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Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE Study

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Abstract

Background—While there have been advances in prophylaxis and management of venous thromboembolism (VTE), there are a dearth of data from the perspective of a community-wide study, on the epidemiology, management, and outcomes of patients with a first episode of deep vein thrombosis (DVT) or pulmonary embolism (PE).

Objectives—The purpose of this population-based observational study was to describe trends in the incidence rates, clinical profile, management, and outcomes for patients with VTE.

Methods—The medical records of Worcester (MA) metropolitan area residents with ICD-9 codes consistent with possible VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors.

Results—A total of 1,567 persons with first-time VTE were identified. Incidence rates (per 100,000) of VTE were stable between 1999 (109) and 2003 (117). A considerable proportion of patients treated for VTE had events of unclear clinical significance (e.g., isolated calf DVT, unconfirmed “possible” PE). By 2003, low-molecular-weight heparin was increasingly utilized as acute therapy and more than 25% of patients with VTE were managed as outpatients. Cumulative rates of recurrent VTE and major bleeding following initial VTE were high (~16% and 12%, respectively, mean follow-up 1,216 days) and did not change significantly between 1999 and 2003.

Conclusions—Our data suggest that while the incidence rates of VTE remain high, and outcomes suboptimal, there have been marked changes in its management. Whether these changes will result in future declines in VTE incidence and/or improved outcomes in the community setting will require further surveillance.

Introduction

Despite advances in the diagnosis and management of venous thromboembolism (VTE), this disease remains an important clinical problem. Indeed, the Leapfrog Group, a consortium dedicated to improved patient safety and quality of care, have cited VTE as the most common preventable cause of hospital death in the United States [1]. The American Public Health Association has stated that “Clinical trials and guidelines for prophylaxis and

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treatment have progressed further and faster than “real-world” preventive efforts and outpatient therapy. The disconnect between evidence and execution as it relates to the prevention of VTE amounts to a public health crisis [2].”

Although awareness of VTE as an important public health issue is growing, our understanding of the clinical epidemiology of this disease state remains limited. The most frequently cited estimates of the magnitude of VTE are based on data collected more than a decade ago [3–5]. Knowledge about the epidemiology of VTE is critical to the effective application of current and future diagnostic and therapeutic interventions.

The purpose of the present population-based observational study is to describe trends in the incidence rates, clinical profile, and outcomes of patients with VTE in the community setting.

METHODS

Patients

Computerized printouts of metropolitan Worcester (MA) residents with healthcare system encounters in which any of 34 ICD-9 diagnosis codes consistent with the potential occurrence of VTE during calendar years 1999, 2001, and 2003 were obtained from each of the 12 hospitals serving residents of the Worcester Standard Metropolitan Statistical Area (SMSA) [6–8]. These data queries were not limited to discharge diagnoses, but also encompassed all outpatient, emergency department, radiology, and laboratory encounters. For the first study cohort, namely, in- and out-patients diagnosed with possible VTE in 1999, the logs and/or computerized billing lists of patients evaluated in area ultrasound departments for potential DVT were also screened. This latter search was performed for purposes of identifying potential cases of VTE in greater Worcester residents 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 outside settings for treatment. Since this further screening process identified only a few additional cases of VTE, and in only 1 of 11 study hospitals, this search was not performed in the other 10 hospitals in our subsequent patient cohorts of 2001 and 2003.

Procedures

The medical records of all identified patients meeting the geographic inclusion criteria were reviewed [6–8]. Trained nurse abstractors using pre-specified criteria performed the validation of each potential case of VTE and characterization of each case of VTE as being either definite, probable, possible, or absent. These criteria were based on a modification of a well-accepted classification schema [4].

The medical records of each patient's current, as well as previous, hospitalization(s) and/or outpatient visit(s) were reviewed to identify whether the index VTE event represented an incident (initial) or a recurrent episode. Information was collected about patients' demographic characteristics, medical history, clinical characteristics, diagnostic test results, and hospital management practices through review of the medical record. Only medical history variables documented in patients' medical records by a physician were abstracted. Medical history variables defined as “recent” were those occurring or active in the 3 months prior to the diagnosis of VTE. An episode of “provoked” VTE was defined as VTE occurring within 3 months of a hospitalization, surgical procedure, pregnancy, trauma, or fracture; “unprovoked” VTE was defined as VTE occurring in the absence of malignancy or any of the above “provoked” variables.

Potential cases of recurrent VTE were classified using similar criteria as that employed for incident cases; the development of a definite or probable recurrence of VTE required the new occurrence of thrombosis in a previously uninvolved venous or pulmonary vessel by ultrasound or radiologic imaging. Cases of recurrent VTE in which demonstration of thrombosis in a previously involved segment could not be confirmed but a diagnosis of recurrent VTE was made by the physician and acute treatment was initiated were classified as possible. Bleeding was defined as any episode of bleeding requiring transfusion of packed red blood cells or that required surgery or resulted in subsequent hospitalization, cerebrovascular accident, myocardial infarction, or death.

The development of a first recurrence of VTE or a bleeding episode was determined through the review of subsequent medical records at the same hospital site as the index event as well as through the screening of medical records from the other participating hospital sites. Information about deaths from all causes was obtained through hospital record reviews and review of death certificates at the Massachusetts Division of Vital Statistics. Follow-up data were available for a maximum of 3 years.

The study coordinator and principal investigator independently audited a random sample of 5% of cases to ensure the accuracy of information collected. This study was approved by the Research Ethics boards of all participating hospitals.

Statistical Analysis

Age-adjusted (overall and sex-specific) incidence rates were calculated based on U.S. census estimates of the greater Worcester population in 2000 ($n = 477,800$; 51% female; 90% Caucasian, 7% Hispanic of any race, 3% African American, 3% Asian). Differences in the distribution of demographic and clinical characteristics as well as treatment practices in patients further stratified according to year of study enrollment were examined using chi-square tests of statistical significance for categorical variables and ANOVA for continuous variables.

Cumulative incidence rates of recurrent episodes of VTE (including DVT and/or PE) and major bleeding (censoring subjects at the time of death or date of last medical record review) and all-cause mortality overall, and according to study year, were estimated using the life-table method. Given their clinical significance, event rates for subsequent (recurrent or new) PE were also estimated. Cox proportional hazards modeling was used to examine changes over time in long-term rates of recurrent VTE, major bleeding, and mortality while controlling for potentially confounding demographic and clinical factors. Variables controlled for in the first regression model included age, sex, VTE risk factors (recent hospitalization, surgery, serious infection, central venous catheter, ICU discharge, hormonal therapy, fracture, congestive heart failure, cardiac procedures), and active cancer (treated, palliative, or metastatic). The second multivariable regression model included all of the previous variables plus VTE type (e.g. DVT vs. PE) and DVT location (upper extremity vs. lower extremity, isolated calf vein versus more proximal DVT).

The study was approved by the institutional review committee of all participating hospitals.

RESULTS

Study Sample Characteristics

After screening more than 7,500 potential cases of VTE, 1,567 Worcester residents were validated as a first time episode of possible, probable, or definite VTE. None of the remaining cases met our prespecified criteria for an acute venous thromboembolic event. The majority of these ineligible cases represented VTE occurring prior to the study year of

interest (e.g., chronic DVT), cases in which VTE was suspected but ruled out, or simple misclassification.

The mean age of the study sample at the time of VTE diagnosis was 64.6 years and 55.9% were woman. Of the 1,567 patients, 1,310 had DVT (97.3% definite, 0.2% probable, 2.6% possible) and 465 had PE (52.0% definite, 22.6% probable, 25.2% possible) (208 patients had both DVT and PE). DVT was isolated to the calf in 127 (9.7%) and to the upper extremity in 186 (14.2%) of patients with DVT.

Incidence Rates of Venous Thromboembolism

The age-adjusted incidence rates of VTE in the greater Worcester population during the period under study (adjusted to 2000 U.S. Census data) was 114 per 100,000 population (95% C.I. 108, 120). The age adjusted incidence rates of DVT and PE, respectively, were 95 per 100,000 (95% C.I. 90, 101) and 34 per 100,000 (95% C.I. 31, 37), respectively. Age and sex-specific rates of VTE, DVT, PE, definite or probable DVT or PE, upper extremity DVT, and isolated calf DVT are provided in Table 1. The incidence rates within each category increased markedly with age (>7–10 fold from age <55 years to >75 years). The incidence rates of VTE in our various age strata were consistently higher in women than in men.

The annual age-adjusted incidence rate of VTE remained essentially unchanged between 1999 (109/100,000) and 2003 (117/100,000) as did the rates of DVT (94/100,000 to 98/100,000) (see Table 2). The incidence rates of PE also remained relatively flat during the years under study (30/100,000 in 1999, 37/100,000 in 2001, and 34/100,000 in 2003). After excluding cases of VTE classified as “possible”, the annual incidence rates of DVT and PE remained relatively unchanged from 1999 to 2003. Incidence rates of VTE, DVT, and PE increased from 1999 to 2003 in younger patients (<65 years of age) but remained stable or slightly declined in patients > 65 years of age.

Clinical Profile of Patients Developing Venous Thromboembolism

Between 1999 and 2003, the mean as well as median age of subjects with incident VTE declined (from 65.5 years to 62.7 years and 71.0 years to 65.0 years, respectively). The 5 most prevalent preexisting medical characteristics for VTE, in order of occurrence, included recent hospitalization, surgical procedure, malignancy, infection, and receipt of a central venous catheter (Table 3). The proportion of patients with a recent hospitalization or malignancy declined between 1999 and 2003.

Characterization of VTE Events

Approximately 72% of patients presented from the community to area hospitals with signs and symptoms suggestive of VTE (“community acquired”) (Table 3). This proportion did not change significantly between our 3 study years. Approximately 20% of all events were classified as unprovoked, 30% were thought to be related to malignancy, and 50% were considered to be provoked by other factors such as a recent hospitalization, surgery, trauma/fracture, or pregnancy. The proportion of patients with unprovoked events of VTE increased over time (17% in 1999 to 26% in 2003) whereas the proportion of patients with malignancy related events declined from 32% to 26%. The proportion of patients with VTE treated as outpatients increased from 22% in 1999 to 29% in 2003.

Diagnostic Modalities and Acute Treatment Practices

Of the 1,310 patients diagnosed with DVT, the vast majority underwent an ultrasound, whereas venograms were rarely performed (Table 4). In patients diagnosed with PE, the use of ventilation-perfusion scans declined markedly over time whereas the use of CT scans increased dramatically. Pulmonary angiography was utilized in only 2% of patients with PE.

Between 1999 and 2003, the proportion of patients receiving unfractionated heparin decreased by more than one third whereas the proportion of patients receiving low-molecular weight heparin (LMWH) increased more than two-fold (Table 4). In approximately one quarter of patients, warfarin was not administered during their hospital encounter or was given entirely in the outpatient setting - this proportion did not change appreciably over time. An increasing proportion of patients were discharged on LMWH (alone or in combination with warfarin therapy) over time - 24.8% in 1999 to 47.5% in 2003. The placement of IVC filters as acute treatment for VTE occurred in approximately 1 in every 9 of patients with VTE during each study year.

Outcomes

Mean follow-up for the entire study cohort was 1,216 days. Long-term rates of recurrent VTE were 17.5%, 17.2% and 15.3% for the 1999, 2001, and 2003 cohorts respectively (Figure 1). After controlling for potentially confounding demographic and clinical differences between the 3 study cohorts, there was a trend towards reduced VTE recurrence in the 2003 cohort (O.R. 0.75, 95% CI 0.54, 1.04) (Table 5). Rates of major bleeding were approximately 12–13% for the 3 study cohorts and did not differ significantly by cohort year (Figure 2, Table 5). Long-term mortality decreased slightly between our initial study cohort of 1999 (43.3%) and the 2003 cohort (37.7%) but this difference was not statistically significant (Figure 3, Table 5). No significant changes in the rates of recurrent events of PE were detected over this period (Table 5).

DISCUSSION

The Worcester Venous Thromboembolism study provides a unique opportunity to describe the magnitude, management, and outcomes of VTE from a broad population-based perspective.

Incidence of Venous Thromboembolism

The age-adjusted incidence rate of VTE observed in the present study (114/100,000) is substantially higher than that reported in the landmark Worcester DVT study of 1986/87 (71/100,000) [3]. Data from an ongoing observational study of VTE in residents of Olmsted County, MN, have also described an increase in the incidence rates of this clinical syndrome over time (96/100,000 in 1986–1990 to 118/100,000 in 1991–1997) [4,5]. In the present study, the incidence rates of VTE remained stable between 1999 and 2003; this finding is not wholly unexpected given the relatively short time interval between these study years. While one must be particularly cautious in comparing incidence rates between a limited number of published studies with differing diagnostic criteria, screening methods, and population characteristics, it is clear that the burden of VTE within these New England and Midwest communities remains substantial and does not appear to be decreasing. Of note, rates of first events of VTE in our study were similar to those observed in an epidemiologic study conducted in Brest District, France between April 1998 and March 1999 (DVT 95/100,000 persons and PE 54/100,000 persons) [9].

It is likely that increasing physician awareness with respect to the diagnosis of VTE, increased utilization of improved non-invasive diagnostic imaging, and increased “screening” for VTE all played a role in the observed increase in incidence rates of VTE in these communities from the 1980s to the 1990s. Conversely, increased utilization of VTE prophylaxis in the community setting may have offset some of these factors, thereby tempering any increase in rates. It remains to be seen whether renewed interest in the prevention of VTE will result in a future decline in the incidence rates of VTE.

VTE subtypes—Unlike prior studies, we were able to provide additional data on the rates of occurrence of specific types of DVT. It must be noted that isolated upper extremity and isolated calf vein thromboses constituted 14% and 10%, respectively, of observed deep vein thromboses in our study. As such, these events represent a considerable proportion of VTE disease burden seen within a community. Excluding these events, our overall age-adjusted incidence of VTE would be closer to that reported in the initial Worcester DVT Study [3].

While it is generally accepted that patients with upper extremity DVT require treatment to prevent extension and/or recurrence of thrombosis [10], the clinical significance of isolated calf vein thromboses detected by compression ultrasound is much less clear. As the specificity of ultrasound for the detection of distal lower extremity thrombosis is significantly lower than for more proximal clot, it is likely that a meaningful proportion of these cases represent “false positives” [12]. Prior studies suggest that only 7–25% of distal lower extremity DVT will propagate more proximally and the likelihood of subsequent PE from truly isolated calf vein DVT is very low [13, 14]. Given this background, it has been suggested that ultrasound examination be limited to the more proximal veins, and if negative, treatment for DVT be withheld and a follow-up ultrasound be performed a week later to evaluate for evolution of clinically important proximal DVT [15]. However, this practice is not the standard of care in most U.S. centers. As such, approximately 10% of patients with DVT in the greater Worcester community were treated for possible thromboses of unclear significance. Given the bleeding risk observed following the development of DVT in our study, this is an important clinical issue that warrants further study.

It is also noteworthy that approximately one quarter of incident cases of PE were classified as “possible”. These data likely reflect the limitations of non-invasive imaging modalities available for the diagnosis of PE during our study years as well as reluctance by physicians to order pulmonary angiography to confirm a diagnosis of PE. The majority of these patients will be anticoagulated for 3–6 months (if not longer) without a firm diagnosis of PE. As such, there is a great need for the development and enhanced application of non-invasive imaging modalities with improved sensitivity and specificity.

Treatment practices

Not surprisingly, we detected substantial increases in the use of LWMH for the acute management of patients with VTE over a comparatively short monitoring period with a concomitant rise in the proportion of patients treated entirely as outpatients. Clinical trials have clearly documented the safety and efficacy of this approach in specific patient subsets with careful monitoring [16–18]. That said, as physicians become increasingly comfortable with the outpatient management of VTE, it will be important to ensure that there is not a “loosening” of the standards by which such patients are selected and followed.

Outcomes

Recurrent VTE—Despite the considerable advances that have been made in the diagnosis and management of VTE over the last few decades, the rates of recurrent episodes of VTE that were observed in the present study were substantial. These rates are higher than those reported in clinical trials of anticoagulant treatment in patients with VTE in whom study inclusion criteria are narrowly defined and therapy is carefully mandated and monitored [19, 20]. Disappointingly, the overall rate of recurrent episodes of VTE observed in our study do not differ significantly from those reported by Prandoni and colleagues in their landmark study of the natural history of VTE more than a decade ago [21]. We did observe a trend towards a declining risk of recurrent VTE noted between our initial and most recent study years of 1999 and 2003. It remains to be seen, however, whether increased utilization of

LMWH, introduction of other novel anticoagulants, and clearer guidelines on the duration of therapy in patients with new onset VTE will result in further declines in VTE recurrence.

Bleeding—In contrast to data obtained in the context of recent randomized clinical trials of VTE treatment in which the occurrence of major bleeding episodes approximates 1% at 3 to 6 months after trial enrollment [19,20,22], the cumulative incidence of major bleeding in our study was approximately 8% in the month following an initial diagnosis of VTE.

Unfortunately, rates of major bleeding remained relatively stable during the years under investigation. These data highlight the difficulties translating the use of anticoagulation strategies derived from clinical trials to the broader community setting in which patients are older and have a greater prevalence of comorbidities that complicates their effective management.

These data suggest that further evaluation of acute, immediate post-discharge, and long-term management practices as they are provided by community practitioners are needed to identify potential deficiencies in care.

Study Limitations

Similar to the design and conduct of any observational study, the present investigation has several limitations. Although we conducted a broad screening for cases of VTE that might have taken place at all 12 greater Worcester hospitals using multiple databases, validated each potential case of VTE, and performed regular audits of randomly selected charts, it is likely that we may have missed some cases of VTE. In addition, due to low autopsy rates in the Worcester community and the limited validity of death certificate data, we have not captured cases of PE resulting in out-of-hospital death. As such, we can only comment on the incidence rates of clinically recognized VTE. Finally, we are unable to control for variables that may confound recurrence rates and/or bleeding complications including influence of genetic risk factors, efficacy of anticoagulation monitoring and compliance with treatment, and influence of other drugs on bleeding complications (e.g. non-steroidal inflammatory agents).

CONCLUSIONS

Our findings provide insights into the incidence of VTE, changing patient profiles, utilization patterns of diagnostic and therapeutic modalities, and short and long-term patient associated outcomes. Although difficult to compare to the results of earlier observational studies, the incidence rates of clinically recognized VTE prompting treatment do not appear to be declining. However, we have identified subsets of patients with unconfirmed PE and/or DVT of unclear clinical significance - these patients comprise a large proportion of the total burden of cases of VTE that occur in a community setting. Improved diagnostic strategies are needed to minimize unnecessary treatment and its associated complications in patients without clinically important VTE. Rates of recurrent VTE and/or major bleeding following a diagnosis of initial VTE remain unacceptably high. Given the ongoing shift to the outpatient management of patients with this prevalent condition, continued monitoring of community-based management and associated VTE outcomes is warranted.

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Figure 1.
Rate of recurrent VTE after initial VTE stratified according to year of diagnosis

Figure 2.
Rate of major bleeding after initial VTE stratified according to year of diagnosis

Figure 3.
Mortality after initial VTE stratified according to year of diagnosis

Table 1

Incidence Rates* of Venous Thromboembolism

	VTE (N = 1,567)	DVT (N = 1,310)	Definite or probable DVT† (N = 1,276)	PE (N = 465)	Definite or probable PE† (N = 348)	Upper Extremity DVT (N = 186)	Isolated Calf DVT (N = 127)
Age Adjusted Rate (95% CI)	114 (108, 120)	95 (90, 101)	93 (88, 98)	34 (31, 37)	25 (23, 28)	14 (12, 16)	9 (8, 11)
Age Specific Rate (yrs)							
<55	43	37	36	11	10	7	5
55-64	207	168	162	67	52	23	15
65-74	336	268	260	112	87	45	26
≥ 75	604	518	504	175	114	47	36
Sex Specific Rates							
Males	103	87	85	30	23	12	9
Females	124	103	100	37	27	15	9

VTE = venous thromboembolism

DVT = deep vein thrombosis

PE = pulmonary embolism

* All rates are per 100,000 population

† Excluding cases of "possible" DVT or PE

Table 2
Incidence Rates* of Venous Thromboembolism by Study Year: The Worcester Venous Thromboembolism Study

	<u>VTE</u>	<u>DVT</u>	<u>Definite or Probable DVT</u> [†]	<u>PE</u>	<u>Definite or Probable PE</u> [†]
1999					
Age Adjusted Rate (95% CI)	109 (100,119)	94 (85,103)	91 (83,100)	30 (25,35)	21 (17,26)
Age Specific Rate (yrs)					
<55	39	33	32	10	8
55–64	146	130	130	35	22
65–74	369	296	278	136	97
≥ 75	625	556	541	150	97
2001					
Age Adjusted Rate (95% CI)	116 (106,126)	94 (86,104)	91 (83,101)	37 (32,43)	26 (22,31)
Age Specific Rate (yrs)					
<55	44	37	37	11	8
55–64	211	163	146	81	68
65–74	303	226	223	108	77
≥ 75	650	537	522	222	131
2003					
Age Adjusted Rate (95% CI)	117 (108,127)	98 (89,107)	96 (87,105)	34 (29,40)	29 (24,34)
Age Specific Rate (yrs)					
<55	47	40	39	14	13
55–64	263	211	209	84	68
65–74	337	282	278	94	87
≥ 75	537	459	450	153	112

VTE = venous thromboembolism

DVT = deep vein thrombosis

PE = pulmonary embolism

* All rates are per 100,000 population

[†] Excluding cases of “possible” DVT or PE

Table 3

Medical Characteristics of Patients with Venous Thromboembolism: The Worcester Venous Thromboembolism Study

Variable	Total Sample (n = 1,567)	1999 Cohort (n = 499)	2001 Cohort (n = 531)	2003 Cohort (n = 537)	P-values for linear trend 1999-2003
Demographic Characteristics					
Mean age ($\pm$ SD, yrs)	64.4 ($\pm$ 28.)	65.5 ($\pm$ 18.4)	65.1 ($\pm$ 17.5)	62.7 ($\pm$ 17.9)	0.028
Median age ($\pm$ SD, yrs)	68.0	71.0	68.0	65.0	
Female (%)	55.8	55.1	57.9	54.4	0.79
Medical Characteristics (%)					
Recent Prior Hospitalization*	41.1	41.7	43.9	37.8	0.037
Recent Surgery*	30.5	32.0	31.8	27.8	0.50
Recent Malignancy*	30.0	32.1	32.2	25.9	0.028
Recent Infection*	26.9	24.5	28.4	27.8	0.24
Recent Central Venous Catheter*	19.9	19.0	20.7	19.7	0.79
Prior IVC filter	6.2	10.8	5.5	2.6	0.033
Recent ICU Discharge*	18.1	17.6	18.6	18.1	0.86
Recent Hormonal Therapy*	6.6	7.6	7.7	4.7	0.053
Recent Fracture*	11.7	12.6	12.2	10.4	0.27
Recent Chemotherapy*	8.4	9.0	8.5	7.8	0.49
Recent Heart Failure*	8.6	6.6	10.7	8.2	0.39
Recent Cardiac Procedures*	4.6	3.6	6.2	3.9	0.85
VTE Characteristics (%)					
Setting of VTE Occurrence					
Hospital Acquired	28.5	28.9	28.4	28.1	0.79
Community Acquired	71.5	71.1	71.6	71.9	0.79
Type of VTE Event (%)					
Unprovoked [†]	19.8	17.2	16.2	25.7	<0.001
Provoked [‡]	50.2	50.7	51.6	48.4	<0.001
Malignancy related	30.0	32.1	32.2	25.9	<0.001
Isolated upper extremity DVT	11.8	12.6	9.8	13.2	0.74

Variable	Total Sample (n = 1,567)	1999 Cohort (n = 499)	2001 Cohort (n = 531)	2003 Cohort (n = 537)	P-values for linear trend 1999-2003
Isolated calf vein DVT	8.1	7.4	10.9	6.0	0.36
DVT (upper/lower) w/o PE	70.2	72.3	68.0	70.4	0.51
PE (with or without DVT)	29.8	27.7	32.0	29.6	0.51
Hospital Encounter					
Admitted to hospital (%)	75.7	77.6	78.2	71.5	0.021
If admitted, length of stay (days)	11.1 (± 15.6)	10.4 (± 14.8)	11.4 (± 16.0)	11.5 (± 15.9)	0.56
Treated only as outpatients (%)	24.3	22.4	21.9	28.5	0.021

IVC = inferior vena cava

VTE = venous thromboembolism

DVT = deep vein thrombosis

* Recent defined as < 3 months

[†] An episode of "provoked" VTE was defined as VTE occurring within 3 months of a hospitalization, surgical procedure, pregnancy, trauma, or fracture. "Unprovoked" VTE was defined as VTE occurring in the absence of malignancy or any of the above "provoked" variables.

Table 4

Diagnostic and Treatment Strategies Utilized in Patients with Venous Thromboembolism

	Total Sample (n=1,567) (n = 941)	1999 Cohort (n=499) (n = 323)	2001 Cohort (n=531) (n = 318)	2003 Cohort (n=537) (n = 300)	P values <u>linear trend</u>
Diagnostic Tests in patients with DVT (%)					
Ultrasound	93.2	94.1	91.8	93.7	0.80
Venogram	2.7	2.5	3.5	2.0	0.73
Diagnostic Tests in patients with PE (%)					
Ventilation-perfusion scan	39.2	60.8	40.5	19.5	<0.001
Pulmonary Angiogram	2.2	2.3	2.4	2.0	0.83
Spiral CT Scan	57.2	26.2	60.7	79.9	<0.001
Initial Hospital Therapy (%)					
IV heparin	52.7	64.3	53.9	40.8	<0.001
SQ LMWH	44.6	27.9	44.8	60.0	<0.001
Other parenteral anticoagulant	2.0	0.8	2.8	2.2	0.11
Warfarin	72.2	71.3	70.6	74.7	0.22
New IVC Filter	11.2	11.0	11.7	10.8	0.033
Discharge Therapy among hospital survivors (%)					
Warfarin alone	41.8	48.7	41.3	36.0	0.86
SQ LMWH alone	7.7	5.9	10.3	6.9	0.86
Both	29.5	18.9	28.2	40.6	0.86
Aspirin	12.1	8.5	14.3	13.4	<0.05

DVT = Deep vein thrombosis

PE = Pulmonary embolism

IV = intravenous

SQ = subcutaneous

LMWH = low molecular weight heparin

IVC = inferior vena cava

Table 5

Adjusted Odds of Selected Outcomes After the Diagnosis of VTE According to Study Year

	<u>% Developing Event</u>	<u>Crude Hazards Ratio</u>	<u>Multivariable Adjusted Hazards Ratio*</u>	<u>Multivariable Adjusted Hazards Ratio[†]</u>
Recurrent VTE				
1999	17.5	1.0	1.0	1.0
2001	17.2	0.97(0.71,1.32)	0.94(0.69,1.28)	0.99(0.72,1.34)
2003	15.3	0.79(0.57,1.09)	0.76(0.54,1.05)	0.75(0.54,1.04)
New or recurrent PE				
1999	3.8	1.0	1.0	1.0
2001	6.0	1.60(0.89,2.88)	1.62(0.89,2.92)	1.63(0.90,2.95)
2003	5.0	1.01(0.53,1.95)	0.98(0.50,1.90)	0.98(0.50,1.90)
Major Bleeding				
1999	12.4	1.0	1.0	1.0
2001	12.7	1.05(0.73,1.49)	1.03(0.72,1.48)	1.04(0.73,1.49)
2003	12.2	0.97(0.68,1.40)	0.98(0.68,1.42)	0.98(0.68,1.41)
Mortality				
1999	43.3	1.0	1.0	1.0
2001	42.8	1.00(0.83,1.21)	1.03(0.85,1.25)	1.04(0.86,1.26)
2003	37.7	0.83(0.69,1.01)	0.90(0.74,1.10)	0.90(0.74,1.10)

* Adjusted for age, sex, VTE risk factors (recent (< 3 months prior to VTE diagnosis) hospitalization, surgery, serious infection, central venous catheter, ICU discharge, hormonal therapy, fracture, congestive heart failure, cardiac procedures), and active cancer (treated, palliative, or metastatic).

[†] Adjusted for above variables plus VTE type (e.g. DVT vs. PE) and DVT location (upper extremity vs. lower extremity, isolated calf vein versus more proximal DVT).