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Declining Long-Term Risk of Adverse Events after First-time Community-presenting Venous Thromboembolism: The Population-based Worcester VTE Study (1999 to 2009)

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Abstract

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

Materials and 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. Patients were followed for up to 3 years after their index event. Total of 2334 WMSA residents diagnosed with first-time community-presenting VTE (occurring in an ambulatory setting or diagnosed within 24 hours of hospitalization) from 1999 through 2009.

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Disclosures

Anderson has received research grants from Sanofi and The Medicines Company. He has served as a consultant to GlaxoSmithKline and Millennium on the design of outcomes studies. Cohen is a medical consultant, and has received consultancy and clinical trial funding from many pharmaceutical companies, including Bayer, Boehringer-Ingelheim, BMS, Daiichi, GlaxoSmithKline, Johnson and Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi, Schering Plough, and Takeda. He is an advisor to the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS, on the prevention of VTE. He is also an advisor to Lifeblood: the thrombosis charity and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism. Other authors have no conflict of interest.

Results—While PE patients were consistently admitted to the hospital for treatment over time, the proportion diagnosed with DVT-alone admitted to the hospital decreased from 67% in 1999 to 37% in 2009 (p value for trend <0.001). Among hospitalized patients, the mean length of stay decreased from 5.6 to 4.8 days (p value for trend <0.001). Between 1999 and 2009, treatment of VTE shifted from warfarin and unfractionated heparin towards use of low-molecular-weight heparins and newer anticoagulants; also, 3-year cumulative event rates decreased for all-cause mortality (41–26%), major bleeding (12–6%), and recurrent VTE (17–9%).

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 needed.

Keywords

venous thromboembolism; adverse events; risk assessment

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, 2], most episodes presently occur in the community [3, 4].

A substantial proportion of patients presenting with VTE in the community have undergone surgery or hospitalization in the preceding 3 months [4–6]. Following changes in health-care services and their delivery [7, 8], hospitalized patients are increasingly being discharged earlier, at increased risk of developing VTE in the community. Thus, it is plausible that the proportion of community-presenting VTE 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 [9–13]. This change in 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 [14].

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

Materials and 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) [4–6]. Computer printouts of all WMSA residents with health-care system encounters in which any of ICD-9 diagnosis code consistent with VTE (e-Table) had been listed in 1999, 2001, 2003,

2005, 2007, and 2009 were screened from all 12 hospitals serving residents of 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 patient survival status.

Informed consent was obtained from all participants and this study was approved by the institutional review committees at participating hospitals (UMass Medical School #10387).

Patients were classified as first-time VTE or previously diagnosed (recurrent) VTE at the time of their index visit based on 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 [4]. Three categories of VTE were defined [6]: (1) cancer-associated VTE (i.e. occurring in the presence of an active malignancy); (2) provoked VTE (i.e. occurring within 3 months of surgery, pregnancy, trauma, fracture, or hospitalization, but not in the presence of active malignancy); and (3) unprovoked (idiopathic) VTE (i.e. occurring in the absence of any provoking factors and active malignancy).

Only first-time community-presenting VTE was examined in this analysis. Patients diagnosed with upper-extremity DVT-alone were excluded due to important differences in the natural history of upper- versus lower-extremity DVT [15, 16].

Recurrence 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 (recurrent PE) segment. Recurrent VTE was classified as the first occurrence of DVT or PE after the index VTE.

In study years 1999, 2001, and 2003, the definition of major bleeding was 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. In the subsequent study years, the definition was modified to be consistent with International Society of Thrombosis and Haemostasis criteria [17].

Statistical Analysis

Cochran-Armitage tests for binomial 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 all cause mortality, recurrent VTE, and major bleeding during 3-year follow-up, multivariable Cox proportional hazard regressions were constructed that controlled for age, sex, diagnosis of PE with/without (±) DVT, and medical history within 3 months before 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). 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=0.05 (2-sided).

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, 2334 (77%), ranging from a low of 74% in 1999 to a high of 80% in 2007, and 77% in 2009 (p value for trend 0.04), were community-presenting and serve as the focus of this report.

Among the 2334 patients, 43% were men, 94% were white, and their mean age was 63.4 ± 18.2 years. One third (32%) was treated only in an ambulatory setting.

Over time, the patients' mean age decreased and an increasing proportion were overweight (Table 1). The frequency of patients with previously diagnosed heart failure, myocardial infarction, stroke, trauma, major fracture, surgery, or non-surgical hospitalization declined, 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 hospital consistently over time. Among the DVT-alone group, the proportion admitted to hospital decreased from 67% in 1999 to 37% in 2009. A decreasing trend in mean length of hospitalization was also detected.

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 receipt of pharmacologic prophylaxis (Fig. 1A). Among patients who had a prior non–surgical-related hospitalization, the proportion that received thromboprophylaxis did not vary, remaining consistently over 80% (Fig. 1B).

Acute Treatment in 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 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 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 hospital or emergency department, the proportion who received LMWH +warfarin increased from 20% in 1999 to 49% in 2009 whereas the proportion receiving warfarin alone decreased from 57% to 27% (Table 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).

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). After adjustment for potentially confounding variables, the rate of major bleeding in 2009 was reduced by more than half compared with that in 1999 (Table 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, a decreasing trend was observed in frequency of recurrent VTE (Table 3).

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. 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 surgical patients.

Between 1999 and 2009, there was an increasing trend in the proportion of PE±DVT among first-time community-presenting VTE. This trend was consistent with both our prior publication [18] and in other reports [19, 20], and may be due to the increased utilization of high-sensitivity diagnostic methods [18] [21].

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 [22]. Although the proportion of cancer-associated VTE remained fairly constant in our study, there was a decrease in the proportion of patients with 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 unaware 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 also 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 [2, 23]. In addition, in 2005, a VTE quality measure was selected as a core measure in the Joint Commission's performance measurement and improvement initiative among hospitalized patients [24]. 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 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 [18]. Thus, increases in the proportion of unprovoked VTE represent a true increase in the population-based rate of diagnosis of unprovoked VTE, perhaps 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/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 [25]. However, among patients at high risk for VTE due to recent surgery/hospitalization in 2009, approximately 20% did not receive any type of VTE prophylaxis during the period of hospitalization/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 [26]. These collective findings suggest that VTE prophylaxis remains markedly underutilized despite the availability of guidelines.

Acute Treatment in Hospital and Ambulatory Settings

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 [9–13, 27]. Accordingly, we observed an increasing trend in 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 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 [27]. Presumably, recent findings and recommendations from randomized clinical trials (RCTs) and guidelines have also influenced clinical practices [28–31].

Outcomes after Index Event

During the past three decades, major advances have occurred in identifying patients at risk for VTE and in diagnostic and treatment strategies [1, 14, 23]. 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 decrease in hospital mortality rates among all hospitalized cases of PE in US acute care hospitals between 1998 and 2005 [19]. Although the 1-month mortality rate in our study decreased, it was not statistically significant, which may due to the lack of statistical power. Despite encouraging declining trends in 3-year all-cause mortality observed between 1999 and 2009, the overall 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 [32]. 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 being PE-related was only 1.4% [33].

The cumulative rates of major bleeding or recurrent VTE in our study were higher than those reported in RCTs of VTE treatment [34], despite 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 [35, 36]. 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 [37–39].

Study Strengths and Limitations

We 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. 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 have been missed. The most important indicator of bleeding (e.g. 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. In addition, the decreasing trend in major bleeding was observed even between 2005 and 2009. 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 on our study outcomes.

Conclusion

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

DVT	deep vein thrombosis
LMWH	low-molecular-weight heparin
PE	pulmonary embolism
UFH	unfractionated heparin
VTE	venous thromboembolism

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Highlights

- The rates of all-cause mortality, major bleeding and recurrent VTE are declining.
- The declining trends may be evidence of improved VTE management strategies.
- However, the frequency of those adverse events remains high in recent years.
- Increase in the frequency of unprovoked VTE supports the need for further research.

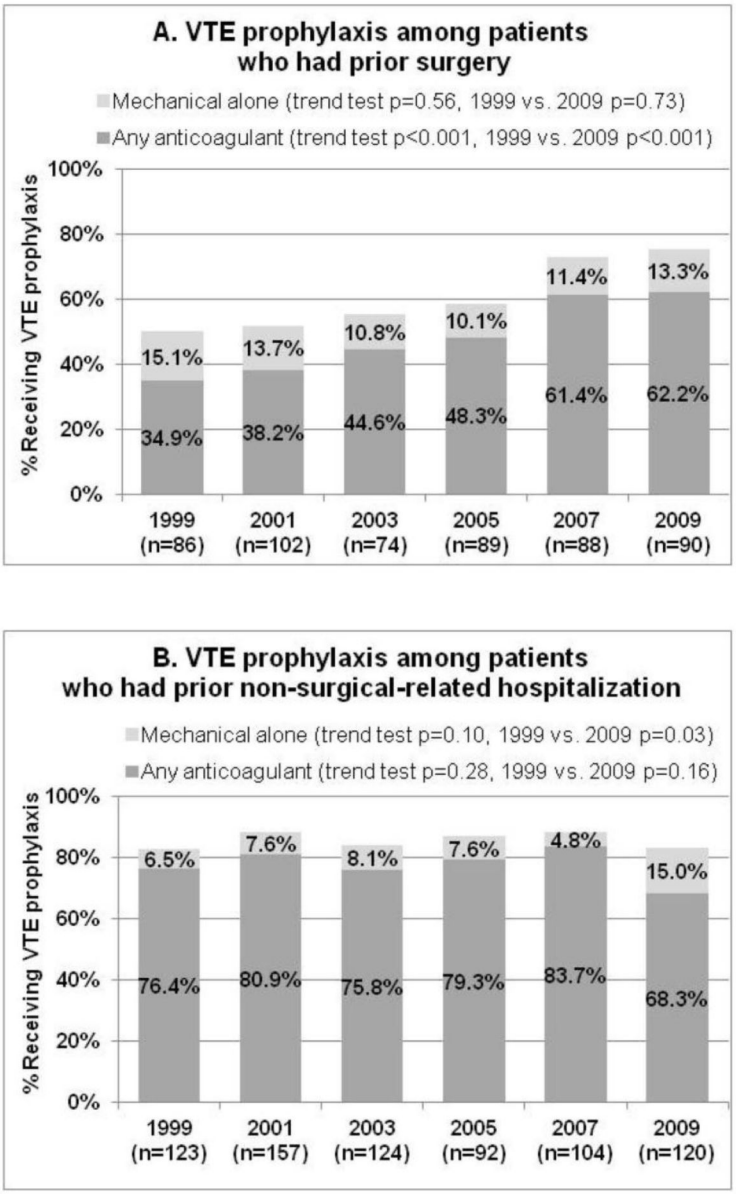

Fig. 1.
VTE prophylaxis before index event: 1999–2009.

Table 1

Characteristics of Patients with First-time Community-presenting VTE: 1999–2009.

Study Year	**1999**	**2001**	**2003**	**2005**	**2007**	**2009**	**p value for Trend**	**p value 1999 vs. 2009**
No. of VTEs	320	362	353	380	431	488		
Demographic characteristics								
Age, years							0.04	0.02
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	0.18	0.62
White	95.7	95.1	93.5	94.3	95.0	92.4	0.10	0.06
Recent[a] medical characteristics prior to index VTE								
BMI, kg/m^2								
<25	34.9	32.7	24.0	35.2	28.4	25.3	0.02	0.01
25–30	25.9	31.5	35.1	29.3	35.3	29.8	0.43	0.30
>30	39.2	35.8	40.9	35.5	36.3	44.9	0.13	0.17
Congestive heart failure	9.4	10.8	8.5	6.8	5.8	4.9	<0.001	0.01
Myocardial infarction	3.4	5.5	4.0	1.3	2.8	2.0	0.013	0.23
Stroke	4.7	4.4	5.1	1.1	1.6	1.0	<0.001	0.001
Cardiac procedure	2.8	5.0	3.1	3.9	3.9	3.9	0.75	0.41
Chronic obstructive pulmonary disease	15.3	20.7	16.4	20.8	24.1	22.7	0.003	0.01
Diabetes	15.6	21.0	17.3	15.3	21.6	16.8	0.82	0.66
Active malignancy	17.8	19.9	11.3	15.0	16.7	17.0	0.64	0.77
Chemotherapy (among active malignancy)	54.4	56.9	60.0	57.9	52.8	41.0	0.07	0.12
Trauma/fracture	16.9	23.2	13.0	8.7	7.2	7.4	<0.001	<0.001
Serious infection	14.4	22.7	22.1	19.5	16.9	14.3	0.10	0.99
Intensive care unit discharge	10.0	9.7	8.2	8.4	9.5	8.6	0.58	0.50
HRT/oral contraceptives (among women)	24.2	23.9	17.9	12.3	8.3	12.4	<0.001	<0.001
Post partum (among women)	2.2	0.9	1.6	2.2	1.3	1.5	0.85	0.72
Surgery before index event	26.9	28.2	21.0	23.4	20.4	18.4	<0.001	0.005

Study Year	1999	2001	2003	2005	2007	2009	p value for Trend	p value 1999 vs. 2009
Hospitalization due to non-surgical illness before index event	38.4	43.4	35.1	24.2	24.1	24.6	<0.001	<0.001
VTE characteristic								
Diagnosis of index event							<0.001	<0.001
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								
Cancer-associated	17.8	19.9	11.3	15.0	16.7	17.0	0.64	0.77
Provoked (non–cancer-associated)[b]	43.4	47.5	37.1	37.1	33.4	36.1	<0.001	0.04
Unprovoked[c]	38.8	32.6	51.6	47.9	49.9	46.9	<0.001	0.02
Hospital encounter								
Admitted to hospital	75.9	71.3	62.3	68.2	66.4	65.0	0.002	<0.001
Length of stay, days							<0.001	<0.001
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	0.17	0.96
Admitted to hospital among patients with lower extremity DVT alone	67.4	56.7	44.4	41.5	39.9	36.9	<0.001	<0.001

All values are %, unless otherwise specified. 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 and active malignancy.

Table 2

Initial Treatment of Patients with First-time Community-presenting VTE: 1999–2009.

Study Year	**1999**	**2001**	**2003**	**2005**	**2007**	**2009**	**p value for Trend**	**p value 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	<0.001	<0.001
SQ LMWH[b]	29.1	45.9	60.1	69.5	73.3	64.5	<0.001	<0.001
Other parenteral anticoagulant[c]	0	1.4	2.5	1.1	3.5	19.3	<0.001	<0.001
IVC filter implanted prior/during index visit	10.0	11.0	9.3	8.9	10.7	7.6	0.23	0.23
Warfarin initiated during initial treatment	76.3	69.9	67.1	55.3	52.7	56.1	<0.001	<0.001
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	0.27	0.18
SQ LMWH	26.2	38.6	48.4	56.4	61.8	63.1	<0.001	<0.001
Combination treatment								
Warfarin with LMWH	19.6	31.6	41.9	45.3	56.0	49.0	<0.001	<0.001
Warfarin with UFH	3.8	2.5	0.4	0	0	0	<0.001	<0.001
Warfarin without LMWH/UFH	56.9	45.3	39.7	31.5	26.0	27.0	<0.001	<0.001
LMWH without warfarin/UFH	6.5	7.0	6.5	11.1	5.5	14.1	0.002	0.002
UFH without warfarin/LMWH	2.3	1.1	0.7	0.3	0.6	0.8	0.08	0.17
None of the above	10.8	12.6	10.8	11.7	11.6	9.2	0.39	0.50

All values are %. 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

Mortality, First Episode of Major Bleeding, and Recurrent VTE after Index Event: 1999–2009.

Study Year	**1999**	**2001**	**2003**	**2005**	**2007**	**2009**	**p value for Trend**	**p value 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	0.67	0.29
Death within 1 year post index	25.7	24.4	20.2	21.2	18.3	19.3	0.007	0.03
Death within 3 years post index	40.9	37.8	30.9	31.6	28.8	26.4	<0.001	<0.001
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	0.63	0.26
Death within 1 year post index	24.2	26.1	22.7	21.7	23.1	26.2	0.84	0.71
Death within 3 years post index	37.5	39.5	30.3	30.8	33.7	33.9	0.40	0.53
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	0.20	0.21
Death within 1 year post index	26.3	23.5	19.0	20.6	13.9	12.9	<0.001	<0.001
Death within 3 years post index	42.4	37.0	31.2	32.3	24.2	19.6	<0.001	<0.001
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	<0.001	0.03
Within 1 year post index	9.1	11.1	9.5	9.1	4.4	4.5	<0.001	0.01
Major bleeding within 3 years post index	11.9	12.2	11.3	12.1	5.8	5.7	<0.001	0.002
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	0.006	0.004
Within 1 year post index	11.4	8.4	8.9	5.6	5.6	5.3	<0.001	0.002
Within 3 years post index	16.9	12.7	11.3	11.3	8.6	8.6	<0.001	<0.001

Study Year	1999	2001	2003	2005	2007	2009	p value for Trend	p value 1999 vs. 2009
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	0.30	0.64
Within 1 year post index	1.6	3.2	2.9	1.6	2.1	0.8	0.09	0.32
Within 3 years post index	3.1	5.0	4.0	3.2	3.7	1.6	0.07	0.16
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								
Within 1 month post index	4.6	1.2	4.0	2.1	1.9	1.4	0.02	0.007
Within 1 year post index	10.4	6.0	7.5	5.0	4.6	4.7	0.001	0.002
Within 3 years post index	15.3	9.4	9.6	10.0	6.5	7.2	<0.001	<0.001
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)		

All values are %, unless otherwise specified. 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).