



## Regular Article

# 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.

**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.

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## 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].

**Abbreviations:** DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RBC, red blood cell; RCT, randomized controlled trial; UFH, unfractionated heparin; VTE, venous thromboembolism; WMSA, Worcester, Massachusetts, metropolitan statistical area.

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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 or 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  $\geq 2$  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 ( $\pm$ ) 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  $\alpha = 0.05$  (2-sided).

## Results

Over the 10-year study period, 3039 WMSA residents were diagnosed with a first episode of acute PE  $\pm$  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  $63.4 \pm 18.2$  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  $\pm$  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  $\pm$  DVT group; and 4.4%, 19%, and 31% among the DVT-alone group. There was a decreasing

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