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Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: population-based Worcester Venous Thromboembolism Study

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Abstract Venous thromboembolism (VTE) 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 after an acute episode; it is particularly high during the acute treatment phase. We sought to quantify the magnitude, identify predictors, and develop risk score calculator of recurrence within 3 years after first-time VTE. This was a population-based surveillance study among residents of central Massachusetts (MA), USA, diagnosed with an acute first-time pulmonary embolism and/or lower-extremity deep vein thrombosis from 1999 to 2009 in hospital and ambulatory settings in all 12 central MA hospitals. Medical records were reviewed and validated. The 2989 study patients were followed for 5836 person-years [mean follow-up 23.4 (median 30) months]. Mean age was 64.3 years, 44 % were men, and 94 % were white. The cumulative incidence rate of recurrent VTE within 3 years after an index VTE was 15 % overall, and 25, 13, and 13 % among patients with active cancer, provoked, or unprovoked VTE, respectively. Multivariable regression indicated that active cancer, varicose vein stripping, and inferior vena cava filter placement were independent predictors of recurrence during both 3-month and 3-year follow-up. A risk score calculator was developed based on the 3-month prognostic model. In conclusion, the rate of VTE recurrence over 3 years of follow-up remained high. The risk score calculator 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.

Keywords Venous thrombosis · Pulmonary embolism · Recurrence · Predictors · Risk assessment · Epidemiology

Introduction

Venous thromboembolism (VTE)—comprising deep vein thrombosis (DVT) and pulmonary embolism (PE)—is associated with increased long-term morbidity, functional disability, and mortality [1]. Despite advances in identification, prophylaxis, and treatment, the annual event rate of VTE has increased over time [2–5].

VTE is a disease with multiple contributory risk factors, which tends to recur [1, 6], especially during the 3 years after an acute episode [7–9]. Limited data from observational studies have suggested that the cumulative recurrence rate after an acute event is approximately 8 % at 90 days, 11–13 % at 1 year, and 20 % at 3 years [10, 11]. In current practice, anticoagulation is recommended for at least 3 months for nearly all patients [6]. However, despite the proven benefits of anticoagulation, a systematic review has indicated that the case-fatality rate of recurrent VTE is >10 % within 3 months of acute treatment [12]. Therefore, understanding who is at risk for a recurrence during the acute treatment phase may help

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clinicians determine the optimal frequency of subsequent clinical surveillance and the appropriate type of outpatient treatment. Furthermore, the decision to continue anticoagulation beyond 3 months continues to be individually tailored [6], yet risk-assessment tools for predicting the long-term risk of VTE recurrence at the individual patient-level remain limited [13]. Inasmuch, identifying short-term and long-term risk factors associated with recurrent events after an acute VTE episode may lead to improved strategies for secondary prevention. A limited number of studies have attempted to quantify the risk of, and factors associated with, VTE recurrence. These studies either focused on a subset of VTE patients or used data from randomized trials, administrative databases, or outdated observational cohorts that may limit their value [10, 11, 14–19].

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 calculator uses characteristics assessed during the index encounter to predict VTE recurrence during the initial 3-month acute treatment period.

Materials and 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) [5, 20–22]. Computer printouts of all WMSA residents with health-care system encounters in which any International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes consistent with VTE [5] had been listed during 1999–2009 on a biennial basis from all 12 hospitals serving residents of the WMSA were used to screen 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 reviewed retrospectively by trained abstractors and validated by clinicians; follow-up was up to 3 years for all independently validated events. National and statewide death registries were reviewed to ascertain survival status of all patients.

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

Definition of index episode of VTE

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 [20]: (1) cancer-associated VTE (occurring in the presence of active malignancy); (2) provoked 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 (occurring in the absence of provoking factors and active malignancy). Whether to classify hormone replacement therapy (HRT) or oral contraceptives (OC) as a provoking factor for VTE is a controversial topic [23–26]. Therefore, we performed a sensitivity analysis by reclassifying HRT/OC as a provoking factor.

In this analysis, only patients with a first-time (incident) episode of VTE were included. Patients diagnosed with upper-extremity DVT alone were excluded due to differences in the natural history of upper- and lower-extremity DVT [27, 28].

Recurrence after index 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 lower/upper extremity venous (recurrent DVT) or pulmonary (recurrent PE) segment.

Potential prognostic factors

Potential prognostic factors included patient demographics at baseline, medical history within 3 months before the index event, index VTE characteristics [PE with or without (±) DVT vs. DVT alone; community presenting vs. hospital-acquired VTE], antithrombotic medication at presentation, type of acute therapy received in a healthcare facility, and treatment setting (in-hospital, at discharge, ambulatory). For patients admitted to hospital, length of stay and international normalized ratio assessed during hospitalization were assessed.

Statistical analysis

The cumulative incidence rate (CIR) of VTE recurrence within 3 years of the 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, as prior

publications suggest that the recurrence rates differ among these groups [6, 13]. 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.

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. 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 (no violations found). Non-linearity of age at the index encounter was assessed by a fractional polynomial technique (no non-linearity found) [29, 30].

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) [31]. We also assessed two-way interactions and co-linearity among the final predictors (none found). Model discrimination was assessed using the Harrell macro for Cox regression (the c-index) [32], while goodness-of-fit (calibration) was assessed by the May–Hosmer method [33]. In addition, 100 replications of bootstrapping using the unrestricted random sampling technique were used to validate the best fitting model internally.

To help clinicians improve management of their patients during the acute treatment phase, a final prognostic model for 3-month VTE recurrence among all patients was used to develop the 3-month risk score calculator based on previous methods [34–38]. A patient risk score was developed as follows: the factor with the smallest logarithmic HR (natural log of HR) was assigned 1 point, with other factors assigned points based on the proportional size of their estimates relative to the smallest logarithmic HR. Individual factor points were summed to provide a total risk score (on a 0–100 scale) for each patient. Calibration was further assessed by comparing predicted to observed risk (using the Kaplan–Meier method) over selected risk score groups, as well as May–Hosmer test.

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).

Results

Over the 10-year study, 2989 WMSA residents were diagnosed with a first episode of acute PE ± DVT (42 %) or lower-extremity DVT alone (58 %). These patients were followed for 5836 person-years [mean ± standard deviation (SD) follow-up 23.4 ± 14.4 (median 30) months]. Mean ± SD age was 64.3 ± 18.0 years, 44 % were men, and 94 % were white (Table 1). The proportions of cancer-associated, provoked, and unprovoked episodes of VTE were 17, 43, and 40 %, respectively.

During follow-up, 329 patients developed a recurrence [85 (26 %) PE and 244 (74 %) DVT]. Among 244 recurrent DVT cases, 161 (66 %) were proximal DVT, 11 (4.5 %) were isolated calf DVT, 17 (7.0 %) were upper-extremity DVT alone, and in 55 (23 %) the location of DVT was undocumented. The CIRs of VTE recurrence were 5.1 % within 3 months and 15 % within 3 years after the index event among all patients (Fig. 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 (Fig. 1b). After we had re-classified 117 patients with HRT/OC (but without other provoking factors or active cancer) from the unprovoked to the provoked group, the proportion of provoked VTE increased to 1408 (47 %) and the proportion of unprovoked VTE decreased to 1084 (36 %). However, the CIRs of recurrent VTE within 3 months or 3 years after an index event were essentially unchanged (Fig. 1c). Furthermore, we stratified the type of index event into PE ± DVT [1251 (42 %)], proximal DVT alone [1525 (51 %)], and isolated calf DVT [213 (7.1 %)]. The CIRs of VTE recurrence within 3 years among the three groups were 13.5, 15.8, and 11.9 %, respectively, but the differences were not statistically significant (log-rank test $p = 0.24$).

Predicting recurrence within 3 years: all patients

Factors associated with a risk of recurrence during 3-year follow-up are shown in Table 2. Five independent predictors of recurrence were identified (c-index 0.62) (Fig. 2a): active cancer (with or without chemotherapy), superficial thrombophlebitis, varicose vein stripping, inferior vena cava (IVC) filter placement; while previous surgery predicted a lower risk of recurrence.

Table 1 Characteristics assessed during index encounter among all patients with first-time VTE

Characteristic	All patients ($n = 2989$)
Age (years)	
Mean ± SD	64.3 ± 18.0
Median (IQR)	67 (51–79)
Men	1319 (44.1)
White	2712 (94.2)
Body mass index (kg/m^2)	
<25	663 (30.8)
25–30	661 (30.7)
>30	826 (38.4)
Current smoker, including quitting within previous 3 months	508 (17.0)
Recent[a] medical history	
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)
Hyperlipidemia	1063 (35.6)
Hypertension	1703 (57.0)
Inflammatory bowel disease (Crohn's disease/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)
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 h	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 non-surgical illness before index event	949 (31.8)
Intubation	535 (17.9)
Surgery before index event	786 (26.3)
VTE characteristic	
PE ± DVT	1251 (41.9)
Lower-extremity DVT alone	1738 (58.1)
Type of VTE event	
Cancer associated	497 (16.6)
Provoked (non-cancer-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	
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)
Patient discharged with subtherapeutic INR (<2.0)	828 (37.4)
Any excessive INRs >3.0 prior to hospital discharge	429 (19.4)

Values are *n* (%) unless otherwise stated

DVT deep vein thrombosis, *HRT* hormone replacement therapy, *INR* international normalized ratio, *IQR* interquartile range, *PE* pulmonary embolism, *SD* standard deviation, *VTE* venous thromboembolism

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

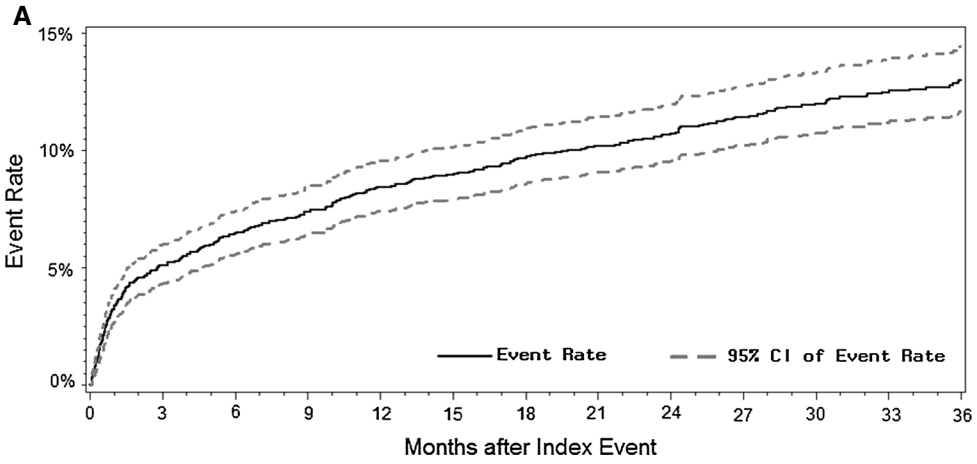
[b] History of surgical procedure, pregnancy, trauma, fracture, or hospitalization within 3 months prior to index visit

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

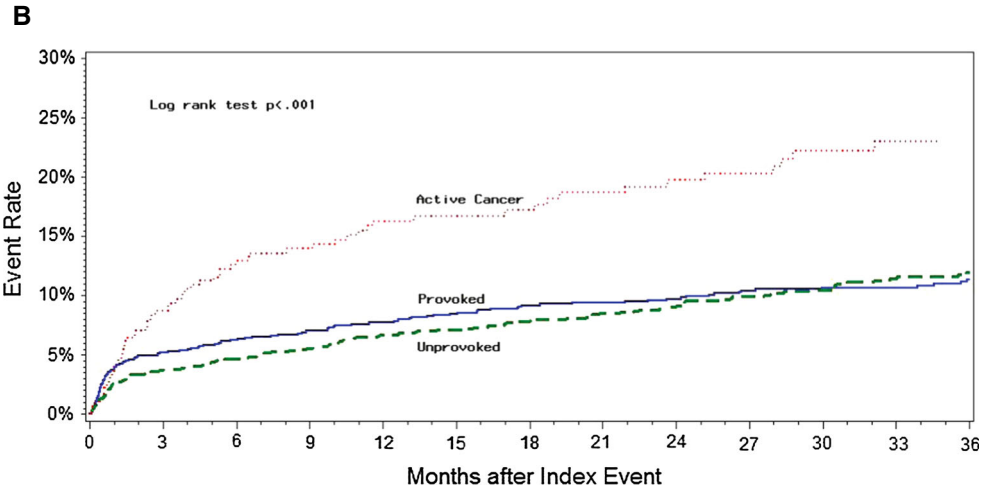
[d] Ambulatory patients presenting to all central Massachusetts hospitals with signs and symptoms consistent with VTE, or diagnosed with VTE within 24 h of hospital presentation

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

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



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



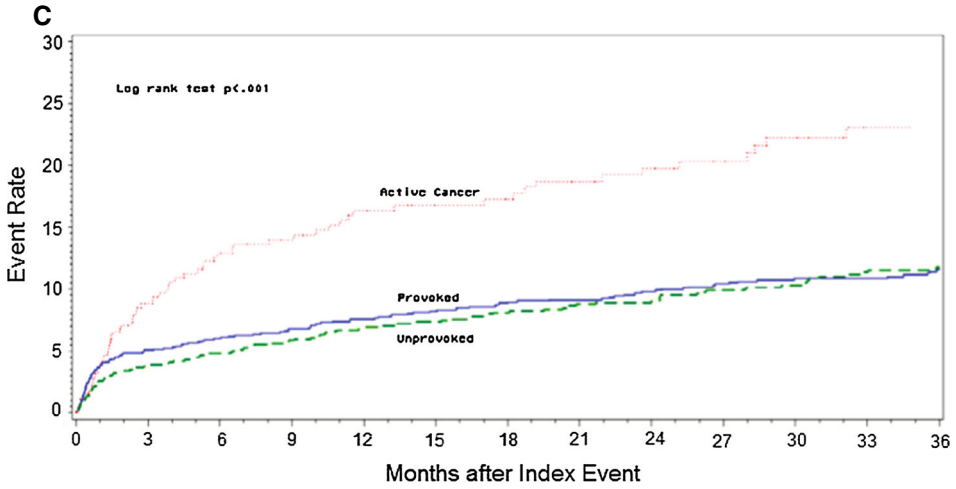
Time from Index Event to Recurrence	0 d	1m	1.5m	3m	6m	9m	1y	2y	3y
Among patients with active cancer									
No. at risk	497	385	359	307	256	227	207	150	82
Cumulative incidence rate, %	0	3.9	6.2	8.7	12.9	13.9	16.3	19.7	24.8
Among patients with provoked VTE									
No. at risk	1291	1127	1093	1046	995	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	1026	1000	968	870	492
Cumulative incidence rate, %	0	2.6	3.0	3.8	4.7	5.6	6.7	9.1	13.1

Fig. 1 Kaplan–Meier estimates of cumulative recurrence of VTE among WMSA residents with **a** first-time VTE diagnosed from 1999 through 2009 in a all patients, **b** stratified by type of index event, and **c** stratified by type of index event (HRT/OC as a provoking factor). *CI* confidence interval, *d* day, *HRT* hormone replacement therapy, *m* month, *OC* oral contraceptives, *VTE* venous thromboembolism, *WMSA* Worcester Metropolitan Statistical Area, *y* year

Predicting recurrence within 3 months: all patients

Factors associated with recurrence within 3 months are shown in Table 2. Five independent predictors of recurrence were identified (c-index 0.64) (Fig. 2b): active cancer, previous major trauma, varicose vein stripping, anticoagulant therapy at admission, and IVC filter placement. Separating the independent predictor "active cancer" into with or without chemotherapy categories did not improve the model performance; the HRs of active cancer with and without chemotherapy were 1.70 (95 % CI 1.01–2.85) and 1.58 (95 % CI 0.96–2.63) versus no-cancer,

Fig. 1 continued



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	1408	1239	1204	1158	1100	1063	1035	918	574
Cumulative incidence rate, %	0	3.8	4.3	5.0	6.0	6.7	7.5	9.8	13.1
Among patients with unprovoked VTE									
No. at risk	1084	1002	985	954	921	892	865	776	421
Cumulative incidence rate, %	0	2.6	3.1	3.9	4.8	5.8	6.9	9.0	13.2

respectively. Thus, "active cancer (with/without chemotherapy)" was used as a covariate in the final predictive model (HR 1.63, 95 % CI 1.11–2.41).

Predicting recurrence within 3 months: patients without active cancer

Among 2492 patients without active cancer (106 recurrent VTE episodes at 3 months), risk factors associated with 3-month recurrence were similar to those for all patients, with the exceptions that stroke was associated with an increased risk of recurrence and warfarin treatment was no longer associated with a decreased short-term risk (Table 2). Four independent predictors of recurrence were identified (c-index 0.64) (Fig. 2c): previous major trauma, varicose vein stripping, anticoagulants at admission, and IVC filter placement.

Predicting recurrence within 3 months: patients with active cancer

Among 497 patients with active cancer (35 recurrent episodes of VTE at 3 months), family history of VTE and compression stockings were associated with an increased 3-month risk of VTE recurrence (Table 2). However, only the single factor of family history of VTE remained an independent predictor of recurrence in multivariable regression.

Risk score calculator for predicting 3-month VTE recurrence

A risk score calculator was developed based on the five independent predictors of VTE recurrence during the first 3 months after the index event among all patients (Fig. 3).

Discussion

We assessed the cumulative risk of VTE recurrence over 3 years among residents of central MA diagnosed with a first-time 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.

Table 2 Characteristics associated with risk of recurrence after index VTE event among all patients with first-time VTE, and within 3 months after index VTE event stratified by active cancer (unadjusted Cox proportional hazards model)

Characteristic	All patients		Stratified by active cancer	
	Entire 3 years ($n = 2989$)	First 3 months ($n = 2989$)	Patients without active cancer ($n = 2492$)	Patients with active cancer ($n = 497$)
Number of recurrent VTEs	329	141	106	35
Demographic characteristics				
Age (per 10-year increment)	**1.07 (1.00–1.13)**	1.03 (0.94–1.13)	0.99 (0.89–1.09)	1.04 (0.81–1.35)
Men	0.98 (0.79–1.22)	1.02 (0.73–1.43)	0.88 (0.60–1.30)	1.55 (0.79–3.02)
White	0.80 (0.53–1.22)	0.99 (0.48–2.02)	1.23 (0.50–3.02)	0.56 (0.17–1.84)
Body mass index (kg/m^2) (ref: <25 kg/m^2)				
25–30	0.85 (0.61–1.17)	1.01 (0.63–1.60)	0.96 (0.55–1.66)	1.25 (0.54–2.88)
>30	0.81 (0.60–1.09)	0.70 (0.43–1.13)	0.79 (0.46–1.36)	0.46 (0.15–1.44)
Current smoker, including quitting within previous 3 months	0.91 (0.70–1.21)	0.85 (0.53–1.35)	0.71 (0.41–1.25)	1.45 (0.63–3.31)
Recent[a] medical history				
Cancer (active) (ref: none)	**2.06 (1.58–2.69)**	**1.66 (1.14–2.44)**	NA	NA
With chemotherapy	**2.63 (1.90–3.62)**	**1.79 (1.08–2.99)**	NA	0.98 (0.51–1.90)
Without chemotherapy	**1.53 (1.03–2.28)**	**1.92 (1.16–3.16)**	NA	Reference
Chronic obstructive pulmonary disease	1.13 (0.86–1.48)	1.23 (0.84–1.81)	1.51 (0.99–2.31)	0.55 (0.21–1.41)
Congestive heart failure	1.01 (0.68–1.50)	1.25 (0.76–2.05)	1.46 (0.86–2.47)	0.65 (0.16–2.69)
Diabetes mellitus	**1.32 (1.01–1.71)**	1.13 (0.76–1.69)	1.21 (0.76–1.92)	0.87 (0.38–1.98)
Family history of VTE	1.26 (0.82–1.94)	1.73 (0.93–3.20)	1.27 (0.59–2.73)	**8.18 (2.88–23.20)**
Hyperlipidemia	0.98 (0.78–1.23)	1.24 (0.89–1.74)	1.23 (0.84–1.82)	1.21 (0.62–2.36)
Hypertension	1.23 (0.98–1.53)	1.12 (0.80–1.57)	1.17 (0.80–1.73)	0.87 (0.44–1.70)
Inflammatory bowel disease (Crohn's disease/ulcerative colitis)	1.17 (0.60–2.27)	1.77 (0.78–4.02)	2.28 (0.999–5.19)	0
Infection	1.03 (0.79–1.34)	0.92 (0.62–1.36)	0.96 (0.61–1.50)	0.80 (0.35–1.84)
Liver disease	0.72 (0.34–1.53)	0.83 (0.31–2.25)	0.66 (0.16–2.66)	0.92 (0.22–3.85)
Major fracture	0.69 (0.43–1.09)	0.88 (0.46–1.67)	1.07 (0.56–2.06)	0
Major trauma	1.31 (0.93–1.87)	**2.08 (1.31–3.31)**	**2.40 (1.48–3.91)**	1.17 (0.16–8.55)
Mixed connective tissue disease (rheumatoid arthritis, lupus, scleroderma, Sjogren's)	0.80 (0.46–1.40)	0.54 (0.20–1.46)	0.69 (0.25–1.86)	0
Myeloproliferative disease	**2.62 (1.17–5.87)**	1.77 (0.44–7.14)	2.64 (0.65–10.69)	0
Myocardial infarction	0.74 (0.39–1.38)	0.95 (0.42–2.15)	1.19 (0.52–2.72)	0
Neurologic disease	0.97 (0.65–1.45)	1.24 (0.71–2.15)	1.48 (0.83–2.64)	0.46 (0.06–3.34)
Paralysis of lower extremity	0.96 (0.55–1.67)	1.34 (0.65–2.72)	1.69 (0.82–3.48)	0
Peripheral artery disease	1.20 (0.81–1.78)	0.87 (0.46–1.66)	0.90 (0.44–1.86)	0.81 (0.19–3.37)
Pulmonary hypertension	1.02 (0.58–1.77)	0.77 (0.31–1.87)	0.78 (0.29–2.12)	0.79 (0.11–5.74)
Renal disease	1.26 (0.90–1.78)	1.19 (0.74–1.94)	1.28 (0.74–2.21)	0.93 (0.33–2.63)
Stroke	1.56 (0.96–2.54)	1.84 (0.97–3.51)	**2.18 (1.10–4.32)**	0.82 (0.11–6.01)
Superficial thrombophlebitis	**1.74 (1.18–2.56)**	1.80 (0.99–3.25)	1.92 (0.999–3.67)	1.57 (0.38–6.52)
Varicose veins	1.14 (0.80–1.63)	1.07 (0.60–1.88)	1.02 (0.53–1.96)	1.46 (0.45–4.78)
Varicose vein stripping	**1.88 (1.22–2.90)**	**2.18 (1.18–4.03)**	**2.37 (1.20–4.69)**	1.59 (0.38–6.62)
HRT/oral contraceptives (among women)	0.90 (0.59–1.36)	1.02 (0.54–1.93)	0.87 (0.41–1.82)	1.98 (0.56–7.03)
Statin therapy	0.97 (0.74–1.26)	1.01 (0.68–1.50)	0.84 (0.52–1.37)	1.46 (0.73–2.94)
Bed rest >48 h	0.88 (0.71–1.13)	0.97 (0.69–1.37)	1.16 (0.79–1.71)	0.54 (0.25–1.19)
Cardiac procedure	0.67 (0.36–1.21)	0.67 (0.27–1.63)	0.83 (0.34–2.03)	0
Central venous catheter	1.21 (0.87–1.78)	1.26 (0.80–1.98)	1.52 (0.90–2.55)	0.62 (0.24–1.60)
Discharged from intensive care unit	0.96 (0.70–1.32)	1.23 (0.81–1.89)	1.33 (0.83–2.15)	0.95 (0.37–2.44)

Table 2 continued

Characteristic	All patients		Stratified by active cancer	
	Entire 3 years ($n = 2989$)	First 3 months ($n = 2989$)	Patients without active cancer ($n = 2492$)	Patients with active cancer ($n = 497$)
Hospitalization due to non-surgical illness before index event	**1.30 (1.03–1.63)**	**1.49 (1.06–2.09)**	**1.62 (1.10–2.39)**	0.71 (0.36–1.42)
Intubation	0.93 (0.69–1.25)	1.14 (0.76–1.73)	1.26 (0.79–2.02)	0.78 (0.32–1.87)
Surgery before index event	**0.76 (0.59–0.98)**	0.82 (0.55–1.22)	0.83 (0.52–1.31)	0.73 (0.34–1.55)
VTE characteristic				
PE ± DVT (ref: lower-extremity DVT alone)	0.86 (0.69–1.08)	0.71 (0.50–1.01)	0.68 (0.45–1.03)	0.72 (0.36–1.41)
Type of VTE event [ref: provoked (non-cancer-associated)][b]				
Cancer associated	**2.03 (1.52–2.72)**	**1.60 (1.06–2.43)**	NA	NA
Unprovoked[c]	0.97 (0.76–1.24)	0.76 (0.51–1.11)	0.76 (0.49–1.16)	NA
Community presenting[d]	0.84 (0.65–1.09)	0.90 (0.62–1.32)	0.89 (0.54–1.47)	1.77 (0.73–4.26)
Admitted to hospital	**1.37 (1.06–1.77)**	1.30 (0.87–1.95)	1.26 (0.80–1.99)	1.32 (0.55–3.19)
Antithrombotic medication at index encounter				
Antiplatelet	0.85 (0.66–1.10)	0.88 (0.60–1.29)	0.88 (0.57–1.35)	0.99 (0.45–2.17)
Anticoagulant	1.62 (0.997–2.65)	**2.26 (1.25–4.08)**	**2.74 (1.43–5.25)**	1.05 (0.25–4.37)
Acute treatment[e]				
Intravenous/subcutaneous unfractionated heparin	1.08 (0.87–1.34)	1.08 (0.77–1.50)	1.10 (0.75–1.62)	0.996 (0.51–1.94)
Subcutaneous low-molecular-weight heparin	0.86 (0.69–1.07)	**0.65 (0.47–0.91)**	**0.65 (0.45–0.96)**	0.68 (0.35–1.33)
Warfarin	0.82 (0.65–1.04)	**0.70 (0.50–0.99)**	0.76 (0.51–1.13)	1.23 (0.63–2.42)
Any anticoagulant therapy[f]	0.83 (0.60–1.15)	**0.62 (0.41–0.94)**	**0.55 (0.34–0.89)**	0.94 (0.39–2.26)
IVC filter implanted prior/during index visit	**2.04 (1.54–2.70)**	**2.73 (1.89–3.95)**	**3.46 (2.28–5.24)**	1.11 (0.48–2.53)
Stocking	1.26 (0.62–2.54)	1.09 (0.35–3.42)	0.44 (0.06–3.12)	**5.88 (1.41–24.50)**
Thrombolytic therapy administered	1.16 (0.93–1.45)	**1.46 (1.05–2.04)**	**1.47 (1.01–2.16)**	1.49 (0.76–2.89)
Among patients admitted to hospital				
Length of stay (per 1-day increment)	1.003 (0.99–1.02)	**1.02 (1.00–1.03)**	**1.02 (1.01–1.04)**	0.99 (0.94–1.04)
Patient discharged with subtherapeutic INR (<2.0)	1.004 (0.80–1.26)	1.05 (0.74–1.49)	1.11 (0.75–1.66)	0.95 (0.44–2.02)
Any excessive INRs >3.0 prior to hospital discharge	0.87 (0.63–1.20)	0.93 (0.57–1.50)	0.84 (0.47–1.49)	1.21 (0.50–2.90)

Bold values indicate statistical significance ($p < 0.05$)

Data are HR (95 % CI)

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 h of hospital presentation

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

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

Cumulative risk of VTE recurrence

The CIRs of VTE recurrence in our study were higher than have been observed in randomized controlled trials (RCTs) [12]. These differences are likely related, in part, to the inclusion criteria employed in 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

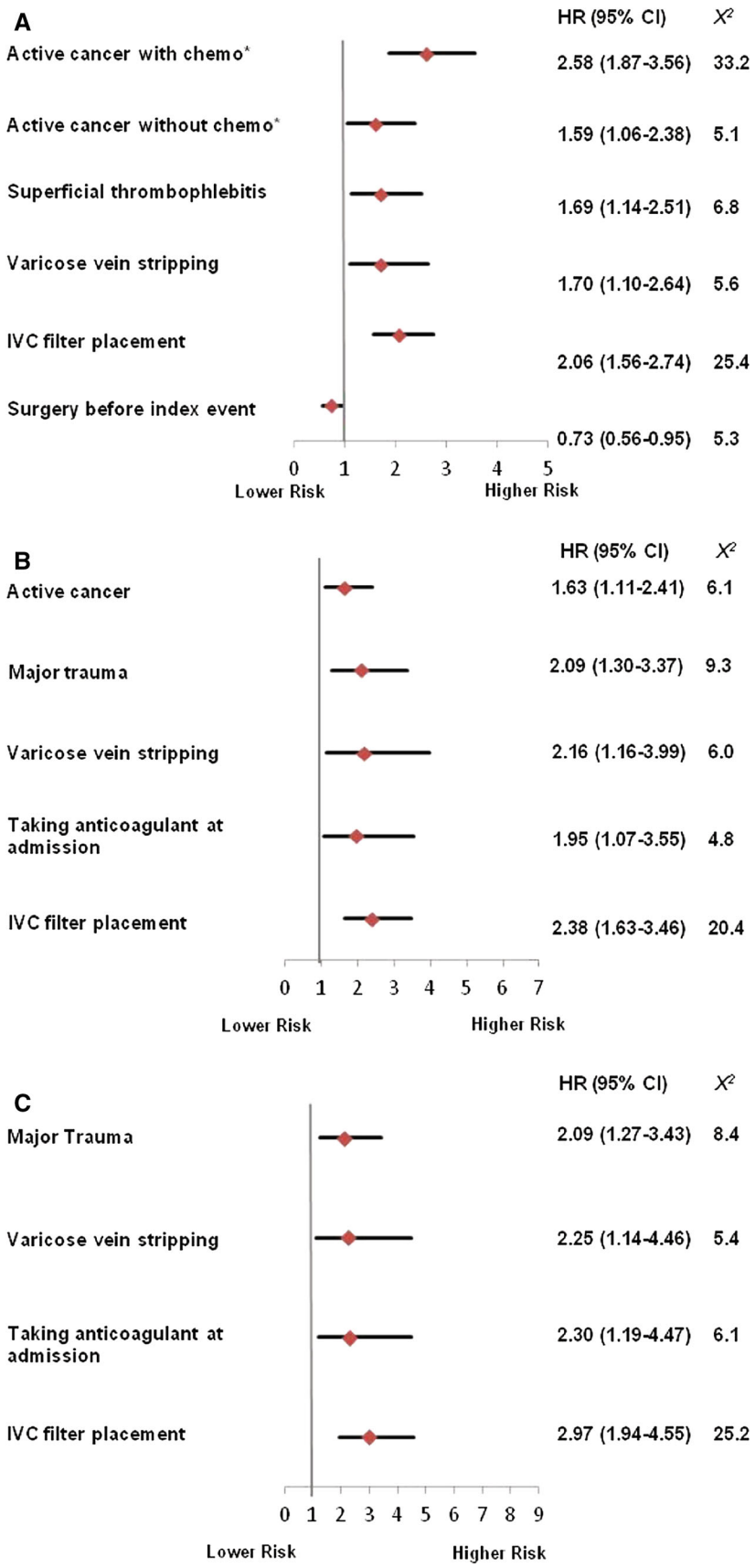
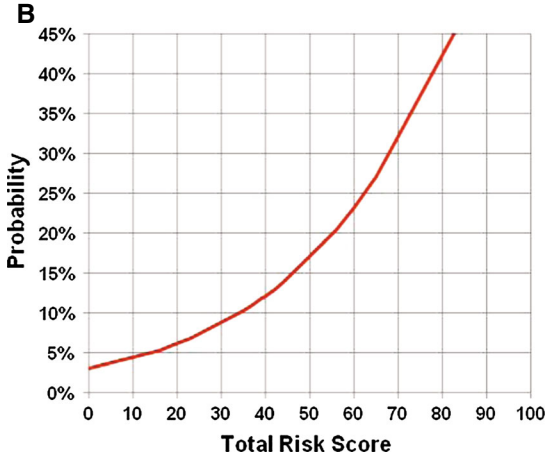


Fig. 2 Independent predictors of VTE recurrence within **a** 3 years, **b** 3 months, and **c** 3 months in patients without active cancer, among WMSA residents with a first-time VTE diagnosed from 1999 through 2009. *Reference group without active cancer. *chemo* chemotherapy, *CI* confidence interval, *HR* hazard ratio, *IVC* inferior vena cava, *VTE* venous thromboembolism, *WMSA* Worcester Metropolitan Statistical Area

A

Predictors	Points
Active cancer (with/without chemo)	16
Taking anticoagulant at admission	19
Major trauma	21
Varicose vein stripping	21
IVC filter implanted	23
Possible maximum total risk score	100

B



C

Risk score category	Patients (N=2989) n (%)	Predicted rate	Observed rate	p-value*
0	1890 (63.2%)	2.9%	3.1%	0.70
>0 to <19	361 (12.1%)	6.6%	5.4%	0.29
19 to <25	503 (16.8%)	7.0%	6.5%	0.69
25+	235 (7.9%)	11.5%	13.2%	0.47

Fig. 3 **a** Risk score calculator for **b** predicted risk of, and **c** observed versus predicted rate of, VTE recurrence during the first 3 months after the index event among all patients. *May–Hosmer goodness-of-fit test. *chemo* chemotherapy, *IVC* inferior vena cava, *VTE* venous thromboembolism

studies have reported higher rates of recurrent VTE after an acute episode of VTE: 8 % at 3 months and 20 % at 3 years [10, 11].

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 >800 patients with VTE, of whom 181 had known cancer at study entry, revealed that the 1-year cumulative incidence of recurrent VTE was threefold higher in patients with cancer versus those without [17]. Historically, recurrence rates after an acute episode of VTE among cancer patients has been higher than among patients without cancer [6, 13, 30]. 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 [16]. In this UK study, the 3-year CIR of recurrent VTE was approximately 5 % higher among patients with an unprovoked index VTE versus those with a provoked episode [16]. However, in our study, we found no suggestion of a difference in the recurrence rate between these two groups. Despite re-classifying HRT/OC as a provoking factor, the results remained unchanged. Further investigations on whether HRT/OC is a provoking factor for VTE are needed, as published findings provide conflicting results [25, 39]. While we recognize that differences between the UK study and our study may be related to the use of an administrative database in the UK study and their inability to robustly differentiate index and recurrent events, this may be at least partly explained by the different practices in the US and UK in managing patients with unprovoked VTE. Although we did not collect data on the duration of long-term treatment in the current study cohort, based on our prior publication that focused on a subset of elderly VTE patients, we found that the median duration of warfarin treatment was >1 year for patients with unprovoked VTE and around 6 months for patients with provoked VTE [40]. This suggests that patients in central MA with unprovoked VTE were protected from recurrence for a much longer period than those with provoked VTE. This prolonged treatment pattern may explain why no differences were found in risk of recurrence within 3 years between our provoked and unprovoked groups. In addition, other studies have reported that approximately 4 % of patients with unprovoked VTE develop a recurrence within 6 months [41, 42], similar to our findings. Furthermore, recently published data from a US population-based case-cohort study demonstrated a similar time-to-event pattern as ours: the CIR of recurrent VTE was higher among provoked than unprovoked cases of VTE within the first 2 years after index event but was lower during the later follow-up period [43]. However, unmeasured time-dependent variables may change the strength of association between baseline factors and outcomes, as the literature has shown that interim hospitalization, active cancer, pregnancy, central venous catheter, and respiratory infection are associated with increased hazards of recurrence, whereas warfarin and aspirin are associated with reduced hazards [43].

Owing to increasing use of objective diagnostic tests in the 2000s, there was an increasing trend in the annual event rate for PE [5, 44]. As such, the proportion of patients diagnosed with first-time PE in our study was higher than in historic data [5, 22]. However, after stratifying type of index event into PE ± DVT, proximal DVT alone, and isolated calf DVT, the CIR of VTE recurrence within

3 years after index event was not statistically different among the groups. There are conflicting reports as to whether type of index event (PE vs. DVT) is a predictor of VTE recurrence, irrespective of follow-up duration [30]; these include no increased risk by type of VTE event [10, 41] and an increased risk for patients with incident PE [12, 13] or proximal DVT [11]. In our study, the index diagnosis was not an independent predictor of recurrence during long-term follow-up. These discrepancies could be related to variations in study design, study criteria, incomplete documentation, and duration of follow-up.

Independent predictors of 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 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 1976–1990, patients with cancer receiving chemotherapy had a more than fourfold increased risk of VTE recurrence within 10 years after the index event compared to patients without cancer, while cancer patients not taking chemotherapy had a twofold increased risk [10]. However, during 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 [6].

With regard to the remaining independent predictors in both the short- 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. having varicose vein stripping, superficial thrombophlebitis prior to index event), stasis of blood flow, and blood hypercoagulability [45].

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 consensus review that IVC placement may increase the risk of early VTE recurrence by as much as 50 % [30]. Patients who received an IVC filter may have been unable to receive anticoagulant treatment due to contraindications [42]. Our prior publication demonstrated that patients who received an IVC filter were older and had more comorbidities [46]. These patients require special attention, as an IVC filter alone is inadequate therapy for acute VTE [30].

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 [6, 13]. We found that patients who had undergone surgery within 3 months before the index event had an approximate 30 % reduction in the risk for recurrence during long-term follow-up versus those who had not undergone surgery; this was because the risk of subsequent recurrence declines after the patient recovers from surgery, and is consistent with the literature [6, 13, 30, 47]. In addition, we found that patients with a recent major trauma had a twofold increased risk of VTE recurrence during the first 3 months. Most of these patients were likely still in recovery from their major trauma, which could extend the period of VTE risk, particularly due to prolonged immobility [45]. Taking anticoagulant therapy at admission was an independent predictor for increased risk of VTE recurrence within 3 months, which could be a proxy for other unmeasured risk factors, including comorbidities and genetic predisposition.

Not surprisingly, several predictors identified in the unadjusted Cox proportional hazards model were no longer predictors in the multivariable model (i.e. adjusted for confounders). For instance, use of graduated compression stockings was a predictor for increased hazard of recurrent VTE within 3 months after the index event among patients with active cancer, but was not an independent predictor in the multivariable model.

Historically, increasing age has been considered to be associated with higher incidence rates of VTE in the general population [5, 22, 45, 48]. 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 [18, 30], others indicate that increasing age is associated with a decreasing risk of recurrence [19, 49]. Moreover, some studies did not identify age as an independent predictor of VTE recurrence after an acute episode [14, 15, 50], similar to the findings in our study. Similarly, evidence on male sex as an independent predictor of recurrent VTE is conflicting [14, 15, 18, 19]. While VIENNA and DASH indicated that male sex was an independent predictor of increased risk of VTE recurrence and the Louzada's model indicated a decreasing risk, the Rodger's model did not identify sex as a predictor for VTE recurrence as what we have found [14, 15, 18, 19]. Again, these discrepancies could be related to variations in study design, selection

criteria, duration of follow-up, and incomplete documentation of the physician's examination for clinical VTE risk factors. Further studies are needed to clarify the reasons for these observed discrepancies [51].

Risk score calculator for predicting VTE recurrence within 3 months of the index event

Realizing that time-dependent characteristics may change over the course of long-term follow-up, we developed a risk score calculator based solely on our 3-month prediction model. Our intention 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 calculator included variables that are readily available to clinicians and uses a simple point system to estimate the risk of VTE recurrence.

Although the results of any prediction models are only 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 calculator differs from currently available calculators that are focused on information assessed at the end of the acute treatment phase and are only applicable to a subset of VTE cases (e.g. DASH, VIENNA, and Rodger et al's model for unprovoked VTE, and Louzada et al's model for cancer-associated VTE) [14, 15, 18, 19]. Owing to differences in the study designs and the inclusion of candidate predictors, not surprisingly, the final sets of predictors differ. Therefore, external validations of these tools are needed.

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 may have missed some cases of asymptomatic VTE. Owing to low autopsy rates in the WMSA and the limited validity of death-certificate data [2, 7], only clinically recognized cases of acute VTE were described and some cases of fatal PE could have been missed. Consistent with other observational studies, unmeasured or inadequately measured variables (e.g. duration of anticoagulant treatment after initial treatment in the clinical facility, changes in dose/type of medication subsequent to initial treatment prescriptions, and changes in medical conditions) may have impacted our findings, despite the inclusion of >50 potential prognostic factors assessed during the index encounter. 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. Moreover, when the sample size is adequate, different prediction models may be developed by stratifying the endpoint (recurrent VTE). Although we conducted internal validation, we recognize that no study can effectively validate itself [52], and external validations are needed to fully assess the model performance. Nevertheless, we believe that our 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.

Conclusions

This population-based study 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 calculator can be used during the initial treatment phase for predicting recurrence during the acute treatment phase. This may help clinicians to determine the optimal frequency of subsequent clinical surveillance and the appropriate outpatient treatment of VTE.

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Compliance with ethical standards

Conflict of interest Professor Anderson received research grants from Sanofi and The Medicines Company; he has served as a consultant to GlaxoSmithKline and Takeda Oncology on the design of outcomes studies. Dr. Cohen reports grants and personal fees from Bayer, Boehringer-Ingelheim, BMS, Daiichi, GSK, Johnson and

Johnson, Pfizer, Portola, Sanofi and XO1, outside the submitted work. All other authors declare that they have no conflict of interest.

References

1. Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ (2006) Hemostasis and thrombosis basic principles and clinical practice, vol 1, 5th edn. Lippincott Williams & Wilkins, Philadelphia
2. Deitelzweig SB, Johnson BH, Lin J, Schulman KL (2011) Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol 86(2):217–220
3. Heit JA (2005) Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 3(8):1611–1617
4. Park B, Messina L, Dargon P, Huang W, Ciocca R, Anderson FA (2009) Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: findings from the nationwide inpatient sample. Chest 136(4):983–990
5. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA (2014) Secular trends in occurrence of acute venous thromboembolism: the Worcester venous thromboembolism study (1985 to 2009). Am J Med 127:829–839
6. Guyatt GH, Akl EA, Crowther M, Schunemann HJ, Gutterman DD, Zelman Lewis S (2012) Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141(2 Suppl):48S–52S
7. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, Melton LJ III (2001) The epidemiology of venous thromboembolism in the community. Thromb Haemost 86(1):452–463
8. Spencer FA, Gore JM, Lessard D, Douketis JD, Emery C, Goldberg RJ (2008) Patient outcomes after deep vein thrombosis and pulmonary embolism: the Worcester Venous Thromboembolism Study. Arch Intern Med 168(4):425–430
9. White RH (2003) The epidemiology of venous thromboembolism. Circulation 107(23 Suppl 1):I4–I8
10. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III (2000) Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 160(6):761–768
11. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A (2007) The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 92(2):199–205
12. Carrier M, Le Gal G, Wells PS, Rodger MA (2010) Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 152(9):578–589
13. Agnelli G, Becattini C (2013) Risk assessment for recurrence and optimal agents for extended treatment of venous thromboembolism. Am Soc Hematol Educ Progr 2013:471–477
14. Eichinger S, Heinze G, Jandeck LM, Kyrle PA (2010) Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation 121(14):1630–1636
15. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, Rodger MA, Zhang J, Lee AY, Meyer G, Wells PS (2012) Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation 126(4):448–454
16. Martinez C, Cohen AT, Bamber L, Rietbrock S (2014) Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 112(2):255–263
17. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100(10):3484–3488
18. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, Vickars L, Ramsay T, Betancourt MT, Kovacs MJ (2008) Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ 179(5):417–426
19. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Douketis J (2012) Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 10(6):1019–1025
20. Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, Becker RC, Goldberg RJ (2006) The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med 21(7):722–727
21. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ (2007) Venous thromboembolism in the outpatient setting. Arch Intern Med 167(14):1471–1475
22. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE (1991) A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 151(5):933–938
23. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR (2005) Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 293(19):2352–2361
24. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA (1999) A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 340(12):901–907
25. Le Gal G, Kovacs MJ, Carrier M, Do K, Kahn SR, Wells PS, Anderson DA, Chagnon I, Solymoss S, Crowther M, Righini M, Lacut K, White RH, Vickars L, Rodger M (2010) Risk of recurrent venous thromboembolism after a first oestrogen-associated episode. Data from the REVERSE cohort study. Thromb Haemost 104(3):498–503
26. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W, Warfarin Optimal Duration Italian Trial Investigators (2001) Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. N Engl J Med 345(3):165–169
27. Spyropoulos AC (2009) Upper vs. lower extremity deep vein thrombosis: outcome definitions of venous thromboembolism for clinical predictor rules or risk factor analyses in hospitalized patients. J Thromb Haemost 7(6):1041–1042
28. Spencer FA, Emery C, Lessard D, Goldberg RJ (2007) Upper extremity deep vein thrombosis: a community-based perspective. Am J Med 120(8):678–684
29. Royston P, Altman D (1994) Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. Appl Stat 43(3):429–467
30. Heit JA (2012) Predicting the risk of venous thromboembolism recurrence. Am J Hematol 87:S63–S67

31. Hosmer DW, Lemeshow S, May S (2008) Applied Survival Analysis, 2nd edn. Wiley, Hoboken, NJ
32. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA (1982) Evaluating the yield of medical tests. JAMA 247(18):2543–2546
33. May S, Hosmer DW (2004) A cautionary note on the use of the Gronnesby and Borgan goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal 10(3):283–291
34. Spyropoulos AC, Anderson FA Jr, Fitzgerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann JF, Tapson V, Froehlich JB, Monreal M, Merli GJ, Pavanello R, Turpie AG, Nakamura M, Piovella F, Kakkar AK, Spencer FA (2011) Predictive and associative models to identify hospitalized medical patients at risk for venous thromboembolism. Chest 140(3):706–714
35. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Granger CB (2006) Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 333(7578):1091
36. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA (2004) A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 291(22):2727–2733
37. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA (2003) Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 163(19): 2345–2353
38. Huang W, Anderson FA, Spencer FA, Gallus A, Goldberg RJ (2013) Risk-assessment models for predicting venous thromboembolism among hospitalized non-surgical patients: a systematic review. J Thromb Thrombolysis 35(1):67–80
39. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY (2008) Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 336(7655):1227–1231
40. Spencer FA, Gurwitz JH, Schulman S, Linkins LA, Crowther MA, Ginsberg JS, Lee AY, Saczynski JS, Anand S, Lessard D, Emery C, Huang W, Goldberg RJ (2014) Venous thromboembolism in older adults: a community-based study. Am J Med 127(6):530–537
41. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS (2000) Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med 160(22):3431–3436
42. Heit JA, Lahr BD, Petterson TM, Bailey KR, Ashrani AA, Melton LJ III (2011) Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-based cohort study. Blood 118(18):4992–4999
43. Heit JA, Lahr BD, Ashrani AA, Petterson TM, Bailey KR (2015) Predictors of venous thromboembolism recurrence, adjusted for treatments and interim exposures: a population-based case-cohort study. Thromb Res 136:298–307
44. Wiener RS, Schwartz LM, Woloshin S (2011) Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 171(9):831–837
45. Anderson FA Jr, Spencer FA (2003) Risk factors for venous thromboembolism. Circulation 107(23 Suppl 1):I9–I16
46. Spencer FA, Bates SM, Goldberg RJ, Lessard D, Emery C, Glushchenko A, Gore JM, White RH (2010) A population-based study of inferior vena cava filters in patients with acute venous thromboembolism. Arch Intern Med 170(16):1456–1462
47. Baglin T, Luddington R, Brown K, Baglin C (2003) Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 362(9383):523–526
48. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 158(6):585–593
49. White RH, Zhou H, Romano PS (1998) Length of hospital stay for treatment of deep venous thrombosis and the incidence of recurrent thromboembolism. Arch Intern Med 158(9):1005–1010
50. Verso M, Agnelli G, Ageno W, Imberti D, Moia M, Palareti G, Pistelli R, Cantone V (2012) Long-term death and recurrence in patients with acute venous thromboembolism: the MASTER registry. Thromb Res 130(3):369–373
51. Poli D, Palareti G (2013) Assessing recurrence risk following acute venous thromboembolism: use of algorithms. Curr Opin Pulm Med 19(5):407–412
52. Altman DG, Vergouwe Y, Royston P, Moons KG (2009) Prognosis and prognostic research: validating a prognostic model. BMJ 338:b605