A POPULATION-BASED PERSPECTIVE ON CLINICALLY RECOGNIZED VENOUS THROMBOEMBOLISM: CONTEMPORARY TRENDS IN CLINICAL EPIDEMIOLOGY AND RISK ASSESSMENT OF RECURRENT EVENTS

A Dissertation Presented

By

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Dedicated to my family

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Abstract

Background: Venous thromboembolism (VTE), comprising the conditions of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common acute cardiovascular event associated with increased long-term morbidity, functional disability, all-cause mortality, and high rates of recurrence. Major advances in identification, 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 prevention and management.

Objectives: To examine recent trends in the epidemiology of clinically recognized VTE and assess the risk of recurrence after a first acute episode of VTE.

Methods: We used population-based surveillance to monitor trends in acute VTE among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA) from 1985 through 2009, including in-hospital and ambulatory settings.

Results: Among 5,025 WMSA residents diagnosed with acute PE and/or lower-extremity DVT between 1985 and 2009 (mean age = 65 years), 46% were men and 95% were white. Age- and sex-adjusted annual event rates (per 100, 000) of clinically recognized acute first-time and recurrent VTE was 142 overall, increasing from 112 in 1985/86 to 168 in 2009, due primarily to increases in PE occurrence. During this period, non-invasive diagnostic VTE testing increased,

while treatment shifted from the in-hospital (chiefly with warfarin and unfractionated heparin) to out-patient setting (chiefly with low-molecular-weight heparins and newer anticoagulants). Among those with community-presenting first-time VTE, subsequent 3-year cumulative event rates of key outcomes decreased from 1999 to 2009, including all-cause mortality (41% to 26%), major bleeding episodes (12% to 6%), and recurrent VTE (17% to 9%). Active-cancer (with or without chemotherapy), a hypercoagulable state, varicose vein stripping, and Inferior vena cava filter placement were independent predictors of recurrence during short- (3-month) and long-term (3-year) follow-up after a first acute episode of VTE. We developed risk score calculators for VTE recurrence based on a 3-month prognostic model for all patients and separately for patients without active cancer.

Conclusions: Despite advances in identification, prophylaxis, and treatment between 1985 and 2009, the disease burden from VTE in residents of central Massachusetts remains high, with increasing annual events. Declines in the frequency of major adverse outcomes between 1999 and 2009 were reassuring. Still, mortality, major bleeding, and recurrence rates remained high, suggesting opportunities for improved prevention and treatment. Clinicians may be able to use the identified predictors of recurrence and risk score calculators to estimate the risk of VTE recurrence and tailor outpatient treatments to individual patients.

Key words: deep vein thrombosis; venous thrombosis; pulmonary embolism; incidence; prevalence; event rate; attack rate; recurrence; adverse events; outcomes research; prognostic/prediction models

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List of Acronyms

Acronym	Definition
VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary embolism
PE±DVT	Pulmonary embolism with or without deep vein thrombosis
WMSA	Worcester metropolitan statistical area
RAM	Risk assessment model
US	United States
MA	Massachusetts
LMWH	Low molecular weight heparin
UFH	Unfractionated heparin
ICD-9	International classification of diseases ninth revision
CI	Confidence interval
HR	Hazard ratio
CIR	Cumulative incidence rate
CTPA	Computed tomography pulmonary angiography
RBC	Red blood cell
RCT	Randomized controlled trial
IVC	Inferior vena cava
UK	United Kingdom

Preface

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

Huang W, Anderson FA Jr., Spencer FA, Gallus A, Goldberg RJ. Risk-assessment Models for Predicting Venous Thromboembolism among Hospitalized Non-Surgical Patients: A Systematic Review. J Thromb Thrombolysis. 2013; 35(1):67-80
PMID: 22826096

The material covered in Chapter II has been recently published in the American Journal of Medicine under the following citation:
Huang W, Goldberg RJ, Anderson FA, Kiefe C, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: The worcester venous thromboembolism study (1985 to 2009). Am J Med. 2014 Sep; 127(9): 829-839 e5. doi: 10.1016/j.amjmed.2014.03.041. Epub 2014 May 6.
PMID: 24813864

Chapter III (submitted to peer-review journal)
Chapter IV (under preparation for submission)

Chapter I. Introduction

1.1 Specific aims

Venous thromboembolism (VTE), comprising the conditions of deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with increased long-term morbidity, functional disability, and mortality.[1] VTE has been estimated to be the third most common cardiovascular disorder in American adults after the acute coronary syndromes and ischemic stroke.[2] Estimates from observational studies conducted more than a decade ago suggested that there are between 150,000 to 300,000 new cases of clinically recognized VTE, and 100,000 to 200,000 VTE-associated deaths, that occur annually in the United States.[3-5] However, recent clinical data on the descriptive epidemiology of VTE are limited.[6] The need for better estimates of the magnitude of VTE was the impetus for two National Institutes of Health-funded, population-based, epidemiologic studies carried out in residents of the Worcester Metropolitan Statistical Area (WMSA), namely the Worcester DVT Study (1986-1990: Cohort-I) and the Worcester VTE Study (1999-2009: Cohort-II).[3,7] Both studies employed population-based surveillance methods to monitor trends in the incidence, management strategies, recurrence, and case-fatality rates of VTE among residents of the WMSA. These studies provide a solid foundation to describe the clinical epidemiology of VTE in residents of central Massachusetts, and changes over time therein.

During the past three decades, there have been major advances in identifying patients at increased risk for VTE, and in the development of improved prophylaxis, diagnostic, and treatment strategies.[6 8-13] These advances have likely changed the clinical epidemiology of VTE. In addition, with recent changes in health care delivery, such as decreasing lengths of acute hospitalization and increasing treatment in the outpatient setting,[14-15] patients are being sent home earlier with major ongoing risk factors for VTE. It is possible that an increasing proportion of VTE is being shifted from the hospital setting to the community setting, and a majority of patients will now be treated as outpatients due to advances in therapeutic strategies.[16] Therefore, it remains of considerable importance to examine secular trends in the clinical epidemiology of VTE, particularly among patients with episodes of VTE that have occurred in the broader community setting.

VTE is a disease with multiple risk factors and this condition is associated with high rates of recurrence.[1, 11] Despite ongoing advances in the therapeutic management of patients with VTE, recurrence is common during the first 2-3 years after the development of this thromboembolic disorder.[17-19] Accordingly, identifying risk factors associated with VTE recurrence will hopefully lead to more effective VTE treatment.

The primary goal of this dissertation project is to describe multi-decade long trends in the magnitude, management, and short- and long-term outcomes of VTE from a broad population-based perspective among residents of central

Massachusetts. In addition, I have developed a risk assessment model (RAM) to estimate the risk of recurrent VTE within 3 years after a first acute episode. To accomplish these objectives, I used data (~ 5000 VTE cases) from the Worcester VTE Study Cohort-I and Cohort-II. The objectives of my dissertation project include the following specific aims:

Aim 1: **Describe secular trends (1985–2009) in VTE prevalence and incidence rates, associated patient characteristics, type of VTE events, occurrence settings, and diagnostic methods utilized.**

H1a: The proportion of patients who develop VTE in the community setting has increased during the years under study.

H1b: The proportion of all VTE patients who underwent an objective diagnostic test to confirm the presence of VTE has increased over time.

H1c: The proportion of patients with objectively diagnosed VTE who underwent a non-invasive confirmatory test has increased between 1985 and 2009.

Aim 2: **Examine recent decade long trends (1999–2009) in the clinical management and long-term outcomes among patients with a first episode of VTE that developed in the community setting.**

H2a: There has been an improvement over time in the use of prior VTE prophylaxis.

H2b: There has been an increased use of low molecular weight heparin over time and in the proportion of patients who receive this treatment in the outpatient setting.

Aim 3: **Develop a RAM to predict the risk of VTE recurrence within 3 years after a first episode of VTE.**

The findings of this dissertation project provide relatively contemporary insights into the clinical epidemiology of VTE from a population-based perspective and provide important data on the evolution and outcomes of diagnostic and therapeutic strategies used in the management of VTE. This information is sorely lacking in the published literature, which may be utilized for the design and testing of interventions to enhance current management practices with the goal of favorably influencing the long-term outcomes of patients with VTE. In addition, following independent validation, the new RAM developed as part of this dissertation to predict recurrent episodes of VTE may serve as a clinical decision support tool to guide clinicians to deliver more effective VTE treatment.

1.2 Significance: disease burden

Venous thromboembolism (VTE) (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) is associated with increased long-term morbidity, functional disability, and mortality.[1] VTE has been estimated to be the third most common cardiovascular disorder in adult Americans after the acute coronary syndromes and ischemic stroke.[2] PE remains a leading cause of death in western countries following hospitalization for childbirth, major surgery, and acute medical conditions.[1] Estimates from observational studies conducted more than a decade

ago suggested that there are between 150,000 to 300,000 new cases of clinically recognized VTE, and 100,000 to 200,000 VTE-associated deaths, that occur annually in the United States.[3-5]

DVT occurs when the deep veins carrying blood back to the heart develop one or more large clots, usually in the lower extremities.[1] Leg pain and swelling may result, but the most serious complication associated with DVT results in a potentially life-threatening PE when part or all of the thrombus breaks loose and embolizes to the pulmonary vessels.[1] Symptoms of PE include chest pain and shortness of breath, leading to sudden death in severe cases.[1] Late sequelae of DVT are a source of substantial morbidity and include venous stasis syndrome, venous leg ulcers, and chronic thromboembolic pulmonary hypertension,[1] which have been shown to negatively impact patient's long-term quality of life.[20-22] In addition, patients with a history of VTE are nearly eight times more likely to develop another episode of VTE as compared to patients without a history of DVT or PE.[23]

In addition to the clinical impact of VTE, the economic burden of this disease is considerable.[24-26] Direct medical costs for the treatment of patients with nonfatal VTE were recently estimated to be between 6-8 billion dollars in the United States.[6 25]

1.3 Significance: clinical epidemiology of VTE

Knowledge of the clinical epidemiology of VTE comes primarily from three National Institutes of Health-funded, population-based, observational studies in the United States.[3, 5, 7] The first two, based in Worcester, Massachusetts (MA), include the Worcester DVT Study (1986-1990: Cohort-I)[3] and the Worcester VTE Study (1999-2009: Cohort-II).[7] A third study, the Rochester Epidemiology Project, is based in Olmsted County, Minnesota.[5] These studies provide the best data to assess the clinical epidemiology of VTE in United States, and changes over time therein, from the more generalizable perspective of a population-based investigation.

Investigators from the Rochester Epidemiology Project retrospectively reviewed the inpatient and outpatient medical records from a population-based inception cohort of 2,218 patients who resided in Olmsted County, Minnesota and who experienced a first episode of DVT or PE during the 25-year period between 1966 and 1990.[5] The overall age- and sex-adjusted annual incidence rate of VTE was 117 per 100,000 population.[5] Overall, the incidence rates of first episodes of VTE were relatively high between 1966 and 1976, declined by 30% between 1977 and 1979, and remained relatively stable from 1980 through 1990.[5] Based on the Worcester VTE Study Cohort-I, during the 18-month period from July, 1985 to December, 1986, the crude annual incidence rate of first episodes of VTE was 71 per 100,000 population.[3] Results of the Worcester VTE Study Cohort-II indicated that the age- and sex-adjusted annual incidence rates

of first episodes of VTE (including upper-extremity DVT) were 104, 116, and 117 per 100,000 population during 1999, 2001, and 2003, respectively.[7,27] However, long-term trends (1985 – 2009) in the Worcester VTE studies have not been assessed.

In 1884, Rudolph Virchow first proposed that thrombosis was the result of at least 1 of 3 underlying etiologic factors: vascular endothelial damage, stasis of blood flow, and blood hypercoagulability.[23] Previous publications based on the Rochester Epidemiology Project, early year cohorts of the Worcester VTE studies, and other epidemiologic studies indicated that risk factors for VTE included male sex, increasing age, obesity, malignancy, prolonged immobility, neurological disease with leg paresis, central vein catheterization or receipt of a transvenous pacemaker, varicose veins, myocardial infarction, respiratory failure, congestive heart failure, pregnancy and the puerperium, oral contraceptives, antiphospholipid antibody syndrome, an inherited thrombophilic condition, persistently increased plasma fibrin D-dimer levels, surgery, trauma, hospital or nursing home confinement, and prior VTE.[1, 23, 28 29-37] In particular, the incidence rates of VTE increase markedly with advancing age.[1, 3, 19, 23, 28] However, current estimates of the clinical epidemiology of VTE are lacking, particularly identification of elevated VTE risk at an individual patient level.[6]

1.4 Significance: trends in the clinical management of VTE

There have been major advances in identifying patients at increased risk for VTE, in the development of improved prophylaxis, and in diagnostic and treatment strategies,[6 8-13] which have likely changed the descriptive clinical epidemiology of VTE.

The evolution of computer imaging technology led to a change in VTE diagnostic strategies. The common diagnostic tests were shifting from invasive imaging (venography and angiography) in the 1980's to the use of noninvasive imaging tests (compression ultrasound imaging, lung scan and computed tomography imaging) in the 1990's. During recent years, the combination of noninvasive imaging, D-dimer measurement, and a clinical probability assessment have become common diagnostic strategies for VTE,[8-10] whose increasing use could have impacted the reported event rates of VTE.

The introduction of the subcutaneous low molecular weight heparins (LMWHs) in the 1990's as an alternative to the treatment requiring dosing monitoring (intravenous unfractionated heparin [UFH] and Vitamin-K antagonists) has dramatically changed the manner in which the initial care of patients with VTE is presently carried out.[38-42] Recently, several orally active small molecules have been evaluated in the treatment of VTE, including a direct thrombin inhibitor and several direct Factor Xa inhibitors.[16] Other novel oral agents are also in development for VTE treatment.[16]

In addition, growing awareness of VTE as an important public health problem served as the impetus for several revisions of evidence-based clinical practice guidelines for appropriate VTE prevention and treatment.[11-13 6, 43] A VTE quality measure was selected as a core measure set for use in the Joint Commission's ORYX program (performance measurement and improvement initiative) in the 2000's.[43] Each of these practice and guideline recommendations could have altered physicians clinical practice patterns.

Therefore, I propose to assess 25-year trends (1985-2009) in VTE event rates, associated patient characteristics, and diagnostic methods utilized by examining data from the Worcester VTE Study Cohort-I and Cohort-II (including unpublished findings from the 1988/89, 2005, 2007, and 2009 cohorts). This research may provide new insights into relatively recent changes in the clinical epidemiology of VTE, reflecting the impact of rapidly evolving clinical practices in the management of VTE.

1.5 Significance: VTE in the community setting

Although hospitalized patients are at particularly high risk for developing VTE,[1, 11] data from early findings of the Worcester VTE Study cohorts suggested that most episodes of VTE occurred in the community setting.[44-45] It is notable that a substantial proportion of these patients had undergone surgery or hospitalization in the preceding 3 months.[3, 7, 45] With recent changes in health care services, including decreasing lengths of acute hospitalization that postpone

medical diagnosis and treatment to the outpatient setting,[14-15] patients are being sent home earlier with potential risk factors for VTE. It is possible that an increasing proportion of VTE is being shifted from the hospital to the community setting. In addition, recent advances in different therapeutic strategies have made it possible to treat most patients on an outpatient basis for longer periods of time.[16]

Therefore, it becomes increasingly important to investigate recent decade long trends (1999-2009) in the clinical management (prior VTE prevention, in-hospital and/or outpatient VTE treatment) and long-term outcomes among patients with a first episode of VTE that occurred in the community setting. This research may provide new insights into the profile and management of patients who experience VTE in the community setting, ultimately representing a significant proportion of failures in VTE prevention after a preceding hospitalization. The findings may generate testable hypotheses and subsequent investigations that will ultimately improve VTE prevention and its treatment.

1.6 Significance: VTE recurrence

VTE is a disease with multiple risk factors, which tends to recur.[1, 11] Despite therapeutic advances in the management of patients with VTE, the cumulative incidence rates of recurrent VTE remain high during the first 2-3 years after the development of this thromboembolic disorder.[17-19] Accordingly,

identifying risk factors associated with VTE recurrence may lead to more effective VTE treatment.

In current practice, the optimal duration of anticoagulation in patients with VTE is based on balancing the risks of recurrence and bleeding during the three month period during which anticoagulation therapy is prescribed following an index episode of VTE.[46] The decision as to continue or discontinue anticoagulation after this period should be individually tailored and balanced against the risk of hemorrhage.[46] Current practice guidelines for the management of VTE shift the focus away from laboratory testing and place stronger emphasis on identifying clinical factors when making treatment decisions.[47-48] Despite substantial progress in identifying the determinants of recurrent VTE,[49-50] prediction of elevated risk in an individual patient is often not feasible in routine care. Therefore, it would advance patient care to develop a robust risk assessment model (RAM) to identify independent predictors of recurrent episodes of VTE by using contemporary and population-based data. This RAM could be used as a clinical decision support tool to guide clinicians to deliver more effective VTE treatment.

1.7 Innovation

The findings of this dissertation project may provide contemporary insights into the clinical epidemiology of VTE from a population-based perspective and may provide important data on the evolution and outcomes of diagnostic and

therapeutic strategies used in the contemporary management of VTE. This information is sorely lacking in the published literature. The findings of this dissertation project may be instrumental in identifying VTE patients at increased risk for the underutilization of specific therapies as well as for early and more long-term adverse outcomes. This information may set the stage for the design and testing of interventions to correct deficiencies in current management practices with the goal of favorably influencing the long-term outcomes of patients with VTE. In addition, following independent validation, the new RAM to predict recurrent episodes of VTE may serve as a clinical decision support tool to guide clinicians to deliver more effective treatment for this increasingly prevalent disorder.

1.8 Approach: overview of methods

The primary goal of this dissertation project is to describe relatively contemporary trends in the clinical epidemiology of clinically recognized VTE and the risk of recurrent events from a population-based perspective. I used data from two National Institutes of Health funded, population-based, epidemiologic studies carried out in Worcester, MA, namely the Worcester DVT Study (1985-1990: Cohort-I)[3] and the Worcester VTE Study (1999-2009: Cohort-II).[7] Both studies included all cases of VTE occurring among residents of the Worcester Metropolitan Statistical Area (WMSA).

1.9 Approach: background of Worcester VTE studies

The Worcester VTE studies employed proven population-based surveillance methods to monitor trends in the incidence, management strategies, recurrence, and short and long-term (up to 3 years after initial episode of VTE) case-fatality rates in residents of the WMSA. Both studies screened all patients with a diagnosis of acute DVT and/or PE based on International Classification of Diseases Ninth revision (ICD-9) consistent with possible VTE (Table 1.1) documented in medical records from all central MA hospitals that provide short-term care for residents of the WMSA.

Prior to 1990, in-hospital treatment was standard clinical practice for all newly diagnosed cases of acute VTE. Therefore, Cohort-I included all VTE patients discharged during two 18-month periods, July 1985 - December 1986 and July 1988 - December 1989. Quarterly hospital discharge reports were used to screen potential patients based on ICD-9 codes listed in Table 1.1, but only objectively confirmed (physician documented) cases of VTE were included.

Cohort-II included hospitalized patients, as well as patients who were not admitted to central MA hospitals, but were diagnosed with VTE based on the results of an outpatient, emergency department, radiology department, or diagnostic laboratory encounter during 1999, 2001, 2003, 2005, 2007, and 2009. In addition, the logs and/or computerized billing lists of patients evaluated in greater Worcester ultrasound departments were screened to identify potential cases of VTE that may have been missed due to coding errors, and to identify

patients referred directly from outside physicians' offices, rehabilitation facilities, and nursing homes for testing who then returned directly to these settings for treatment. Data on index and follow-up events were collected at the same time when the medical records were reviewed, approximately three-years after the index event (i.e., the length of follow-up is 3 years for all included patients). National and statewide death registries were reviewed on an annual basis to ascertain the survival status of all study patients.

Definition of index VTE

Although both Worcester VTE studies used ICD-9 codes to screen and identify potentially eligible cases of acute DVT and/or PE, there were slight differences in ICD-9 codes due to the refining of ICD-9 codes over the years (Table 1.1). In addition, Cohort-II included patients with upper extremity DVT.

In Cohort-I, data were collected only from medical records that included a written hospital discharge diagnosis of acute DVT and/or PE. For cases with ICD-9 codes that were not specific for VTE, particularly the 900 series, cases were validated based on lung scan, venography, impedance plethysmography (ICD-9 codes 88.62, 88.66, 88.68) or pulmonary angiography (ICD-9 code 88.43) test results.

In Cohort-II, cases identified by ICD-9 codes were validated and classified by trained data abstractors based on pre-specified criteria as either definite, probable, possible, or absent (Table 1.2). The criteria were developed based on

a modification of a classification schema proposed by Silverstein et al.[5] Only the cases identified as definite, probable, and possible were included in Cohort-II.

Potential cases of recurrent VTE as the index event were classified using criteria similar to those used for first-time cases if the patient had a prior VTE noted in their medical records.

Definition of Adverse Events after Index VTE in Cohort-II

Recurrence was classified using criteria similar to those employed for the index event, but required occurrence of thrombosis in a previously uninvolved venous (recurrent DVT) or pulmonary segment (recurrent PE). Recurrent VTE was classified as the first occurrence of DVT or PE after the index VTE.

Episodes of major bleeding that may have occurred for patients in the study years of 1999, 2001, and 2003 were defined as any episode of bleeding requiring transfusion of ≥2 units of packed red blood cells (RBCs), or causing a prolonged or subsequent hospitalization (e.g., stroke, myocardial infarction) or death. To be consistent with International Society of Thrombosis and Haemostasis criteria,[51] the definition for major bleeding was revised for the 2005, 2007, and 2009 cohorts as the following: clinically overt bleeding resulting in death; located in a critical site (intracranial, intraocular, retroperitoneal, intra-articular, pericardial, muscular with compartment syndrome); required transfusion of ≥2 units of packed RBCs; or resulted in a hemoglobin drop of ≥20 g/L.

Data collection and management

The medical records of all identified patients meeting the diagnostic and geographic inclusion criteria were reviewed retrospectively by trained data abstractors and validated by clinicians. Standard data abstraction forms were developed for the medical record review. Both studies collected information on patient's socio-demographic characteristics, risk factors for VTE, previous and concurrent medical conditions, diagnostic methods, therapeutic interventions, and outcomes for up to a 3 year period of follow-up. For some major medical events that occurred prior to the index event, Cohort-II only included historical information for the prior 3 months, compared to the collection of historical data over the preceding 6 months for patients included in Cohort-I. In situations where patients had been assigned several possible VTE related ICD-9 codes, or had received care from multiple hospitals for a single VTE event, potential duplicate cases were eliminated in the master database after data collection.

1.10 Approach: methods for aim 1

To assess 25-year trends (1985-2009) in event rates of VTE, including trends in patient characteristics and diagnostic methods, data from patients included in Cohort-I and Cohort-II were used. However, cases of upper-extremity DVT alone identified in Cohort-II were excluded in this dissertation, since the natural history and management of upper-extremity DVT differs from that of acute lower-extremity DVT.[52-53] In addition, Cohort-I did not include patients with upper-extremity DVT alone.

Prior to 1990, in hospital treatment was standard clinical practice for all newly diagnosed cases of acute VTE. Outpatient initiation of treatment was considered to be unsafe.[16] Accordingly, Cohort-I did not include cases treated without hospitalization to initiate anticoagulant therapy.

Event rates

Data from the United States Census Bureau for individuals residing in the WMSA were used as the denominator to calculate various event rates including first-time and recurrent VTE. The population estimates per US Census conducted in 1985 and 2000 for the city and towns included in the Worcester VTE studies are listed in Table 1.3. These crude rates were used to calculate age- and sex-adjusted rates by the direct adjustment method.[54]

Patient socio-demographic characteristics

Age was calculated as the difference between the date of the index VTE event and date of birth. In addition, age was grouped into several age categories, namely <40 years, 40-49, 50-59, 60-69, 70-79, and 80 years and older, in order that my results can be compared to published 25-year trends (1966 – 1990) from the Rochester Epidemiology Project.[5] Sex and race were compared as well.

Clinical factors

Hospital length of stay wascalculated as the difference between the dates of hospital discharge and admission. Data on medical history were examined, including use of hormone therapy (diffreent than comorbid conditions), diabetes,

DVT, PE, active malignancy, paralysis of lower extremities, parturition, severe burns, multiple trauma, fracture, congestive heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, and major surgery.

Signs and symptoms of VTE

These included leg symptoms of pain, swelling, tenderness, positive Holman's sign, redness, warmth, leg ulcers, or calf circumference, and chest symptoms of dyspnea or chest pain, hemoptysis, syncope, elevated jugular pressure, pleural friction rub, hypotension, tachycardia, and central cyanosis. A Yes/no question related to whether VTE was suspected at the time of hospital admission, emergency room visit, or outpatient visit was collected which was used to identify patients who developed VTE in the community setting.

Objective diagnostic methods

Objective diagnostic testing methods were reported separately for DVT and PE. Tests employed for the diagnosis of VTE were categorized as either invasive (venogram and pulmonary angiogram) or non-invasive (impedance plethysmography, duplex/ultrasound scan, lung scan, computed tomography imaging).

Analysis methods

Annual event rates of VTE were reported per 100,000 population. The number of first-time VTE served as the numerator for the calculation of event rates of first episodes of VTE (incidence rate), while the number of recurrent episodes of VTE served as the numerator for the calculation of event rates of

recurrent VTE. The 1985 Census data for the WMSA (*n*=379,953) were used as the denominator for calculation of 1985–1989 annual crude event rates and 2000 Census data of the WMSA (*n*=477,598) were used as the denominator for calculation of 1999–2009 annual crude event rates.[3, 7] These crude rates were used to calculate age- and sex-adjusted rates by the direct adjustment method.[54] Since the WMSA population was approximately 90% white during the years under study, the age and sex distribution of the 2000 United States white (reference) population was used to calculate age- and sex-adjusted rates.[5] Confidence interval (CI) estimates were based on the Poisson distribution. Trends in rates during the years under study were assessed by Poisson regression. Annual case counts were modeled using the SAS procedure GENMOD with a logarithmic link function and a log (population) offset term. A main effects model included a term for sex, age group (<40, 40–49, 50–59, 60–69, 70–79, ≥80 years), and study period. Separate models were constructed for episodes of first-time or recurrent VTE, overall, and separated into PE (with or without DVT) and DVT-alone.

Patient characteristics and diagnostic tests were reported as frequencies and percentages for categorical variables and as means (standard deviations) or medians (interquartile ranges) for continuous variables. The Cochran-Armitage tests and linear regression models were used to test for linear trends over time among categorical variables and continuous variables, respectively. Comparisons between the 2009 cohort with the 1985/86 cohort were performed

using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was specified as α=.05 (two-sided).

1.11 Approach: methods for aim 2

The primary objectives of this aim are to assess recent decade long trends (1999–2009) in the clinical management and long-term outcomes among patients with an initial episode of VTE that developed in the community setting. The working definitions of a first-time VTE, and VTE occurring in the community setting, were the same as the definition used in Aim 1.

Clinical management practices included prior VTE prophylaxis status among patients who underwent prior surgery or a non-surgical-related hospitalization. In the early 1990s, with the introduction of subcutaneous LMWHs, which did not require dose adjustment (LMWHs replaced UFH), the outpatient treatment of VTE was made possible.[38-42] Therefore, trends in the adoption of new treatment methods were examined, including initial treatment setting (in-hospital or outpatient clinic) and type of therapy (UFH, warfarin, or LMWH).

Decade long trends in adverse event rates of all-cause mortality, major bleeding episodes, and recurrent VTE within 3 years of the index event were assessed.

Analysis plan:

Categorical variables were reported as frequencies and percentages and continuous variables as means, standard deviations, medians, and interquartile ranges. Cochran-Armitage tests for binomial variables, Mantel-Haenzel tests for multinomial variables, and linear regression models for continuous variables were used to examine trends during the years under study. Differences in the characteristics, management, and outcomes of patients diagnosed with VTE in 2009 versus those in 1999 were examined using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

To further evaluate whether study year at the time of VTE presentation was associated with our pre-specified outcomes over our 3-year follow-up, including occurrence of recurrent VTE, major bleeding, and all-cause mortality, Kaplan-Meier curves with log-rank tests and multivariable Cox proportional hazard regressions were constructed. Multivariable Cox proportional hazard regressions controlled for age, sex, index diagnosis of VTE (PE with/without (±) DVT vs. DVT alone), and medical history within 3 months before the index event. Patients who experienced a major bleeding episode before the development of a recurrent VTE over the course of follow-up were excluded from the recurrent VTE regression model; patients with recurrent VTE prior to major bleeding during follow-up were excluded from the major bleeding regression model. All follow-up data were censored at the last contact (3 years) for mortality, and death or the

last contact (3 years) for major bleeding and recurrent VTE following the index event.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was specified as α=.05 (2-sided).

1.11 Approach: methods for aim 3

Due to the availability of data on long-term follow-up, only data from Cohort-II were used for this analysis. In addition, only identified first episodes of VTE were included. Risk factors associated with recurrence after index event were identified. Evidence-based RAMs were developed to predict VTE recurrence during short- (3 months) and long-term (3 years) follow-up after the index event. Risk score calculator(s) based on the 3-month prognostic model were created.

Outcome

Recurrent VTE following an index event (defined in section 1.9) was the primary outcome for this analysis. The risk period was divided into short-term (3 months post index event) and long-term (3 years post index event).

Potential risk factors

The candidate predictors included patient demographics, medical history, recent clinically recognized VTE risk factors, and initial treatment (including initial and chronic outpatient anticoagulant therapy).

Analysis methods

The distributions of patient characteristics were assessed during the index encounter (potential risk factors) and were described using means, standard deviations, medians and inter-quartile ranges for continuous variables; these data were presented as percentages for categorical variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) generated by the unadjusted Cox proportional hazard regression were used to illustrate the relationship of potential prognostic factors to time to recurrent episodes of VTE.

Cumulative incidence rate (CIR) of VTE recurrence within 3 years after the patient's index event were estimated using the Kaplan-Meier methods. Data were censored at death or last contact (3 years) following the index event.

Prognostic models for predicting risk of VTE recurrence after the index event were developed using these methods: the full model included all potential risk factors identified by unadjusted Cox proportional hazard regressions with $p \leq 0.1$; multivariable Cox regression backwards selection procedures were used to select final independent predictors ($p<0.05$). Proportional hazards assumptions were assessed by a test of the interaction between log (time metric) and each predictor. The linearity of age at index encounter were assessed by the fractional polynomial technique.[55] Possible 2-way interactions among the final risk predictors were assessed. Model discrimination was assessed using the Harrell macro for Cox regression (the c-index),[56] while goodness-of-fit (calibration) was assessed by the May-Hosmer methods.[57]

The final prognostic model for predicting 3-month VTE recurrence was used to develop the 3-month risk score calculator based on methods commonly used in published studies.[58-62] The risk score was calculated as follows: the factor with the smallest logarithmic HR (natural log of HR) was assigned 1 point, with other factor scores based on the size of their estimates relative to the smallest logarithmic HR; Individual predictor scores were summed to give a total risk score (on a 0-100 scale) for each patient. The accuracy of calibration was demonstrated by comparing model-predicted to observed VTE risk (using the Kaplan-Meier method) over the full range of VTE risk scores.[57]

Since use of the maximum sample size leads to the best unbiased estimates, it is least likely to cause a type II error. In addition, no study can effectively validate itself: “a true evaluation of generalisability (also called transportability) requires evaluation on data from elsewhere”.[63] Therefore, internal validation of the model results by using a split sample technique was not attempted.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was specified as $\alpha=0.05$ (two sided).

1.12 Sample size and power estimates

All calculations were performed using the PASS software version 11 with a two-sided $\alpha=0.05$.

Sample size estimates

Previous publications from the Worcester VTE studies indicated that there were 615 cases in the 1985/86 group, 618 cases in the 1988/89 cohort and approximately 1,800 cases in the1999/01/03 cohorts.[3, 7, 27] I anticipate that at least an additional 1,800 additional cases will be included in the 2005/07/09 patient cohorts. Previous publications from Cohort-II indicated that 14% of VTE cases were upper-extremity DVT,[52] and approximately 12% of recurrent VTE cases presented as the index event.[18, 27] After excluding either upper-extremity DVT in Cohort-II or recurrent VTE, the estimated sample sizes for each aim are listed in Table 1.4.

For Aim-3, the cumulative VTE recurrence rate within 3-years since the index event is approximately 17% based on previously published data.[18] Therefore, the estimated total number of recurrent VTE events accumulated within 3-years after the index event will be approximately 450.

Based on previous publications, the expected survival or mortality rates are approximately 10% within 30 days, and 30% within 3-years, following the index event.[18]

Power estimates for analysis of patient characteristics and clinical management practices

The estimated sample size for each aim suggests that the sample size is more than adequate to estimate differences between patient subsets for a variety of endpoints (e.g., individual diagnostic and treatment modalities). Table 1.5 provides the 95% confidence interval estimates for proportions in the expected

range of sample sizes in the proposed aims. The widths of these confidence intervals suggest that considerable precision is possible.

Power estimates for hypothesis tests

For all five hypothesis tests of study aims 1 and 2, chi-square tests were used to compare two independent binomial proportions, P1 and P2. The null hypothesis is that P1=P2. The alternative hypothesis is P1≠P2. Based on the projected sample size, a minimum of 400 patients would be available in each group. Table 1.6 provides estimates of the minimum detectable difference in proportions for power of 80% and $\alpha=0.05$ for the expected range of proportions and available sample sizes.

Power estimates for Cox proportional hazards model

The sample estimates indicate that at least 2,700 VTE cases are available for aim-3. Due to the methods employed to capture follow-up events in Cohort-II, the rate of missing data should be very low. Inasmuch, it is likely that the number of individuals included in this analysis will be more than 2,700 with an expected 17% recurrence rate. The estimated power for a range of hazard ratios (HR) is provided in Table 1.7, which suggests that this analysis will be adequately powered to detect an HR of 1.3 or larger.

1.14 Tables

Table 1.1: ICD-9 Codes Used to screen and Identify VTE Cases

ICD-9 Code	Description	Cohort I	Cohort II
Deep venous thrombosis			
451.1	Of deep vessels of lower extremities	X	X
451.11	Femoral vein phlebitis	X	X
451.19	Deep phlebitis-leg nec	X	X
451.81	Iliac thrombophlebitis	X	X
451.83	Of deep veins of upper extremities		X
451.89	Thrombophlebitis nec		X
451.9	Thrombophlebitis nos		X
453.1	Thrombophlebitis migrans		X
453.2	Oth inf vena cava thromb	X	X
453.8	Acute venous embolism and thrombosis of other specified veins	X	X
453.9	Venous thrombosis nos	X	X
671.3 (0,1,3)	Deep phlebothrombosis antepartum	X	X
671.4 (0,2,4)	Deep phlebothrombosis postpartum	X	X
671.9 (0 to 4)	Unspecified venous complications	X	X
673.2 (0 to 4)	Obstetrical blood-clot embolism		X
673.24	Obstetrical blood-clot embolism		X
996.73	Other complications; due to renal dialysis device, implant, graft		X
996.74	Other complications; due to other vascular device, implant, graft		X
997.2	Peripheral vascular complications, Phlebitis or thrombophlebitis during or resulting from a procedure, Excludes:, the listed conditions due to:, implant or catheter device	X	X
999.2	Complication of medical care; other vascular complications, Thromboembolism following infusion, perfusion, or transfusion, Thrombophlebitis following infusion, perfusion, or transfusion	X	
Pulmonary embolism			
415.1	Pulmonary embolism and infarction	X	X
415.11	Iatrogen pulm emb/infarc		X
415.19	Pulm embol/infarct nec		X
639.6	Embolism	X	
996.7	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft	X	

Table 1.2: Criteria for classification of VTE events

Classification	Description
Deep vein thrombosis	
Definite	if confirmed by venography, compression/Duplex ultrasound, CT scan, MRI scan, or at autopsy
Probable	if the above tests were not performed, or were indeterminate, but impedance plethysomography, radionuclide venography, or radiolabelled fibrinogen scan test results were reported as positive.
Possible	if all of these confirmatory tests were not performed, or were indeterminate, and 2 of the following criteria were satisfied – medical record indicates that the physician made a diagnosis of DVT, signs and/or symptoms of DVT were documented, and the patient underwent therapy with anticoagulants, or an IVC filter was placed.
Pulmonary embolism	
Definite	if confirmed by pulmonary angiography, spiral CT scan, MRI scan, or pathology.
Probable	if the above tests were not performed, or were indeterminate, but ventilation-perfusion scan findings were of high probability.
Possible	if all of the above confirmatory tests were not performed, or were indeterminate, and 2 of the following criteria were satisfied – medical record indicates that the physician made a diagnosis of PE, signs and/or symptoms of PE were documented, and the patient underwent therapy with anticoagulants, or an IVC filter was placed.

Table 1.3: US Census Estimates for Towns included in Worcester VTE Study

Towns	ZIP CODE	Y1985	Y2000
Auburn	01501	14,468	15,901
Barre*	01005	-	5,113
Berlin	01503	2,217	2,380
Boylston	01505	3,450	4,008
Brookfield	01506	2,556	3,051
Charlton	01507	7,490	11,263
Clinton*	01510	-	13,435
Douglas*	01516	-	7,045
Dudley*	01570-01571	-	10,036
East Brookfield	01515	1,915	2,097
Grafton	01529	11,867	14,894
Holden	01520	13,555	15,621
Leicester	01524	9,567	10,471
Millbury	01597	11,672	12,784
North Brookfield	01535	4,142	4,683
Northborough	01532	10,766	14,013
Northbridge	01534	12,285	13,182
Oxford	01540	11,895	13,352
Paxton	01612	8,690	4,386
Princeton*	01541	-	3,353
Rutland*	01543	-	6,353
Shrewsbury	01545	22,653	31,640
Spencer	01562	11,289	11,691
Sterling	01564	5,832	7,257
Sutton	01590	6,345	8,250
Upton	01568	4,164	5,642
Uxbridge	01569	8,633	11,156
Webster	01570	14,824	16,415
West Boylston	01583	6,057	7,481
Westborough	01581	13,132	17,997
Worcester	01601-01610	160,489	172,648
Total		**379,953**	**477,598**

*Towns were not considered as Worcester Statistical Metropolitan Area in 1985

Table 1.4: Sample Size Estimates

Cohort	85/86	88/89	99/01/03	05/07/09	Total
Total enrolled	615	618	1800	1800	4833
Aim-1 sample*	615	618	1548	1548	4329
Aim-2 sample[§]	0	0	1362	1362	2724
Aim-3 sample[§]	0	0	1362	1362	2724

*excluding upper-extremity DVT;
[§]excluding recurrent VTE as index event.

Table 1.5: Expected Widths of 95% confidence Intervals for One Proportion

Sample size	P=0.5	P=0.4	P=0.3	P=0.2	P=0.1
100	0.098	0.096	0.090	0.078	0.059
500	0.044	0.043	0.040	0.035	0.026
1000	0.031	0.030	0.028	0.025	0.019
2000	0.022	0.021	0.020	0.018	0.013
3000	0.018	0.018	0.016	0.014	0.011
4000	0.015	0.015	0.014	0.012	0.009
5000	0.014	0.014	0.013	0.011	0.008

Width=1.96*SQRT((p*(1-p))/n)

Table 1.6: Minimum Detectable Differences for the Stated N and base Proportion (P1)

N per group	P1=0.5	P1=0.4 or 0.6	P1=0.3 or 0.7	P1=0.2 or 0.8	P1=0.1 or 0.9
400	0.0981	0.0981	0.0938	0.0845	0.0671
500	0.0879	0.0800	0.0837	0.0751	0.0593
600	0.0804	0.0804	0.0763	0.0683	0.0537
800	0.0697	0.0697	0.0659	0.0587	0.0459
1000	0.0624	0.0624	0.0588	0.0523	0.0407
2000	0.0442	0.0442	0.0413	0.0366	0.0281

α=0.05 and β=0.20

Table 1.7: Cox Regression Power Analysis

Power	Regression Coefficient	Hazard Ratio
90%	0.3041	1.355
80%	0.2629	1.301
70%	0.2331	1.262

α=0.05; Sample size = 2700; Event Rate= 17%

Chapter II. Secular Trends in Occurrence of Acute Venous Thromboembolism: The Worcester VTE Study (1985 to 2009)

2.1 Abstract

Background: The clinical epidemiology of venous thromboembolism (VTE) has changed recently due to advances in identification, prophylaxis, and treatment. We described secular trends in the occurrence of VTE among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA).

Methods: Population-based methods were used to monitor trends in event rates of first-time or recurrent episodes of pulmonary embolism (PE) and/or deep vein thrombosis (DVT) in 5025 WMSA residents diagnosed with acute PE and/or lower-extremity DVT during 9 annual periods between 1985 and 2009. Medical records were reviewed by abstractors and validated by clinicians.

Results: Age- and sex-adjusted annual event rates for first-time VTE increased from 73 (95% CI 64–82) per 100,000 in 1985/1986 to 133 (122–143) in 2009, due mostly to an increase in PE. The rate of recurrent VTE decreased from 39 (32–45) in 1985/1986 to 19 (15–23) in 2003, and then increased to 35 (29–40) in 2009. There was an increasing trend in the use of non-invasive diagnostic testing, with about half of tests being invasive in 1985/1986 and almost all being non-invasive by 2009.

Conclusions: Despite advances in identification, prophylaxis, and treatment between 1985 and 2009, the annual event rates of VTE have increased and

remain high. While these increases 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.

2.2 Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with increased long-term morbidity, functional disability, and all-cause mortality.[1] Over three decades ago, VTE was estimated to be the third most common acute cardiovascular event after the acute coronary syndromes and ischemic stroke.[2] Recent data on the clinical epidemiology of VTE are, however, limited.[6]

Considerable variation exists in estimates of the annual incidence rates of VTE, derived from population-based studies and hospital discharge or health-insurance claims databases.[6] Major advances have occurred in identifying patients at increased risk for VTE, in thromboprophylaxis, and in diagnostic methods and treatments.[6, 8-13] Growing awareness of VTE as an important public-health problem became the impetus for evidence-based guidelines for appropriate VTE prevention and treatment, which have been revised over time.[43, 64] These advances have likely influenced the reported frequency of VTE.

Using data from the Worcester VTE study (1985 to 2009), we describe 25-year trends in event rates, patient characteristics, and use of various diagnostic

approaches among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA) diagnosed with clinically recognized acute VTE.

2.3 Methods

The Worcester VTE study employed population-based surveillance methods to monitor trends in event rates of VTE (first-time or recurrent episodes of PE and/or DVT), including management strategies, case-fatality rates, and recurrences after the index event among WMSA residents.[3, 7, 27, 44] Reflecting the evolution of the standard of care for the treatment of acute VTE, Cohort-I included all hospital inpatients discharged with a primary/secondary diagnosis of VTE during two 18-month periods, July 1985 to December 1986, and July 1988 to December 1989. Cohort-II included hospitalized patients and outpatients diagnosed with VTE based on outpatient, emergency department, radiology department, or diagnostic laboratory encounter during 1999, 2001, 2003, 2005, 2007, and 2009. Medical records were reviewed by trained abstractors and validated by clinicians.

This study was approved by the institutional review committee at participating hospitals.

VTE Definition

Both cohorts used International Classification of Disease, 9th revision, codes to identify eligible acute cases of PE and/or DVT (Table 1.1). There were slight differences in our study populations due to the refinement of these codes

over the years. In addition, Cohort-II included patients diagnosed with upper-extremity DVT alone. These were excluded in the present analyses due to important differences in the natural history of upper-extremity and lower-extremity DVT.[52-53]

Patients were classified as either 'first-time' if the index event was a first-time episode, or as 'recurrent' at the time of the index visit if the patient had a prior episode of VTE noted in their medical records.

Data Analysis

Annual event rates of VTE are reported per 100,000 population. The number of first-time VTE episodes served as the numerator for calculation of event rates of first-time VTE (incidence rate), while the number of cases of recurrent VTE served as the numerator for calculation of the event rates of recurrent VTE. The 1985 United States (US) Census data of the WMSA (*n*=379,953) were used as the denominator for calculation of 1985–1989 annual crude event rates and 2000 Census data of the WMSA (*n*=477,598) were used as the denominator for the calculation of 1999–2009 annual crude event rates.[3, 7] These crude rates were used to calculate age- and sex-adjusted rates by the direct adjustment method.[54]

Since the WMSA population was approximately 90% white during the years under study, the age and sex distribution of the 2000 United States white (reference) population was used to calculate age- and sex-adjusted rates.[5] Confidence interval (CI) estimates were based on the Poisson distribution.

Trends in rates during the years under study were assessed by Poisson regression. Annual case counts were modeled using the SAS procedure GENMOD with a logarithmic link function and a log (population) offset term. A main effects model included a term for sex, age group (<40, 40–49, 50–59, 60–69, 70–79, ≥80 years), and study period. Separate models were constructed for episodes of first-time or recurrent VTE, overall, and separated into PE with or without DVT (±DVT) and DVT alone.

Patient characteristics and diagnostic tests are reported as frequencies and percentages for categorical variables, and as means (standard deviations) or medians (interquartile ranges) for continuous variables. The Cochran-Armitage tests and linear regression models were used to test for linear trends over time among categorical variables and continuous variables, respectively. Comparison of the 2009 cohort with the 1985/86 cohort was performed using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was pre-specified as α=.05 (two-sided).

2.4 Results

During the study period (1985–2009), 5487 WMSA residents were diagnosed with acute PE and/or DVT (1235 from Cohort-I, 4252 from Cohort-II). After excluding 462 (10.9%) patients diagnosed with upper-extremity DVT alone

in Cohort-II, 5025 patients with a diagnosis of acute PE±DVT or lower-extremity DVT alone were examined in the present analyses. This included 3887 (77.4%) first-time VTE and 1138 (22.6%) episodes of recurrent VTE. Increases in the proportion of first-time episodes of VTE were observed over time from approximately two-thirds in the initial cohort to nearly 80% in the 2009 cohort (trend *P*<.001, Table 2.1).

Patient Characteristics at Index Visit

Among the 5025 patients diagnosed with VTE, 46% were men, 95% were white, and their mean age was 64.6 (±17.8) years. Patients diagnosed with first-time VTE tended to be younger and include an increasing proportion of ethnic minorities over the study period, but no changes were apparent in the recurrent VTE group (Table 2.1). Increases in body mass index and diabetes, whereas declines were observed in the frequency of prior congestive heart failure, stroke, and malignancy, in patients with first-time and recurrent VTE. Among patients with first-time VTE, there was a decrease in the proportion of patients who had recent surgery, trauma, or major fracture during the years under study.

The proportion of patients with community-accquired VTE remained approximately 80% over time among patients presenting with first-time VTE, but decreased from approximately 91% to 78% among those diagnosed with recurrent VTE at the time of their index visit (*P for trend* =.001). Overall, the proportion of patients admitted to the hospital for treatment of VTE, or who developed index VTE during hospitalization for another diagnosis, decreased

from 100% to approximately 70% during the years under study. Among hospitalized patients, the mean length of stay during the index hospitalization decreased markedly over time in all patient groups.

Annual Event Rates

Among residents of the WMSA during the period 1985 to 2009, the overall age- and sex-adjusted annual event rate (per 100,000) was 108 (95% CI, 98 to 118) for first-time VTE and 34 (95% CI, 28 to 40) for recurrent VTE. Further stratifying VTE into PE±DVT and DVT alone, the overall age- and sex-adjusted annual event rate (per 100,000) was 41 (95% CI, 35 to 47) for first-time PE±DVT, 66 (95% CI, 59 to 74) for first-time DVT alone, 9.6 (95% CI, 6.6–12.6) for recurrent PE±DVT, and 25 (95% CI, 20 to 29) for recurrent DVT alone.

There were increases over time in the age- and sex-adjusted annual event rates of first-time VTE from 73/100,000 to 133/100,000 (P<.001, Figure 2.1A). Poisson regression indicated an approximate 40% increase in first-time VTE from 1985 to 2001, which remained essentially unchanged in the early 2000s, followed by an additional 50% increase by 2009 (Table 2.2). Although the pattern of first-time VTE observed in WMSA between the late 1980s and early 2000s was similar in PE±DVT and DVT alone groups, the increasing trend in the late 2000s predominantly reflected an increase in the age- and sex-adjusted annual event rate of first-time PE±DVT, which increased from 35/100,000 in 2003 to 65/100,000 in 2009 (P<.001, Figure 2.1A).

Trends in the age- and sex-adjusted annual event rates of recurrent VTE were U-shaped (Figure 2.1B). Poisson regression indicated an approximate 40% decrease in the event rates of recurrent VTE between the mid-1980s and 1999, which remained relatively unchanged in the early 2000s, then increased in the late 2000s (Table 2.2). Similar trends were found for those with PE±DVT and DVT alone (Figure 2.1B).

Crude and adjusted annual event rates for each study period, as well as by VTE type, are shown in Table 2. These rates increased markedly with age regardless of VTE type, sex, or study period (Table 2.2S).

Objective Diagnostic Tests

The proportion of patients undergoing at least one objective (either invasive or non-invasive) diagnostic test rose, with rates of non-invasive testing increasing from 60–70% in 1985/86 to nearly 100% in 2009, while the rates of invasive testing plunged from over 50% to near zero (Table 2.3). In particular, there was a marked increase in the use of computed tomography and magnetic resonance imaging scans in the late 2000s (Table 2.3).

2.5 Discussion

The Worcester VTE study provides a unique opportunity to examine 25-year trends in the magnitude, characteristics, and diagnostic workup for VTE from the perspective of a well-characterized population. The disease burden from VTE in this central Massachusetts population remains high, with a trend towards

increasing annual event rates as well as substantial changes in patient characteristics and methods used to diagnose VTE between 1985 and 2009.

Disease Burden

The age- and sex-adjusted annual event rates of clinically recognized acute first-time and recurrent VTE was 142/100,000 during the entire study period, increasing from 112/100,000 in 1985/86 to 168/100,000 in 2009. It is higher than the incidence of the leading two cancers (126/100,000 for prostate cancer and 124/100,000 for breast cancer) and >15 times higher than the incidence rate of HIV (8.3/100,000) in white Americans.[65] The age- and sex-adjusted annual event rate of clinically recognized acute PE±DVT was 78/100,000 in 2009, nearly equivalent to the annual incidence of ischemic stroke (88/100,000) in white individuals reported by the American Heart Association during that period.[54]

With increased long-term morbidity and functional disability, and high rates of recurrence and mortality among VTE patients,[1] this disorder remains a major national health problem.

Trends in Occurrence

Between 1985 and 2009, the annual event rates of first-time VTE nearly doubled, and first-time PE±DVT nearly tripled, with inconsistent patterns noted among patients with recurrent VTE.

Our study is the first population-based surveillance project of VTE to provide data about trends in annual event rates of first-time and recurrent VTE

between 1985 and 2009. Data from the Rochester Epidemiology Project (REP), the study with the most similar design to ours, indicated a 23% increase in the age- and sex-adjusted annual event rate of first-time VTE from 96/100,000 in 1986–1990 to 118/100,000 in 1991 to 1997.[5, 66] These results are similar to the 30% increase in the age- and sex-adjusted annual event rate of first-time VTE observed in our study between 1985 and 1999.

In the US Nationwide Inpatient Sample, the number of patients with first-time and recurrent PE±DVT discharged from US acute care hospitals approximately doubled between 1998 and 2005,[67] consistent with our findings. A retrospective study based on estimates derived from commercial insurance and Medicare databases of insured US residents observed a 33% increase in annual event rates of first-time and recurrent VTE between 2002 and 2006.[68] This increase was larger than the approximate 20% increase in the age- and sex-adjusted annual event rates of first-time and recurrent VTE observed in the present study (from 131/100,000 in 2001 to 154/100,000 in 2007). These results, based on commercial insurance and Medicare databases, may be limited due to their reliance on administrative databases without actual chart review and independent diagnostic validation.

Both the Rochester Epidemiology Project and our study indicated that the frequency of VTE increased markedly with advancing age regardless of study year, VTE type, or sex. Given the aging of the United States population,[69] the

projected disease burden of VTE is expected to more than double between 2006 and 2050.[68]

Possible Contributory Factors to Observed Trends

Observed increases in the frequency of VTE during the study period are likely to be multifactorial. First, the use of one or more non-invasive diagnostic methods for the detection of VTE increased from approximately two-thirds of patients in 1985 to nearly all in 2009. In particular, the introduction of computed tomography pulmonary angiography (CTPA) closely parallels the observed increases in the annual event rate of first-time and recurrent PE±DVT observed in our study. The proportion of PE±DVT patients who underwent a CTPA test increased from approximately 25% in 1999 to 85% in 2009. During this period, the annual event rate of first-time and recurrent PE±DVT more than doubled.

A time-trend analysis using the Nationwide Inpatient Sample and Multiple Cause-of-Death databases demonstrated that the introduction of CTPA was associated with changes consistent with a rising frequency of PE in the US [70]. Clearly, we are detecting more cases of VTE during recent years than were detected (or were detectable) in the decades before the introduction of newer technology. A more difficult question to address is how much of this increase represents small, clinically insignificant PEs? Following the introduction of high-resolution multiple-detector CTPA, systematic reviews and meta-analyses have suggested an increase in the diagnosis of subsegmental PEs of unclear clinical significance through the use of these newer testing modalities.[71] Because most

of these subsegmental PEs are treated, their importance remains a key healthcare and resource issues. Further study of this issue is warranted.

With expanded access to higher resolution diagnostic imaging, a growing awareness of VTE as an important public-health problem may have led clinicians to refer additional patients for evaluation.[72] Our findings indicate that the proportion of patients who received any form of objective diagnostic testing has increased over time.

In addition to changes in the diagnosis of VTE, the increases in annual event rates of VTE observed in WMSA residents could also be related to changes in population characteristics over time. As the US population ages and becomes less active and more obese,[65, 69] it may lead to further increases in risk of developing VTE.

Although the development and implementation of evidence-based practice guidelines for VTE prevention and treatment may have reduced the annual event rate of VTE among 'high-risk' patients, including those with a recent history of a surgical procedure, pregnancy, trauma, fracture, and hospitalization,[48] this would not be expected to impact patients without obvious recent provocations who would be less likely to have received enhanced VTE prophylaxis compared with high-risk patients.

Our findings demonstrate that the proportion of patients with community-accquired first-time VTE has remained relatively constant, at approximately 80%, during the 25-year period under study. A prior publication from our study

suggests that approximately 40% of patients with community-acquired VTE had a hospitalization or surgery in the 3 months before their index visit.[45] Further work identifying and providing prophylaxis to high-risk patients being discharged from hospital is needed. With respect to the remaining 60% (with unprovoked VTE), research aimed at better understanding such patients by risk and identifying possible "minor" triggers for a VTE event may provide additional opportunities for prophylaxis.

Interestingly, although the annual event rate of recurrent VTE remained relatively unchanged between 1985 and 2009, the trend was U-shaped. The decreasing trend observed between the late 1980s and 1999 could be due to improved treatment strategies.[32, 38-42, 73] However, given increases in the annual event rates of first-time VTE and high recurrence of this thromboembolic disorder,[1, 11] it was not surprising that the annual event rates of recurrent VTE also increased in the WMSA during the late 2000s.

Study Strengths and Limitations

The Worcester VTE study employed rigorous population-based surveillance methods to describe the clinical epidemiology of acute VTE in the WMSA. Although we conducted broad screening for cases of VTE using multiple databases, validated each potential case of VTE, and performed regular chart audits, it is possible that this study may have missed some cases. Owing to low autopsy rates in the WMSA, and the limited validity of death-certificate data, only clinically recognized cases of acute VTE were described and some cases of fatal

PE could be missed. Further, regional differences may exist in the diagnostic workup of patients presenting with signs and symptoms of VTE. Since the WMSA is predominantly a white population, additional population-based studies in minority and economically disadvantaged populations are needed.

2.6 Conclusions

Despite advances in identification, prophylaxis, and treatment between 1985 and 2009, the annual event rate of VTE has increased and remains high. While these increases 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.

2.7 Tables and figures

Table 2.1 Characteristics of patients with venous thromboembolism in the Worcester venous thromboembolism study (1985–2009)

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test	1985/86 vs. 2009
First-time venous thromboembolism at index visit, n (% of total venous thromboembolism)	405 (65.6)	442 (71.5)	435 (80.7)	482 (82.4)	466 (84.1)	482 (79.3)	542 (77.7)	633 (79.7)	<.001	<.001
Demographic characteristics										
Age (years)									.001	.04
Mean (standard deviation)	65.9 (17.2)	66.4 (17.4)	66.4 (17.7)	65.8 (17.3)	63.0 (17.9)	62.7 (18.9)	65.0 (18.1)	63.7 (17.8)		
Median (interquartile range)	69 (60–78)	70 (60–78)	72 (54–80)	69 (54–81)	65 (50–78)	65 (48–79)	68 (52–80)	65 (50–80)		
Men (%)	48.6	45.5	43.4	41.9	46.8	41.3	47.6	44.6	.34	.75
White (%)	97.5	98.2	95.4	93.5	93.6	94.8	95.7	92.5	<.001	.001
Recent* medical characteristics (%)										
Body mass index class										
<25 kg/m^2	42.1	44.2	35.3	32.9	26.0	36.5	28.9	26.9	<.001	<.001
25–30 kg/m^2	35.1	28.8	27.4	31.4	33.3	28.4	35.2	29.5	.80	.11
>30 kg/m^2	22.8	27.1	37.3	35.6	4.7	35.1	35.9	43.6	<.001	<.001
Congestive heart failure	20.2	11.5	13.1	14.9	11.2	10.0	9.2	7.4	<.001	<.001
Myocardial infarction	4.9	3.4	5.1	7.3	6.4	4.1	3.0	2.5	.25	.04
Stroke	4.2	6.6	6.4	7.1	5.6	2.7	2.2	2.2	.001	.07
Chronic obstructive pulmonary disease	23.2	15.8	17.0	21.4	16.7	21.8	24.7	23.7	.04	.86

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test	1985/86 vs. 2009
Diabetes	14.3	16.5	17.0	22.4	18.0	17.2	23.4	18.8	.005	.06
Malignancy	30.4	23.3	19.3	19.9	12.7	15.6	16.8	19.0	<.001	<.001
Trauma/fracture	12.8	13.8	17.7	21.0	13.5	9.8	8.9	9.5	.006	.09
Hormone replacement therapy/oral contraceptives†	4.3	4.6	21.1	21.4	14.9	10.6	7.4	10.9	.008	.01
Post partum†	3.8	1.7	2.4	1.1	1.2	2.5	1.1	1.4	.08	.07
Any surgery, including index admission	34.6	30.5	29.2	30.5	25.8	28.2	23.2	22.7	<.001	<.001
Venous thromboembolism characteristics (%)										
Type of venous thromboembolism event										
Pulmonary embolism alone	24.2	22.2	15.9	20.5	18.9	28.4	29.9	28.8	<.001	.11
Pulmonary embolism and deep vein thrombosis	8.2	6.6	15.6	14.7	15.2	18.9	19.6	19.7	<.001	<.001
Lower-extremity deep vein thrombosis alone	67.7	71.3	68.5	64.7	65.9	52.7	50.5	51.5	<.001	<.001
Community acquired	78.0	80.1	73.6	75.1	75.8	78.8	79.5	77.1	.68	.73
Hospital encounter,										
Admitted to hospital§ (%)	100	100	77.7	77.2	70.8	74.3	73.1	71.1	<.001	<.001
If admitted, length of stay, days									<.001	<.001
Mean (standard deviation)	15.3 (24.1)	15.1 (15.5)	9.0 (10.0)	10.1 (11.5)	9.6 (10.8)	8.5 (11.0)	7.2 (8.6)	6.9 (8.0)		
Median (interquartile range)	10 (8–19)	10 (7–16)	6 (4–9)	6 (4–10)	6 (4–10)	5 (3–9)	5 (3–8)	5 (3–8)		
Recurrent venous thromboembolism at index	212 (34.4)	176 (28.5)	104 (19.3)	115 (19.3)	88 (15.9)	126 (20.7)	156 (22.4)	161 (20.3)	<.001	<.001

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test	1985/86 vs. 2009
visit, n (% of total venous thromboembolism)										
Patient characteristics										
Age (years)									.10	.17
Mean (standard deviation)	62.6 (17.3)	61.1 (19.0)	64.1 (16.6)	64.7 (17.2)	65.4 (17.7)	63.8 (18.0)	66.9 (15.5)	64.9 (16.8)		
Median (interquartile range)	66 (49–75)	67 (48–75)	69 (51–77)	67 (51–80)	71 (54–79)	64 (49–80)	69 (57–80)	67 (53–79)		
Men (%)	45.8	55.1	47.1	47.0	50.0	48.4	50.0	51.6	.83	.27
White (%)	96.2	97.2	90.7	93.6	95.4	96.0	94.7	92.4	.08	.10
Recent* medical characteristics (%)										
Body mass index class										
<25 kg/m^2	39.0	38.6	33.8	30.9	28.1	34.8	28.9	27.6	.01	.04
25–30 kg/m^2	30.8	36.2	36.4	35.8	35.1	28.1	31.6	30.6	.60	.97
>30 kg/m^2	30.1	25.2	29.9	33.3	36.8	37.1	39.5	41.8	.002	.04
Congestive heart failure	18.9	9.7	8.7	13.9	6.8	4.0	10.7	8.1	<.001	.003
Myocardial infarction	2.8	0.6	3.8	3.5	6.8	1.6	3.8	3.7	.14	.63
Stroke	4.2	1.7	9.6	5.2	6.8	1.6	0.6	1.2	.26	.12
Chronic obstructive pulmonary disease	25.9	19.3	19.2	20.9	10.2	26.2	32.7	29.8	.13	.41
Diabetes	15.6	11.4	17.3	16.5	13.6	19.0	19.2	26.7	.003	.01
Malignancy	25.9	25.0	11.5	13.9	9.1	15.1	19.2	16.8	<.001	.03
Trauma/fracture	4.2	5.1	12.5	12.2	12.5	8.7	4.5	8.1	.07	.12
Hormone replacement therapy/oral	3.5	6.3	36.4	26.2	6.8	9.2	2.6	6.4	.32	.45

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test	1985/86 vs. 2009
contraceptives†										
Post partum†	2.6	0	0	0	0	0	0	0	.01	.27
Any surgery, including index admission	15.6	16.5	17.3	15.7	10.2	21.4	16.7	17.4	.61	.64
Venous thromboembolism characteristics (%)										
Type of venous thromboembolism event										
Pulmonary embolism alone	16.5	15.3	12.5	20.0	13.6	16.7	17.3	23.6	.10	.09
Pulmonary embolism and deep vein thrombosis	9.4	10.2	13.5	9.6	8.0	11.1	12.8	13.7	.20	.20
Lower-extremity deep vein thrombosis alone	74.1	74.4	74.0	70.4	78.4	72.2	69.9	62.7	.02	.02
Community acquired	91.0	91.5	86.5	85.2	86.4	82.5	82.7	77.6	<.001	<.001
Hospital encounter§ (%)										
Admitted to hospital	100	100	78.8	63.5	68.2	70.6	65.4	73.3	<.001	<.001
If admitted, length of stay, days									<.001	<.001
Mean (standard deviation)	11.9 (11.3)	10.9 (7.8)	7.4 (8.4)	7.0 (9.3)	6.4 (7.0)	6.7 (5.9)	9.5 (10.4)	6.3 (8.0)		
Median (interquartile range)	9 (7–13)	9 (7–13)	5 (4–8)	5 (3–8)	4 (2–7)	5 (3–8)	6 (3–10)	3 (2–7)		

*Recent defined as <6 months in 1980s cohort, <3 months in 1999–2007 cohort. †Among women. §Reflecting the standard care for the treatment of acute venous thromboembolism in 1980s, cohorts 85/86 and 88/89 included only inpatients diagnosed with acute venous thromboembolism.

Table 2.2 Annual event rates (per 100,000) of clinically recognized acute venous thromboembolism among Worcester metropolitan statistical area residents (1985–2009)

	Rate (95% confidence interval)							
	1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
First-time venous thromboembolism at index visit								
Crude	71 (63–80)	78 (69–87)	91 (83–100)	101 (92–110)	98 (89–107)	101 (92–110)	113 (104–123)	133 (123–143)
Adjusted*	73 (64–82)	81 (72–91)	95 (86–104)	106 (96–115)	103 (94–112)	105 (95–114)	119 (109–129)	133 (122–143)
Incidence rate ratio †	Reference group	1.1 (0.9–1.3)	1.3 (1.1–1.5)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.6 (1.4–1.8)	1.9 (1.6–2.2)
First-time pulmonary embolism ± deep vein thrombosis at index visit								
Crude	23 (19–28)	22 (18–27)	29 (24–34)	36 (31–41)	33 (28–39)	48 (42–54)	56 (50–63)	64 (57–72)
Adjusted*	24 (19–29)	23 (18–28)	30 (25–35)	37 (32–43)	35 (30–41)	50 (44–57)	59 (52–66)	65 (58–72)
Incidence rate ratio †	Reference group	1.0 (0.7–1.3)	1.2 (1.0–1.6)	1.5 (1.2–2.0)	1.4 (1.1–1.9)	2.1 (1.6–2.7)	2.4 (1.9–3.1)	2.8 (2.2–3.5)
First-time deep vein thrombosis alone at index								
Crude	48 (41–55)	55 (48–63)	62 (56–70)	65 (58–73)	64 (57–72)	53 (47–60)	57 (51–64)	68 (61–76)
Adjusted*	49 (42–56)	58 (50–66)	65 (58–72)	68 (61–76)	68 (60–75)	54 (48–61)	60 (53–67)	68 (60–75)
Incidence rate ratio †	Reference group	1.1 (0.9–1.4)	1.3 (1.1–1.6)	1.4 (1.1–1.6)	1.3 (1.1–1.6)	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.4 (1.2–1.7)

	Rate (95% confidence interval)							
	1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
Recurrent venous thromboembolism at index visit								
Crude	37 (31–44)	31 (26–37)	22 (18–26)	24 (20–29)	18 (15–23)	26 (22–31)	33 (28–38)	34 (29–39)
Adjusted*	39 (32–45)	32 (27–38)	23 (19–28)	25 (21–30)	19 (15–23)	28 (23–32)	35 (29–40)	35 (29–40)
Incidence rate ratio †	Reference group	0.8 (0.6–1.1)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.6)	0.7 (0.6–0.9)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Recurrent pulmonary embolism ± deep vein thrombosis at index visit								
Crude	10 (7–13)	8 (5–11)	6 (4–8)	7 (5–10)	4 (2–6)	7 (5–10)	10 (7–13)	13 (10–16)
Adjusted*	10 (7–13)	8 (5–11)	6 (4–8)	8 (5–10)	4 (2–6)	8 (5–10)	11 (8–14)	13 (10–17)
Incidence rate ratio †	Reference group	0.8 (0.5–1.3)	0.6 (0.4–1.0)	0.7 (0.5–1.2)	0.4 (0.2–0.7)	0.8 (0.5–1.2)	1.0 (0.7–1.6)	1.3 (0.9–2.0)
Recurrent deep vein thrombosis alone at index visit								
Crude	28 (23–33)	23 (19–28)	16 (13–20)	17 (14–21)	14 (11–18)	19 (15–23)	23 (19–27)	21 (17–26)
Adjusted*	29 (23–34)	24 (19–29)	17 (13–21)	18 (14–22)	15 (12–19)	20 (16–24)	24 (20–29)	21 (17–25)
Incidence rate ratio†	Reference group	0.8 (0.6–1.1)	0.6 (0.4–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.7)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	0.8 (0.6–1.0)

*Directly age- and sex-adjusted to the 2000 United States white population. †Based on Poisson regression adjusted by age and sex.

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
First-time venous thromboembolism at index visit								
Female residents (per age group in years)								
<40	11 (6–19)	13 (7–20)	13 (8–20)	18 (12–26)	22 (15–30)	30 (22–41)	21 (14–30)	23 (16–32)
40s	10 (2–31)	32 (14–65)	56 (35–83)	85 (59–118)	63 (42–93)	98 (70–133)	66 (44–96)	87 (61–121)
50s	53 (27–94)	74 (42–121)	119 (82–166)	122 (85–171)	134 (95–184)	115 (79–162)	126 (88–175)	176 (130–232)
60s	161 (113–224)	168 (118–231)	198 (139–274)	282 (210–371)	180 (124–253)	264 (194–351)	246 (179–330)	240 (174–323)
70s	280 (204–377)	331 (247–435)	357 (275–456)	351 (270–449)	392 (306–496)	309 (233–402)	368 (285–469)	440 (348–549)
80+	443 (321–597)	480 (353–639)	640 (513–789)	647 (520–797)	493 (383–626)	578 (458–720)	732 (596–891)	794 (651–958)
Female, crude	70 (59–82)	81 (69–94)	100 (88–113)	114 (101–128)	101 (89–114)	115 (103–129)	116 (103–130)	143 (128–158)
Female, adjusted*	70 (58–81)	82 (70–95)	103 (91–116)	118 (104–132)	105 (92–118)	118 (104–131)	120 (106–134)	138 (123–152)
Male residents (per age group in years)								
<40	17 (10–26)	16 (10–24)	20 (13–28)	12 (8–19)	18 (12–26)	21 (14–30)	20 (14–29)	23 (16–32)
40s	49 (24–88)	38 (17–74)	51 (32–78)	67 (44–97)	91 (64–126)	62 (40–91)	99 (71–135)	145 (110–187)
50s	70 (38–119)	93 (56–148)	94 (62–138)	149 (107–203)	181 (134–239)	153 (111–207)	149 (107–203)	196 (147–257)
60s	230 (165–313)	202 (141–280)	220 (153–306)	247 (176–338)	316 (234–418)	247 (176–338)	412 (317–527)	392 (300–503)
70s	373 (263–513)	459 (336–612)	424 (320–553)	333 (241–449)	333 (241–449)	341 (248–458)	333 (241–449)	300 (213–410)
80+	469 (282–737)	488 (296–760)	571 (405–785)	751 (557–992)	457 (310–651)	490 (337–689)	898 (683–1159)	816 (613–1067)
Male, crude	73 (61–86)	74 (62–88)	81 (70–94)	87 (76–100)	94 (82–107)	86 (74–98)	111 (98–125)	121 (108–136)
Male, adjusted*	77 (64–90)	80 (67–94)	86 (74–99)	93 (80–106)	101 (87–114)	91 (78–104)	119 (104–133)	127 (112–142)
All residents								
All, crude	71 (63–80)	78 (69–87)	91 (83–100)	101 (92–110)	98 (89–107)	101 (92–110)	113 (104–123)	133 (123–143)
All, adjusted†	73 (64–82)	81 (72–91)	95 (86–104)	106 (96–115)	103 (94–112)	105 (95–114)	119 (109–129)	133 (122–143)

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009) (continued)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
First-time pulmonary embolism±deep vein thrombosis at index visit								
Female residents (per age group in years)								
<40	5 (2–10)	5 (2–10)	1 (0–5)	4 (2–9)	9 (5–15)	18 (12–26)	9 (5–15)	9 (5–15)
40s	0 (0–0)	6 (1–26)	34 (19–57)	21 (10–40)	29 (15–50)	45 (27–70)	48 (29–74)	42 (25–67)
50s	11 (2–34)	39 (18–75)	42 (22–73)	46 (25–78)	54 (31–87)	57 (34–92)	65 (39–102)	80 (51–120)
60s	62 (35–104)	46 (23–83)	54 (27–98)	114 (71–174)	66 (35–114)	132 (85–196)	90 (53–145)	162 (109–232)
70s	69 (35–122)	106 (62–169)	119 (75–180)	107 (66–165)	131 (84–194)	125 (80–187)	184 (128–258)	256 (187–341)
80+	140 (78–235)	148 (83–244)	146 (91–224)	270 (191–371)	154 (97–233)	231 (159–326)	385 (289–504)	331 (243–442)
Female, crude	21 (16–29)	26 (20–34)	30 (24–38)	40 (33–49)	37 (30–45)	53 (44–62)	58 (49–68)	71 (61–82)
Female, adjusted*	21 (15–27)	27 (20–34)	31 (24–39)	42 (33–50)	38 (30–46)	54 (45–64)	60 (50–70)	69 (59–80)
Male residents (per age group in years)								
<40	3 (1–8)	3 (1–7)	6 (3–11)	2 (1–6)	4 (2–9)	10 (5–16)	7 (4–13)	7 (3–12)
40s	24 (9–55)	10 (2–33)	8 (2–21)	13 (5–29)	27 (14–47)	35 (19–58)	35 (19–58)	62 (40–91)
50s	27 (10–61)	23 (8–56)	31 (15–59)	63 (37–100)	55 (31–90)	79 (50–119)	59 (34–95)	94 (62–138)
60s	86 (49–141)	49 (23–93)	76 (40–131)	110 (65–174)	110 (65–174)	151 (97–225)	268 (193–362)	192 (131–274)
70s	107 (55–191)	122 (65–209)	175 (111–262)	133 (79–211)	133 (79–211)	158 (98–242)	183 (118–272)	166 (105–252)
80+	206 (94–399)	113 (38–268)	180 (95–311)	245 (143–394)	114 (51–224)	196 (107–332)	424 (284–612)	441 (297–631)
Male, crude	25 (18–33)	18 (13–25)	27 (21–34)	31 (24–38)	30 (23–37)	43 (35–52)	54 (45–64)	57 (48–67)
Male, adjusted*	27 (19–35)	20 (13–27)	29 (22–36)	33 (25–41)	32 (25–40)	46 (37–55)	59 (48–69)	60 (50–71)
All residents								
All, crude	23 (19–28)	22 (18–27)	29 (24–34)	36 (31–41)	33 (28–39)	48 (42–54)	56 (50–63)	64 (57–72)
All, adjusted†	24 (19–29)	23 (18–28)	30 (25–35)	37 (32–43)	35 (30–41)	50 (44–57)	59 (52–66)	65 (58–72)

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009) (continued)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
First-time deep vein thrombosis alone at index								
Female residents (per age group in years)								
<40	7 (3–13)	8 (4–15)	11 (7–18)	13 (8–21)	13 (8–20)	13 (8–20)	12 (7–19)	14 (9–22)
40s	10 (2–31)	26 (10–56)	21 (10–40)	63 (42–93)	34 (19–57)	53 (33–80)	19 (8–36)	45 (27–70)
50s	42 (20–80)	35 (15–70)	76 (48–116)	76 (48–116)	80 (51–120)	57 (34–92)	61 (36–97)	96 (63–139)
60s	99 (62–149)	122 (80–177)	144 (95–210)	168 (114–239)	114 (71–174)	132 (85–196)	156 (104–225)	78 (44–129)
70s	211 (146–297)	225 (157–313)	238 (172–320)	244 (177–327)	262 (193–348)	184 (128–258)	184 (128–258)	184 (128–258)
80+	303 (205–433)	332 (229–468)	493 (383–626)	378 (283–495)	339 (250–451)	347 (256–460)	347 (256–460)	462 (356–591)
Female, crude	48 (39–59)	55 (45–66)	70 (60–81)	74 (64–85)	64 (55–75)	63 (53–73)	57 (49–68)	72 (62–83)
Female, adjusted†	49 (39–59)	55 (45–66)	72 (61–83)	76 (65–87)	67 (56–77)	63 (53–73)	60 (50–70)	69 (58–79)
Male residents (per age group in years)								
<40	13 (8–21)	13 (7–21)	14 (9–21)	10 (6–17)	13 (8–20)	12 (7–19)	13 (8–20)	16 (10–24)
40s	24 (9–55)	28 (11–59)	43 (25–68)	54 (34–81)	64 (42–94)	27 (14–47)	64 (42–94)	83 (57–116)
50s	43 (19–83)	70 (38–119)	63 (37–100)	86 (56–128)	126 (88–175)	75 (46–114)	90 (59–133)	102 (68–147)
60s	144 (94–212)	152 (101–222)	144 (92–216)	137 (87–208)	206 (142–290)	96 (55–157)	144 (92–216)	199 (136–282)
70s	265 (175–386)	337 (234–471)	250 (172–352)	200 (131–292)	200 (131–292)	183 (118–272)	150 (92–232)	133 (79–211)
80+	263 (131–474)	375 (212–619)	392 (257–573)	506 (350–709)	343 (219–514)	294 (180–454)	473 (324–670)	375 (244–553)
Male, crude	48 (39–59)	56 (46–68)	54 (45–64)	56 (47–67)	64 (54–75)	43 (35–52)	57 (48–68)	65 (55–76)
Male, adjusted*	50 (39–60)	61 (49–72)	58 (48–68)	60 (49–70)	69 (58–80)	45 (36–54)	60 (50–70)	67 (56–78)
All residents								
All, crude	48 (41–55)	55 (48–63)	62 (56–70)	65 (58–73)	64 (57–72)	53 (47–60)	57 (51–64)	68 (61–76)
All, adjusted†	49 (42–56)	58 (50–66)	65 (58–72)	68 (61–76)	68 (60–75)	54 (48–61)	60 (53–67)	68 (60–75)

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009) (continued)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
Recurrent venous thromboembolism at index visit								
Female residents (per age group in years)								
<40	9 (5–16)	5 (2–10)	4 (1–8)	3 (1–7)	1 (0–5)	4 (1–8)	2 (1–6)	5 (2–10)
40s	45 (23–82)	19 (7–46)	8 (2–21)	16 (7–33)	11 (4–25)	32 (17–54)	11 (4–25)	11 (4–25)
50s	18 (5–45)	32 (13–66)	34 (17–63)	38 (20–68)	23 (10–47)	34 (17–63)	42 (22–73)	31 (14–58)
60s	95 (60–145)	66 (37–109)	66 (35–114)	36 (15–74)	42 (19–82)	42 (19–82)	84 (48–137)	78 (44–129)
70s	119 (73–186)	96 (55–158)	77 (43–128)	77 (43–128)	89 (52–143)	83 (48–136)	101 (61–158)	119 (75–180)
80+	185 (111–290)	111 (57–197)	108 (62–176)	170 (109–252)	77 (40–137)	139 (85–215)	223 (153–316)	185 (122–271)
Female, crude	38 (31–48)	26 (20–34)	22 (17–29)	25 (19–32)	18 (13–24)	27 (21–34)	32 (25–39)	32 (25–39)
Female, adjusted*	40 (31–49)	27 (20–35)	24 (17–30)	26 (19–32)	19 (13–25)	27 (21–34)	33 (26–41)	32 (25–39)
Male residents (per age group in years)								
<40	10 (5–17)	16 (10–24)	3 (1–7)	3 (1–7)	5 (2–10)	6 (3–11)	3 (1–7)	5 (2–10)
40s	28 (11–59)	17 (5–44)	27 (14–47)	21 (10–40)	11 (4–25)	19 (8–37)	21 (10–40)	37 (21–61)
50s	35 (15–72)	51 (25–93)	20 (7–43)	71 (43–109)	31 (15–59)	43 (23–75)	75 (46–114)	59 (34–95)
60s	111 (68–172)	74 (40–125)	48 (21–94)	41 (17–85)	27 (9–65)	76 (40–131)	124 (76–191)	131 (81–200)
70s	201 (124–308)	172 (102–273)	158 (98–242)	92 (49–158)	83 (43–148)	83 (43–148)	158 (98–242)	108 (61–180)
80+	131 (48–295)	188 (82–374)	65 (22–155)	114 (51–224)	180 (95–311)	228 (131–373)	163 (84–290)	196 (107–332)
Male, crude	36 (28–45)	36 (28–45)	21 (16–28)	23 (18–30)	19 (14–25)	26 (20–33)	34 (27–42)	36 (29–44)
Male, adjusted*	38 (28–47)	38 (29–47)	23 (16–29)	25 (18–31)	20 (14–26)	28 (21–35)	37 (29–45)	37 (29–45)
All residents								
All, crude	37 (31–44)	31 (26–37)	22 (18–26)	24 (20–29)	18 (15–23)	26 (22–31)	33 (28–38)	34 (29–39)
All, adjusted†	39 (32–45)	32 (27–38)	23 (19–28)	25 (21–30)	19 (15–23)	28 (23–32)	35 (29–40)	35 (29–40)

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009) (continued)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
Recurrent pulmonary embolism±deep vein thrombosis at index visit								
Female residents (per age group in years)								
<40	2 (0–6)	0 (0–0)	1 (0–5)	1 (0–5)	0 (0–0)	1 (0–3)	1 (0–5)	1 (0–5)
40s	6 (1–26)	6 (1–26)	0 (0–0)	3 (0–12)	3 (0–12)	5 (1–17)	3 (0–12)	3 (0–12)
50s	7 (1–28)	7 (1–28)	23 (10–47)	19 (7–42)	8 (2–25)	11 (3–31)	8 (2–25)	4 (0–18)
60s	30 (12–61)	13 (3–37)	24 (8–57)	6 (1–28)	6 (1–28)	12 (2–38)	36 (15–74)	42 (19–82)
70s	32 (12–72)	28 (9–66)	12 (2–38)	30 (11–65)	30 (11–65)	18 (5–48)	24 (8–57)	59 (31–105)
80+	37 (11–94)	59 (23–127)	23 (6–62)	39 (15–84)	8 (1–36)	54 (24–106)	54 (24–106)	108 (62–176)
Female, crude	9 (6–14)	7 (4–12)	7 (4–11)	8 (5–12)	4 (2–7)	7 (5–11)	9 (6–13)	14 (10–20)
Female, adjusted*	9 (5–14)	8 (4–12)	7 (4–11)	8 (4–12)	4 (2–7)	8 (4–11)	9 (6–13)	15 (10–20)
Male residents (per age group in years)								
<40	3 (1–7)	2 (1–6)	1 (0–3)	1 (0–3)	1 (0–3)	0 (0–0)	1 (0–3)	2 (1–6)
40s	7 (1–27)	0 (0–0)	0 (0–0)	0 (0–0)	3 (0–12)	8 (2–21)	8 (2–21)	5 (1–17)
50s	8 (1–31)	16 (4–44)	8 (2–25)	16 (5–37)	8 (2–25)	20 (7–43)	24 (10–49)	20 (7–43)
60s	29 (11–65)	16 (4–46)	14 (3–44)	14 (3–44)	0 (0–0)	21 (6–55)	41 (17–85)	48 (21–94)
70s	57 (22–123)	72 (31–143)	33 (11–79)	42 (16–91)	8 (1–39)	25 (7–67)	50 (21–103)	42 (16–91)
80+	56 (11–180)	19 (1–113)	16 (1–76)	49 (14–131)	65 (22–155)	49 (14–131)	49 (14–131)	49 (14–131)
Male, crude	10 (6–15)	8 (5–14)	4 (2–8)	6 (4–10)	4 (2–7)	7 (4–11)	11 (7–16)	11 (7–16)
Male, adjusted*	11 (6–16)	9 (5–14)	5 (2–8)	7 (3–11)	4 (1–7)	8 (4–12)	12 (7–16)	12 (7–16)
All residents								
All, crude	10 (7–13)	8 (5–11)	6 (4–8)	7 (5–10)	4 (2–6)	7 (5–10)	10 (7–13)	13 (10–16)
All, adjusted†	10 (7–13)	8 (5–11)	6 (4–8)	8 (5–10)	4 (2–6)	8 (5–10)	11 (8–14)	13 (10–17)

Table 2.2s Annual event rates (per 100,000) of clinical recognized acute venous thromboembolism among Worcester metropolitan statistical area residents by sex and age (1985–2009) (continued)

	Rate (95% CI) 1985/1986	1988/1989	1999	2001	2003	2005	2007	2009
Recurrent deep vein thrombosis alone at index visit								
Female residents (per age group in years)								
<40	7 (4–14)	5 (2–10)	2 (1–6)	1 (0–5)	1 (0–5)	3 (1–7)	1 (0–3)	4 (1–8)
40s	39 (18–74)	13 (3–36)	8 (2–21)	13 (5–29)	8 (2–21)	26 (14–47)	8 (2–21)	8 (2–21)
50s	11 (2–34)	25 (9–56)	11 (3–31)	19 (7–42)	15 (5–36)	23 (10–47)	34 (17–63)	27 (12–53)
60s	66 (37–109)	53 (28–92)	42 (19–82)	30 (11–66)	36 (15–74)	30 (11–66)	48 (23–90)	36 (15–74)
70s	87 (48–146)	69 (35–122)	65 (35–113)	48 (22–90)	59 (31–105)	65 (35–113)	77 (43–128)	59 (31–105)
80+	148 (83–244)	52 (19–116)	85 (45–147)	131 (79–205)	69 (34–127)	85 (45–147)	170 (109–252)	77 (40–137)
Female, crude	29 (22–37)	19 (14–26)	15 (11–21)	17 (13–23)	14 (10–19)	19 (14–25)	23 (17–29)	18 (13–23)
Female, adjusted*	30 (22–38)	19 (13–25)	16 (11–21)	18 (12–23)	15 (10–19)	20 (14–25)	24 (18–30)	17 (12–23)
Male residents (per age group in years)								
<40	7 (3–13)	13 (8–21)	2 (1–6)	2 (1–6)	4 (2–9)	6 (3–11)	2 (1–6)	3 (1–7)
40s	21 (7–49)	17 (5–44)	27 (14–47)	21 (10–40)	8 (2–21)	11 (4–25)	13 (5–29)	32 (18–54)
50s	27 (10–61)	35 (15–72)	12 (3–31)	55 (31–90)	24 (10–49)	24 (10–49)	51 (29–85)	39 (20–70)
60s	82 (46–136)	58 (29–104)	34 (13–75)	27 (9–65)	27 (9–65)	55 (26–104)	82 (45–140)	82 (45–140)
70s	143 (81–237)	100 (50–181)	125 (73–201)	50 (21–103)	75 (37–137)	58 (26–114)	108 (61–180)	67 (31–126)
80+	75 (19–211)	169 (70–348)	49 (14–131)	65 (22–155)	114 (51–224)	180 (95–311)	114 (51–224)	147 (73–268)
Male, crude	26 (19–34)	27 (20–36)	17 (12–23)	17 (12–23)	15 (11–21)	19 (14–25)	23 (17–30)	25 (19–32)
Male, adjusted*	27 (19–35)	29 (21–37)	18 (12–24)	18 (12–23)	16 (11–21)	20 (14–26)	25 (18–32)	25 (19–32)
All residents								
All, crude	28 (23–33)	23 (19–28)	16 (13–20)	17 (14–21)	14 (11–18)	19 (15–23)	23 (19–27)	21 (17–26)
All, adjusted†	29 (23–34)	24 (19–29)	17 (13–21)	18 (14–22)	15 (12–19)	20 (16–24)	24 (20–29)	21 (17–25)

*Directly age–adjusted to the 2000 U.S. white population.
†Directly age– and sex–adjusted to the 2000 US white population.

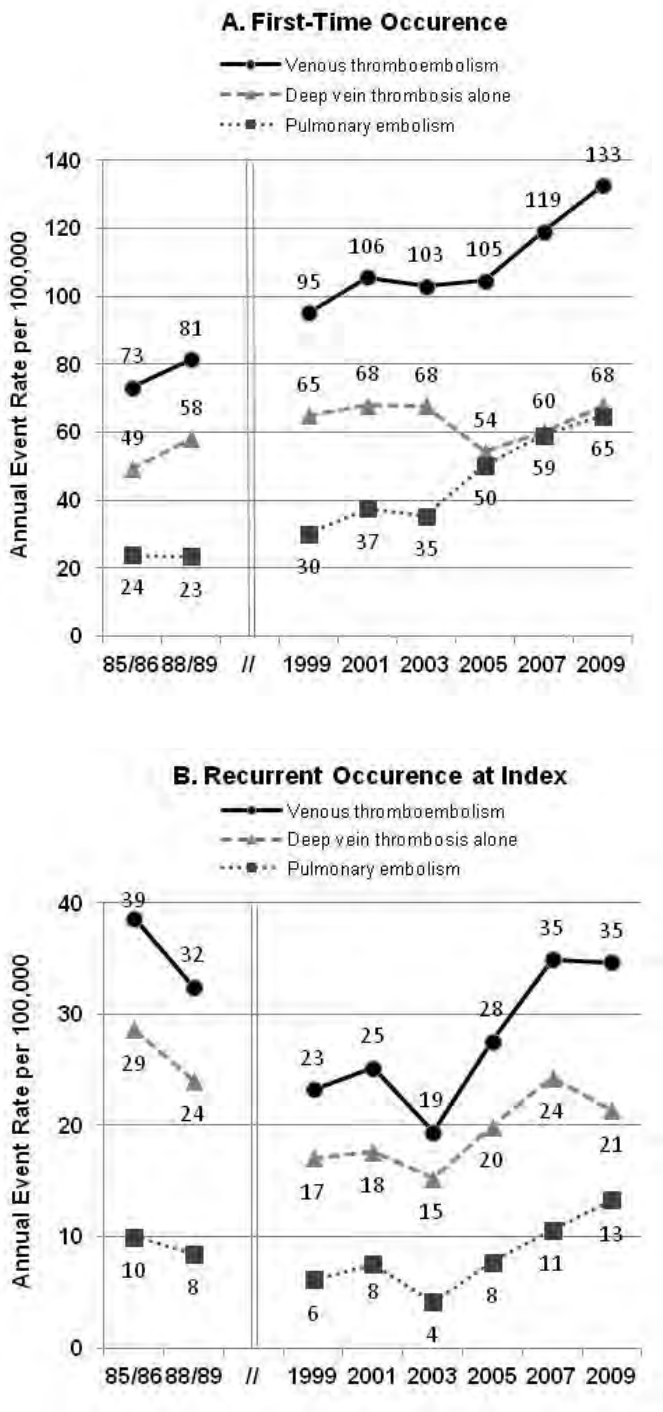
Table 2.3 Diagnostic methods for venous thromboembolism: the Worcester venous thromboembolism study (1985–2009)

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend Test	1985/86 vs 2009
First-time event at index, n (%)	n=405	n=442	n=435	n=482	n=466	n=482	n=542	n=633		
Any invasive* diagnostic method	237 (58.5)	206 (46.6)	6 (1.4)	18 (3.7)	9 (1.9)	14 (2.9)	11 (2.0)	15 (2.4)	<.001	<.001
Any non-invasive diagnostic method	285 (70.4)	335 (75.8)	406 (93.3)	456 (94.6)	453 (97.2)	477 (99.0)	535 (98.7)	615 (97.2)	<.001	<.001
Diagnostic tests in patients with deep vein thrombosis (%)	n=307	n=344	n=366	n=383	n=378	n=345	n=380	n=451		
Venogram	67.8	54.9	0.5	1.6	0.8	2.0	1.1	0.7	<.001	<.001
Impedance plethysmography	57.7	53.2	0	0	0	0	0	0	<.001	<.001
Duplex/ultrasound scan	0.3	36.3	92.9	91.6	94.4	93.0	91.3	97.8	<.001	<.001
Computed tomography	0	0	3.3	7.0	6.9	4.9	10.3	2.9	<.001	.003
Magnetic resonance imaging	0	0	0	0	0.3	7.8	9.2	0.7	<.001	.28
Any of above tests	94.8	96.8	95.4	95.6	97.6	99.4	100	99.1	<.001	<.001
Diagnostic tests in patients with pulmonary embolism (%)	n=131	n=127	n=137	n=170	n=159	n=228	n=268	n=307		
Pulmonary angiogram	16.8	11.0	2.2	2.4	2.5	2.6	2.6	3.9	<.001	<.001
Lung scan	80.9	88.2	59.1	40.0	19.5	24.1	11.2	7.5	<.001	<.001
Spiral computed tomography	0	0	24.8	60.6	79.2	80.7	86.9	87.3	<.001	<.001
Magnetic resonance imaging	0	0	0	0	0	0.4	0	0.3	.33	1.0
Any of above tests	90.1	93.7	92.7	95.3	97.5	98.7	97.8	96.4	<.001	.008
Recurrent event at index, n (%)	n=212	n=176	n=104	n=115	n=88	n=126	n=156	n=161		

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend Test	1985/86 vs 2009
Any invasive* diagnostic method	108 (50.9)	63 (35.8)	0	1 (0.9)	1 (1.1)	6 (4.8)	6 (3.8)	1 (0.6)	<.001	<.001
Any non-invasive diagnostic method	126 (59.4)	122 (69.3)	97 (93.3)	107 (93.0)	85 (96.6)	124 (98.4)	153 (98.1)	158 (98.1)	<.001	<.001
Diagnostic tests in patients with deep vein thrombosis (%)	n=177	n=149	n=91	n=92	n=76	n=105	n=129	n=123		
Venogram	49.7	39.6	0	1.1	1.3	3.8	2.3	0	<.001	<.001
Impedance plethysmography	47.5	49.7	0	0	0	0	0	0	<.001	<.001
Duplex/ultrasound scan	0	32.2	94.5	92.4	93.4	96.2	89.1	97.6	<.001	<.001
Computed tomography	0	0	1.1	1.1	6.6	2.9	7.0	4.1	<.001	.01
Magnetic resonance imaging	0	0	0	0	0	6.7	11.6	4.1	<.001	.01
Any of above tests	83.6	87.9	94.5	94.6	98.7	99.0	99.2	99.2	<.001	<.001
Diagnostic tests in patients with pulmonary embolism (%)	n=55	n=45	n=27	n=34	n=19	n=35	n=47	n=60		
Pulmonary angiogram	12.7	4.4	0	0	0	2.9	6.4	0	.004	.005
Lung scan	65.5	88.9	66.7	44.1	31.6	22.9	8.5	13.3	<.001	<.001
Spiral computed tomography	0	0	25.9	58.8	63.2	74.3	85.1	78.3	<.001	<.001
Magnetic resonance imaging	0	0	0	0	0	0	0	0	Not applicable	Not applicable
Any of above tests	76.4	95.6	92.6	94.1	89.5	97.1	97.9	96.7	.001	.001

*Invasive tests including venogram and pulmonary angiogram.

Figure 2.1 Age- and sex-adjusted annual event rates of (a) first-time and (b) recurrent clinical recognized acute VTE among WMSA residents (1985 to 2009). DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism; WMSA = Worcester, Massachusetts, metropolitan statistical area.



Chapter III. Trends in Clinical Management and Outcomes of First-time Community-presenting Episodes of Venous Thromboembolism: The Worcester VTE Study (1999 to 2009)

3.1 Abstract

Background: Contemporary trends in health-care delivery are shifting the management of venous thromboembolism (VTE) events (deep vein thrombosis [DVT] and pulmonary embolism [PE]) from the hospital to the community, which may have important implications for its prevention, treatment, and outcomes.

Methods: Population-based surveillance study monitoring trends in clinical epidemiology among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA) diagnosed with an acute VTE in all 12 WMSA hospitals. All patients were followed for up to 3 years after their index event.

Results: A Total of 2234 WMSA residents were diagnosed with first-time community-presenting VTE (those occurring in an ambulatory setting or diagnosed within 24 hours of hospitalization) in biennial epriods between 1999 and 2009. The proportion of VTE patients with PE increased from 30% in 1999 to 48% in 2009 (*P* for trend <.001), and nearly all PE patients were admitted to the hospital for treatment over time. However, in the DVT-alone group, the proportion of patients admitted to the hospital decreased from 67% in 1999 to 37% in 2009 (*P* for trend <.001). Among hospitalized patients, the mean length of stay decreased from 5.6 to 4.8 days (*P* for trend <.001). The proportion of VTE

provoked by prior surgery, pregnancy, trauma, fracture, or hospitalization, but not in the presence of active malignancy, decreased from 43% in 1999 to 36% in 2009. Between 1999 and 2009, treatment of VTE shifted from warfarin and unfractionated heparin towards increased use of low-molecular-weight heparins and newer anticoagulants; 3-year cumulative event rates decreased for all-cause mortality (41% to 26%), major bleeding (12% to 6%), and recurrent VTE (17% to 9%).

Conclusions: A decade of change in VTE management was accompanied by improved long-term outcomes. However, rates of adverse events remained fairly high in our population-based surveillance study, implying that new risk-assessment tools to identify individuals at increased risk for developing major adverse outcomes over the long-term are still needed.

3.2 Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with increased morbidity, functional disability, and mortality.[1] Although hospitalized patients are at high risk for developing VTE,[1, 48] most episodes presently occur in the community.[44-45]

A substantial proportion of patients presenting with VTE in the community have undergone surgery or hospitalization in the preceding 3 months.[3, 7, 45] Following recent changes in health-care services and their delivery,[14-15] hospitalized patients are increasingly being discharged earlier, placing them at

increased risk for developing VTE in the community setting. Thus, it is possible that the proportion of community-presenting VTE has increased over time. In addition, advances in therapeutic strategies have made it feasible to treat most patients with VTE as outpatients earlier and for longer periods.[32, 39-40, 42, 73] This change in clinical practice may have influenced subsequent short- and long-term outcomes. However, data generated from robust population-based surveillance studies describing changing trends in the clinical epidemiology of VTE are limited.[6]

Using data from the Worcester VTE study (1999-2009), we examined decade-long trends in the clinical management and short- and long-term outcomes of patients diagnosed with first-time community-presenting VTE.

3.3 Methods

The Worcester VTE study employed population-based surveillance methods to monitor trends in event rates of first-time or recurrent PE and/or DVT, management strategies, case-fatality rates, and recurrences after the index event among residents (n=477,598 per 2000 Census data) of the Worcester, Massachusetts, metropolitan statistical area (WMSA).[3, 7, 45] Computer printouts of all WMSA residents with health-care system encounters in which any of ICD-9 diagnosis codes consistent with VTE (Table 1.1) had been listed in 1999, 2001, 2003, 2005, 2007, and 2009 were screened from all 12 hospitals serving residents of the WMSA. Data queries encompassed all inpatient, outpatient ,

emergency department, radiology department, and diagnostic laboratory encounters. Data on index and follow-up events in medical records were reviewed by trained abstractors and validated by clinicians retrospectively; follow-up was up to 3 years for all independently validated patients. National and statewide death registries were reviewed to ascertain the survival status of all patients.

This study was approved by the institutional review committees at participating hospitals.

Definition of Index VTE

Several ICD-9 diagnosis codes were used to screen and identify eligible acute cases of PE and/or DVT (Table 1.1). Patients were classified as first-time VTE or previously diagnosed (recurrent) VTE at the time of their index visit based on whether they had a history of VTE noted in their medical records. Ambulatory patients presenting to all central MA hospitals with signs and symptoms consistent with VTE, or diagnosed with VTE within 24 hours of hospital presentation, were considered as community-presenting VTE patients.[45] Three etiologic categories of VTE were defined:[7] (1) cancer-associated VTE was a VTE occurring in the presence of an active malignancy; (2) provoked VTE was a VTE occurring within 3 months of surgery, pregnancy, trauma, fracture, or hospitalization, but not in the presence of active malignancy; and (3) unprovoked (idiopathic) VTE was a VTE occurring in the absence of any provoking factors and active malignancy.

Only first-time community-presenting episodes of VTE were examined in this analysis. Patients diagnosed with upper-extremity DVT alone were excluded due to important differences in the natural history of upper-extremity versus lower-extremity DVT.[52-53]

Adverse Events after Index VTE

Recurrence of VTE was classified using criteria similar to those employed for the index event, but required the occurrence of thrombosis in a previously uninvolved venous (recurrent DVT) or pulmonary segment (recurrent PE). Recurrent VTE was classified as the first occurrence of DVT or PE after the index VTE.

Episodes of major bleeding that may have occurred for patients in the study years of 1999, 2001, and 2003 were defined as any episode of bleeding requiring transfusion of ≥2 units of packed red blood cells (RBCs), or causing a prolonged or subsequent hospitalization (including stroke, myocardial infarction) or death. To be consistent with International Society of Thrombosis and Haemostasis criteria,[51] our definition for major bleeding was revised for the 2005, 2007, and 2009 cohorts as the following: clinically overt bleeding resulting in death; located in a critical site (intracranial, intraocular, retroperitoneal, intra-articular, pericardial, muscular with compartment syndrome); required transfusion of ≥2 units of packed RBCs; or resulted in a hemoglobin drop of ≥20 g/L.

Statistical Analysis

Categorical variables are reported as frequencies and percentages and continuous variables as means, standard deviations, medians, and interquartile ranges. Cochran-Armitage tests for binomial variables, Mantel-Haenzel tests for multinomial variables, and linear regression models for continuous variables were used to examine trends during the study years. Differences in the characteristics, management, and outcomes of patients diagnosed with VTE in 2009 versus those in 1999 were examined using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

To further evaluate whether study year at the time of VTE presentation was associated with our pre-specified outcomes during the 3-year follow-up, including occurrence of recurrent VTE, major bleeding, and all-cause mortality, Kaplan-Meier curves with log-rank tests and multivariable Cox proportional hazard regressions were constructed. Multivariable Cox proportional hazard regressions controlled for age, sex, diagnosis of PE with/without (±) DVT, and medical history within 3 months before the index event (congestive heart failure, myocardial infarction, stroke, cardiac procedure, chronic obstructive pulmonary disease, diabetes, active cancer, serious infection, trauma, major fracture, surgery, non-surgical-related hospitalization). Patients who experienced major bleeding before the development of a recurrent VTE over the course of follow-up were excluded from the recurrent VTE regression model; patients with recurrent VTE prior to major bleeding during follow-up were excluded from the major

bleeding regression model. All follow-up data were censored at the last contact (3 years) for mortality, and at the earliest of death or the last contact (3 years) for major bleeding and recurrent VTE following the index event.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was pre-specified as α=.05 (2-sided).

3.4 Results

Over the 10-year study period, 3039 WMSA residents were diagnosed with a first episode of acute PE±DVT or lower-extremity DVT alone. Of these, 2,334 (77%), ranging from a low of 74% in 1999 to a high of 80% in 2007, and 77% in 2009 (*P* for trend .04), were community-presenting and serve as the focus of this report.

Patient Characteristics

Among the 2, 334 patients, 43% were men, 94% were white, and their mean age was 63.4(±18.2) years. One third (32%) of patients were treated only in an ambulatory setting.

Patient baseline characteristics are shown in Table 3.1. Over time, the mean age of patients decreased and an increasing proportion were overweight. There was a decline in the frequency of patients with previously diagnosed heart failure, myocardial infarction, stroke, trauma, major fracture, surgery, or non-surgical hospitalization, with an increased frequency of patients with previously diagnosed chronic obstructive pulmonary disease. Although there was no

detectable trend in the proportion of cancer-associated VTE, the proportion of provoked VTE decreased, concomitant with increases in the proportion of persons with unprovoked VTE. The proportion of patients diagnosed with PE±DVT rose from 30% in 1999 to 48% in 2009, and nearly all were admitted to area hospitals over time. Among the DVT-alone group, the proportion admitted to the hospital decreased from 67% in 1999 to 37% in 2009. A decreasing trend in mean length of hospitalization was detected as well.

Prior VTE Prophylaxis

Overall, 43% of patients had either surgery or a non-surgical-related hospitalization during the 3 months preceding the index VTE. Among patients who underwent prior surgery, the proportion who received perioperative VTE prophylaxis increased from 50% in 1999 to 76% in 2009, primarily due to increases in the receipt of pharmacologic prophylaxis (Figure 3.1A). Among patients who had a prior non-surgical-related hospitalization, the proportion that received thromboprophylaxis did not vary, remaining consistently over 80% (Figure 3.1B).

Acute Treatment in the Hospital or Ambulatory Care Settings

Between 1999 and 2009, the proportion of patients who received low-molecular-weight heparin (LMWH) more than doubled, and the proportion who received unfractionated heparin (UFH) decreased (Table 3.2). We observed a declining trend in the initiation of warfarin during initial treatment, while there were no statistically significant changes in the use of inferior vena cava filters

during the years under study (Table 3.2). The proportion of patients who received any form of parenteral anticoagulant therapy other than UFH or LMWH increased dramatically, primarily due to use of fondaparinux.

At discharge from the hospital or emergency department, the proportion of patients who received LMWH increased from 26% in 1999 to 63% in 2009 whereas the proportion receiving warfarin alone decreased from 57% to 27% (Table 3.2).

Outcomes after Index Event

Overall (the entire 10 years) cumulative mortality rates at 30 days, 1 year, and 3 years, respectively, were 6.8%, 21%, and 32% among all patients; 10%, 24%, and 34% among the PE±DVT group; and 4.4%, 19%, and 31% among the DVT-alone group. There was a decreasing trend in all-cause mortality, primarily among patients diagnosed with DVT-alone (Table 3.3, Figure 3.2A).

Overall cumulative rates of major bleeding were 5.1%, 7.6%, and 9.5%, respectively, at 30 days, 1 year, and 3 years. The cumulative rates of major bleeding at 30 days, 1 year, and 3 years all decreased from 1999 to 2009 (Table 3.3, Figure 3.2B). After adjustment for a variety of potentially confounding variables, the rate of major bleeding in 2009 was reduced by more than half compared with that in 1999 (Table 3.3).

Among all VTE patients, overall cumulative recurrence rates of VTE were 2.9%, 7.2%, and 11% (0.6%, 2.0%, and 3.3% for recurrent PE; 2.4%, 6.1%, and

9.3% for recurrent DVT), respectively, at 30 days, 1 year, and 3 years. During the study period, a decreasing trend was observed in the frequency of recurrent VTE (Table 3.3, Figure 3.2 C and D).

3.5 Discussion

Among residents of central Massachusetts diagnosed with a first-time community-presenting VTE between 1999 and 2009, we observed significant decreases in all-cause mortality, major bleeding episodes, and recurrent VTE within 3 years of the index event. However, despite these encouraging trends, the frequency of major adverse events remained relatively high. These changes occurred concurrent with a number of other historical trends, most notably an increase in the occurrence of unprovoked VTEs, a change in anticoagulant treatment strategies, and an increase in the use of VTE prophylaxis for patients who had undergone surgery.

Patient Characteristics

Between 1999 and 2009, there was an increasing trend in the proportion of PE±DVT among first-time community-presenting VTE. This increasing trend was consistent with the findings from our prior publication, which focused on all patients diagnosed with first-time or recurrent VTE at the time of their index health encounter,[74] as well as with published findings from the US Nationwide Inpatient Sample, commercial insurance, and Medicare databases.[67-68] This

increasing trend may be due, in part, to the increased utilization of newer, high-sensitivity, diagnostic methods.[74 71]

The overall proportion of cancer-associated VTE (nearly 20%) and proportion of patients (43%) with a surgery or a non-surgical-related hospitalization within 3 months preceding the index event are consistent with those from another population-based observational study conducted among residents of Olmsted Country, Minnesota, during 1976-1990.[75]

Although the proportion of cancer-associated VTE remained constant in our study, there was a decrease in the proportion of patients who had a history of trauma, major fracture, surgery, or hospitalization for a non-surgical illness within 3 months before their index VTE. Thus, the proportion of VTE that are not easily predictable or preventable (i.e., unprovoked) increased. We are not aware of studies reporting similar secular trends, and we hypothesize that declines in the proportion of provoked VTE could be related to observed improvements in perioperative management including VTE prophylaxis among patients who had prior surgery and possibly due to the increased use of sensitive diagnostic tests.

Prior VTE Prophylaxis

Growing awareness of VTE as a public-health problem has become the impetus for evidence-based practice guidelines for VTE prevention.[48, 64] In 2005, a VTE quality measure was selected as a core measure set in the Joint Commission's performance measurement and improvement initiative among hospitalized patients.[43] These changes could have influenced clinical practice

towards a measurable improvement in practices and outcomes in patients at recognized “high” risk for VTE. Indeed, the proportion of patients who received any form of thromboprophylaxis among patients who had prior surgery increased from 50% in 1999 to 76% in 2009 in our study; although these prophylaxis measures were not associated with a reduction in the overall rates of index VTE, possibly due to competing factors (see below), increases in overall perioperative prophylaxis likely contributed to the observed decline in provoked VTE.

In a prior publication, we documented that the overall rate of VTE per 100,000 WMSA residents increased from 1999 through 2009.[74] Thus, increases in the proportion of unprovoked VTE represent a true increase in the population-based rate of diagnosis of unprovoked VTE, which may be attributable to improved diagnostic approaches or to poorly understood increases in VTE risk factors. Further research is needed to better understand factors affecting the development of VTE in the community setting and to identify additional triggers and risk factors.

Despite declining trends in the proportion of VTE patients who were either hospitalized or had surgery in the 3 months before their index event, this proportion was still approximately 40% in 2009. These patients were likely to have been considered at the “highest” risk for developing VTE because they had a VTE episode within 3 months after their surgery or hospitalization. This may explain why we observed a higher rate of VTE prophylaxis among these patients compared with the findings of a cross-sectional study based on all inpatients in a

sample of US hospitals.[76] However, among patients recognized as being at high risk for VTE due to recent surgery or hospitalization in 2009, approximately 20% did not receive any type of VTE prophylaxis during the period of hospitalization or surgery.

A prospective registry of ,5451 patients diagnosed with ultrasound-confirmed DVT from 183 US sites revealed that only 42% of patients who had hospital-acquired DVT received prophylaxis within 30 days before their index event.[77] These collective findings suggest that VTE prophylaxis remains markedly underutilized despite the availability of evidence-based consensus guidelines.

Acute Treatment in Hospital and Ambulatory Settings

Use of LMWH has changed the landscape of VTE treatment by enabling home treatment and providing an alternative long-term anticoagulant in populations in whom warfarin is less effective, difficult to manage, or contraindicated.[32, 39-40, 42, 73, 78] Accordingly, we observed an increasing trend in the use of LMWH, with a corresponding decrease in initial treatment with UFH and warfarin during the acute period. These practice changes may have influenced the proportion of patients admitted to the hospital for treatment among WMSA residents diagnosed with DVT alone. Early studies evaluating outpatient treatment of DVT have determined this practice to be safe and effective.[78] Presumably, recent findings and recommendations from randomized clinical trials (RCTs) and guidelines have influenced clinical practice as well.[79-82]

Outcomes after Index Event

During the past three decades, major advances have occurred in identifying patients at risk for VTE and in the utilization of diagnostic and treatment strategies.[1, 6, 64] The observed declining trends in all-cause mortality, major bleeding, and recurrent VTE within 3 years of the index event may be evidence of improved patient outcomes based on these advances.

A study based on the US Nationwide Inpatient Sample detected a similar decreasing trend in hospital mortality rates among all hospitalized cases of PE in US acute care hospitals between 1998 and 2005.[67] However, despite encouraging declining trends in all-cause mortality observed between 1999 and 2009, the 3-year cumulative all-cause mortality rate was still 26% in 2009. While we cannot comment on cause-specific mortality, we suspect that most of these deaths were due to the influence of comorbid conditions.[65] Indeed, an ongoing international multicenter VTE-treatment registry reported that the 3-month all-cause mortality in patients with proven symptomatic acute VTE was 7.9%, whereas deaths considered as PE-related was only 1.4%.[83]

The cumulative rates of major bleeding or recurrent VTE in our study were higher than those reported in RCTs of VTE treatment,[84] in spite of the declining rates observed over time. These differences are likely related, in part, to the inclusion criteria employed in RCTs, resulting in a more narrowly defined, “less ill” population. In addition, therapy is more carefully monitored in RCTs than in the uncontrolled setting of community practice. Indeed, other observational

studies have reported higher rates of recurrent VTE: 5% at 1 month, 11-13% at 1 year, 20% at 3 years, and 30-40% at 10 years after an acute episode of VTE.[31, 85] Further research is needed to develop safer and more effective treatment strategies that balance the benefits of treatment against the increased risk of bleeding. Furthermore, point-of-care, patient-specific, robust prognostic prediction models may be particularly helpful in guiding treatment decisions.[86-88]

Study Strengths and Limitations

The study employed population-based surveillance methods to describe the clinical epidemiology of VTE in WMSA residents, along with prevention and treatment data and changes over time therein. Although we conducted broad screening for cases of VTE using multiple databases, validated each potential case of VTE, and performed regular chart audits, we may have missed some cases of asymptomatic VTE. Due to the low autopsy rates in the WMSA, and the limited validity of death-certificate data, [3, 7] only clinically recognized cases of acute VTE were described and some cases of fatal PE could have been missed. The most important indicator of bleeding such as the need for ≥2 units of packed RBCs was present in both versions of the definition of major bleeding, so the decline in major bleeding was likely to be real. We did not collect information on the use of long-term anticoagulation; therefore, we could not assess the impact of use of various anticoagulation strategies, including the duration of therapy, on our principal study outcomes.

3.6 Conclusions

This population-based study in residents of central Massachusetts confirms that most first-time VTE develop in the community setting and that this trend increased between 1999 and 2009. We detected an increase in incidence rates of unprovoked VTE, indicating the need to identify novel risk factors for this event. While the decreasing frequency of major adverse outcomes is reassuring, mortality, major bleeding, and recurrence rates remained high, suggesting that current treatment strategies are less than optimal. New risk-assessment tools to estimate the true risks and benefits associated with VTE prevention and treatment at the individual patient-level are needed.

3.7 Tables and figures

Table 3.1 Characteristics of Patients with Community-presenting First-time VTE: 1999-2009

Study Year	1999	2001	2003	2005	2007	2009	*P* for Trend	*P* 1999 vs. 2009
No. of VTEs	320	362	353	380	431	488		
Demographic characteristics								
Age, y							.04	.02
Mean±SD	65.9±18.1	64.6±17.4	62.3±17.9	61.9±19.1	63.3±18.3	63.0±18.2		
Median (IQR)	71 (52-80)	66 (51-79)	64 (50-77)	64 (47-79)	66 (50-79)	65 (49-79)		
Men, %	41.9	38.7	46.2	40.0	47.1	43.6	.18	.62
White, %	95.7	95.1	93.5	94.3	95.0	92.4	.10	.06
Recent[a] medical characteristics prior to index VTE, %								
BMI, kg/m^2							.03	.04
<25	34.9	32.7	24.0	35.2	28.4	25.3	.02	.01
25-30	25.9	31.5	35.1	29.3	35.3	29.8	.43	.30
>30	39.2	35.8	40.9	35.5	36.3	44.9	.13	.17
Congestive heart failure	9.4	10.8	8.5	6.8	5.8	4.9	<.001	.01
Myocardial infarction	3.4	5.5	4.0	1.3	2.8	2.0	.013	.23
Stroke	4.7	4.4	5.1	1.1	1.6	1.0	<.001	.001
Cardiac procedure	2.8	5.0	3.1	3.9	3.9	3.9	.75	.41
Chronic obstructive pulmonary disease	15.3	20.7	16.4	20.8	24.1	22.7	.003	.01
Diabetes	15.6	21.0	17.3	15.3	21.6	16.8	.82	.66
Active malignancy	17.8	19.9	11.3	15.0	16.7	17.0	.64	.77
Chemotherapy (among active malignancy)	54.4	56.9	60.0	57.9	52.8	41.0	.07	.12
Trauma/fracture	16.9	23.2	13.0	8.7	7.2	7.4	<.001	<.001
Serious infection	14.4	22.7	22.1	19.5	16.9	14.3	.10	.99
Intensive care unit discharge	10.0	9.7	8.2	8.4	9.5	8.6	.58	.50
HRT/oral contraceptives (among women)	24.2	23.9	17.9	12.3	8.3	12.4	<.001	<.001
Post partum (among women)	2.2	0.9	1.6	2.2	1.3	1.5	.85	.72

Study Year	1999	2001	2003	2005	2007	2009	*P* for Trend	*P* 1999 vs. 2009
Surgery before index event	26.9	28.2	21.0	23.4	20.4	18.4	<.001	.005
Hospitalization due to non-surgical illness before index event	38.4	43.4	35.1	24.2	24.1	24.6	<.001	<.001
VTE characteristic, %								
Diagnosis of index event							<.001	<.001
PE±DVT	30.0	34.3	33.7	48.7	48.3	47.7		
Lower extremity DVT alone	70.0	65.7	66.3	51.3	51.7	52.3		
Type of VTE event							<.001	.06
Cancer-associated	17.8	19.9	11.3	15.0	16.7	17.0	.64	.77
Provoked (non-cancer-associated)[b]	43.4	47.5	37.1	37.1	33.4	36.1	<.001	.04
Unprovoked[c]	38.8	32.6	51.6	47.9	49.9	46.9	<.001	.02
Hospital encounter, %								
Admitted to hospital	75.9	71.3	62.3	68.2	66.4	65.0	.002	<.001
Length of stay, days							<.001	<.001
Mean±SD	5.6±4.8	6.8±6.4	6.0±5.6	5.4±5.9	4.9±4.0	4.8±5.1		
Median (IQR)	5 (3-7)	5 (3-8)	5 (3-7)	4 (3-6)	4 (2-6)	4 (2-6)		
Admitted to hospital among patients with PE±DVT	95.8	99.2	97.5	96.2	94.7	95.7	.17	.96
Admitted to hospital among patients with lower extremity DVT alone	67.4	56.7	44.4	41.5	39.9	36.9	<.001	<.001

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; HRT, hormone replacement therapy; ICU, intensive care unit; IQR, inter-quartile range; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.
[a]Recent defined as < 3 months and prior to index VTE.
[b]Provoked VTE was defined as VTE occurring with a history of a surgical procedure, pregnancy, trauma, fracture, or hospitalization within 3 months prior to index visit.
[c]Unprovoked VTE was defined as VTE occurring in the absence of any of the above "provoking" factors or active malignancy (cancer-associated).

Table 3.2 Initial Treatment of Patients with First-time VTE Developed in a Community Setting: 1999-2009

Study Year	1999	2001	2003	2005	2007	2009	*P* for Trend	*P* 1999 vs. 2009
No. of VTEs	320	362	353	380	431	488		
Acute treatment methods[a], %								
IV/SQ UFH	65.9	52.8	41.1	35.8	33.9	29.9	<.001	<.001
SQ LMWH[b]	29.1	45.9	60.1	69.5	73.3	64.5	<.001	<.001
Other parenteral anticoagulant[c]	0	1.4	2.5	1.1	3.5	19.3	<.001	<.001
IVC filter implanted prior/during index visit	10.0	11.0	9.3	8.9	10.7	7.6	.23	.23
Warfarin initiated during initial treatment	76.3	69.9	67.1	55.3	52.7	56.1	<.001	<.001
Discharge medication among hospital/ED survivors, %	n = 260	n = 285	n = 277	n = 298	n = 327	n = 382		
Warfarin	80.4	79.3	81.9	76.8	82.0	75.9	.27	.18
SQ LMWH	26.2	38.6	48.4	56.4	61.8	63.1	<.001	<.001
Combination treatment								
Warfarin with LMWH	19.6	31.6	41.9	45.3	56.0	49.0	<.001	<.001
Warfarin with UFH	3.8	2.5	0.4	0	0	0	<.001	<.001
Warfarin without LMWH/UFH	56.9	45.3	39.7	31.5	26.0	27.0	<.001	<.001
LMWH without warfarin/UFH	6.5	7.0	6.5	11.1	5.5	14.1	.002	.002
UFH without warfarin/LMWH	2.3	1.1	0.7	0.3	0.6	0.8	.08	.17
None of the above	10.8	12.6	10.8	11.7	11.6	9.2	.39	.50

Abbreviations: ED, emergency department; IV, intravenous; IVC, inferior vena cava; LMWH, low molecular weight heparin; SQ, subcutaneous; UFH, unfractionated heparin.
[a]Initial therapy in health-care facility (inhospital or ambulatory settings); may receive more than one parenteral anticoagulant.
[b]Enoxaprain, dalteparin, tinzaparin.
[c]Fondaprinux, danaparoid, hirudin, argatroban, other.

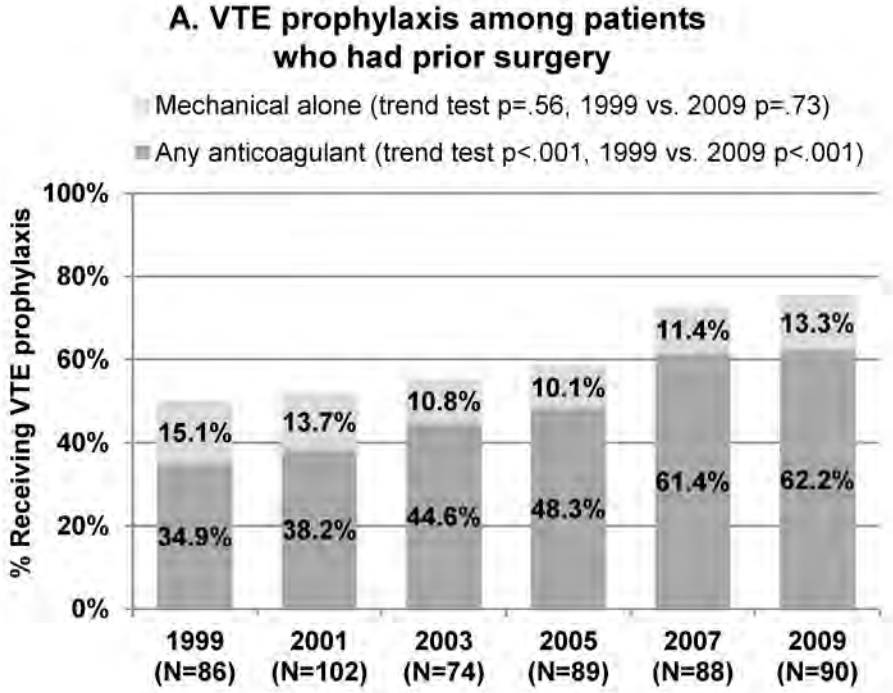
Table 3.3 Mortality, First Episode of Major Bleeding, and Recurrent VTE after Index Event: 1999-2009

Study Year	1999	2001	2003	2005	2007	2009	*P* for Trend	*P* 1999 vs. 2009
No. of VTEs	320	362	353	380	431	488		
All patients with VTE								
Death within 1 month post index, %	8.1	6.9	4.6	7.7	7.4	6.1	.67	.29
Death within 1 year post index, %	25.7	24.4	20.2	21.2	18.3	19.3	.007	.03
Death within 3 years post index, %	40.9	37.8	30.9	31.6	28.8	26.4	<.001	<.001
Hazard ratio (95% CI)[a]	Ref	0.83 (0.64-1.07)	0.82 (0.63-1.06)	0.85 (0.65-1.10)	0.79 (0.61-1.03)	0.66 (0.51-0.85)		
Patients with PE±DVT	**n = 96**	**n = 124**	**n = 119**	**n = 185**	**n = 208**	**n = 233**		
Death within 1 month post index, %	13.2	10.1	6.7	10.8	11.1	9.0	.63	.26
Death within 1 year post index, %	24.2	26.1	22.7	21.7	23.1	26.2	.84	.71
Death within 3 years post index, %	37.5	39.5	30.3	30.8	33.7	33.9	.40	.53
Hazard ratio (95% CI)[a]	Ref	0.97 (0.58-1.48)	1.04 (0.64-1.69)	1.08 (0.69-1.71)	1.05 (0.68-1.63)	0.91 (0.59-1.40)		
Patients with DVT alone	**n = 224**	**n = 238**	**n = 234**	**n = 195**	**n = 223**	**n = 255**		
Death within 1 month post index, %	6.0	5.2	3.5	4.6	4.0	3.5	.20	.21
Death within 1 year post index, %	26.3	23.5	19.0	20.6	13.9	12.9	<.001	<.001
Death within 3 years post index, %	42.4	37.0	31.2	32.3	24.2	19.6	<.001	<.001
Hazard ratio (95% CI)[a]	Ref	0.84 (0.61-1.14)	0.72 (0.53-0.99)	0.76 (0.54-1.06)	0.68 (0.48-0.96)	0.52 (0.36-0.74)		
Major bleeding								
Within 1 month post index, %	6.8	8.2	7.2	4.3	2.3	3.5	<.001	.03
Within 1 year post index, %	9.1	11.1	9.5	9.1	4.4	4.5	<.001	.01
Major bleeding within 3 years post index, %	11.9	12.2	11.3	12.1	5.8	5.7	<.001	.002
Hazard ratio (95% CI)[a]	Ref	0.96 (0.60-1.53)	1.01 (0.63-1.62)	0.97 (0.60-1.55)	0.48 (0.28-0.83)	0.43 (0.25-0.75)		
Recurrent VTE								
Within 1 month post index, %	5.2	1.7	5.4	2.4	2.1	1.6	.006	.004
Within 1 year post index, %	11.4	8.4	8.9	5.6	5.6	5.3	<.001	.002
Within 3 years post index, %	16.9	12.7	11.3	11.3	8.6	8.6	<.001	<.001
Hazard ratio (95% CI)[a]	Ref	0.72 (0.46-1.12)	0.61 (0.38-0.96)	0.62 (0.39-0.97)	0.53 (0.34-0.85)	0.52 (0.33-0.85)		
Recurrent PE after index VTE								
Within 1 month post index, %	0.7	0.6	1.4	0.5	0.2	0.4	.30	.64
Within within 1 year post index, %	1.6	3.2	2.9	1.6	2.1	0.8	.09	.32
Within within 3 years post index, %	3.1	5.0	4.0	3.2	3.7	1.6	.07	.16
Hazard ratio (95% CI)[a]	Ref	1.59 (0.67-3.75)	1.51 (0.63-3.61)	0.96 (0.38-2.44)	1.40 (0.58-3.37)	0.73 (0.27-1.96)		
Recurrent DVT after index VTE								

Study Year	1999	2001	2003	2005	2007	2009	*P* for Trend	*P* 1999 vs. 2009
Within 1 month post index, %	4.6	1.2	4.0	2.1	1.9	1.4	.02	.007
Within within 1 year post index, %	10.4	6.0	7.5	5.0	4.6	4.7	.001	.002
Within within 3 years post index, %	15.3	9.4	9.6	10.0	6.5	7.2	<.001	<.001
Hazard ratio (95% CI)[a]	Ref	0.55 (0.33-0.89)	0.47 (0.28-0.79)	0.57 (0.35-0.93)	0.39 (0.23-0.66)	0.40 (0.24-0.67)		

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; Ref, reference group; VTE, venous thromboembolism.
[a]Results from Cox proportional hazards model adjusted by age, sex, diagnosis of PE with/without (±) DVT, and medical conditions within 3 months before the index event (congestive heart failure, myocardial infarction, stroke, cardiac procedure, chronic obstructive pulmonary disease, diabetes, active cancer, serious infection, trauma, major fracture, surgery, non-surgical-related hospitalization)

Figure 3.1 VTE Prophylaxis before Index Event: 1999-2009



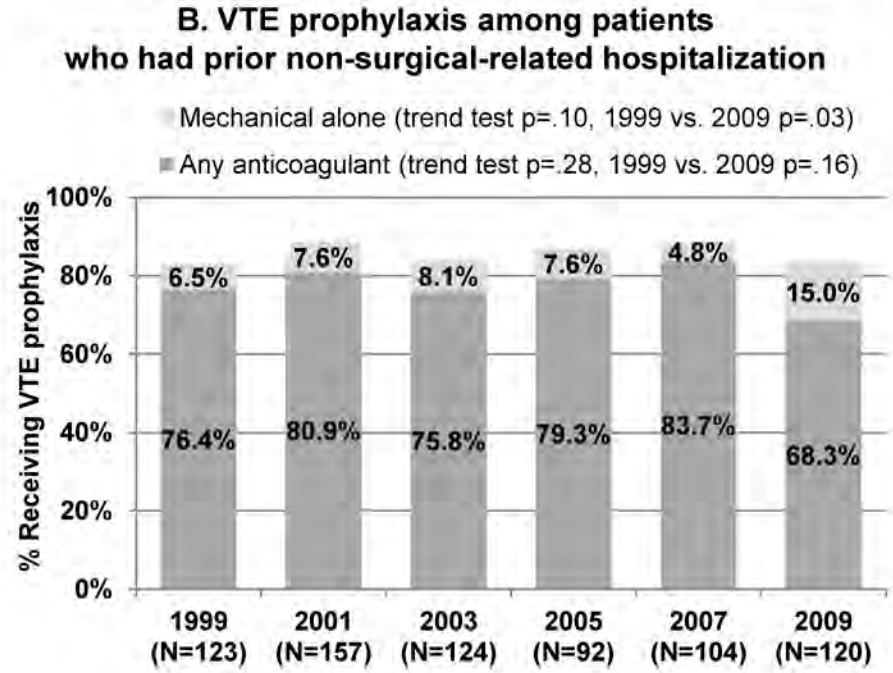
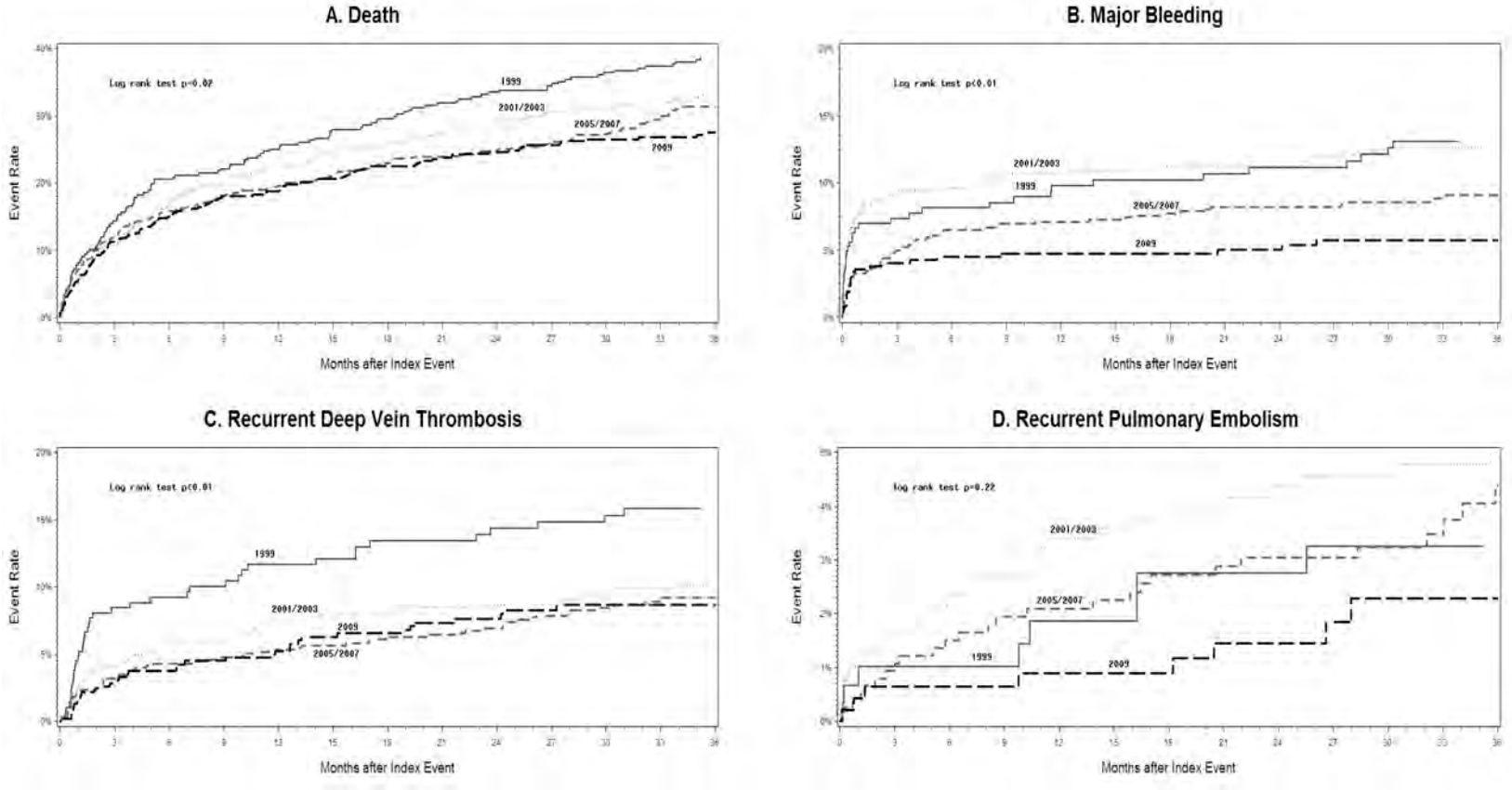


Figure3.2 Cumulative Incidence of (A) Death, (B) Major Bleeding, (C) Recurrent DVT, (D) Recurrent PE after Index VTE: 1999-2009
Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism
Kaplan-Meier curves by secular period account for censoring



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Chapter IV. Predicting Recurrence after First-time Acute Venous Thromboembolism

4.1 Abstract

Background: Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has multiple risk factors and tends to recur. Despite the benefits of anticoagulation, the prevalence of, and case-fatality rate associated with, recurrent VTE remains a concern over several years after an acute episode; it is particularly high during the acute treatment phase. Therefore, identifying individual risk factors associated with recurrence may lead to more effective secondary prevention and enhanced prognosis.

Methods: Population-based surveillance study with 3-year follow-up among residents of central Massachusetts diagnosed with an acute first-time PE and/or lower-extremity DVT from 1999 through 2009 at in-hospital and ambulatory settings in all 12 central MA hospitals. Medical records were reviewed by trained abstractors and validated by clinicians.

Results: The 2,989 study patients were followed for a total of 5,836 person-years with mean follow-up duration of 23.4(±14.4) months. Mean age of the study popualtion was 64.3(±18.0) years, and 44% were men. The Kaplan-Meier estimated cumulative incidence rate of recurrent VTE within 3 years after an index VTE was 15%. Multivariable Cox proportional hazard regression indicated that active cancer (with/without chemotherapy), a hypercoagulable state,

varicose vein stripping, and inferior vena cava filter placement were independent predictors of recurrence during short- (3-month) and long-term (3-year) follow-up. Risk score calculators were developed based on the 3-month prognostic models. **Conclusions:** Several independent predictors were identified that may be useful for estimating risk of VTE recurrence at the individual patient-level. The risk score calculators may assist clinicians at the index encounter in determining the frequency of clinical surveillance and appropriate outpatient treatment of VTE during the acute treatment phase.

4.2 Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with increased long-term morbidity, functional disability, and all-cause mortality.[1] VTE has been estimated to be the third most common acute cardiovascular event after acute coronary syndromes and ischemic stroke.[2] Despite advances over the past three decades in VTE identification, prophylaxis, and treatment, the annual event rate of VTE has increased over time.[66-68, 74]

VTE is a disease with multiple contributory risk factors which tends to recur,[1, 48] especially during the first three years after an acute episode.[17-19] Data from a limited number of observational studies have suggested that the cumulative recurrence rate after an acute event is approximately 8% at 90 days, 11-13% at 1 year, 20% at 3 years, and 30-40% at 10 years.[31, 85] In current

practice, anticoagulation treatment is recommended for at least 3 months for nearly all patients.[48] However, despite the proven benefits of anticoagulation, a systematic review indicated that the case-fatality rate of recurrent VTE is greater than 11% during the initial 3 months of acute treatment.[84]

Therefore, understanding who is at risk for developing a recurrence during the acute treatment phase may help clinicians to determine the optimal frequency of subsequent clinical surveillance and the appropriate type of outpatient treatment. Furthermore, the decision to continue or discontinue anticoagulation beyond 3 months (extended treatment phase) continues to be individually tailored,[48] yet risk assessment tools for predicting the long-term risk of VTE recurrence at the individual patient-level remain limited.[87]

Inasmuch, , identifying short- and long-term risk factors associated with recurrent events after an acute episode of VTE may lead to improved strategies for VTE secondary prevention. A limited number of published studies have attempted to quantify the risk of, and factors associated with, VTE recurrence. These studies have either focused on a subset of VTE patients or used data from randomized clinical trials, administrative databases, or outdated observational cohorts that may limit their value.[31, 85, 89-94]

We used population-based surveillance methods to monitor residents of central Massachusetts diagnosed with an acute first-time episode of PE and/or lower-extremity DVT on a biennial basis between 1999 and 2009. We followed these individuals for 3 years to quantify the magnitude of recurrent events and

identify predictors of short- and long-term recurrence after the index episode. Our risk score calculators use characteristics assessed during the index encounter to predict VTE recurrence during the initial 3-month acute treatment period.

4.3 Methods

The Worcester VTE study employed population-based surveillance methods to monitor trends in annual event rates of acute episodes of PE and/or DVT, management strategies, case-fatality rates, and recurrences after the index event among all residents of the Worcester metropolitan statistical area (WMSA) (n=478,000 per 2000 Census data).[3, 7, 45, 74]

Computer printouts of all WMSA residents with health-care system encounters in which any ICD-9 diagnostic codes consistent with VTE (Table 1.1) had been listed during 1999 to 2009 on a biennial basis from all 12 hospitals serving residents of the WMSA were used to screen and identify index events. Data queries encompassed all inpatient, outpatient, emergency department, radiology department, and diagnostic laboratory encounters. Medical records related to the index and follow-up events were retrospectively reviewed by trained abstractors and validated by clinicians; follow-up was up to 3 years for all independently validated events. National and state-wide death registries were reviewed to ascertain the survival status of all study patients.

The institutional review committee at each participating hospital approved this study.

Definition of Index Episode of VTE

Several ICD-9 diagnosis codes were used to screen and identify eligible acute cases of PE and/or (±) DVT (Table 1.1). Patients were classified as first-time VTE or previously diagnosed (recurrent) VTE at the time of their index visit based on whether they had a history of VTE noted in their medical records. Three etiologic categories of VTE were defined:[7] (1) cancer-associated VTE was classified as a VTE occurring in the presence of an active malignancy; (2) provoked VTE was a VTE occurring within 3 months of surgery, pregnancy, trauma, fracture, or hospitalization, but not in the presence of active malignancy; and (3) unprovoked (idiopathic) VTE was classified as a VTE occurring in the absence of any provoking factors and active malignancy.

In the present analyses, only patients with a first-time (incident) episode of VTE were included. Patients diagnosed with upper-extremity DVT alone were excluded due to important differences in the natural history of upper-extremity versus lower-extremity DVT.[52-53]

Recurrence after Index Episode of VTE

Through the retrospective review of medical records, a recurrent episode of VTE after the patient's index event was defined as a first occurrence of thrombosis in a previously uninvolved venous (recurrent DVT) or pulmonary segment (recurrent PE). Due to lack of adequate sample size (Table 4.1s), a multivariable model using recurrent PE as the endpoint was not conducted.

Potential Prognostic Factors

Potential prognostic factors included patient demographic characteristics, medical history within 3 months prior to the index event, type of diagnosis (PE±DVT versus DVT alone), clinical characteristics assessed during the index encounter, and acute therapy in a health-care facility (in-hospital/at discharge or ambulatory settings).

Statistical Analysis

The distributions of various patient characteristics assessed during the index encounter were described using mean, standard deviation, median and inter-quartile range for continuous variables and frequency with percent for categorical variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) generated by the unadjusted Cox proportional hazards regression models were used to describe the relationship of potential prognostic factors to time-to-recurrent VTE.

The cumulative incidence rate (CIR) of VTE recurrence within 3 years after the patient's index event was estimated using the Kaplan-Meier method. Data were censored at the time of death or last medical contact (in survivors) up to 3 years following the index event. The log-rank test was used to compare CIRs of VTE recurrence among cancer-associated, provoked, and unprovoked episodes of VTE since prior publications suggest that the recurrence rate among these three groups are different.[48-49, 87]

Since each potential prognostic factor was assessed during the index VTE encounter, and possible unmeasured time-dependent risk factors (e.g. duration of treatment) may have impacted our results, separate prognostic models for predicting short-term (3-month) and long-term (3-year) risks of recurrence were developed. In addition, due to differences between VTE patients with and without active cancer in the risk of recurrence and in patient management practices during the acute treatment period, sensitivity analyses were conducted and a separate 3-month prognostic model among non-cancer patients was developed. Although we attempted to develop a 3-month prognostic model among cancer patients, due to the lack of statistical power, a multivariable Cox regression model could not be constructed. Therefore, three prognostic models for predicting risk of VTE recurrence after the index event (predicting 3-year risk and 3-month risk among all patients; predicting 3-month risk among patients without active cancer) were reported in the current study.

The methods used to develop the prognostic models were as follows: the full model included all potential prognostic factors identified by unadjusted Cox proportional hazard regression analyses with p-values ≤0.1; multivariable Cox regression with backward selection was then used to select the final independent predictors ($p<0.05$). Proportional hazards assumptions were assessed by a test of the interaction between log (time metric) and each predictor (not violated). The linearity of age at the index encounter was assessed by a fractional polynomial technique (not violated).[55] Furthermore, the plots for the coefficients of the age

categories generated from adding the age category as a covariate to the best fitting model were examined to examine whether age made an additional contribution to the best fitting models.

The existence of influential outliers was examined by plotting the Scaled Score Residuals versus each predictor to identify subjects who may have influenced the value of a single coefficient and by plotting the likelihood displacement versus the Martingale Residual to identify subjects who may have influenced the vector of coefficients (no subjects were excluded).[95] We also assessed 2-way interactions and co-linearity among the final predictors (not found). Model discrimination was assessed using the Harrell macro for Cox regression (the c-index),[56] while goodness-of-fit (calibration) was assessed by the May-Hosmer method.[57] In addition, 100 replications of bootstrapping using the unrestricted random sampling technique were used to validate the best fitting model internally; 95%CIs of the c-index were also reported.

To help clinicians improve the management of their patients during the acute treatment phase, the final prognostic models for predicting 3-month VTE recurrence among all patients, and separately among patients without active cancer, were used to develop the 3-month risk score calculators based on methods previously used in published studies.[58-62] The risk score was calculated as follows: the factor with the smallest logarithmic HR (natural log of HR) was assigned 1 point, with other factor scores based on the size of their estimates relative to the smallest logarithmic HR; Individual predictor scores were summed

to give a total risk score (on a 0-100 scale) for each patient. The accuracy of calibration was demonstrated by comparing predicted to observed risk (using the Kaplan-Meier method) over the full range of risk scores. The correlation of predicted risk generated by two risk calculators for the same patient was assessed.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was pre-specified as $\alpha=0.05$ (two sided).

4.4 Results

Over the 10-year study period, a total of 2,989 WMSA residents were diagnosed with a first episode of acute PE±DVT (42%) or lower-extremity DVT alone (58%) . These patients were followed for a total of 5,836 person-years with mean follow-up duration of 23.4(±14.4) (median=30) months. Their mean age was 64.3(±18.0) years, 44% were men, and 94% were white. The proportions of cancer-associated, provoked, and unprovoked episodes of VTE were 17%, 43%, and 40%, respectively. Individual risk factors assessed during the index encounter are shown in Table 4.1.

During the follow-up period, 329 patients developed a recurrent VTE; the Kaplan-Meier estimated CIRs of VTE recurrence were 5.1% within 3 months and 15% within 3 years after the index event among all patients (Figure 4.1A). The CIRs of VTE recurrence among patients with active cancer, provoked, and

unprovoked VTE were 8.7%, 5.2%, and 3.8% within 3 months and 25%, 13%, and 13%, within 3 years, respectively (Figure 4.1B).

Predicting Recurrence within 3 Years for All Patients

HRs and 95% CIs generated from unadjusted Cox regression models for more than 50 potential risk factors for recurrent VTE within 3 years are presented in Table 4.2. Advanced age, active cancer (with/without chemotherapy), diabetes mellitus, a hypercoaguable state (as indicated in medical records), myeloproliferative disease, superficial thrombophlebitis, varicose vein stripping, prior nonsurgical-related hospitalization before index event, admission to hospital at the pateint's index encounter, and inferior vena cava (IVC) filter placement were associated with an increased risk of recurrence during this period; undergoing surgery before the index event was associated with a decreased long-term risk of recurrence (Table 4.2). In the mulivariable Cox regression analyses, six factors were identified as independent predictors of VTE recurrence during the 3-year follow-up (c-index 0.616[0.614-0.619]; Figure 4.2A): active cancer with/without chemo, hypercoaguable state, superficical thrombophlebitis, varicose vein stripping, IVC filter placement, and prior sugery within 3 months of the index event.

Predicting Recurrence within 3 Months for All Patients

The unadjusted Cox regression model identified active cancer (with/without chemotherapy), hypercoaguable state, major trauma, varicose vein stripping, prior nonsurgical-related hospitalization before the index event, taking

an anticoagulant at admission, and receipt of thrombolytic therapy or inferior vena cava (IVC) filter placement to be associated with an increased risk of recurrence within 3 months after the index event; receipt of subcutaneous low-molecular-weight heparin (LMWH) or warfarin during the initial treatment period was associated with decreased short-term risk of recurrence (Table 4.2).

In the mulivariable Cox regression analyses, seven factors were identified as independent predictors of VTE recurrence during the first 3 months after the index event (c-index 0.670[0.668-0.675], Figure 4.2B): active cancer, major trauma within 3 months before index event, hypercoaguable state, varicose vein stripping, diagnosed with DVT-alone at index encounter, taking anticoagulant therapy at admission, and IVC filter placement.

Separating the independent predictor “active cancer” into with/without chemotherapy categories did not improve the model performance (c-index decreased 0.004), and the HRs of active cancer with chemotherapy and active cancer without chemotherapy were 1.70 (1.01-2.86) and 1.62 (0.98-2.69) versus no-cancer, respectively. Thus, ‘active cancer (with/without chemotherapy)’ was used as a covariate in the final predictive model (HR: 1.66 [1.12-2.45]).

Predicting Recurrence within 3 Months for Patients without Active Cancer

Among 2,492 patients without active cancer (106 recurrent episodes at 3 months), the risk factors associated with 3 month recurrence were similar to those identified for all patients from the unadjusted Cox regression analysis, with the exception that stroke was associated with an increased risk of recurrence

and receiving treatment with warfarin was no longer associated with a decreased short-term risk of recurrence (Table 4.3). In the multivariable Cox regression analyses, five factors were identified as independent predictors of recurrence during the first 3 months after the index event (c-index 0.648 [0.646-0.654], Figure 4.2C): major trauma within 3 months before index event, a hypercoaguable state, varicose vein stripping, taking anticoagulants at admission, and IVC filter placement. The index diagnosis (PE±DVT vs. DVT alone) was no longer an independent predictor compared with the prognostic model based on all patients.

Predicting Recurrence within 3 Months for Patients with Active Cancer

Among 497 patients with active cancer (35 recurrent episodes of VTE at 3 months), only a family history of VTE and receiving stockings during the initial treatment period were significiantly associated with increasing 3 month risk of VTE recurrence based on unadjusted Cox regression findings (Table 4.3). In the multivariable adjusted regression model, only a family history of VTE was identified as an independent predictor of recurrent VTE. Therefore, a risk score calculator was not developed for these patients.

Age and VTE Recurrence

The unadjusted Cox regression model indicated that the HR of age per 10-year increase was 1.07 (1.00-1.13) for VTE recurrence during the entire 3 year follow-up period (Table 4.2), 1.03 (0.94-1.13) for VTE recurrence within the first 3 months after the index event among all patients (Table 4.2), and 0.99

(0.89-1.09) for VTE recurrence within the first 3 months after the index event among patients without active cancer (Table 4.3). The multivariable adjusted Cox regression model indicated that age was neither an independent predictor for VTE recurrence within 3 months nor within 3 years after the index VTE event. In addition, the plots of the coefficients of the age categories generated by adding age category as a covariate into the best fitting models provided convincing evidence that, after taking into account the contributions of the other predictors in the best fitting model, age made no apparent contribution to predict VTE recurrence (Figure 4.3 A/B/C).

Risk Score Calculators for Predicting 3-month VTE Recurrence

A risk calculator was developed based on the seven independent predictors of VTE recurrence during the first 3 months after the index event among all patients. A total risk score (range 0-100 points) was obtained by summing the individual points for each predictor (Figure 4.4A). Based on the predicted risk, each risk predictor was classified into one or two levels (Class-A and Class-B, Figure 4.4.A). The predicted versus observed probability of VTE recurrence within 3 months, based on the total risk score category, showed good model calibration (Figure 4.4B). Figure 4.4C provided a visual illustration of the predicted probability based on the number of risk predictors and risk class.

Another risk calculator was developed based on the five independent predictors of VTE recurrence during the first 3 months after the index event among patients without active cancer. A total risk score (range 0-100 points) was

obtained by summing the individual points for each of the predictors (Figure 4.5A). Based on the predicted risk, each risk predictor was classified into one or two levels (Class-A and Class-B, Figure 4.5.A).The predicted versus observed probability of VTE recurrence within 3 months based on the total risk score category, and a visual decision tree based on the number of risk predictors and risk class, are illustrated in Figures 4.5B and 4.5C.

We used the two risk calculators to generate two different predicted risks for VTE recurrence for the same l patient without active cancer. In comparing the individual patient-level predicted risk of VTE recurrence generated by the two caculators, the r-square value was 0.83 (Figure 4.6), which indicated excellent correlation between the two calculators.

4.5 Discussion

We assessed the cumulative risk of VTE recurrence over a 3-year follow-up period among residents of central MA diagnosed with a first-time episode of PE and/or lower-extremity DVT between 1999 and 2009 on a biennial basis. Despite advances in treatment, the 3-year CIR of VTE recurrence remained high in our population-based surveillance study, particularly among patients with active cancer. We systematically evaluated a large number of patient characteristics assessed during the patient's index encounter as potential risk predictors, and identified several independent predictors of VTE recurrence

during the acute (3 month) treatment phase and the long-term (3 year) follow-up window among patients diagnosed with a first confirmed episode of VTE.

Cumulative Risk of VTE Recurrence

The CIRs of VTE recurrence in our study were higher than have been observed in previous randomized clinical trials (RCTs) of VTE treatment.[84] These differences are likely related, in part, to inclusion criteria employed in the RCTs, resulting in a more narrowly defined "healthier" population. In addition, anticoagulant therapy is monitored more carefully in RCTs than in an uncontrolled community practice setting. Indeed, compared with our findings, published observational studies have reported higher rates of recurrent VTE after an acute episode of VTE: 8% at 3 months and 20% at 3 years.[31, 85]

After stratifying the patient's index event into cancer-associated, provoked, and unprovoked VTE, the CIR of VTE recurrence was highest among patients with active cancer. Consistent with our findings, a prospective analysis of more than 800 patients with VTE, in whom 181 had known cancer at the time of study entry, revealed that the 1-year cumulative incidence of recurrent VTE was three-fold higher in patients with cancer compared to those without.[92]

Historically, the recurrence rates after an acute episode of VTE among cancer patients has been higher than among patients without cancer.[48-49, 87] Our estimated 3-year CIR of recurrent VTE among individuals with a provoked VTE was similar to the 3-year CIR generated from a population-based cohort study including all non-cancer-associated first-time VTE patients identified through the

United Kingdom (UK) primary care database between 2001 and 2011.[91] In this UK study, the 3-year CIR of recurrent VTE was approximately 5% higher among patients with an unprovoked index VTE compared to those with a provoked episode.[91] However, in our study, we found no suggestion of a difference in the recurrence rate between these two groups. This may be related to the use of an administrative database in the UK study and their inability to robustly differentiate between index and recurrent events, or to document different practice patterns in managing persons with unprovoked VTE. Indeed, other studies have also reported that approximately 4% of patients with unprovoked VTE develop a recurrence within 6 months,[96-97] which is similar to our findings.

Independent Predictors of VTE Recurrence

After systematically evaluating a large number of characteristics assessed during the index encounter, it was not surprising that active cancer was strongly associated with an increased risk of VTE recurrence over both the short- and long-term follow-up. Based on relative model chi-square values (indicating the relative predictive strength of a model's risk predictors), patients with active cancer undergoing chemotherapy were at greatest risk for recurrence during our long-term follow-up. In a population-based observational study conducted among residents of Olmsted County, Minnesota, over the period 1976 to 1990, patients with cancer receiving chemotherapy had a more than four-fold increased risk of VTE recurrence within 10 years after the index event, while cancer patients not taking chemotherapy had a two-fold increased risk, compared to patients without

cancer.[31] However, during a 3-month follow-up, we observed no additional increase in the risk of VTE recurrence due to receipt of chemotherapy in patients with active cancer. We hypothesize that VTE patients with active cancer who were not undergoing chemotherapy may have received as much clinical monitoring as those undergoing chemotherapy during the acute VTE treatment phase consistent with the recommendations of contemporary guidelines. [48]

With regard to the remaining independent predictors in both the short-term and long-term prediction models, these predictors are consistent with the three underlying factors associated with the development of venous thrombi that were first proposed by Virchow in 1884: vascular endothelial damage(i.e., varicose vein stripping, superficial thrombophlebitis), stasis of blood flow, and blood hypercoagulabiltiy (i.e., hypercoagulable state).[23]

Based on relative model chi-square values, IVC filter placement was a strong independent predictor for VTE recurrence over both short and long-term follow-up. This finding is supported by data in a recent expert concensus review that IVC placement may increase the risk of early VTE recurrence by as much as 50%.[49] Patients who received an IVC filter may have been unable to receive anticoagulant treatment due to contraindications to anticoagulation.[97] Our prior publication demonstrated that patients who received an IVC filter were older and had more comorbidities.[98] These patients require special attention, as an IVC filter alone is inadequate therapy for acute VTE.[49]

The role of “transient” risk factors (associated with a reduced risk of recurrence in the long-term or increased risk of recurrence in the short-term) is widely acknowledged.[48, 87] We found that patients who had undergone recent surgery within 3 months before index event had an approximate 30% reduction in the risk for recurrence during long-term follow-up after the index event compared with those who had not undergone surgery as the risk of subsequent recurrence declines after the patient recovers from surgery, which is consistant with the previously published literature.[29 49 48, 87] In addition, we found that patients with a recent major trauma had a two-fold increased risk of VTE recurrence during the first 3 months. Most of these patients were likely still in recovery from their major trauma during the 3 months after the index event, which could prolong the period of VTE risk, particularly due to prolonged immobility.[23]

In recent publications, there are conflicting findings as to whether the type of the index event (PE vs. DVT) is a predictor of VTE recurrence, irrespective of the duration of follow-up ;[49] these include no increased risk by type of VTE event,[31, 96] or an increased risk for patients with incident PE[84, 87] or proximal DVT.[85] In our study, the index diagnosis (PE±DVT vs. DVT alone) was not an independent predictor of recurrence during long-term follow-up. However, patients diagnosed with DVT alone had an approximate 40% higher risk for developing a recurrence over the first 3-months of follow-up compared with patients diagnosed with PE±DVT based on the model built on all patients.

This finding may be explained by the higher 30-day mortality rate among

PE patients compared with patients who had DVT alone,[18] as a greater proportion died before they had the opportunity to develop a recurrence. On the other hand, patients with DVT alone may have received less treatment or less effective treatment. In a prior publication, we showed that nearly 20% of patients with DVT alone did not receive either unfractionated heparin or low-molecular-weight heparin during acute treatment compared with 12% among the PE±DVT group.[18] In addition, an index diagnosis of VTE was the only independent predictor of 3-month recurrence that dropped out after we stratified patients into those with and without active cancer. This may be due to insufficient statistical power or to unmeasured and/or competing clinical factors that overpowered the VTE diagnosis at the time of the index encounter among patients without active cancer.

Taking anticoagulant therapy at admission was idenfied as an independent predictor for increased risk of VTE recurrence within 3 months, which could be a proxy for other unmeasured risk factors, including commorbidities and genetic predisposition. Historically, increasing age has been considered to be a factor associated with higher incidence rates of VTE in the general population.[3, 5, 23, 74] However, there are conflicting findings as to whether age is an independent predictor of VTE recurrence in the published literature. While some studies indicate that advancing age is associated with an increased risk of VTE recurrence,[49, 93] some studies indicate that increasing age is associated with a decreasing risk of VTE recurrence.[99 94] Moreover, some

studies did not identify age as an independent predictor of VTE recurrence after an acute episode of VTE,[89 90, 100] similar to the findings observed in our study. These discrepancies could be related to variations in study design, the inclusion/exclusion criteria of cohort selection, incomplete documentation of the physicians examination for clinical VTE risk factors, and duration of follow-up. Further studies are needed to clarify the reasons for these observed discrepancies.[101]

Risk Score Calculators for Predicting VTE Recurrence within 3 Months after the Index Event

Realizing that time-dependent characteristics may change over the course of long-term follow-up, we developed risk score calculators based solely on our 3-month prediction models, separately for all patients with first-time VTE and for the subset of persons without active cancer. Our intent was to develop a risk assessment tool for use at the index encounter to enable clinicians to tailor individual patient management practices during acute VTE treatment. Our risk calculators included variables that are readily available to clinicians and use a simple point system to estimate the risk of VTE recurrence.

Although the results of any prediction models are only as generalizable to populations similar to the one from which they were derived, we believe that our models are robust, based on our population-based study design, the comprehensive list of patient and clinical characteristics assessed during the

index encounter, and internal validation. We hope that our calculator may serve as a tool to assist clinicians at the time of the index encounter to better determine the optimum frequency of subsequent clinical surveillance and the appropriate anticoagulant agents after initial treatment at clinical facilities. Our risk calculators differ from currently available calculators that are focused on information assessed at the end of the acute treatment phase and are only applicable to either cancer-associated or unprovoked VTE.[89-90, 94, 102]

Our sensitivity analyses indicate that our final risk calculator derived from all patients with first-time VTE has excellent correlation with a more limited risk calculator that was derived solely from patients without active cancer. Thus, our risk calculator based on all patients seems the best choice, based on its better discrimination (c-index 0.67 vs. 0.65) and the practical advantage of using a single, broad model at the bedside for all patients with an initial confirmed VTE.

Study Strengths and Limitations

This study employed population-based surveillance methods to systematically monitor the clinical epidemiology of VTE among residents of central MA. We conducted broad screening for cases of VTE using multiple databases, validated each potential case of VTE, and performed regular chart audits; nonetheless, we recognize that we may have missed some cases of asymptomatic VTE. Due to low autopsy rates in the WMSA, and the limited validity of death-certificate data,[3, 7] only clinically recognized cases of acute VTE were described and some cases of fatal PE could have been missed. Consistent

with the design and results of other observational studies, unmeasured, or inadequately measured variables may have impacted our findings, despite the inclusion of more than fifty potential prognostic factors assessed during the index encounter. Unmeasured variables that may have impacted our findings include unknown duration of anticoagulant treatment after initial treatment in clinical facility and any changes in dose or type of medication subsequent to initial treatment prescriptions. Further refinement of our prediction model may require the inclusion of additional time-dependent risk factors and perhaps biomarkers to increase precision; and of anticoagulation strategy and adherence to it at 3 months. Although we have conducted internal validation on our findings to show that our best fitting models are robust, we recognize that no study can effectively validate itself: "a true evaluation of generalizability requires evaluation on data from elsewhere".[63] Therefore, external validations of our models are needed to fully assess the model performance. Nevertheless, we believe that our current risk score discrimination allows separation of patients into broad, clinically meaningful categories and provides guidance for improving decisions on patient management from the index encounter through the patient's acute treatment.

4.6 Conclusions

This population-based study in residents of central Massachusetts has quantified the risk of developing a recurrent episode of VTE over a 3-year follow-up among patients with a first episode of VTE. We have identified independent

predictors of recurrence that will be useful in the design of future studies focused on estimating the true risks and benefits associated with VTE treatment at the individual patient-level. Our risk score calculators are designed to be used during the initial treatment phase for predicting recurrence during the entire acute treatment phase. This may help clinicians to determine the optimal frequency of subsequent clinical surveillance and the appropriate outpatient treatment of VTE.

4.7 Tables and figures

Table 4.1 Patient Characteristics Assessed during Index Encounter among All Patients Diagnosed with First-Time VTE

Characteristics	All patients (N=2989)
Demographic characteristics	
Age, y	
Mean±SD	64.3±18.0
Median (IQR)	67 (51-79)
Men, n (%)	1319 (44.1)
White, n (%)	2712 (94.2)
BMI, kg/m^2	
<25	663 (30.8)
25-30	661 (30.7)
>30	826 (38.4)
Current smoker, including quitting within 3 months	508 (17.0)
Recent[a] medical history, n (%)	
Cancer (active)	497 (16.6)
With chemotherapy	*254 (51.1)*
Without chemotherapy	*243 (48.9)*
Chronic obstructive pulmonary disease	633 (21.2)
Congestive heart failure	316 (10.6)
Diabetes mellitus	579 (19.4)
Family history of VTE	141 (4.7)
Hypercoagulable state	42 (1.4)
Hyperlipidemia	1063 (35.6)
Hypertension	1703 (57.0)
Inflammatory bowel disease (Crohn's/ulcerative colitis)	75 (2.5)
Infection	723 (24.2)
Liver disease	101 (3.4)
Major fracture	237 (7.9)
Major trauma	239 (8.0)
Mixed connective tissue disease (rheumatoid arthritis, lupus, scleroderma, Sjogren's)	152 (5.1)
Myeloproliferative disease	25 (0.8)
Myocardial infarction	135 (4.5)
Neurologic disease	246 (8.2)
Paralysis of lower extremity	131 (4.4)
Peripheral artery disease	242 (8.1)
Pulmonary hypertension	136 (4.6)
Renal disease	347 (11.6)
Stroke	123 (4.1)
Superficial thrombophlebitis	151 (5.1)

Characteristics	All patients (N=2989)
Varicose veins	262 (8.8)
Varicose vein stripping	117 (3.9)
HRT/oral contraceptives	232 (13.9)
Statin therapy	671 (22.5)
Bed rest >48 hours	1144 (38.3)
Cardiac procedure	156 (5.2)
Central venous catheter	384 (12.9)
Discharged from intensive care unit	466 (15.6)
Hospitalization due to nonsurgical illness before index event	949 (31.8)
Intubation	535 (17.9)
Surgery before index event	786 (26.3)
VTE characteristic, n (%)	
PE±DVT	1251 (41.9)
Lower extremity DVT alone	1738 (58.1)
Type of VTE event	
Cancer associated	497 (16.6)
Provoked (noncancer-associated)[b]	1291 (43.2)
Unprovoked[c]	1201 (40.2)
Community presenting[d]	2299 (76.9)
Admitted to hospital	2214 (74.1)
Antithrombotic medication at index encounter, n (%)	
Antiplatelet	838 (28.0)
Anticoagulant	121 (4.1)
Acute treatment[e]	
Intravenous/subcutaneous unfractionated heparin	1284 (43.0)
Subcutaneous low-molecular-weight heparin	1748 (58.5)
Warfarin	2040 (68.3)
Any anticoagulant therapy[f]	2601 (87.0)
Inferior vena cava filter implanted prior/during index visit	379 (12.7)
Stocking	58 (1.9)
Thrombolytic therapy administered	1151 (38.5)
Among patients admitted to hospital	**N=2214**
Length of stay, days	
Mean±SD	8.5±10.1
Median (IQR)	5 (3-9)
Hypercoagulable workup abnormal	162 (5.4)
Patient discharged with subtherapeutic INR (<2.0)	828 (37.4)
Any excessive INRs >3.0 prior to hospital discharge	429 (19.4)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; HRT, hormone replacement therapy; INR, international normalized ratio; IQR, inter-quartile range; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a] Within previous 3 months and prior to index VTE.

[b] History of surgical procedure, pregnancy, trauma, fracture, or hospitalization within 3 months prior to index visit.
[c] Absence of any of the above "provoking" factors or active malignancy (cancer-associated).
[d] Ambulatory patients presenting to all central Massachusetts hospitals with signs and symptoms consistent with VTE, or diagnosed with VTE within 24 hours of hospital presentation
[e] Acute therapy in a health-care facility (inhospital/at discharge or ambulatory setting); may include more than one anticoagulant.
[f] Intravenous/subcutaneous unfractionated heparin, subcutaneous low-molecular-weight heparin, Warfarin,other

Table 4.1s Frequency of Recurrent Events after Index Encounter

Index Event (N=2989)	Recurrent Event after Index Event		
	within **3 months** after Index Event		
	VTE (n=141)	**PE (n=32)**	DVT (n=119)
PE only (n=729)	17 (2.3%)	4 (0.6%)	15 (2.1%)
DVT only (n=1738)	93 (5.4%)	23 (1.3%)	74 (4.3%)
PE and DVT (n=522)	31 (5.9%)	5 (1.0%)	30 (5.8%)
	within **3 months** after Index Event		
	VTE (N=141)	**PE (n=32)**	DVT (n=119)
PE±DVT (n=1251)	48 (3.8%)	23 (1.3%)	74 (4.3%)
DVT alone (n=1738)	93 (5.4%)	9 (0.7%)	45 (3.6%)
	Recurrence within **3 years** after Index Event		
	VTE (n=329)	**PE (n=88)**	DVT (n=281)
PE only (n=729)	51 (7.0%)	19 (2.6%)	38 (5.2%)
DVT only (n=1738)	208 (12.0%)	55 (3.2%)	178 (10.2%)
PE and DVT (n=522)	70 (13.4%)	14 (2.7%)	65 (12.5%)
	Recurrence within **3 years** after Index Event		
	VTE (N=329)	**PE (n=88)**	DVT (n=281)
PE±DVT (n=1251)	121 (9.7%)	33 (2.6%)	103 (8.2%)
DVT alone (n=1738)	208 (12.0%)	55 (3.2%)	178 (10.2%)

Table 4.2 Patient Characteristics Associated with the Risk of Recurrence after Index VTE Event among All Patients Diagnosed with First-Time VTE (Unadjusted Cox Proportion Hazard Model)

Characteristics	Entire 3 years N=2989	First 3 months N=2989
# of recurrent VTEs	**329**	**141**
	HR (95% CI)	**HR (95% CI)**
Demographic characteristics		
Age, y (per 10-y increment)	**1.07 (1.00-1.13)**	1.03 (0.94-1.13)
Men	0.98 (0.79-1.22)	1.02 (0.73-1.43)
White	0.80 (0.53-1.22)	0.99 (0.48-2.02)
BMI, kg/m^2 (ref: <25 kg/m^2)		
25-30	0.85 (0.61-1.17)	1.01 (0.63-1.60)
>30	0.81 (0.60-1.09)	0.70 (0.43-1.13)
Current smoker, including quitting within 3 months	0.91 (0.70-1.21)	0.85 (0.53-1.35)
Recent[a] medical history		
Cancer (active) (ref: none)	**2.06 (1.58-2.69)**	**1.66 (1.14-2.44)**
With chemotherapy	**2.63 (1.90-3.62)**	**1.79 (1.08-2.99)**
Without chemotherapy	**1.53 (1.03-2.28)**	**1.92 (1.16-3.16)**
Chronic obstructive pulmonary disease	1.13 (0.86-1.48)	1.23 (0.84-1.81)
Congestive heart failure	1.01 (0.68-1.50)	1.25 (0.76-2.05)
Diabetes mellitus	**1.32 (1.01-1.71)**	1.13 (0.76-1.69)
Family history of VTE	1.26 (0.82-1.94)	1.73 (0.93-3.20)
Hypercoaguable state	**2.71 (1.44-5.08)**	**3.28 (1.45-7.44)**
Hyperlipidemia	0.98 (0.78-1.23)	1.24 (0.89-1.74)
Hypertension	1.23 (0.98-1.53)	1.12 (0.80-1.57)
Inflammatory bowel disease (Crohn's/ulcerative colitis)	1.17 (0.60-2.27)	1.77 (0.78-4.02)
Infection	1.03 (0.79-1.34)	0.92 (0.62-1.36)
Liver disease	0.72 (0.34-1.53)	0.83 (0.31-2.25)
Major fracture	0.69 (0.43-1.09)	0.88 (0.46-1.67)
Major trauma	1.31 (0.93-1.87)	**2.08 (1.31-3.31)**
Mixed connective tissue disease (rheumatoid arthritis, lupus, scleroderma, Sjogren's)	0.80 (0.46-1.40)	0.54 (0.20-1.46)
Myeloproliferative disease	**2.62 (1.17-5.87)**	1.77 (0.44-7.14)
Myocardial infarction	0.74 (0.39-1.38)	0.95 (0.42-2.15)
Neurologic disease	0.97 (0.65-1.45)	1.24 (0.71-2.15)
Paralysis of lower extremity	0.96 (0.55-1.67)	1.34 (0.65-2.72)
Peripheral artery disease	1.20 (0.81-1.78)	0.87 (0.46-1.66)
Pulmonary hypertension	1.02 (0.58-1.77)	0.77 (0.31-1.87)
Renal disease	1.26 (0.90-1.78)	1.19 (0.74-1.94)
Stroke	1.56 (0.96-2.54)	1.84 (0.97-3.51)
Superficial thrombophlebitis	**1.74 (1.18-2.56)**	1.80 (0.99-3.25)

Characteristics	Entire 3 years N=2989	First 3 months N=2989
# of recurrent VTEs	**329**	**141**
	HR (95% CI)	**HR (95% CI)**
Varicose veins	1.14 (0.80-1.63)	1.07 (0.60-1.88)
Varicose vein stripping	**1.88 (1.22-2.90)**	**2.18 (1.18-4.03)**
HRT/oral contraceptives (among women)	0.90 (0.59-1.36)	1.02 (0.54-1.93)
Statin therapy	0.97 (0.74-1.26)	1.01 (0.68-1.50)
Bed rest >48 hours	0.88 (0.71-1.13)	0.97 (0.69-1.37)
Cardiac procedure	0.67 (0.36-1.21)	0.67 (0.27-1.63)
Central venous catheter	1.21 (0.87-1.78)	1.26 (0.80-1.98)
Discharged from intensive care unit	0.96 (0.70-1.32)	1.23 (0.81-1.89)
Hospitalization due to nonsurgical illness before index event	**1.30 (1.03-1.63)**	**1.49 (1.06-2.09)**
Intubation	0.93 (0.69-1.25)	1.14 (0.76-1.73)
Surgery before index event	0.76 (0.59-0.98)	0.82 (0.55-1.22)
VTE characteristic		
PE±DVT (ref: lower extremity DVT alone)	0.86 (0.69-1.08)	0.71 (0.50-1.01)
Type of VTE event (ref: provoked [noncancer-associated])[b]		
Cancer associated	**2.03 (1.52-2.72)**	**1.60 (1.06-2.43)**
Unprovoked[c]	0.97 (0.76-1.24)	0.76 (0.51-1.11)
Community presenting[d]	0.84 (0.65-1.09)	0.90 (0.62-1.32)
Admitted to hospital	**1.37 (1.06-1.77)**	1.30 (0.87-1.95)
Antithrombotic medication at index encounter		
Antiplatelet	0.85 (0.66-1.10)	0.88 (0.60-1.29)
Anticoagulant	1.62 (0.997-2.65)	**2.26 (1.25-4.08)**
Acute treatment[e]		
Intravenous/subcutaneous unfractionated heparin	1.08 (0.87-1.34)	1.08 (0.77-1.50)
Subcutaneous low-molecular-weight heparin	0.86 (0.69-1.07)	0.65 (0.47-0.91)
Warfarin	0.82 (0.65-1.04)	0.70 (0.50-0.99)
Any anticoagulant therapy[f]	0.83 (0.60-1.15)	0.62 (0.41-0.94)
IVC filter implanted prior/during index visit	**2.04 (1.54-2.70)**	**2.73 (1.89-3.95)**
Stocking	1.26 (0.62-2.54)	1.09 (0.35-3.42)
Thrombolytic therapy administered	1.16 (0.93-1.45)	**1.46 (1.05-2.04)**
Among patients admitted to hospital		
Length of stay (per 1-day increment)	1.003 (0.99-1.02)	**1.02 (1.00-1.03)**
Hypercoagulable workup abnormal	0.95 (0.60-1.51)	1.20 (0.61-2.35)
Patient discharged with subtherapeutic INR (<2.0)	1.004 (0.80-1.26)	1.05 (0.74-1.49)
Any excessive INRs >3.0 prior to hospital discharge	0.87 (0.63-1.20)	0.93 (0.57-1.50)

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; HRT, hormone replacement therapy; INR, international normalized ratio; IVC, inferior vena cava; PE, pulmonary embolism; ref., reference group; VTE, venous thromboembolism.

[a] Within previous 3 months and prior to index VTE.

[b] History of surgical procedure, pregnancy, trauma, fracture, or hospitalization within 3 months prior to index visit.

[c] Absence of any of the above “provoking” factors or active malignancy (cancer-associated).

[d] Ambulatory patients presenting to all central Massachusetts hospitals with signs and symptoms consistent with VTE, or diagnosed with VTE within 24 hours of hospital presentation

[e] Acute therapy in a health-care facility (inhospital/at discharge or ambulatory setting); may include more than one anticoagulant

[f] Intravenous/subcutaneous unfractionated heparin, subcutaneous low-molecular-weight heparin, Warfarin,other

Table 4.3 Patient Characteristics Associated with the Risk of Recurrence within 3 months after Index VTE Event Stratified by patients with/without active cancer (Unadjusted Cox Proportion Hazard Model)

Characteristics	Patients without active cancer N=2492	Patients with active Cancer N=497
VTE Recurrent within 3-month after index	**106**	**35**
	HR (95% CI)	**HR (95% CI)**
Demographic characteristics		
Age, y (per 10-y increment)	0.99 (0.89-1.09)	1.04 (0.81-1.35)
Men	0.88 (0.60-1.30)	1.55 (0.79-3.02)
White	1.23 (0.50-3.02)	0.56 (0.17-1.84)
BMI, kg/m^2 (ref: <25 kg/m^2)		
25-30	0.96 (0.55-1.66)	1.25 (0.54-2.88)
>30	0.79 (0.46-1.36)	0.46 (0.15-1.44)
Current smoker, including quitting within 3 months	0.71 (0.41-1.25)	1.45 (0.63-3.31)
Recent[a] medical history		
Cancer (active) (ref: none)	NA	NA
With chemotherapy	NA	0.98 (0.51-1.90)
Without chemotherapy	NA	reference
Chronic obstructive pulmonary disease	1.51 (0.99-2.31)	0.55 (0.21-1.41)
Congestive heart failure	1.46 (0.86-2.47)	0.65 (0.16-2.69)
Diabetes mellitus	1.21 (0.76-1.92)	0.87 (0.38-1.98)
Family history of VTE	1.27 (0.59-2.73)	**8.18 (2.88-23.20)**
Hypercoaguable state	**3.66 (1.49-8.98)**	2.16 (0.30-15.81)
Hyperlipidemia	1.23 (0.84-1.82)	1.21 (0.62-2.36)
Hypertension	1.17 (0.80-1.73)	0.87 (0.44-1.70)
Inflammatory bowel disease (Crohn's/ulcerative colitis)	2.28 (0.999-5.19)	0
Infection	0.96 (0.61-1.50)	0.80 (0.35-1.84)
Liver disease	0.66 (0.16-2.66)	0.92 (0.22-3.85)
Major fracture	1.07 (0.56-2.06)	0
Major trauma	**2.40 (1.48-3.91)**	1.17 (0.16-8.55)
Mixed connective tissue disease (rheumatoid arthritis, lupus, scleroderma, Sjogren's)	0.69 (0.25-1.86)	0
Myeloproliferative disease	2.64 (0.65-10.69)	0
Myocardial infarction	1.19 (0.52-2.72)	0
Neurologic disease	1.48 (0.83-2.64)	0.46 (0.06-3.34)
Paralysis of lower extremity	1.69 (0.82-3.48)	0
Peripheral artery disease	0.90 (0.44-1.86)	0.81 (0.19-3.37)
Pulmonary hypertension	0.78 (0.29-2.12)	0.79 (0.11-5.74)
Renal disease	1.28 (0.74-2.21)	0.93 (0.33-2.63)
Stroke	**2.18 (1.10-4.32)**	0.82 (0.11-6.01)
Superficial thrombophlebitis	1.92 (0.999-3.67)	1.57 (0.38-6.52)

Characteristics	Patients without active cancer N=2492	Patients with active Cancer N=497
VTE Recurrent within 3-month after index	**106**	**35**
	HR (95% CI)	**HR (95% CI)**
Varicose veins	1.02 (0.53-1.96)	1.46 (0.45-4.78)
Varicose vein stripping	**2.37 (1.20-4.69)**	1.59 (0.38-6.62)
HRT/oral contraceptives	0.87 (0.41-1.82)	1.98 (0.56-7.03)
Statin therapy	0.84 (0.52-1.37)	1.46 (0.73-2.94)
Bed rest >48 hours	1.16 (0.79-1.71)	0.54 (0.25-1.19)
Cardiac procedure	0.83 (0.34-2.03)	0
Central venous catheter	1.52 (0.90-2.55)	0.62 (0.24-1.60)
Discharged from intensive care unit	1.33 (0.83-2.15)	0.95 (0.37-2.44)
Hospitalization due to nonsurgical illness before index event	**1.62 (1.10-2.39)**	0.71 (0.36-1.42)
Intubation	1.26 (0.79-2.02)	0.78 (0.32-1.87)
Surgery before index event	0.83 (0.52-1.31)	0.73 (0.34-1.55)
VTE characteristic		
PE±DVT (ref: lower extremity DVT alone)	0.68 (0.45-1.03)	0.72 (0.36-1.41)
Type of VTE event (ref: provoked [noncancer-associated])[b]		
Cancer associated	NA	NA
Unprovoked[c]	0.76 (0.49-1.16)	NA
Community presenting[d]	0.89 (0.54-1.47)	1.77 (0.73-4.26)
Admitted to hospital	1.26 (0.80-1.99)	1.32 (0.55-3.19)
Antithrombotic medication at index encounter		
Antiplatelet	0.88 (0.57-1.35)	0.99 (0.45-2.17)
Anticoagulant	**2.74 (1.43-5.25)**	1.05 (0.25-4.37)
Acute treatment[e]		
Intravenous/subcutaneous unfractionated heparin	1.10 (0.75-1.62)	0.996 (0.51-1.94)
Subcutaneous low-molecular-weight heparin	**0.65 (0.45-0.96)**	0.68 (0.35-1.33)
Warfarin	0.76 (0.51-1.13)	1.23 (0.63-2.42)
Any anticoagulant therapy[f]	**0.55 (0.34-0.89)**	0.94 (0.39-2.26)
IVC filter implanted prior/during index visit	**3.46 (2.28-5.24)**	1.11 (0.48-2.53)
Stocking	0.44 (0.06-3.12)	**5.88 (1.41-24.50)**
Thrombolytic therapy administered	**1.47 (1.01-2.16)**	1.49 (0.76-2.89)
Among patients admitted to hospital		
Length of stay (per 1-day increment)	**1.02 (1.01-1.04)**	0.99 (0.94-1.04)
Hypercoagulable workup abnormal	1.41 (0.71-2.79)	0
Patient discharged with subtherapeutic INR (<2.0)	1.11 (0.75-1.66)	0.95 (0.44-2.02)
Any excessive INRs >3.0 prior to hospital discharge	0.84 (0.47-1.49)	1.21 (0.50-2.90)

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; HRT, hormone replacement therapy; INR, international normalized ratio; IVC, inferior vena cava; PE, pulmonary embolism; ref., reference group; VTE, venous thromboembolism.

[a] Within previous 3 months and prior to index VTE.

[b] History of surgical procedure, pregnancy, trauma, fracture, or hospitalization within 3 months prior to index visit.

[c] Absence of any of the above “provoking” factors or active malignancy (cancer-associated).

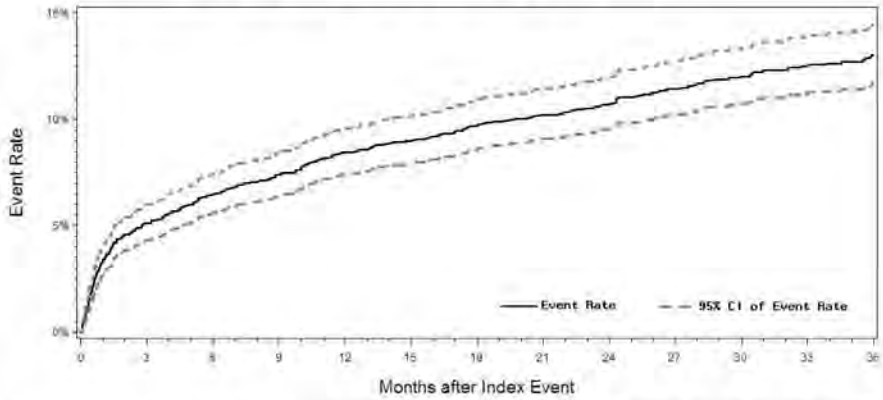
[d] Ambulatory patients presenting to all central Massachusetts hospitals with signs and symptoms consistent with VTE, or diagnosed with VTE within 24 hours of hospital presentation

[e] Acute therapy in a health-care facility (inhospital/at discharge or ambulatory setting); may include more than one anticoagulant

[f] Intravenous/subcutaneous unfractionated heparin, subcutaneous low-molecular-weight heparin, Warfarin,other

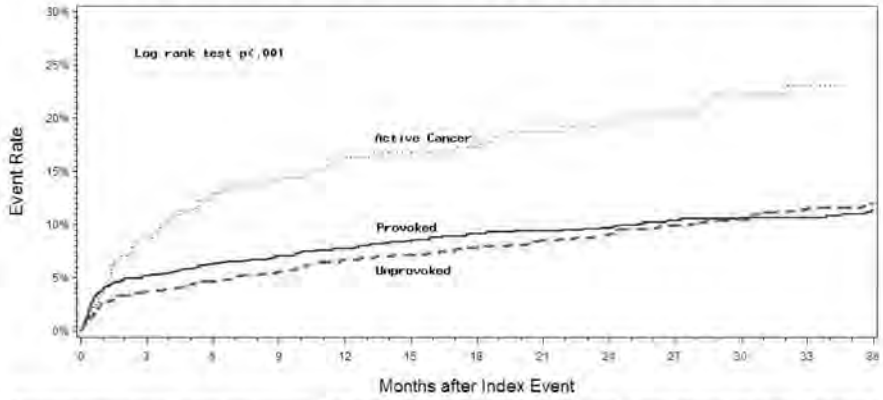
Figure 4.1 Kaplan-Meier estimates of cumulative recurrence of VTE among WMSA residents with a first-time VTE diagnosed from 1999 through 2009.
VTE: venous thromboembolism; WMSA: Worcester, Massachusetts, metropolitan statistical area.

A. VTE Recurrence among all Patients



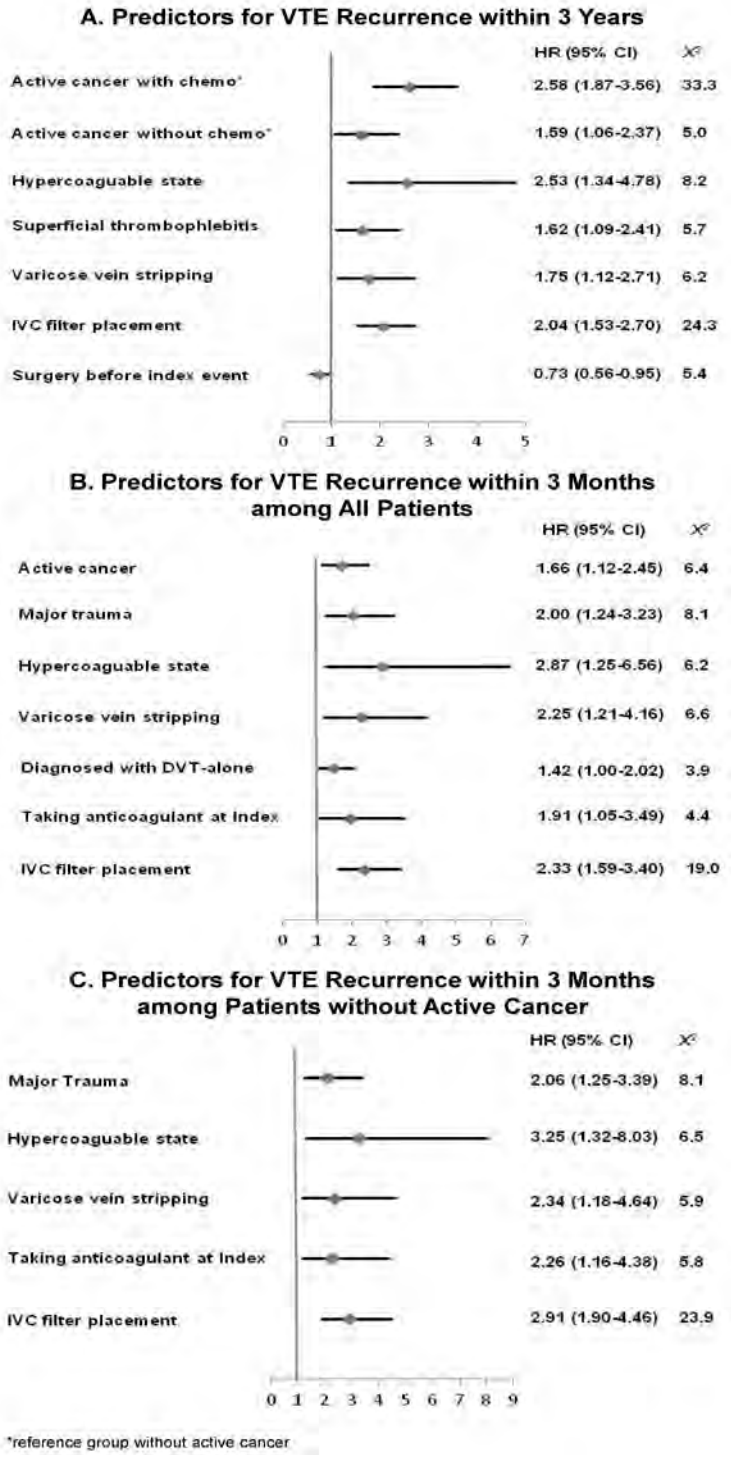
Time from Index Event to Recurrence	0 d	1m	1.5m	3m	6m	9m	1y	2y	3y
No. at risk	2989	2626	2550	2419	2277	2182	2107	1844	1077
Cumulative incidence rate, %	0	3.3	4.1	5.1	6.5	7.4	8.4	10.7	14.5

B. VTE Recurrence Stratified by Type of Index Event



Time from Index Event to Recurrence	0 d	1m	1.5m	3m	6m	9m	1y	2y	3y
Among patients with active cancer									
No. at risk	497	385	359	307	256	227	207	150	82
Cumulative incidence rate, %	0	3.9	6.2	8.7	12.9	13.9	16.3	19.7	24.8
Among patients with provoked VTE									
No. at risk	1291	1127	1093	1046	994	955	932	824	503
Cumulative incidence rate, %	0	3.9	4.5	5.2	6.2	7.1	7.8	9.7	13.0
Among patients with unprovoked VTE									
No. at risk	1201	1114	1098	1066	1025	1000	968	870	492
Cumulative incidence rate, %	0	2.6	3.0	3.8	4.7	5.6	6.7	9.1	13.1

Figure 4.2 Multivariable Cox Proportional Hazard Regression of Independent Predictors of VTE recurrence among WMSA residents with a first-time VTE diagnosed from 1999 through 2009.
VTE: venous thromboembolism; WMSA: Worcester, Massachusetts, metropolitan statistical area.



*reference group without active cancer

Figure 4.3 Plots for the coefficients of age categories generated by adding age category as a covariate in the best fitting models
VTE: venous thromboembolism

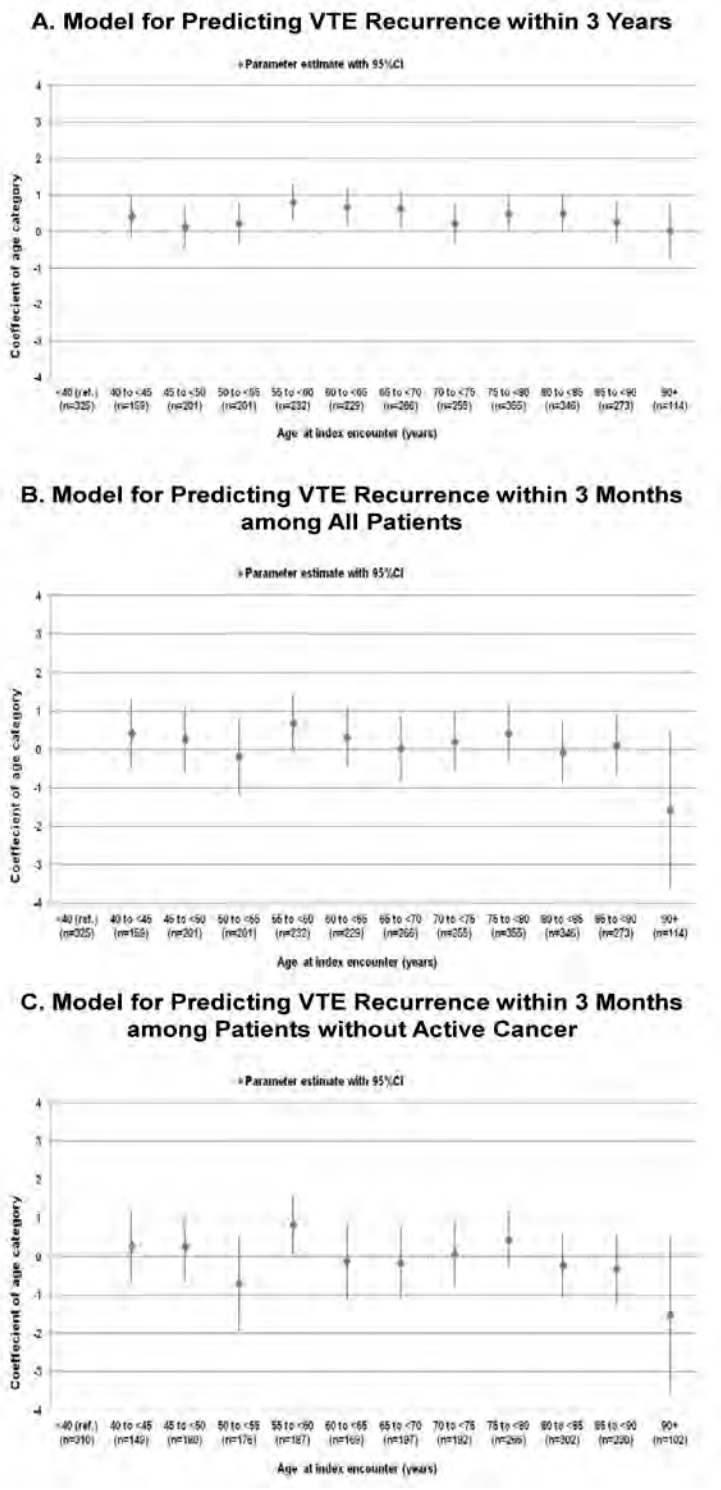


Figure 4.4 Risk Score Calculator for predicting VTE recurrence during first 3 months after index event among all patients
VTE: venous thromboembolism

A. Risk Score Calculator

Class	Predictors	Points
A	Diagnosed with DVT-alone at index visit	10
A	Active cancer (with/without chemo)	11
B	Taking anti-coagulant at admission	13
B	Major trauma	14
B	Varicose vein stripping	16
B	IVC filter implanted	16
B	Hypercoaguable state	20
Possible maximum total risk score		100

B. VTE Recurrence Rate: Observed vs. Predicted

Risk score category	Patients (N=2989) n (%)	Predicted rate	Observed rate	p-value*
0	781 (26.1%)	1.7%	2.3%	0.27
>0 to <13	1251 (41.9%)	3.8%	3.7%	0.78
13 to <37	830 (27.8%)	7.3%	6.8%	0.56
37+	127 (4.2%)	15.0%	16.1%	0.75

*May-Hosmer goodness-of-fit test

C. Decision Tree

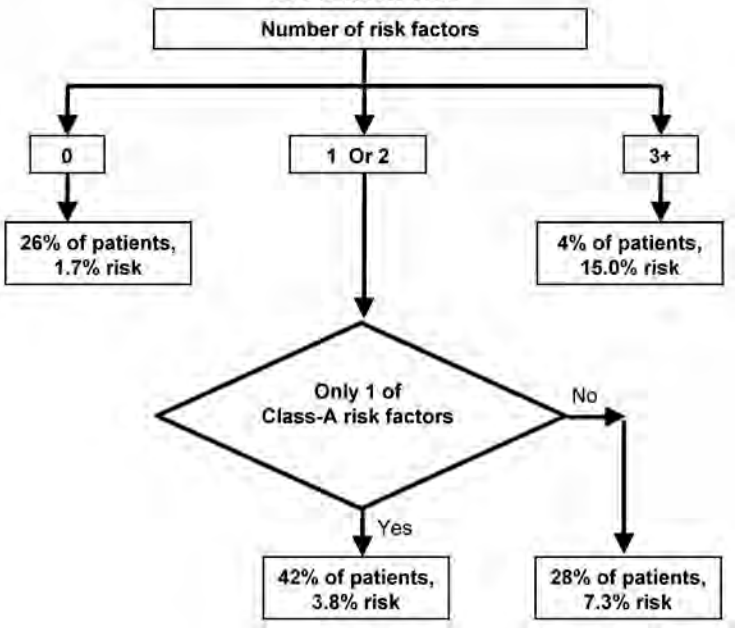
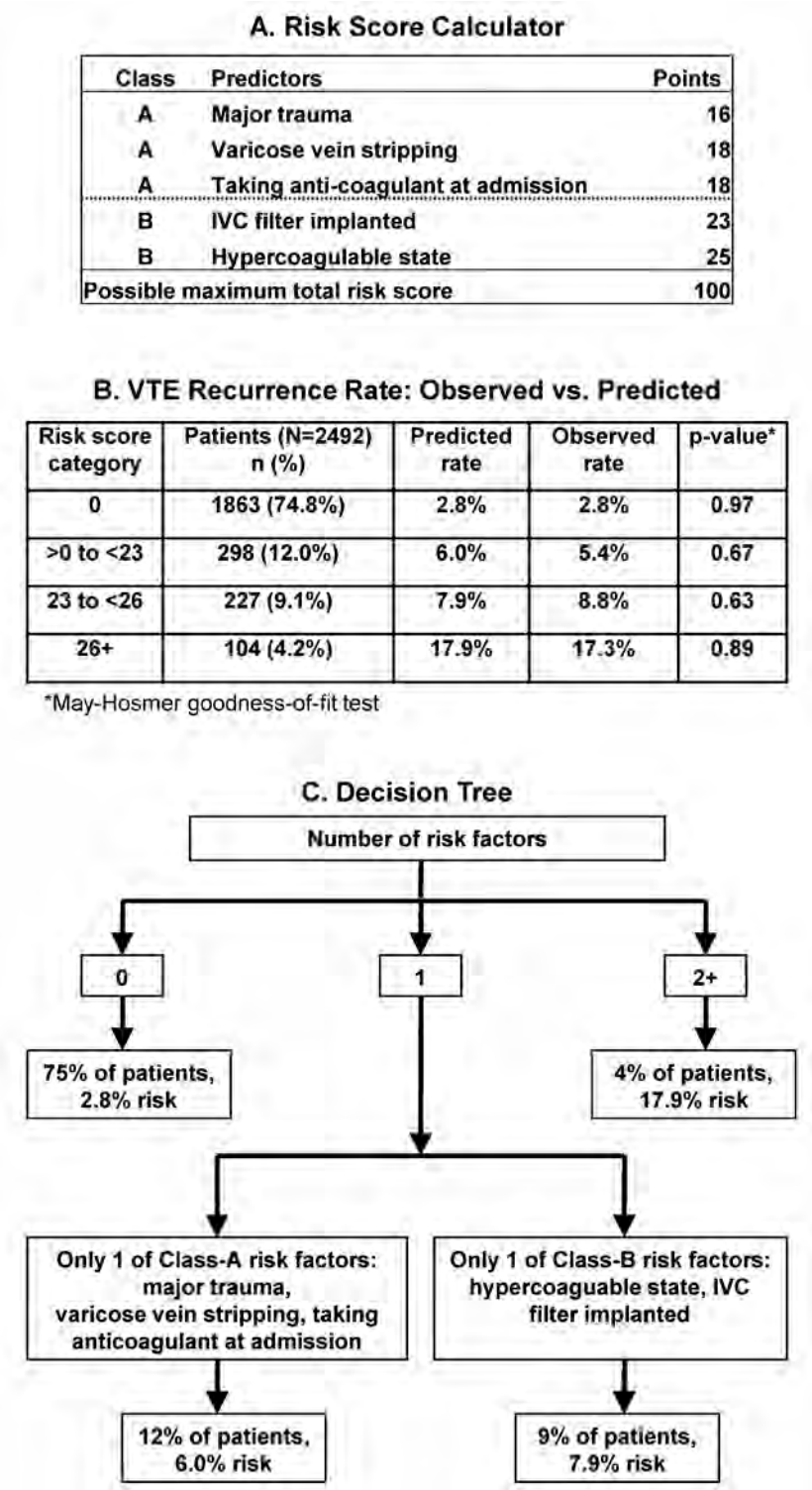


Figure 4.5 Risk Score Calculator for predicting VTE recurrence during first 3 months after index event among patients without active cancer
VTE: venous thromboembolism



A. Risk Score Calculator

Class	Predictors	Points
A	Major trauma	16
A	Varicose vein stripping	18
A	Taking anti-coagulant at admission	18
B	IVC filter implanted	23
B	Hypercoagulable state	25
Possible maximum total risk score		100

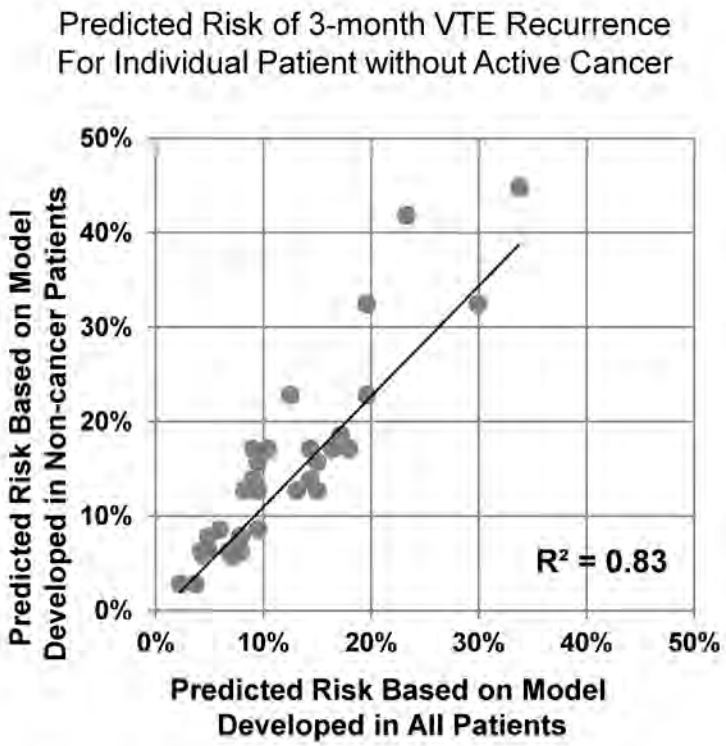
B. VTE Recurrence Rate: Observed vs. Predicted

Risk score category	Patients (N=2492) n (%)	Predicted rate	Observed rate	p-value*
0	1863 (74.8%)	2.8%	2.8%	0.97
>0 to <23	298 (12.0%)	6.0%	5.4%	0.67
23 to <26	227 (9.1%)	7.9%	8.8%	0.63
26+	104 (4.2%)	17.9%	17.3%	0.89

*May-Hosmer goodness-of-fit test

C. Decision Tree

Figure 4.6 Predicted risk of 3-month VTE recurrence for the same patients generated by two Risk Score Calculators
VTE: venous thromboembolism
Each data point represents individual patient without active cancer



Chapter V. Conclusions

5.1 Summary of findings

The primary objectives of this dissertation were to examine contemporary trends in the epidemiology of clinically recognized VTE and to assess the risk of recurrence, and factors associated with a recurrent event, after a first (incident) episode of VTE from a potentially more generalizable population-based perspective.

Among 5,025 WMSA residents diagnosed with acute PE and/or lower-extremity DVT during 9 annual periods between 1985 and 2009, 46% were men, 95% were white, and their mean age was 65 years old. The age- and sex-adjusted annual event rates for first-time VTE increased from 73 (95% CI 64–82) per 100,000 in 1985/1986 to 133 (122–143) in 2009, due chiefly to an increase in PE. The annual event rate of recurrent VTE decreased from 39 (32–45) in 1985/1986 to 19 (15–23) in 2003, and then increased to 35 (29–40) in 2009. There was an increasing trend in the use of non-invasive diagnostic testing in this population during the years under study, with about half of tests being invasive in 1985/1986 and almost all being non-invasive by 2009. The proportion of patients with community-presenting VTE remained approximately 80% over time among patients presenting with first-time VTE. Treatment of VTE shifted from in-hospital treatment with warfarin and unfractionated heparin towards out-patient treatment with low-molecular-weight heparin and newer anticoagulants.

Among the 2,334 patients who were diagnosed with first-time community-presenting VTE between 1999 and 2009, 43% had either surgery or a non-surgical-related hospitalization during the 3 months preceding the index episode of VTE. Among patients who underwent prior surgery, the proportion who received perioperative VTE prophylaxis increased from 50% in 1999 to 76% in 2009, primarily reflecting an increase in the receipt of pharmacologic prophylaxis. Among patients who had a prior non-surgical-related hospitalization, the proportion who received thromboprophylaxis did not vary over time, remaining consistently over 80%. The proportion of patients with provoked VTE decreased during the years under study concomitant with increases in the proportion of individuals with unprovoked VTE.

Among patients diagnosed with first-time community-presenting VTE between 1999 and 2009, the 3-year cumulative event rates of key outcomes after their index VTE decreased, including all-cause mortality (41%-26%), major bleeding (12%-6%), and recurrent VTE (17%-9%). Overall, however, the cumulative incidence rates of recurrence within 3-years after a first episode of acute VTE remained at 15%, which were particularly high among patients with active-cancer (25%) compared to patients with provoked (13%) or unprovoked VTE (13%). In the mulivariable Cox regression analyses, 6 factors were identified as independent predictors of VTE recurrence during the entire 3-year follow-up period (c-index 0.62) and 7 independent predictors were identified for predicting risk of VTE recurrence during the first 3-months after a first-time acute episode of

VTE (c-index 0.69). Active-cancer (with/without chemotherapy), a hypercoagulable state, varicose vein stripping, and Inferior vena cava filter placement were indepedant predictors of recurrence during short- (3-month) and long-term (3-year) follow-up after first-time VTE. Risk caculators were developed based on the 3-month prognostic model among all patients and separately in patients without active cancer. These risk scores could assist clinicians at the time of the index encounter to better determine the appropriate timing of further clinical surveillance and the appropriate duration of outpatient treatment to prevent recurrent episodes of VTE.

5.2 Study strengths and limitations

The Worcester VTE study employed rigorous population-based surveillance methods to describe the clinical epidemiology of acute VTE and prior prophylaxis use among individuals residing in the WMSA. Although we conducted broad screening for cases of VTE using multiple databases, validated each potential case of VTE, and performed regular chart audits, it is possible that this study may have missed some cases. Owing to low autopsy rates in the WMSA, and the limited validity of death-certificate data,[3, 7] only clinically recognized cases of acute VTE were described and some cases of fatal PE could have been missed. Further, regional differences may exist in the diagnostic workup of patients presenting with signs and symptoms of VTE. Since the WMSA

is predominantly a white population, additional population-based studies in minority populations are needed.

In keeping with the findings from other observational studies, unmeasured variables may have impacted our findings. For example, we did not collect information on the use of anticoagulation beyond what was recommended immediately after the index VTE; therefore, we could not assess the impact of use of various anticoagulation strategies, including the duration of therapy, on our study outcomes. Further refinement of our prognostic model may require the inclusion of additional risk factors and biomarkers to increase its precision; and of anticoagulation strategy and adherence to it at 3 months. Nevertheless, we believe that our current risk score discrimination allows separation of patients into broad categories that are clinically meaningful and may provide novel guidance that is relevant for improving decisions on patient management from the index encounter through the patient's phase of acute treatment.

5.3 Implications and future research directions

Despite advances in the identification, prophylaxis, and treatment of pateinst with VTE between 1985 and 2009, the results of this dissertation indicate that the disease burden from VTE in residents of central Massachusetts remains high, with a trend towards increasing frequency of these events. While these increases may be partially due to increased sensitivity of diagnostic methods, especially for PE, they also imply that current prevention and treatment

strategies are less than optimal. The findings of an increase in the proportion of patients with unprovoked VTE indicate the need to better understand factors affecting the development of VTE in the community setting and to identify novel risk factors for this thrombotic disorder.

Although the decreasing frequency of major adverse outcomes in our study population between 1999 and 2009 was encouraging, mortality, major bleeding, and recurrence rates remained high among WMSA residents diagnosed with first-time community-presenting VTE. In particular, the 3-year cumulative recurrent rate of VTE after a first acute episode of VTE was doubled among patients with active cancer compared to patients without active cancer; these findings suggest the need for subsequent intervention studies focused on patients with cancer, particularly those undergoing chemotherapy. The independent predictors of recurrence identified in this dissertation will be useful in the design of future studies focused on estimating the true risks and benefits associated with VTE treatment at the individual patient-level. Risk calculators are designed to be used at the time of initial treatment for predicting the likelihood of recurrence during the entire 3-month acute treatment phase and may help clinicians to determine the subsequent frequency of clinical surveillance and the appropriate outpatient treatment of VTE.

In conclusion, the Worcester VTE study provides a unique opportunity to examine secular trends in the magnitude, characteristics, diagnostic workup, treatment patterns, and long-term outcomes associated with VTE from the

perspective of a well-characterized population. This information is sorely lacking in the published literature. The findings of this dissertation set the stage for the design and systematic assessment of interventions designed to enhance the use of current management practices with the goal of favorably influencing the long-term outcomes and quality of life of patients with VTE.

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