), respectively.

Conclusion: When coupled with relevant imaging codes, VTE diagnostic codes obtained from administrative data provide a relatively sensitive and very specific method to ascertain acute VTE.

Keywords: Validation, Venous Thrombosis, Pulmonary Embolism, ICD, Sensitivity

2.2. Introduction

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), is the third most common acute cardiovascular condition after myocardial infarct and stroke.[1, 2] Population-based studies report an annual incidence of clinically recognized acute VTE, including both DVT and PE, between 1.0 and 1.5 per 1,000 adults.[3-5] VTE recurs in about 20% of patients after 5 years, but the rate varies depending on the presence of risk factors.[6]

To better assess the population burden of acute VTE, administrative healthcare databases such as hospital discharge abstract databases, pharmacy records, and physician or medical services claims databases are increasingly being used in epidemiologic research [7-9] mainly because they allow for rapid identification of large patient cohorts and provide comprehensive data at reasonable cost. Based on Alberta Health (AH) administrative databases, we established a provincial venous thromboembolism database (AB-VTE; inpatient data, outpatient data from ambulatory data, claims data from Alberta Health Services (AHS), registry data, vital statistics and Alberta Blue Cross data) from 2000 to 2010. These databases include demographic information, procedure codes, and International Classification of Diseases (ICD) diagnosis codes, which can be used to identify patients diagnosed with venous thromboembolism as well as other relevant comorbidities and treatments. However, assignments of ICD codes are subject to errors resulting from limitations in available clinical data, diagnostic errors, and coding errors made by human operators. Before analysis can take place, it is imperative to assess the validity of this cohort by examining the accuracy of using administrative data to ascertain acute VTE.

Using a random sample selected from all patients who received imaging studies to exclude acute VTE at one centre, we sought to evaluate the accuracy of using a combination of ICD diagnostic codes and imaging codes for identifying acute DVT and PE diagnoses within our administrative database by comparison to the gold standard of physician diagnosis obtained by chart review.

2.3. Methods

We used an algorithm comprised of one imaging ICD code (VTE related imaging, defined below) and one VTE related diagnostic code to identify incident VTE cases.

2.3.1. Study population

The University of Alberta Health Research Ethics Board (Pro00048871) approved this study. Using the University of Alberta Hospital (UAH) radiology database, a sample of probable VTE patients, ≥ 18 years old, who underwent imaging to diagnose VTE, were chosen randomly from the period January 1, 2000 to December 31, 2010. Regardless of the results of the radiological investigation, all patient charts were reviewed to confirm the presence or absence of VTE. For cases with suspected pulmonary embolism, the use of computerized tomographic angiography (CTA) and/or ventilation perfusion (V/Q) scan were the two modalities of choice. For suspected DVT cases, we relied solely on the lower limb compression duplex ultrasound (CUS).

2.3.2. Chart review (gold standard)

For all identified patients, a trained abstractor with a medical background (who was blinded to patient diagnostic codes during abstraction) used a standardized

data collection form to abstract information from the entire medical record. Data elements include documented symptomatic VTE, diagnostic modality, and timing of the objective confirmation of the event. Patients were considered to have PE, if they were symptomatic at presentation and have a positive imaging test (positive CTA scan or high probability V/Q scan). In patients with suspected DVT, an event was considered positive if the patient was symptomatic at presentation and CUS showed a proximal DVT.

2.3.3. Health administrative data sources

Once patients were classified as having or not having VTE as per our gold standard reference, corresponding discharge abstract database (DAD) or ambulatory care administrative records were obtained for each patient. Discharge abstract database records all admissions to acute care facilities with most responsible diagnosis, up to 25 other diagnoses or comorbidities, and procedures in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (January 1, 2000 to March 31, 2002) or International Classification of Diseases, 10th Revision (ICD-10-CA) (April 1, 2002 to December 31 2010); while the ambulatory care database (using ICD-9-CM from January 1, 2000 to March 31, 2002 and ICD-10-CA from April 1, 2002 to December 31, 2010) tracks all visits to hospital-based physicians' offices (i.e., specialist offices) and the ED and allows for coding of up to 6 conditions for the fiscal years 2000 to 2002 and 10 conditions from 2003 to 2005.

2.3.4. Sample size and statistical analysis

We aimed for a sample size that would allow us to detect a sensitivity and specificity of approximately 0.80 with 95% confidence intervals (CI) within 0.1 of the

estimate. To estimate the accuracy of our algorithm, we compared the current estimates of PE and/or DVT prevalence among patients tested with imaging for PE which ranged from 19% to 79% and for DVT about 23%.[10, 11] A calculated sample of 627 patients screened for PE by CTA or V/Q scans and 615 patients screened by CUS for lower limb DVT was required to detect a sensitivity and specificity of 80% with a 95% CI width of 10%.[12] Total number of required cases was 1366 after accounting for 10% missing charts. DVT and PE occurrence was determined if there were a priori defined ICD codes for DVT, in any diagnostic field, (ICD-9 CM: 451.1. 451.2, 451.8, 451.9, 453.2, 453.8, and 453.9; ICD-10-CA: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1) and PE (ICD-9 CM: 415.0 and 415.1; ICD-10-CA: I26.9, I26.0). For VTE events, we used the combination of PE and DVT diagnostic codes. For patients admitted to hospital (inpatient administrative records), we relied on the presence of the ICD diagnosis and imaging codes that occurred in the same medical act. While in patients diagnosed in emergency department and outpatient clinics (ambulatory care records), we used a 7 days window. A post hoc sensitivity analysis was done to examine the accuracy of imaging procedure codes coupled with ICD codes for VTE recorded only in principle discharge diagnosis fields (first two fields). The gold standard diagnosis was determined from review of the patient chart. Descriptive statistics were used to characterize the study population. We also computed sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value (PPV), and negative predictive value (NPV) of the algorithm with corresponding 95% CIs. All analyses were carried out with SPSS® 21.0 (SPSS Inc., Chicago, IL, USA).

2.4. Results

We randomly sampled 1361 patients with probable VTE, 712 patients with suspected PE and 649 patients with suspected DVT. The median age for all patients was 67 years (IQR 54-76), and 734 (53.9%) were female. Based on chart review, 147 patients (20.65%) were diagnosed as having PE and 105 (16.18%) were diagnosed as having DVT [including 227 patients (17%) with both DVT and PE] (Table 2.1). All cases of PE identified by chart review were confirmed with either VQ or CT scan. All cases of DVT identified by chart review were confirmed by compression ultrasonography.

Applying the predefined ICD diagnostic codes to the 1361 patients, we identified 258 (18.96%) patients with VTE, 156 (21.91%) patients with PE and 102 (15.72%) patients with DVT. For identifying patients with VTE by discharge diagnoses (in all diagnosis positions) in the administrative data, the diagnostic statistics were: sensitivity 75% (95% CI: 69.18-80.22), specificity 93.78% (95% CI: 92.19-95.13), positive likelihood ratio 12.05 (95% CI: 9.49-15.31), negative likelihood ratio 0.27 (95% CI: 0.22–0.33), PPV 73.26% (95% CI: 67.41–78.56%) and NPV 94.29% (95% CI: 92.75–95.58). For identifying patients with PE, the diagnostic statistics were: sensitivity 74.83% (95% CI: 67.01-81.62), specificity 91.86% (95% CI: 89.29-93.98), positive likelihood ratio 9.19 (95% CI: 6.86-12.31), negative likelihood ratio 0.27 (95% CI: 0.21–0.36), PPV 70.51% (95% CI: 62.69–77.53%) and NPV 93.35% (95% CI: 90.94–95.27). Lastly, for identifying patients with DVT, the diagnostic statistics were: sensitivity 75.24% (95% CI: 65.86-83.14), specificity 95.77% (95% CI: 93.72-97.30), positive likelihood ratio 17.8 (95% CI: 11.75-26.94), negative likelihood ratio 0.26 (95% CI: 0.19–0.36), PPV 77.45% (95% CI: 68.11–85.31%) and NPV 95.25% (95% CI: 93.11–96.87).

A post hoc sensitivity analysis using VTE, PE or DVT in only the primary discharge diagnosis field was done in an attempt to increase PPV in our data (Table 2.3). We found that the selective use of primary diagnosis fields resulted in an increase in the PPV to 83.07% (76.95-88.12) for VTE, 83.76% (95% CI: 78.81%, 89.93%) for PE and to 81.94% (95% CI: 71.10%, 90.01%) for DVT. However, the sensitivity of the test dropped significantly to 62.30% (56.00-68.31) for VTE, 66.67% for PE and in DVT cases to 56.19%.

Tables 2.2 and 2.3 summarize the performance of the algorithm in any diagnosis position, and in the principal diagnosis position of VTE, respectively.

2.5. Discussion

Our study explored the validity of using ICD discharge diagnoses when coupled with an imaging procedure code from health administrative data to identify patients presenting with acute venous thromboembolism. We found that about 19% of all patients who were radiologically investigated for VTE, at a tertiary care facility, are found to have positive imaging studies. The identification of ICD codes, in any diagnosis position, with one procedure code was moderately sensitive but remarkably specific with good predictive abilities for VTE, PE and DVT. Additionally, using ICD discharge diagnoses with an imaging procedure code to ascertain acute VTE gave reliable estimates of numbers and proportions as well as a reasonable degree of validity, despite imperfect diagnostic accuracy. Furthermore, the use of principle diagnosis fields only, resulted in moderate increase in PPVs at the expense of the test sensitivities. The use of ICD codes (in any position) with the imaging procedure codes resulted in a good balance between sensitivity, specificity and predictive values. The approach of using imaging procedure codes combined with ICD discharge codes is an

improvement over the use of ICD discharge codes alone, which have been shown in a recent systematic review to yield a very low PPV of 30-40%.[13] Our study expands on prior published literature, and suggests that ICD codes in Canadian administrative data are moderately sensitive but have a good specificity for identifying acute DVT/PE events.[14-16] Additional criteria could be added to enhance positive predictive value, such as prescription of an anticoagulant, but this would come at the cost of further reduction in sensitivity and negative predictive value.[17]

Our diagnostic statistic estimates should be considered in the context of the data used. The PPV and sensitivity estimates depend on the accuracy and completeness of the discharge abstract databases, which vary substantially from system to system. The Alberta Health Discharge Abstract Database allows 25 diagnosis or comorbidity codes, and procedure codes (using ICD-9-CM for 1994-2002 and ICD-10-CA for 2002-2010); and the Ambulatory Care Database (using ICD-9-CM for 1994-2002 and ICD-10-CA for 2002-2010) tracks all visits to hospital-based physician offices (i.e., specialist offices) and the emergency department and allows for coding of up to 6 conditions for the years 2000 to 2002 and 10 conditions from 2003 to 2010. It is likely that some diagnostic codes were recorded on the basis of patient complaints and physician examinations. All cases of VTE identified by chart review were symptomatic and were treated with anticoagulant treatment or inferior vena cava filter, making failure to code the most likely cause for the absence of ICD diagnosis codes for these cases in our study. The utilization of our algorithm (i.e., combining imaging codes with diagnostic codes) to identify actual cases maximizes predictive ability and specificity.

It is likely that when ICD codes are used alone for case identification, there is under-coding of both PE and DVT. Previous literature shows that in addition to missing data issues, coders generally abstract diagnoses from physician notes rather than from diagnostic imaging test reports.[18, 19] Therefore, a clot found on lower limb compression ultrasonography would not trigger coding of DVT unless this diagnosis is explicitly documented by the physician in the chart. This may also explain the lower sensitivity of ICD codes for PE in patients with acute respiratory failure or exacerbation of COPD because the clinical presentation the two conditions frequently overlap.[18]

Only a few studies have assessed the validity of hospital discharge diagnosis codes for identifying VTE, and none have utilized a procedure code with the diagnosis codes to identify events. Differences in sensitivity across studies are likely due to heterogeneity in the study population, recruitment period, and the choice of gold standard reference. The selection of a surgical cohort and the nature of VTE may explain the lower sensitivity reported by Zahn et al.[20] Nevertheless, our sensitivity estimates are consistent with those reported by Heckbert et al[21] and even compare favourably with those reported by Tagalakis et al[16] during a 60 day window period. This also extends the findings of previous studies that showed that coding sensitivity had been preserved in the transition from ICD-9-CM to ICD-10 for other conditions.[22]

Several limitations of our study deserve mention. First, estimating the accuracy of ICD discharge diagnosis codes for PE and DVT alone was not within the scope of the present study. Second, our study was not powered to determine statistically significant differences in the sensitivity of ICD discharge diagnosis codes alone, and the results of our analyses should be considered to be only supportive of

the use of imaging procedure codes along with specific VTE ICD diagnosis codes. Third, we were not able to review medical charts and ask clinicians and coders for the reasons for omitting appropriate discharge diagnosis codes in patients with objectively confirmed DVT or PE because of the retrospective design of our study. Fourth, our study sample was drawn from one major hospital in Canada and we cannot exclude that the results would be different in other countries or settings. Though our study has limitations, our data support that when coupled with a relevant diagnostic imaging code, VTE diagnostic codes from administrative data provide a relatively sensitive and remarkably specific method of ascertaining acute VTE.

2.6. Conclusion

We found that the combination of an imaging procedure code with ICD diagnostic codes drawn from administrative data is a valid approach for ascertaining acute VTE. Our data support the use of administrative data to perform epidemiological research about acute VTE.

Table 2.1. Characteristics of patients with clinical suspicion for acute PE (N = 712) and/or DVT (N = 649) (Total: N = 1,361)

Characteristics	Frequency
Age in years, median (IQR)	
All patients	67 (54-76)
PE	68 (56-77)
DVT	64 (52-74)
Female, n (%)	
All patients	734 (53.9)
PE	409 (57.4)
DVT	325 (50.1)
VTE confirmed by objective diagnostic test, n (%)	
PE	147 (20.65)
DVT	105 (16.18)
VTE documented by ICD diagnostic codes, n (%)	
PE	156 (21.91)
DVT	102 (15.72)
PE: Pulmonary Embolism, DVT: Deep Vein Thrombosis, IQR: Interquartile Range.	

Table 2.2. Accuracy of ICD-9 CM and ICD-10 hospital discharge diagnosis codes *(in any discharge diagnosis positions)* coupled with radiology diagnostic codes for identifying patients with acute symptomatic PE and DVT

Test	VTE (95% CI)	PE (95% CI)	DVT (95% CI)
Sensitivity	75.00% (69.18-80.22)	74.83% (67.01-81.62)	75.24% (65.86-83.14)
Specificity	93.78% (92.19-95.13)	91.86% (89.29-93.98)	95.77% (93.72-97.30)
Positive likelihood ratio	12.05 (9.49-15.31)	9.19 (6.86-12.31)	17.8 (11.75-26.94)
Negative likelihood ratio	0.27 (0.22-0.33)	0.27 (0.21-0.36)	0.26 (0.19-0.36)
Positive predictive value	73.26% (67.41-78.56)	70.51% (62.69-77.53)	77.45% (68.11-85.31)
Negative predictive value	94.29% (92.75-95.58)	93.35% (90.94-95.27)	95.25% (93.11-96.87)

ICD-9 CM and ICD-10 hospital discharge diagnosis codes, *in any diagnosis position*, were combined with radiology diagnostic codes to identify acute events.

Table 2.3. Accuracy of ICD-9 CM and ICD-10 hospital discharge diagnosis codes *(in principle discharge positions)* coupled with radiology diagnostic codes for identifying patients with acute symptomatic PE and DVT

Test	VTE (95% CI)	PE (95% CI)	DVT (95% CI)
Sensitivity	62.30% (56.00-68.31)	66.67% (58.43-74.22)	56.19% (46.17-65.86)
Specificity	97.11% (95.95-98.02)	96.64% (94.80-97.96)	97.61% (95.95-98.72)
Positive likelihood ratio	21.59 (15.14-30.78)	19.19 (12.56-31.30)	23.51 (13.39-41.29)
Negative likelihood ratio	0.39 (0.33-0.46)	0.34 (0.27-0.43)	0.45 (0.36-0.56)
Positive predictive value	83.07% (76.95-88.12)	83.76% (75.81-89.93)	81.94% (71.10-90.01)
Negative predictive value	91.89% (90.18-93.39)	91.76% (89.26-93.85)	92.03% (89.51-94.10)

ICD-9 CM and ICD-10 hospital discharge diagnosis codes, in principle diagnosis positions, were combined with radiology diagnostic codes to identify acute events.

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CHAPTER 3

Secular trends in incidence and mortality of acute venous thromboembolism: The AB-VTE population based study.

3.1. Abstract

Background: Venous thromboembolism (VTE) is a major cause of morbidity and mortality, and comprehensive studies profiling the epidemiology and pattern of health services use are needed. In this study we provide contemporary estimates of VTE incidence and case fatality over the past decade.

Methods: We developed a population-based VTE dataset by linking 6 administrative health databases in Alberta, Canada from April 1, 2002 to March 31, 2012. We defined acute symptomatic cases using a validated algorithm and used Poisson regression to model annual VTE counts.

Results: We identified 31,656 cases of acute symptomatic VTE between April 1, 2002, and March 31, 2012. The age and sex adjusted incidence rate of VTE was 1.38 (95% CI: 1.37, 1.40) per 1000 person-years. For pulmonary embolism (PE) it was 0.38 (95% CI: 0.36, 0.40) per 1000 person-years and for deep vein thrombosis (DVT) it was 1.0 (95% CI: 0.99, 1.1) per 1000 person-years. The adjusted model showed no significant change in the incidence of VTE during the study period. The 30-day case fatality rate of VTE was 2.0% (95% CI: 1.89, 2.21) and was almost doubled in patients with PE 3.9% (95% CI: 3.50, 4.33). The 1-year case fatality was 9.2% (95% CI: 8.88, 9.52) for VTE and 12.9% (95% CI: 12.2, 13.6) for patients with PE. The case fatality increased with increasing subject age. The 1-year and 5-years survival after first acute VTE were similar in patients with unprovoked and provoked events.

However, in patients with cancer associated thrombosis, the 1-year and 5-years survival was 66% (95% CI: 64.71% to 67.29%) and 46% (95% CI: 43.28% to 48.72%) respectively.

Conclusion: The incidence of acute venous thromboembolism remained unchanged over a 10-years period. However, the case fatality of VTE is substantial.

Keywords: VTE, AB-VTE, Epidemiology, Case-fatality, Deep Vein Thrombosis, Pulmonary embolism, Vein Thrombosis.

3.2. Introduction

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep vein thrombosis (DVT), is a chronic disease associated with short and long-term morbidity and mortality. VTE is the third most common cardiovascular condition over the last 3 decades.[1] However, recent population-based data on VTE epidemiology are limited.

Estimates of annual VTE incidence range from 0.75 to 2 per 1,000 individuals in the population.[2-5] Between 60,000 and 300,000 deaths secondary to PE occur annually in the United States, and as many as 200,000 of those deaths occur in hospitals. The in-hospital death rate from pulmonary embolism exceeds the in-hospital death rate from myocardial infarction.[3, 6-8] Furthermore, up to 2,000,000 new DVTs occur each year within the US.[6]

Each year, the direct medical costs for the treatment of patients with nonfatal VTE are estimated to be between 5.8 to 7.8 billion US dollars.[9] Despite the large disease and economic burden of VTE, there is a lack of systematic surveillance for it and, therefore, several public health agencies have recognized that the true burden of venous thrombosis is unknown and have highlighted the importance of obtaining contemporary population-based estimates of incidence and mortality.[9] There is a need for comprehensive epidemiological studies profiling the epidemiology and patterns of health services use, and how these measures compare to other populations.

In this Canadian study, we aimed to provide contemporary population-based estimates of VTE incidence and case fatality in the province of Alberta over the last decade.

3.3. Methods

3.3.1. Study design and setting

This is a retrospective cohort study based on linking several administrative health databases in Alberta, Canada from April 1, 2002 to March 31, 2012. Alberta is a culturally diverse province in Western Canada with an estimated population of over 4 million in 2014.[10] Health care in Alberta is publicly funded for all residents under the Alberta Health Care Insurance Plan (AHCIP) provided by the provincial government of Alberta, which covers 99% of Alberta residents.[11]

3.3.2. Data sources and cohort definition

The Alberta-VTE (AB-VTE) database was developed by linking 6 de-identified provincial administrative databases, including 1) the ambulatory care database which covers emergency department and outpatient clinic visits (April 1, 2002 to March 31, 2014); 2) the hospital inpatient discharge database (April 1, 2002 to March 31, 2014); 3) the physician claims database (April 1, 2002 to March 31, 2014); 4) the Alberta Blue Cross database for prescriptions of patients ≥ 65 years old (April 1, 2002 to March 31, 2014); 5) the population registry database (April 1, 2002 to March 31, 2014); and 6) Vital Statistics (i.e., death registry from January 1, 2002 to December 31, 2012). Both ambulatory care and inpatient discharge databases contain information on patient demographics, comorbidities, measurable outcomes of admission (e.g. length of hospitalization, cost), and up to 10 and 25 diagnostic as well as 10 and 20 procedure codes, respectively. They also provide information on diagnosis, procedure, location of service, and provider specialty. Alberta Vital Statistics data records information on deaths that occur within Alberta.

The study subjects consisted of all residents of Alberta (age >18 years) from April 1, 2002 – March-31, 2012 that had a physician encounter or hospitalization associated with an ICD diagnosis code for VTE. Patients were defined as having definite acute VTE if they had one health care encounter with a diagnosis of VTE within a 7-day window of a pre-specified VTE related imaging code. A case is considered to be incident acute DVT if the diagnosis is recorded as (ICD-9 CM: 451.1. 451.2, 451.8, 451.9, 453.2, 453.8, and 453.9; ICD-10: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1) and incident acute PE (ICD-9 CM: 415.0 and 415.1; ICD-10: I26.9, I26.0) without a DVT or PE code up to 2 antecedent years (washout period). The accuracy of this algorithm to detect acute symptomatic VTE has been previously validated against chart audits in Alberta,[12] with very high specificity (97.11%) and positive predictive value (83.07%), and acceptable sensitivity (62.30%). For cases identified from the ambulatory care or physician claim databases, the date of diagnosis is the date of imaging procedure while for cases identified in the inpatient discharge data the date of diagnosis will be the date of admission.

3.3.3. Risk factors and comorbidities

A comorbidity was considered to be present if it was reported a year prior to the index visit by any of the following data sources: 1) the ambulatory care visit record; or 2) the inpatient admission concurrent to the visit. We categorized all VTE events based on the presence of major risk factors for thrombosis in the period before VTE occurrence. Major risk factors were cancer (within 1 year before VTE), major surgery, major trauma, or hip fracture (up to 3 months preceding VTE), and recent (within 3 months from delivery) or ongoing pregnancy. A greater than 3 days

hospitalization for indications other than those stated above in the last 3 months preceding VTE occurrence were also identified. The VTE was considered unprovoked if these risk factors were absent. If one or more risk factor was identified, then the event was further categorized as a cancer associated or provoked event accordingly. Mortality data was provided by Alberta Vital Statistics.

3.3.4. Statistical analysis

The study population was followed from study entry until death, emigration from the province, or end of the study (March 31, 2012), whichever occurred first. Descriptive summaries were used to report patient demographics and comorbidities. Data were summarized by means and standard deviations or by frequencies and percentages.

Overall incidence rates of VTE, DVT, and PE were calculated by dividing the number of new cases by the total person-years at risk in the Alberta population covered by AHCIP between April 1, 2004 and March 31, 2012 (www.health.alberta.ca).[13] The numerator for the incidence rate was the number of new PE or DVT cases. The denominator was the person-years at risk in the Alberta population covered by AHCIP during the study period. Overall 30-day, 3 months, and 1-year case fatalities were calculated as the proportion of the total number of all-cause deaths that occurred between the beginning of the study and the end of the study among VTE cases.

VTE cases were deemed incident cases in the first fiscal year in which they met the case definition, and cases were considered incident only once. VTE, PE, and DVT crude incidence rates were age and sex adjusted using the direct standardization method and 2008 Albertan census. All incidence rates were expressed as VTE, PE and

DVT cases per 1000 persons-years. Crude- and age- and sex- adjusted incidence rate ratios (IRR) and associated 95% confidence intervals (CIs) was reported to compare rates between both genders. Trends in rates during the years under study were assessed using the likelihood-based trend test based on the Poisson distribution with a logarithmic link function and a log (population) offset term.[14] To compare the adjusted rate of VTE between genders and age groups, a Poisson regression model purposefully included sex, age groups and study period. Interaction terms between variables in the main effect model were tested for their significance by using likelihood ratio test. Statistically significant interaction terms were included into the main effect model to build the final model. Model goodness-of-fit was assessed based on the model deviance and degrees of freedom.[15]

A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using STATA (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

3.4. Results

3.4.1. Patient characteristics

During the study period (2004-2012), 31,656 Alberta residents were diagnosed with an incident acute venous thromboembolic event, among which 8,641 (37.5%) and 23,015 (62.5%) were PE (with or without DVT) and DVT, respectively. At the index visit, 55.9% of the patients were female. The mean age was 57.4 (± 18.4) years and 47% were 60 years and older. In this cohort, 55% of VTE cases were unprovoked events and only 16.3% were associated with cancer (Table 3.1).

3.4.2. Events rate

The crude age and sex- specific incidence rate for VTE, PE and DVT are summarized in Table 3.2. For VTE, the age and sex adjusted incidence rate of VTE was 1.38 (95% CI: 1.37, 1.40) per 1000 person-years. For pulmonary embolism (PE) it was 0.38 (95% CI: 0.36, 0.40) per 1000 person-years and for deep vein thrombosis (DVT) it was 1.0 (95% CI: 0.99, 1.1) per 1000 person-years. The crude and adjusted incidence rate of VTE, PE and DVT increased with age in both genders (Table 3.2 and 3.3). After adjusting for age, sex, study period and allowing for significant interactions in the final model, the incidence rate of VTE was mainly greater in women compared to men, but these differences were not statistically significant, except in the younger age group (18 to 39 years) (Table 3.4).

3.4.3. Trends in VTE incidence

Overall, the adjusted model showed no significant trend in the incidence of VTE during the study period. In men, the crude and adjusted VTE annual incidence rate showed an approximate 8% decline in the event rate between the period 2004 and 2012. In contrast, the crude and adjusted annual incidence in women was relatively unchanged during the study period (Figure 3.1). Throughout the study period, these rates increased markedly with age with a greater increase in men regardless of the event type, sex or study period (Table 3.3 and Figures 3.2, 3.3).

3.4.4. Case fatality rate

Among the 31,656 patients with acute VTE, 647 patients died during the first 30 days, resulting in an overall 30-day case fatality rate of 2.0% (95% CI: 1.89, 2.21). In patients with PE, the cases fatality at 30-days was 3.9% (95% CI: 3.50, 4.33). The

1-year case fatality was 19.6% (95% CI: 8.88, 9.52) for VTE and 12.9% (95% CI: 12.2, 13.6) in patients with PE (Table 3.5).

3.4.5. All-cause mortality

Patients with first incident unprovoked venous thromboembolism had a 96% one-year survival (95% CI: 95.71% to 96.29%) and 88% 5-years survival (95% CI: 87.34% to 88.66%). In patients with VTE provoked by major risk factors other than cancer, the one-year and 5-years survival was 94% (95% CI: 93.51% to 94.49%) and 83% (95% CI: 81.92% to 84.08%) respectively. Lastly, patients with cancer-associated thrombosis, the one-years survival was 66% (95% CI: 64.71% to 67.29%) and the 5-years survival was 46% (95% CI: 43.28% to 48.72%) (Figure 3.4).

3.5. Discussion

We developed a provincial VTE database based on a previously validated VTE identification algorithm[12] and found that the age and sex adjusted incidence rate of VTE was 1.38 per 1000 person-years. This translates to nearly 48,000 first venous thromboembolic events annually in Canada, about half of which are unprovoked and 16% of which are secondary to cancer. The adjusted incidence rates increased with age and were more than threefold higher in those 80 years and older in both sexes. Younger women had a significantly higher rate of acute VTE than younger men, but this difference disappeared in other age groups.

This finding was first noted by Silverstein et al[16] among younger women in their childbearing age and may relate to differential exposure to clinical risk factors by sex and age (e.g., pregnancy, delivery, or oral contraceptive use among younger women). Of note, rates of first events of VTE in our study were similar to those

observed in an epidemiologic study conducted in the province of Quebec, Canada between January 2000 and December 2009 (VTE 1.24/1000 person-years and PE 0.45/1000 persons).[17] Also, these estimates are also similar to rates from older population studies. [18, 19]

To our knowledge, this study is the first population-based data to report trends in annual VTE event rates until 2012. Overall, the adjusted model showed no significant change in the incidence of VTE during the study period. A study based on the Worcester Venous Thromboembolism study demonstrated that the incidence of VTE between 1999 and 2003 remained stable,[20] consistent with our observation. Due to our relatively short study time, which contributes imprecision to estimates of a trend, this finding was not wholly unexpected. However, in men, we observed an approximate 8% decrease in the incidence of VTE during the study period; while the annual incidence of VTE in women was unchanged.

It is likely that the increase in physician awareness with respect to the diagnosis of VTE, increased utilization of improved non-invasive diagnostic imaging, and all participated in maintaining the observed incidence rates of VTE in Alberta. Additionally, the increased recognition of major provoking risk factors such as major surgery and hospitalization and the subsequent creation of DVT prophylactic strategies have helped to offset some of the risk factors, thereby tempering any increase in rates. Revived interest in the prevention of VTE might result in a future decline in the incidence of VTE.

The short-term case fatality rate in our population was high. In patients with DVT, the 3-month case fatality was 3.4% and it was doubled in patients presenting with PE. After 1 year, about 13% of patients with PE died compared to 7.8% in

patients with DVT. In agreement with previous cohort studies,[17, 19, 21] we noted that the case fatality after VTE increases proportionally with age. In patients with PE, for example, the 30-day case fatality in patients 80 years and older was almost double those younger than 40. This relation was maintained even after a year in both PE and DVT cases. Older patients carry higher comorbidity status and less reserve to tolerate events with significant impact on cardiovascular function. These results confirm that elderly patients with VTE have a poor prognosis and may require more careful management and follow up. Overall, VTE carries substantial mortality risk and prompt and appropriate diagnosis and treatment are warranted. Risk reduction and appropriate VTE prophylaxis strategies should also be employed to reduce the burden of disease.

Our study has limitations. First, this was a secondary analysis of previously collected data, and the data set may be prone to misclassification bias. However, our case-defining algorithm was validated against chart reviews and was found to be very specific. Second, we used a washout period during the analysis to properly classify incident cases. Finally, we believe some cases of fatal PEs are undiagnosed and therefore missed.

This population-based data captures the entire population receiving VTE related services (inpatients and outpatients) in Alberta and therefore our estimates are considered generalizable. To our knowledge, this work is the most comprehensive population data that provides contemporary estimates of VTE epidemiology and trends over the last decade.

3.6. Conclusion

The incidence of acute VTE is consistent with prior population based estimates and remained unchanged between 2004 and 2012. Young women have a significantly higher incidence of VTE than age matched men, but this difference disappears with increasing age. Acute VTE is associated with significant case-fatality across gender and age though is more striking in the elderly population. These epidemiologic differences may help streamline effective VTE educational and prophylactic strategies.

Table 3.1. Patient Demographics, Comorbidities and Risk Factors.

	VTE		PE		DVT	
	N	%	N	%	N	%
Overall	31,656		8,641		23,015	
Age (Year)						
18-39	6107	19.3%	1792	20.7%	4315	18.7%
40-59	10683	33.7%	2569	29.7%	8114	35.3%
60-79	10632	33.6%	3058	35.4%	7574	32.9%
≥ 80	4234	13.4%	1222	14.1%	3012	13.1%
Female	17681	55.9%	4979	57.6%	12702	55.2%
Comorbidities (< 1 year)						
Acute Myocardial Infarction	1277	4.0%	552	6.4%	725	3.2%
Congestive Heart Failure	1783	5.6%	771	8.9%	1012	4.4%
Peripheral Vascular Disease	919	2.9%	286	3.3%	633	2.8%
Cerebrovascular Accident	1118	3.5%	349	4.0%	769	3.3%
Chronic Obstructive Pulmonary Disease	3499	11.1%	1472	17.0%	2027	8.8%
Peptic Ulcer Disease	424	1.3%	142	1.6%	282	1.2%
Liver Disease	501	1.6%	156	1.8%	345	1.5%
Diabetes Mellitus	3692	11.7%	1124	13.0%	2568	11.2%
Renal Disease	1196	3.8%	406	4.7%	790	3.4%
Malignancy - except skin	5158	16.3%	1718	19.9%	3440	14.9%
Anemia	2640	8.3%	947	11.0%	1693	7.4%
Thrombocytopenia	326	1.0%	103	1.2%	223	1.0%
Hypertension	6137	19.4%	2154	24.9%	3983	17.3%
Neurological Disease	1055	3.3%	308	3.6%	747	3.2%
Risk Factors (<91 Days)						
Caesarean Section	307	1.0%	103	1.2%	204	0.9%
Recent Hospitalization (≥3 days)	9520	30.1%	3831	44.3%	5689	26.7%
Ongoing Pregnancy	1220	3.9%	358	4.1%	862	3.7%
Recent Delivery	698	2.2%	204	2.4%	494	2.1%
Fractured Hip	226	0.7%	64	0.7%	162	0.7%

Hip Joint Replacement	408	1.3%	86	1.0%	322	1.4%
Knee Joint Replacement	639	2.0%	158	1.8%	481	2.1%
Major Trauma	706	2.2%	176	2.0%	530	2.3%
Major Surgery	3255	10.2%	924	10.7%	2320	10.1%
Cancer Provoked Events	5158	16.3%	1718	19.9%	3440	14.9%
Non-cancer Provoked Events	11868	37.5%	4356	50.4%	7512	32.6%
Unprovoked Events	17413	55.0%	3644	42.2%	13769	59.8%

VTE: venous thromboembolism, PE: Pulmonary Embolism, DVT: Deep Vein Thrombosis, CI: Confidence Interval.

Table 3.2. Crude Incidence rate per 1000 Person-Year for Symptomatic Venous Thromboembolism, Pulmonary Embolism and Deep Vein Thrombosis According to Gender and Age Group.

			VTE		PE		DVT	
		Person-Year	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
Men	Overall	10,784,899	13975	1.30 (1.27,1.32)	3662	0.34 (0.33,0.35)	10313	0.96 (0.95,0.98)
	18-39	4,626,999	1898	0.41 (0.39,0.43)	442	0.1 (0.09,0.10)	1456	0.31 (0.30,0.33)
	40-59	4,138,657	5303	1.28 (1.25,1.32)	1242	0.30 (0.28,0.32)	4061	0.98 (0.95,1.01)
	60-79	1,715,589	5162	3.01 (2.93,3.09)	1484	0.23 (0.21,0.25)	1746	0.79 (0.75,0.82)
	≥80	303,654	1612	5.31 (5.05,5.57)	494	1.63 (1.49,1.78)	1118	3.68 (3.47,3.90)
Women	Overall	10,939,268	17681	1.62 (1.59,1.64)	4979	0.46 (0.44,0.47)	12702	1.16 (1.14,1.18)
	18-39	4,594,254	4209	0.92 (0.89,0.94)	1350	0.29 (0.28,0.31)	2859	0.62 (0.6,0.65)
	40-59	4,050,008	5380	1.33 (1.29,1.36)	1327	0.33 (0.31,0.35)	4053	1 .00(0.97,1.03)
	60-79	1,790,518	5470	3.05 (2.97,3.14)	1574	0.88 (0.84,0.92)	3896	2.18 (2.11,2.25)
	≥80	504,488	2622	5.20 (5.0,5.40)	728	1.44 (1.34,1.55)	1894	3.75 (3.59,3.93)
Total	Overall	21,724,167	31656	1.46 (1.44,1.47)	8641	0.4 (0.39,0.41)	23015	1.06 (1.05,1.07)
	18-39	9,221,253	6107	0.66 (0.65,0.68)	1792	0.19 (0.19,0.2)	4315	0.47 (0.45,0.48)
	40-59	8,188,665	10683	1.3 (1.28,1.33)	2569	0.31 (0.3,0.33)	8114	0.99 (0.97,1.01)
	60-79	3,506,107	10632	3.03 (2.98,3.09)	3058	0.87 (0.84,0.9)	7574	2.16 (2.11,2.21)
	≥80	808,142	4234	5.24 (5.08,5.40)	1222	1.51 (1.43,1.60)	3012	3.73 (3.60,3.86)

VTE: venous thromboembolism, PE: Pulmonary Embolism, DVT: Deep Vein Thrombosis, IR: Incidence Ratio, CI: Confidence Interval.

Table 3.3. Adjusted Incidence Rate of VTE in Men and Women Stratified by Sex*

	Patient-Years		VTE events			
Age	Men	Women	Men	Women	IRR**	95% CI
18-39	4,626,999	4,594,254	1898	4209	0.45	(0.42, 0.47)
40-59	4,138,657	4,050,008	5303	5380	0.96	(0.93, 1.00)
60-79	1,715,589	1,790,518	5162	5470	0.99	(0.95, 1.03)
≥80	303,654	504,488	1612	2622	1.02	(0.96, 1.09)

*Adjusted for year of diagnosis and significant interactions; ** incidence rate ratio.

Table 3.4. Thirty-Day, 3-months and 1-Year Case fatality by Age Group and Type of First Event.

		30-Day			3-months			1-Year		
	Patients at risk	Number of Deaths	CFR	95% CI	Number of Deaths	CFR	95% CI	Number of Deaths	CFR	95% CI
VTE										
Overall	31656	647	2.0%	(1.89, 2.21)	1391	4.4%	(4.17,4.63)	2912	9.2%	(8.88,9.52)
18-39	6107	15	0.2%	(0.14,0.4)	29	0.5%	(0.32,0.68)	17	0.7%	(0.38,1.04)
40-59	10683	124	1.2%	(0.97,1.38)	315	2.9%	(2.64,3.29)	61	1.7%	(1.34,2.24)
60-79	10632	304	2.9%	(2.55,3.19)	681	6.4%	(5.95,6.89)	179	3.7%	(3.23,4.33)
≥ 80	4234	204	4.8%	(4.19,5.51)	366	8.6%	(7.81,9.53)	439	7.4%	(6.77,8.13)
PE										
Overall	8641	337	3.9%	(3.50, 4.33)	609	7.0%	(6.52,7.61)	1117	12.9%	(12.2,13.6)
18-39	1792	9	0.5%	(0.23,0.95)	18	1.0%	(0.6,1.58)	31	1.7%	(1.18,2.45)
40-59	2569	63	2.5%	(1.89,3.13)	127	4.9%	(4.14,5.85)	232	9.0%	(7.95,10.2)
60-79	3058	159	5.2%	(4.44,6.05)	298	9.7%	(8.72,10.8)	557	18.2%	(16.8,19.6)
≥ 80	1222	106	8.7%	(7.16,10.3)	166	13.6%	(11.7,15.6)	297	24.3%	(21.9,26.8)
DVT										
Overall	23015	310	1.3%	(1.2,1.5)	782	3.4%	(3.17,3.64)	1795	7.8%	(7.46,8.15)
18-39	4315	6	0.1%	(0.05,0.3)	11	0.3%	(0.13,0.46)	47	1.1%	(0.8,1.45)
40-59	8114	61	0.8%	(0.58,0.96)	188	2.3%	(2,2.67)	386	4.8%	(4.3,5.24)
60-79	7574	145	1.9%	(1.62,2.25)	383	5.1%	(4.57,5.57)	828	10.9%	(10.2,11.6)
≥ 80	3012	98	3.3%	(2.65,3.95)	200	6.6%	(5.78,7.59)	534	17.7%	(16.3,19.1)

VTE: venous thromboembolism, PE: Pulmonary Embolism, DVT: Deep Vein Thrombosis, CFR: Case Fatality Rate, CI: Confidence Interval.

Figure 3.1. Annual event rates of clinical recognized acute venous thromboembolism among residents of Alberta, Canada, stratified by sex (2004-2012).

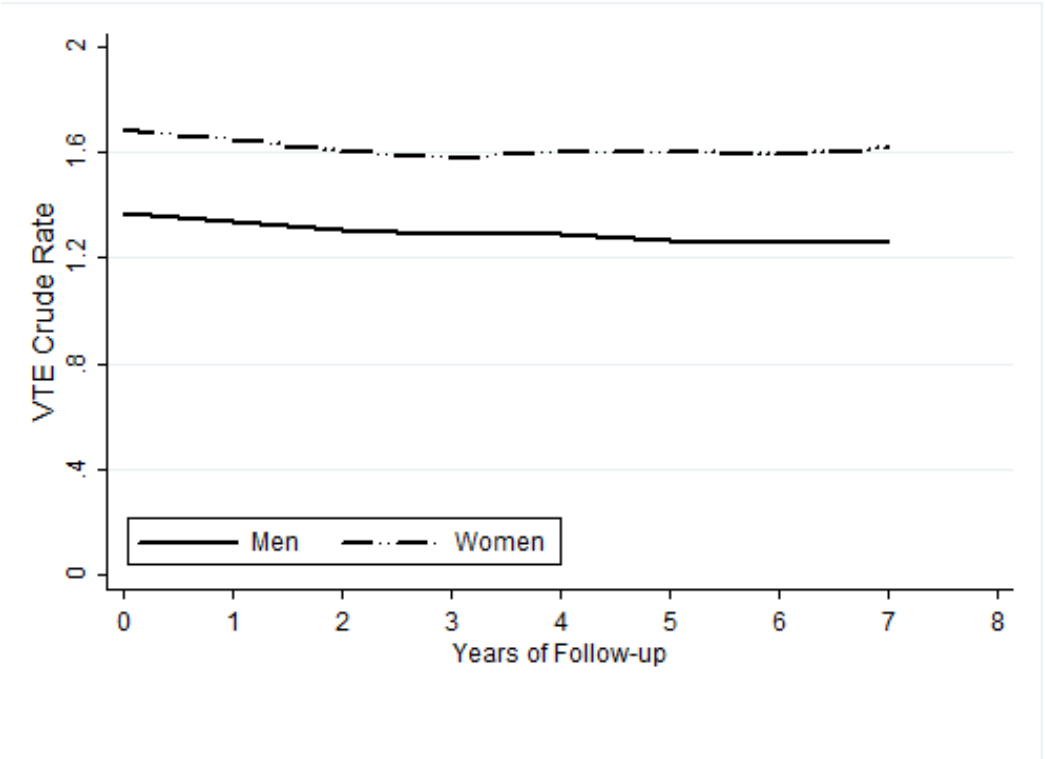


Figure 3.2. Annual event rates of acute venous thromboembolism in men, stratified by age groups (2004-2012).

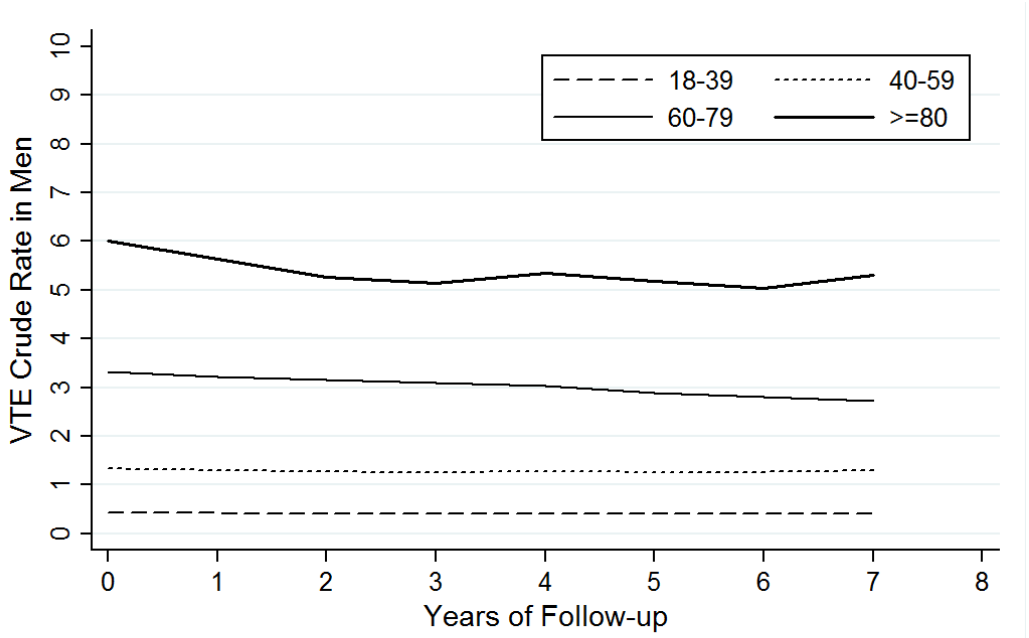


Figure 3.3. Annual event rates of acute venous thromboembolism in women, stratified by age groups (2004-2012).

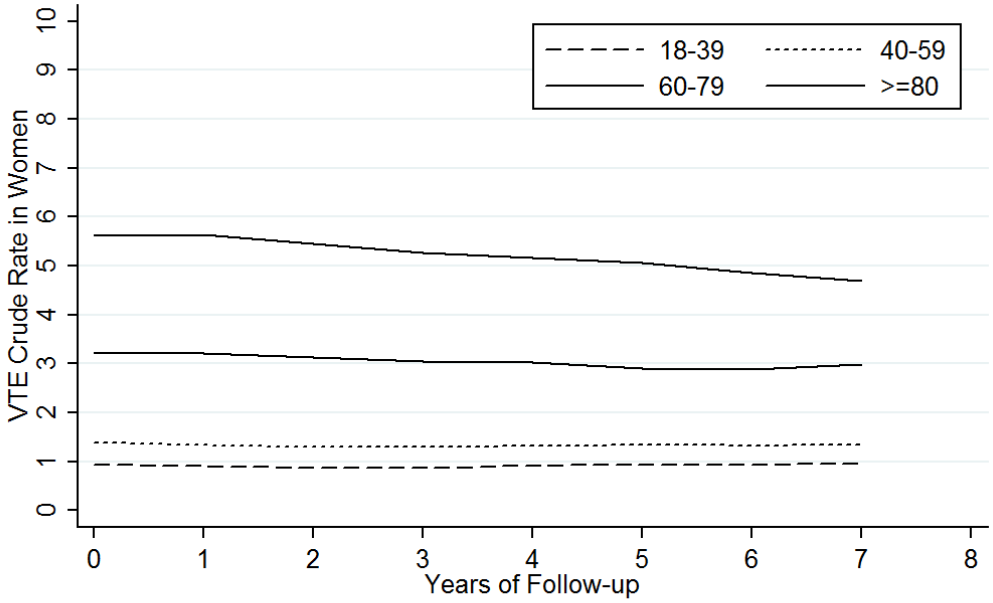
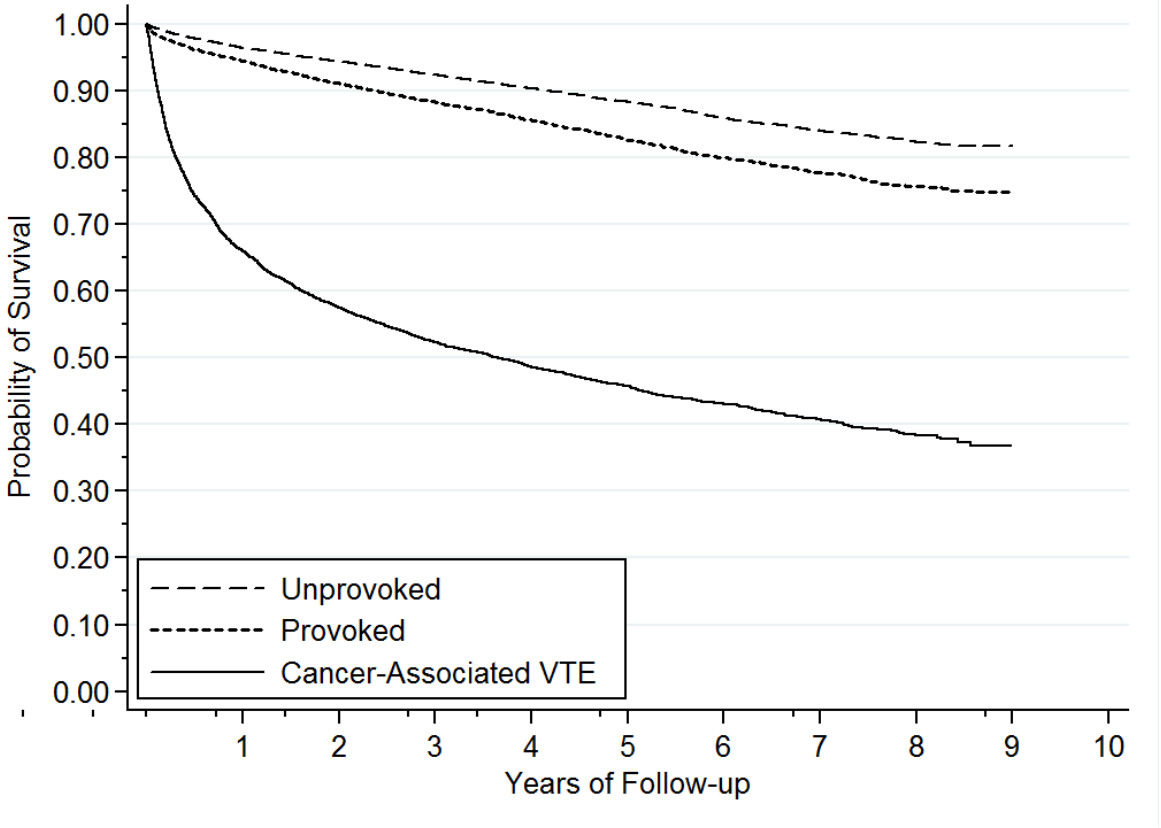


Figure 3.4. Overall survival probability after first acute VTE stratified by risk factors during the period (2004-2012).



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Chapter 4

Short- and Long-Term Mortality after Pulmonary Embolism in Patients with and without Cancer

4.1. Abstract

Background: Pulmonary embolism (PE) is a major cause of mortality and morbidity. It is known that the risk of death varies by provoking factors, however, it is unknown if the risk of death persists beyond the initial diagnosis among patients with cancer and other provoked patients. In this study, we aimed to investigate the effect of cancer on overall, short- and long-term mortality in a cohort of consecutive incident PE patients.

Methods: Using the administrative health care databases of the Canadian province of Alberta, we identified all incident cases of pulmonary embolism between 2004 and 2012 and stratified them by provoking factors (unprovoked, provoked, and cancer-associated). Multivariate Cox survival model was used to estimate the hazard ratios of short- and long-term death.

Results: We identified 8641 patients with PE, among which 42.2% were unprovoked, 37.9% were provoked and 19.9% were cancer–associated. The 1-year and 5-year survival probabilities were 61% (95% CI: 57-64) and 39% (95% CI: 36-43) in cancer-associated PE patients, 93% (95% CI: 92-94) and 80% (95% CI: 78-81) in provoked PE patients, and 94% (95% CI: 93-95) and 85% (95% CI: 83-87) in unprovoked PE patients, respectively. Compared to patients with unprovoked events both short-term and long-term survival in patients with cancer associated PE have significantly higher

observed risk of all-cause mortality in all age groups, P-value <0.001. In contrast, patients with provoked events had similar short- and long-term hazard of death.

Conclusion: PE is still a common condition with a high mortality in all risk groups, however, patients with cancer have a substantial risk of short-term mortality compared to patients with unprovoked PE.

Keywords: AB-VTE, Pulmonary Embolism, Venous Thromboembolism, Cancer, Mortality.

4.2. Introduction

Acute pulmonary embolism (PE) is a common and potentially fatal disease (1, 2). Due to population aging and improvement in diagnostic techniques, PE has been diagnosed increasingly more often in the last few years (3) and it is considered a major cause of mortality, morbidity, and hospitalization with 10%–30% of all patients suffer mortality within 30 days (1, 4). Despite advances in the diagnosis and management of PE, short- and long-term mortality rates remain high (5, 6). In the acute phase, mortality seems to be directly related to the characteristics of the thromboembolic event (i.e., clot burden) and to the rate of its short-term recurrence. Distinctively, the long-term prognosis of PE may be more influenced by the presence of underlying comorbidities or provoking factors (7, 8).

Several studies have shown that the mortality of PE is greatest during the short-term period but even patients who survive beyond this period have an increased risk of death compared to the general population (3, 9). It is unknown if the risk of death persists in the short- and long-term beyond the initial diagnosis among cancer-associated and provoked patients. In this study, we aimed to investigate the effect of cancer on overall, short- and long-term mortality in a cohort of consecutive incident PE patients diagnosed from 2004 to 2012.

4.3. Materials and methods

4.3.1. Study design and data sources

The University of Alberta Health Research Ethics Board (Pro00044383) approved this study. In this retrospective study, six uniquely de-identified administrative health databases in Alberta, Canada, were linked to identify adults (age

≥18 years) diagnosed with incident PE. The databases include: 1) the ambulatory care database which covers emergency department and outpatient clinic visits (April 1, 2002 to March 31, 2014); 2) the hospital inpatient discharge database (April 1, 2002 to March 31, 2014); 3) the physician claims database (April 1, 2002 to March 31, 2014); 4) the Alberta Blue Cross database for prescription information on patients ≥65 years old (April 1, 2002 to March 31, 2014); 5) the population registry database (April 1, 2002 to March 31, 2014); and 6) Vital Statistics (i.e., death registry from January 1, 2002 to December 31, 2012).

4.3.2. Data elements and variables definition

The combined databases provide information on patient demographics, comorbidities, outcomes of admission (e.g. length of hospitalization, cost), and the Tenth Revision, Clinical Modification (ICD-10-CA) diagnosis and procedure codes. It also provides information about the data of diagnosis, procedure, location of service, and provider specialty. Additionally, the Alberta Vital Statistics records information on deaths that occur within Alberta.

To select incident PE cases, we used a validated algorithm comprised of the presence of PE ICD-10 diagnosis with concurrent imaging codes without a PE code up to 2 antecedent years (washout period). The sensitivity and specificity for identifying patients with PE using this algorithm in our data was 74.83% (95% confidence interval [CI]: 67.01–81.62) and 91.86% (95% CI: 89.29–93.98), respectively (10).

4.3.3. Risk factors and comorbidities

Comorbidities were defined as those present at the time of the incident emergency department/hospital/outpatient visit at which the diagnosis of PE was made and were identified based on ICD codes entered for that index visit and all other contacts with the health care system in the 1 year prior to the index PE visit (using the hospitalization, ambulatory care, and physician claims databases)(11, 12). Risk factors were defined as 1) the presence of cancer (within a year preceding the index PE visit); 2) if the patient had major surgery, major trauma, or hip fracture within the last 3 months preceding the diagnosis of PE, or; 3) had recent (within 3 months from delivery) or ongoing pregnancy. A hospitalization more than 3 days for indications other than those stated above in the last 3 months preceding VTE occurrence also was identified. The VTE event was considered unprovoked if risk factors were absent. If one or more risk factors were identified, then the venous thromboembolic event was defined as either provoked or cancer-associated, if cancer was identified in the year preceding the VTE event. The primary end point was all-cause mortality. Death was determined through the Alberta Vital Statistics data, which does not contain information on cause of death. Short-term death was defined as three months or less whereas long-term is defined as more than 3 months.

4.3.4. Statistical analysis

Patients were stratified into three groups according to the presence or absence of risk factors to unprovoked (absence of risk factors), provoked, or cancer-associated. Variables were summarized as means and standard deviations or frequencies and percentages, accordingly. Kaplan-Meier curves were constructed to describe PE survival stratified by the provoking risk factors. Log-rank tests were used

to assess differences in survival between the three groups. Post hoc tests comparing the curves by pairs were performed when the log-rank test was statistically significant.

Multivariate Cox proportional-hazard regression models were used to estimate hazard ratios (HR) for mortality after PE diagnosis for people with provoked events and cancer-associated events compared to individuals with unprovoked events as the reference group while adjusting for the following covariates at baseline: age group (≤50, 51-70, and >70 years and over), sex (female, male), year of diagnosis, and presence of comorbidities. The time dependent variable in the models was 3 months since PE diagnosis. Three months are considered the period to complete treatment of an acute episode of pulmonary embolism (13). Another Cox proportional hazards model was used to estimate the effect of predictors on short- and long-term mortality adjusting for age groups as above, sex, year of diagnosis and provoking factor. Censoring for the analysis occurred upon the date of death or March 31, 2012, whichever came first. After the univariate variables testing, confounding identification, all first-order interaction terms between age, gender and risk factors were tested one at a time. Significant interaction terms ($p < 0.05$) were incorporated in the HR estimates. Log-likelihood ratio tests were used to evaluate whether adjusted Cox regression models that included interaction terms provided a significantly better fit than the main-effects Cox regression models.

All mortality outcomes were reported with 95% confidence intervals (CI) around the estimates. A two-sided P value less 0.05 was considered statistically significant. Statistical analyses were performed STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP)

4.4. Results

A total of 8641 consecutive adults were newly diagnosed with pulmonary embolism between April 1, 2004 and March 31, 2012 (34,854 person-years) with a median follow-up of 8 years, of which 42.2% where unprovoked, 37.9% were provoked and 19.9% were cancer-associated. The median age is 59 years (IQR 43-74 years), and 57.6% were men. Baseline characteristics differed substantially depending on provoking factors (Table 4.1). Patients with no identified provoking factors (i.e., unprovoked PE group) were younger and had less comorbidities than those with provoked and cancer-associated events.

Patients with cancer-associated PE had a 1-year survival of 60% (95% CI: 57%-64%) and 5-year survival of 39% (95% CI: 36%-43%). Further, patients with provoked PE events secondary to major risk factors other than cancer had 1-year survival of 93% (95% CI: 92%-94%) and 5-year survival of 80% (95% CI: 78%-81%) and patients with unprovoked PE had a 1-year survival of 94% (95% CI: 93%-95%) and 5-year survival of 85% (95% CI: 83%-87%) (Figure 4.1). Both patients with unprovoked and provoked PE events have a median survival time of 8 years compared to 2.18 years in patients with cancer-associated events (median study follow-up is 8 years).

The predictive analysis of short- and long-term mortality in patients with PE was performed using the variables listed in Table 4.2, plus the year of diagnosis. In females, both short- and long-term follow-up in patients with cancer-associated PE have significantly higher observed risk of all-cause mortality, P-value <0.001, compared to patients with unprovoked PE (Table 4.3). Moreover, this difference was evident across all age groups. Additionally, there was no significant difference in the hazard ratio of death during the short- or long-term follow-up in patients with

provoked PE in comparison to the unprovoked PE. Similarly, male patients with cancer provoked PE events had a significant higher risk of death in the short-term phase compared to patients with unprovoked PE and in all age categories. On the other hand, in comparison to unprovoked PE men with provoked PE had no difference in hazard of death in the short- and long-term follow-up except in men aged 51 to 70 years. As shown Table 4.3, male patients in the 51 to 70 years age group, the HR of all-cause mortality during the first 3 month was 1.22 (95% CI: 0.47-3.18) for provoked PE patients compared to HR of 1.68 (95% CI: 1.11-2.55) during the long-term follow-up.

4.5. Discussion

This study is the first to evaluate the short- and long-term survival in patients with pulmonary embolism in patients with and without cancer. We found that the 1-year survival in patients with PE was the lowest in patients with cancer with a median survival of 2 years. In addition, patients with cancer provoked pulmonary embolism have a higher risk of dying during the first 3 months of diagnosis compared to patients with unprovoked events.

Similar to major VTE registries, provoked PE (cancer and non-cancer) was more common than the unprovoked PE in the AB-VTE cohort (14, 15). These finding suggests that optimizing thromboprophylaxis in these settings in all patient groups might substantially lower the incidence of thrombosis (16). In contrast to patients with cancer-associated PE, the 1-and 5-year survival in patients with unprovoked events and events provoked by major risk factors other than cancer, were somewhat similar. This is explained by the fact that in the common group of patients with an unprovoked VTE the risk of recurrence has been consistently higher than provoked VTE after

discontinuing anticoagulants, especially over the medium term (1–2 years), but the prognostic differences between patients with unprovoked and provoked PE starts to become smaller with time, but the differences persists (17). Despite the similarity, the proportion of mortality at 5-years is about 1 in 5 patients which emphasizes that acute PE is an important clinical problem with a poor prognosis for short-term and long-term survival.

A 20-year review of data from 1979–1998 found that the age-adjusted death rate for PE was 94 per million individuals (18). Extrapolating to today's Canadian population suggests that an estimated 3290 people die each year from this disease. But it is noted that PE is often undiagnosed, and thus the true death rate is almost certainly substantially higher. In fact, community-based epidemiological studies suggest that roughly one in five individuals die almost immediately from PE, while 40% die within 3 months (4, 19). Additionally, the great improvement in myocardial infarction (MI) and stroke mortality trends (20, 21) suggest that PE is likely going to be the leading cause of death in the near future and that much more efforts should be dedicated to PE management in order to achieve successful trends in mortality, similar to those observed with MI and stroke.

The mortality rate was highest in patients with cancer, compared to patients who present with unprovoked PE. In cancer patients, the risk of death was significantly higher during the acute phase (first 3 months) which may be explained by the clinical deterioration after PE (22) and the presence of thrombosis signifying more advanced cancer. In addition, we found that patients with events provoked by temporary risk factors have similar risk of death in the acute phase and long-term

(17). However, this result should be interpreted with caution because as in most registries, neither diagnostic work-ups nor therapy were controlled.

The present study has several limitations. First, AB-VTE registry is an observational registry, not a randomized trial. In addition, there is no external control of the data entered, and there is no external adjudication of the events. Second, treatment varied with local practice and patients were not treated with a standardized anticoagulant regimen. The strength of the present study is its large size, involving a cohort of more than 8000 patients, followed for nearly a decade and thus should more closely reflect current populations in terms of age demographics and the prevalence of baseline comorbidities. In addition, a validation study allowed us to confirm the diagnosis of VTE and this minimizes a major misclassification bias in our study.

In summary, we found that PE is still a common condition with a high mortality in all risk groups, however, patients with cancer have a substantial risk of short- and long-term mortality.

Table 4.2. Baseline characteristics of patients with unprovoked, provoked and Cancer-asscoaited incident PE in Alberta, Canada.

	Overall	**Unprovoked PE**	**provoked PE**	**Cancer-associated PE**
	Number (%)	Number (%)	Number (%)	Number (%)
N	8641	3644 (42.2)	3279 (37.9)	1718 (19.9)
Age groups				
≤ 50	3111 (36)	1672 (45.9)	1214 (37.0)	225 (13.1)
51-70	2864 (33.1)	1141 (31.3)	970 (29.6)	753 (43.8)
>70	2666 (30.9)	831 (22.8)	1095 (33.4)	740 (43.1)
Female	4979 (57.6)	2189 (60.1)	1920 (58.6)	870 (50.6)
Comorbidities (< 1 years)				
Acute Myocardial Infarction	552 (6.4)	122 (3.3)	298 (9.1)	132 (7.7)
Congestive Heart Failure	771 (8.9)	180 (4.9)	404 (12.3)	187 (10.9)
Peripheral Vascular Disease	286 (3.3)	52 (1.4)	172 (5.2)	62 (3.6)
Cerebrovascular Accident	349 (4.0)	83 (2.3)	179 (5.5)	87 (5.5)
Dementia	184 (2.1)	32 (0.9)	115 (3.5)	37 (2.2)
Chronic Obstructive Pulmonary Disease	1472 (17.0)	422 (11.6)	671 (20.5)	379 (22.1)
Connective Tissue Disease	195 (2.3)	63 (1.7)	97 (3.0)	35 (2.0)
Peptic Ulcer Disease	142 (1.6)	36 (1.0)	68 (2.1)	38 (2.2)
Liver Disease	924 (10.7)	41 (1.1)	60 (1.8)	55 (3.2)
Diabetes Mellitus	1124 (13)	360 (9.9)	492 (15.0)	272 (15.8)
Renal Disease	406 (4.7)	100 (2.7)	206 (6.3)	100 (5.8)
Valvular Heart disease	201 (2.3)	45 (1.2)	108 (3.3)	48 (2.8)
Anemia	947 (11.0)	143 (3.9)	445 (13.6)	359 (20.9)
Thrombocytopenia	103 (1.2)	16 (0.4)	45 (1.4)	42 (2.4)
Hypertension	2154 (24.9)	468 (12.8)	1103 (33.6)	583 (33.9)
Neurological Disease	308 (3.6)	64 (1.8)	161 (4.9)	83 (4.8)
Risk Factors (<91 Days)				
Caesarean Section	103 (1.2)	0 (0.0)	99 (3.02)	4 (0.23)
Recent Hospitalization (≥3 days)	3831 (44.3)	0 (0.0)	2791 (85.1)	1040 (60.5)
Ongoing Pregnancy	358 (4.1)	0 (0.0)	353 (10.8)	5 (0.3)
Recent Delivery	204 (2.4)	0 (0.0)	200 (6.1)	4 (0.2)
Fractured Hip	64 (0.7)	0 (0.0)	57 (1.7)	7 (0.4)
Hip Joint Replacement	86 (1.0)	0 (0.0)	78 (2.4)	8 (0.5)
Knee Joint Replacement	158 (1.8)	0 (0.0)	142 (4.3)	16 (0.9)
Major Trauma	176 (2.0)	0 (0.0)	159 (4.8)	17 (1.0)
Major Surgery	924 (10.7)	0 (0.0)	618 (18.8)	306 (17.8)

Table 4.2. Multivariate predictors of mortality in patients with pulmonary embolism before and after 3 months of diagnosis.

	Short-term (≤ 3 months)		**Long-term (> 3 months)**	
	HR	95% CI	HR	95% CI
Acute Myocardial Infarction	1.07	(0.77-1.49)	1.01	(0.85-1.20)
Congestive Heart Failure	1.40	(1.06-1.84)	1.57	(1.36-1.82)
Peripheral Vascular Disease	1.43	(0.96-2.12)	1.32	(1.07-1.62)
Dementia	1.24	(0.75-2.06)	1.89	(1.51-2.36)
Chronic Obstructive Pulmonary Disease	1.26	(1.01-1.56)	1.44	(1.28-1.62)
Peptic Ulcer Disease	0.89	(0.48-1.62)	1.09	(0.79-1.50)
Liver Disease	1.78	(1.11-2.84)	1.10	(0.79-1.54)
Diabetes Mellitus	1.17	(0.91-1.49)	1.17	(1.02-1.34)
Para or hemiplegia	1.29	(0.69-2.40)	1.88	(1.31-2.70)
Renal Disease	1.04	(0.72-1.51)	1.34	(1.11-1.62)
Anemia	1.04	(0.81-1.33)	1.23	(1.07-1.41)
Hypertension	0.89	(0.72-1.11)	0.90	(0.79-1.01)
Neurological Disease	1.49	(1.00-2.20)	1.43	(1.14-1.80)
HR: Hazard Ratio; CI: confidence interval. Adjusted for diagnosis year.				

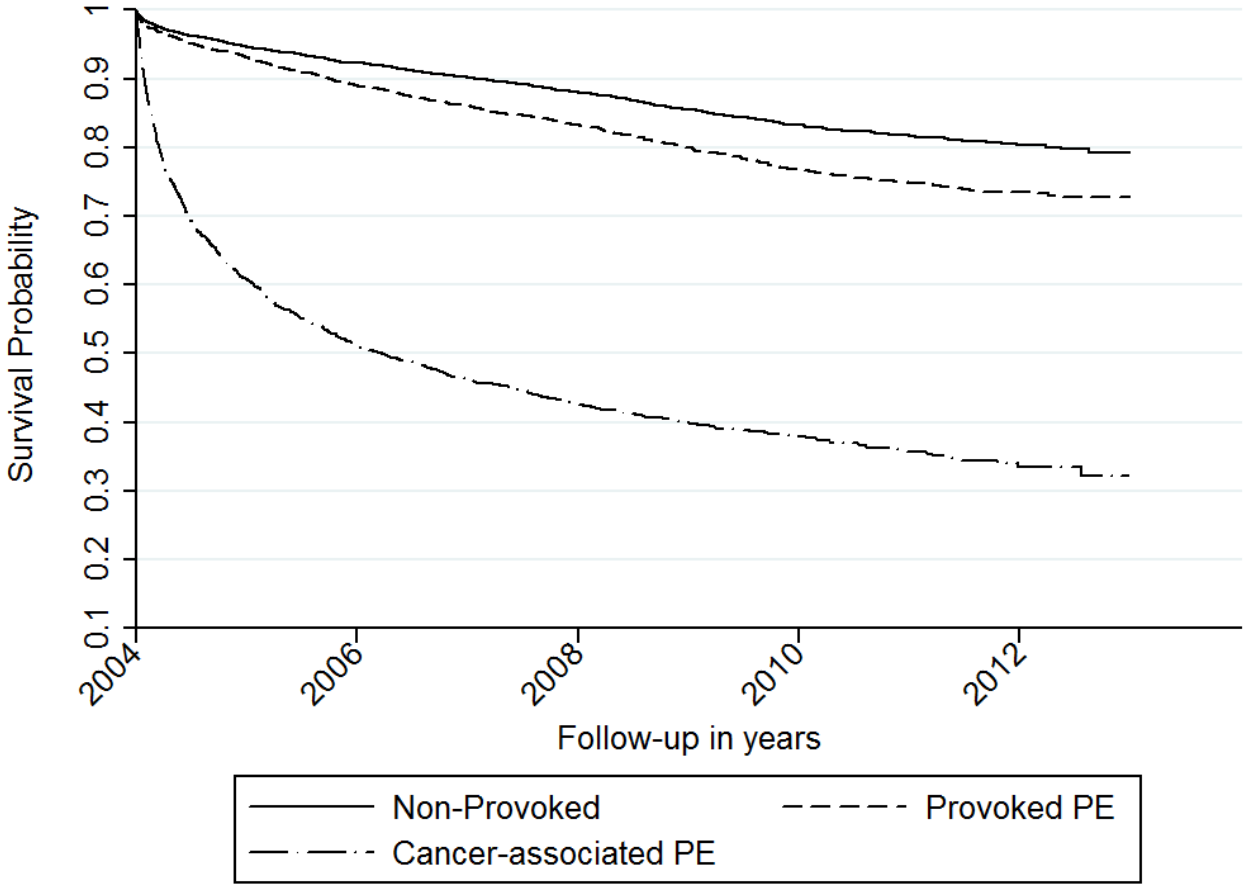
Table 4.3. Multivariate Cox regression analysis of short- and long-term all-cause mortality hazard ratios in patients with unprovoked, provoked and cancer-associated PE in Alberta, Canada.

	Short-term (≤ 3 months)		Long-term (> 3 months)		P-Value*
	HR	95% CI	HR	95% CI	
Female					
Age ≤ 50					
Unprovoked	1		1		
Provoked	0.96	(0.38-2.43)	1.28	(0.82-2.02)	0.56
Cancer	17.85	(8.69-36.66)	12.92	(8.37-19.94)	<0.001
Age 51-70					
Unprovoked	1		1		
Provoked	0.94	(0.48-1.86)	1.30	(0.96-1.76)	0.23
Cancer	9.61	(5.80-15.91)	7.07	(5.43-9.20)	<0.001
Age >70					
Unprovoked	1		1		
Provoked	0.92	(0.54-1.59)	1.07	(0.87-1.31)	0.78
Cancer	5.70	(3.63-8.93)	2.03	(1.06-2.53)	<0.001
Male					
Age ≤ 50					
Unprovoked	1		1		
Provoked	1.25	(0.41-3.81)	1.66	(0.98-2.80)	0.16
Cancer	23.23	(8.99-60.01)	16.71	(10.05-27.79)	<0.001
Age 51-70					
Unprovoked	1		1		
Provoked	1.22	(0.47-3.18)	1.68	(1.11-2.55)	0.044
Cancer	12.50	(5.42-28.84)	9.15	(6.21-13.48)	<0.001
Age >70					
Unprovoked	1		1		
Provoked	1.20	(0.52-2.80)	1.38	(0.98-1.95)	0.17
Cancer	7.41	(3.36-16.31)	2.63	(1.85-3.74)	<0.001

HR: Hazard Ratio; CI: confidence interval; Unprovoked: Patients with non-provoked PEs events; Provoked: Patients with Provoked PEs; Cancer: Patients with cancer-associated PEs. Adjusted for age, sex, diagnosis year, acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, renal disease, valvular heart disease, anemia, thrombocytopenia, hypertension, and neurological disease.

*For comparison between short-term and long-term hazard ratios.

Figure 5: Overall survival probability after pulmonary embolism stratified by risk factors.



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Chapter 5

DISCUSSION AND CONCLUSIONS

5.1. Summary and interpretation of the results

The preceding chapters of this dissertation reviewed research on the epidemiology of venous thromboembolism (VTE) in the population of Alberta, Canada, in a variety of settings. The primary objectives were to examine contemporary trends in the epidemiology of clinically recognized VTE and to assess mortality, and factors associated mortality, after a first (incident) episode of VTE from a potentially more generalizable population-based perspective.

Since a highly specific definition of VTE using data from both primary and secondary care health care settings is required to accurately estimate the incidence of VTE, we validated the case-identifying algorithm to accurately ascertain patients presenting with acute venous thromboembolism and minimize misclassification bias that could potentially render all subsequent analysis invalid. We found the identification of ICD codes, in any diagnosis position, with one VTE-related procedure code was moderately sensitive but remarkably specific with good predictive abilities for VTE, PE and DVT. Additionally, using ICD discharge diagnoses with an imaging procedure code to ascertain acute VTE gave reliable estimates of numbers and proportions as well as a reasonable degree of validity, despite imperfect diagnostic accuracy. Results of the validation study provided a rationale and justification for conducting more epidemiological studies using this kind of data.

Additionally, the subsequent retrospective cohort studies based on linkage of administrative health data in Alberta provide a substantial contribution to our knowledge about the incidence rate, trend, and mortality in patients with VTE.

5.2. Incidence and case-fatality of acute venous thromboembolism

Among 31656 Alberta residents diagnosed with acute PE and/or lower extremity DVT during 8 annual periods between 2004 and 2012, the community age and sex adjusted incidence rate of VTE in our population was 1.46 per 1000 person-years, about half of which are unprovoked and 16% of which are secondary to cancer. The adjusted incidence rates increased with age and were more than threefold higher in those 80 years and older in both sexes. Furthermore, the overall adjusted model showed no significant trend in the incidence of VTE during the study period. Among patients with acute VTE, the overall 30-day case fatality rate was 2.0% (95% CI: 1.89, 2.21), 3.9% (95% CI: 3.50, 4.33) in patients with PE and 1.3% (95% CI: 1.2, 1.5) in patients with DVT. The 1-year case fatality increased markedly to 19.6% (95% CI: 8.88, 9.52) for VTE and 12.9% (95% CI: 12.2, 13.6) in patients with PE.

5.3. Short- and long-term mortality after pulmonary embolism

In this study, we aimed to investigate the effect of cancer on overall, short- and long-term mortality in a cohort of consecutive incident PE patients diagnosed from 2004 to 2012 after adjusting for important sociodemographic and clinical prognostic factors. A total of 8641 consecutive adults were newly diagnosed with pulmonary embolism between April 1, 2004 and March 31, 2012 (34,854 person-years) with a median follow-up of 8 years, of which 42.2% where unprovoked, 37.9% were provoked and 19.9% were cancer-associated PEs.

In line with previous studies, it is estimated consistently that ~20% to 30% of all first venous thromboembolic events are cancer associated. White and coworkers used the California discharge data set to identify a cohort of 21 002 patients hospitalized with incident venous thrombosis in 1996. Of these patients, again ~20% (4368) were reported to have cancer-associated venous thrombosis.[1] In a second study, medical records of residents from the Worcester metropolitan area were obtained for a total of 1399 subjects with a confirmed episode of VTE. Of these patients, 29% had a recent or active malignant neoplasm.[2] In a more recent registry, the RIETE registry, which included >35 000 consecutive symptomatic venous thrombosis patients from 2001 to 2011, active cancer was reported in 6075 patients (17%).[3]

We found that the 1-year survival in patients with PE was the lowest in patients with cancer with a median survival of 2 years. And patients with cancer provoked pulmonary embolism have a higher risk of dying during the first 3 months of diagnosis compared to patients with unprovoked events. In addition, the proportion of mortality at 5-years is about 1 in 5 patients in patients with provoked and unprovoked events which emphasizes that acute PE is an important clinical problem with a poor prognosis for short-term and long-term survival.

Results of this study are similar to those reported in a retrospective analysis of all-cause mortality in patients with VTE in Quebec in which this population had a higher mortality rate in patients with cancer-associated events, as well as, high a similar mortality profile among provoked venous thromboembolism cases compared with unprovoked venous thromboembolism cases.[4]

In cancer patients, the risk of death was significantly higher during the acute phase (first 3 months) which may be explained by the clinical deterioration after PE (22) and the presence of thrombosis signifying more advanced cancer.

5.4. Strengths and limitations of this research

The AB-VTE database is a de-identified individual-level, longitudinal data, by fiscal year, obtained from the administrative health databases under the custodianship of Alberta Health: the Alberta Health Care Insurance Plan (AHCIP) registry, the Alberta Physician Claims Assessment System, the Morbidity and Ambulatory Care Reporting (MACAR) system, Alberta Vital Statistics. Deterministic data linkage across the AHCIP, MACAR, Physician Claims and Vital Statistics databases was based on an encrypted unique personal health number (PHN). Health care in Alberta is publicly funded for all residents under AHCIP. Virtually all Alberta residents (about 99%)[5] are covered by the AHCIP.

Research presented in this dissertation is one of the first studies in Canada, and the first one in Alberta to provide a comprehensive longitudinal assessment of the epidemiology and health services use in VTE. The retrospective cohort design with database linkage constituted a cost efficient and valid method to evaluate the population and outcomes of interest. Additionally, it involved a large number of people with wide coverage and continuity of data over a relatively long follow-up period. Given the research questions and study design, multivariate analyses was the optimal way to address confounding in the study. This research used a validated algorithm to identify VTE cases in the study population. The algorithm has been previously validated to identify adults with VTE, with acceptable predictive performance.[6]

As with all observational research, there are a number of limitations inherent to the design and data sources, such as the quality of administrative data and underreporting of key information, potential bias in the selection of the study cohorts, and misclassification bias in the definition of incident VTE cases. As of the quality of administrative data, the effect of potential confounders, including family history, body mass index, treatments, and laboratory data, were not fully adjusted for in the multivariate analyses because no direct information on these factors is captured in the administrative health databases that were used. Misclassification bias affecting the status of exposure (i.e., having VTE) is almost inevitable in VTE research.[7] Underestimation of the "true" incidence in the community of VTE can potentially arise from missed fatal PEs, under-recognition of the diagnosis in symptomatic cases; and incomplete ascertainment of objectively verified cases. However, we used a validated combined ICD code and VTE related imaging code to mitigate this issue. Further, because the AHCIP is free tax-supported health care for all inhabitants, hospitals have no financial incentive to deny imaging work-up to patients of low socioeconomic position.

5.5. Study significance and implications

Notwithstanding the above limitations, this research is one of the first in Canada and the first in Alberta to provide the most comprehensive evidence to date on the epidemiology and health services use for VTE.

Based on the event rate of 1.46 per 1,000 population per year and with a population of some 35 million,[8] there will be 51,000 episodes of VTE annually in Canada, yielding an incidence approximately equal to that of strokes.[9] Almost forty percent of cases in this study were due solely to recent hospitalization for medical

and/or surgical reasons or surgical interventions, and were therefore, potentially preventable through appropriate thromboprophylactic measures. These estimates are similar to the reported incidence in the general population in this age-group in older population studies.[10, 11]

Knowing the local incidence of VTE has important clinical and economic implications. It allows health planners to allocate resources accordingly so that clinical and social services are adequately placed to meet the demands of managing both the acute problem and longer term consequences of VTE. It also provides local data for pharmaco-economic evaluations of preventive strategies and to target risk groups with the most cost-effective measures.

5.6. Future Research Directions

The AB-VTE database provides multiple opportunities for future research. Several lines of research include assessing the quality of administrative databases in defining recurrent events. Also, evaluating health care inequalities between urban and rural health care facilities, differences in access to VTE treatment as well as adherence to clinical practice guidelines.

Additionally, by linking medication data (Pharmaceutical Information Network, PIN) and laboratory data (Data Integration, Measurement and Reporting, DIMR) to the existing AB-VTE cohort, we can assess the rate of recurrent VTE on therapeutic anticoagulation, after withdrawal of anticoagulation, major bleeding on anticoagulation and mortality after incident VTE.

5.7. Conclusion

Venous thromboembolism is a disease with significant morbidity and mortality. Despite advances in identification, prophylaxis, and treatment in the last decade, the annual event rate of VTE remains high. While this may be partially due to increased sensitivity of diagnostic methods, especially for PE, it may also imply that current prevention and treatment strategies are less than optimal.

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