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ORIGINAL ARTICLE

Incident thrombus location and predicting risk of recurrent venous thromboembolism

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Abstract

Background: Understanding venous thromboembolism (VTE) recurrence risk is central to determining the appropriate treatment course. Whether this risk varies after discontinuing anticoagulation or overall by type of incident event (pulmonary embolism [PE] vs deep vein thrombosis [DVT]) and by the detailed location of the DVT needs further clarification.

Methods: In this population-based inception cohort of incident VTE cases with follow-up by electronic health record review, incident DVT was categorized as distal, popliteal, or iliofemoral. We used the Fine-Gray regression model to describe the predictive association of the thrombus location with the risk of recurrence before death.

Results: Among 2766 participants with an incident event from 2002 to 2010, 1713 (62%) ceased anticoagulation and were followed for recurrent events; 301 events were observed during the 4.5 years of follow-up. Relative to participants with an incident thrombus in an iliofemoral location and no PE, those with a thrombus in a popliteal location and no PE had a similar risk of recurrence (adjusted subdistribution hazard ratio [aSHR], 0.82 [95% confidence interval (CI), 0.57–1.19]), while those with a thrombus in a distal location and no PE and those with a thrombus that included a PE had lower risk of recurrence: aSHR, 0.34 (95% CI, 0.20-0.57); and aSHR, 0.58 (95% CI 0.45-0.76), respectively.

Conclusions: The findings of this population-based inception cohort confirm that the risk of recurrent VTE after discontinuing anticoagulants is similar after iliofemoral and popliteal DVT but is lower after distal DVT. Recurrence may be lower after PE than proximal DVT.

KEYWORDS
deep vein thrombosis, follow-up studies, humans, pulmonary embolism, recurrence, venous thromboembolism

Essentials

- The location of a first clot in the veins may be help identify the risk of a recurrent clot.
- We followed adults with a first clot in different veins and identified recurrent clots.
- Recurrences are more likely in those with a first clot in/above the knee than a clot below the knee.
- They may also be more likely to have recurrent clots than those with a lung clot.

1 | INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two primary manifestations of venous thromboembolism (VTE). An individual who has experienced an incident (first) VTE is more likely to experience a VTE in the future.[1,2] Prior research has provided wide-ranging incidence estimates for VTE recurrence, with the best estimates coming from community-based studies where there is nearly complete ascertainment of events in the defined population. A meta-analysis of VTE recurrence rates from randomized controlled trials and from cohort studies found that recurrence was highest the first year following an incident event (8.6-12.1 per 100 person-years) and that at 10 years, cumulative risk of recurrence was 36%.[3]

Understanding predictors of VTE recurrence is central to determining the appropriate course of treatment for an individual, in particular with regard to the duration of anticoagulation and the possibility of long-term secondary VTE prevention. Direct and vitamin K oral anticoagulants, which are commonly used to treat VTE, carry significant risk of morbidity and mortality related to major bleeds, and optimizing the duration of use in individual patients is challenging.[4] Multivariable risk-assessment scales for VTE recurrence have been built for use in determining appropriate treatment approaches for specific subgroups of patients with VTE, especially among patients with unprovoked incident VTE. These scales include the HERDOO2 scoring system,[5] the Vienna prediction model,[6] the Leiden Thrombosis Recurrence Risk Prediction (L-TRRiP) model, and the DASH score.[7] These risk-rating scoring approaches use data on demographic and clinical factors such as sex,[5,6] age,[5,7] body mass index (BMI),[5] type of VTE (DVT or PE),[6] presence of abnormal levels of D-dimer,[5,7] use of exogenous estrogens,[7] and the presence of postthrombotic syndrome (Table S1).[5]

Variations in the risk of recurrent VTE appear to exist according to the incident VTE type (PE vs DVT) and/or the incident DVT location and help to guide the duration of anticoagulation after a VTE episode.[3] DVT is traditionally categorized into proximal (popliteal or higher) and distal (below the popliteal trifurcation). However, confirmation and more granular data of this risk stratification in a contemporary population-based sample would be valuable. While the risk of recurrent VTE is lower after distal than proximal DVT, the absolute risk may still be important in some subgroups of patients, such as those with cancer.[8] Most risk prediction models exclude those with a distal VTE and only the Vienna Prediction Model and the L-TRRiP model include location of the first VTE in calculation of recurrence risk.[6,9]

In this article, we describe the incidence of VTE recurrence in a population-based inception cohort and characterize its relative risk by the presence of PE or DVT and the DVT location using a more refined categorization than the standard distal-proximal levels. Our primary analyses characterize the relative risk after discontinuing anticoagulation, whereas secondary analyses characterize the relative risk after the time of the incident event. In exploratory analyses, we investigated the predictive role that provoked/unprovoked status of the incident event may have on modifying incidence and relative risks of recurrence after discontinuation of anticoagulation.

2 | METHODS

2.1 | Setting and design

This population-based, incident VTE inception cohort was formed of cases from the Heart and Vascular Health (HVH) case-control study of VTE, details of which have been published previously.[10–12] The HVH study was set within Group Health Cooperative (GHC), now Kaiser Permanente Washington (KPWA), which serves Western Washington State.[12] GHC was an integrated healthcare delivery system in which members received virtually all their care within the unified GHC system. The HVH study has been approved by the GHC/KPWA institutional review board.

2.2 | Cohort of incident VTE

The VTE cases were combined from two studies and included men aged 30 to 89 years and women aged 18 to 89 years who experienced an incident VTE from January 2002 through December 2010. All subjects were members of GHC at the time of their incident VTE. Using an International Classification of Diseases, Ninth Revision code screen, trained medical record abstractors reviewed the complete health record (outpatient, inpatient, provider notes, laboratory measures, pharmacy records) to identify eligible incident events, both provoked and unprovoked, through 2014.[10] Importantly, this study was based on clinical diagnoses and care delivered by GHC providers, so asymptomatic events not detected by the provider could not be included in the study data. Qualifying events could not be catheter related and required confirmatory imaging including Doppler or duplex ultrasound, computed tomography, pulmonary angiography, or ventilation-perfusion scan, or supporting clinical evidence of an incident VTE with a physician diagnosis.[10,11] Ninety-eight percent of qualifying events included imaging. For these analyses, we included all confirmed diagnoses of VTE, excluding only

participants with an upper-extremity DVT (n = 56) and those who died on the day of the incident VTE or otherwise had no follow-up in the GHC record (n = 22).

Incident DVT location was identified using imaging information and categorized as distal, popliteal, or iliofemoral, according to the most proximal location of the thrombus. Distal thrombi are those in the leg that extended only to the peroneal, posterior tibial, or muscular calf veins; popliteal thrombi are extending to the popliteal veins; and iliofemoral thrombi are those that extended into the deep femoral, femoral, common femoral, pelvic, and iliac veins, as well as the vena cava. We used available imaging and physician diagnoses to document the occurrence of combined DVT and PE. Among those whom we classified using existing medical records as having a DVT only, 6.9% had PE imaging diagnostics conducted, but suggestive respiratory symptoms would have led to physician PE diagnoses in case of positive imaging for proximal DVT. Conversely, 38.3% of those whom we classified as having a PE without a DVT had DVT imaging diagnostics conducted. Incident events were also categorized by their presumed etiology: unprovoked or provoked. Provoked events were identified based on recent pregnancy, hospitalization, surgery, or cancer diagnosis or treatment from medical record review; hospitalization or major fracture from hospital inpatient diagnosis codes; and estrogen use from pharmacy records (Table S2). The provoked subset was further divided into provoked noncancer (known major or minor transient risk factors, with no cancer diagnosis or treatment within 2 years prior) events and provoked cancer-related (prevalent cancer or cancer treatment at the time of incident VTE or in the 2 years prior, with or without known transient risk factors) events.

2.3 | Recurrent VTE

The full health record of each GHC member with an incident VTE was reviewed to identify recurrences from the time of their incident event through last date of health care follow-up documentation in the health record, disenrollment from GHC, death, or end of study follow-up (December 2014).[12] Recurrent events were defined as detection of a thrombus in a new location any time after the incident event or a thrombus occurring in the same location ≥14 days after the incident event. Qualifying recurrent events required both physician diagnosis and supporting imaging; symptoms alone were not sufficient to qualify an event as a recurrent VTE. For these analyses, eligible recurrent events were those that occurred after discontinuation of anticoagulation.

2.4 | Covariates

Covariate details were collected primarily from the health record and were supplemented by telephone interview data collected from surviving and consenting individuals (49.4%). Age was defined as the subject's age at the time of the incident VTE event. Race was by self-report; in the absence of self-report, this information was collected from the health record. Race was categorized as White, Black, or other/unknown; we could not subdivide these categories further due to small numbers of other races. Smoking status was based on the participant's smoking status at the time of their incident VTE event and was categorized as never smoker, former smoker, or current smoker. BMI (weight [kg]/height [m]^2) was calculated using the most recent height and weight recorded in the medical record at the time of the incident event. Among women, menopausal status at the time of the incident VTE was determined from the health record. A woman was considered postmenopausal if notation of the cessation of menses was included in the health record, hormone therapy had been initiated, lab tests suggested the woman was postmenopausal, or the woman had undergone a bilateral oophorectomy. In the absence of this information, women ≥55 years of age were assumed to be postmenopausal. We also tracked current anticoagulation use during follow-up based on pharmacy data to identify those who stopped anticoagulation therapy. Less than 1% of participants had missing information for any covariate, so we imputed missing values by multiple imputation (n = 10) using chained equations.[13] We did not have updated covariate data at the discontinuation of anticoagulation.

2.5 | Analyses

For the primary analysis, time zero for each participant was the date of discontinuation of anticoagulation therapy after their incident VTE event. We calculated 1- and 5-year cumulative incidence proportions overall and separately by the values of key characteristics including incident thrombus location, sex, age, and etiology group. To illustrate recurrence burden and the competing risk of death before recurrence, a cumulative incidence plot was created displaying the proportions of subjects who had experienced a recurrent event, had died without a recurrent event, or were still alive over time for all participants combined. Cumulative incidence plots for recurrence were also created separately by etiology and by the location of the incident thrombus.

We used the Fine-Gray regression model to describe the association of incident thrombus location with the cumulative incidence of recurrence while adjusting for incidence and recurrence risk factors.[14] Incident thrombus location was categorized into five groups: iliofemoral DVT without concomitant PE (reference); popliteal DVT without PE; distal DVT without PE; unknown DVT location without PE; and PE with or without diagnosed DVT.

Adjustments were made for variables identified a priori as VTE risk factors to control for potential confounding and index event bias; these included age (linear), BMI (linear), race (White, Black, other/missing), smoking (never, former, current), menopausal status (female—pre/perimenopausal, female—postmenopausal, male), and presence of minor transient risk factor (yes/no), presence of major transient risk factor (yes/no), and/or recent cancer before the incident event. In secondary analyses, we examined the predictive relative risk associated with incident VTE location among all participants, setting time zero to be the time of their incident event.

As exploratory analyses, we tested for effect modification of the five-category thrombus location analysis by the three categories of the incident event etiology: unprovoked; provoked, noncancer; and provoked, cancer related.

All analyses were conducted using Stata 13.1 statistical software (StataCorp, College Station, TX, USA). Graphs were prepared using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Table 1 (upper) provides participant characteristics by the primary incident VTE location classification for the 2766 participants with an incident VTE event. There were slightly more women than men, and the majority of participants were White. At the time of their incident VTE, the mean age of the population was 65.5 years, and the

TABLE 1 Study population demographic and clinical characteristics by thrombus location of incident VTE event

Upper table Characteristic	Cohort at time of incident event (n = 2766)	Stratified by thrombus location of incident VTE event				
		Ilio/femoral DVT without PE (n = 691)	Popliteal DVT without PE (n = 258)	Distal DVT without PE (n = 235)	Unknown DVT location without PE (n = 98)	PE with or without DVT (n = 1484)
Female, n (%)	1542 (55.8)	376 (54.4)	129 (50.0)	124 (52.8)	62 (63.3)	851 (57.4)
Race, n (%)						
White	2480 (89.7)	636 (92.0)	225 (87.2)	220 (93.6)	83 (84.7)	1316 (88.7)
Black	140 (5.1)	20 (2.9)	12 (4.7)	4 (1.7)	10 (10.2)	94 (6.3)
Other/Unknown	146 (5.3)	35 (5.1)	21 (8.1)	11 (4.7)	5 (5.1)	74 (5.0)
Age, y, mean (SD)	65.5 (15.1)	66.2 (15.3)	60.7 (14.0)	60.8 (14.5)	68.0 (14.7)	66.5 (15.0)
BMI, kg/m^2, mean (SD)	30.2 (7.7)	29.2 (6.8)	29.8 (6.4)	30.7 (6.4)	29.7 (8.3)	30.7 (8.3)
VTE etiology, n (%)						
Unprovoked	1265 (45.7)	324 (46.9)	145 (56.2)	107 (45.5)	38 (38.8)	651 (43.9)
Provoked, noncancer	827 (29.9)	182 (26.3)	67 (26.0)	87 (37.0)	23 (23.5)	468 (31.5)
Provoked, cancer related	674 (24.4)	185 (26.8)	46 (17.8)	41 (17.5)	37 (37.8)	365 (24.6)
Anticoagulant use within 30 days after incident VTE, n (%)	2696 (97.5)	685 (99.1)	256 (99.2)	222 (94.5)	91 (92.9)	1442 (97.2)
Censored prior to cessation of anticoagulant, n (%)	983 (36.5)	253 (36.9)	75 (29.3)	41 (18.5)	36 (39.6)	578 (40.1)
Recurrent VTE	141 (14.3)	41 (16.2)	19 (25.3)	8 (19.5)	6 (16.7)	67 (11.6)
Death	383 (39.0)	109 (43.1)	25 (33.3)	13 (31.7)	18 (50.0)	218 (37.7)
Disenrollment	53 (5.4)	12 (4.7)	3 (4.0)	6 (14.6)	0	32 (5.5)
Anticoagulated throughout follow-up[a]	406 (41.3)	91 (36.0)	28 (37.3)	14 (34.2)	12 (33.3)	261 (45.2)
Lower table	**Cohort at anticoagulation Discontinuation (n = 1713)**	**Ilio/femoral DVT without PE (n = 432)**	**Popliteal DVT without PE (n = 181)**	**Distal DVT without PE (n = 181)**	**Unknown DVT location without PE (n = 55)**	**PE with or without DVT (n = 864)**
Follow-up time, y, median (IQR)	4.5 (2.0-6.0)	3.9 (1.9-5.9)	4.8 (2.7-6.2)	5.1 (2.5-6.4)	3.7 (0.91-5.2)	4.5 (2.0-6.0)
Max follow-up time, y	11.0	10.1	10.0	11.0	8.4	10.2
Recurrent events, n (%)	301 (17.6)	108 (25.0)	40 (22.1)	17 (9.4)	10 (18.2)	126 (14.6)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a]End of follow-up is defined as the earliest of the last date of follow-up documentation in the health record or end-of-study follow-up (December 2014).

mean BMI was 30.2 kg/m^2. Among the 2766 with an incident VTE event, 2696 (97.5%) had initiated anticoagulation use within 30 days after the event. Among these, 1713 (63.5%) participants ceased anticoagulation (average duration of anticoagulation treatment was 11.0 months) and were eligible for follow-up; 983 (36.5%) participants were not eligible for follow-up for the following reasons: 406 (41.3%) were anticoagulated throughout follow-up; 383 (39.0%) died while on anticoagulation; 141 (14.3%) had a recurrent event while on anticoagulation; and 53 (5.4%) disenrolled from GHC while on anticoagulation. Among the 1713 eligible for follow-up (Table 1 lower), 849 (49.6%) had experienced an incident DVT without PE (432 [50.9%] iliofemoral location; 181 [21.3%] popliteal; 181 [21.3%] distal; and 55 [6.5%] unidentified location) and 864 (50.4%) had experienced an incident PE with or without a diagnosed DVT. The median follow-up time was 4.5 (interquartile range, 2.0-6.0) years, during which there were 301 (17.6%) recurrent VTE events among the 1713 in follow-up. For the 1498 subjects who survived with no event observed, there were 5.2 median years of follow-up to the last date of documentation of health care and 6.1 median years of follow-up to the date of chart review.

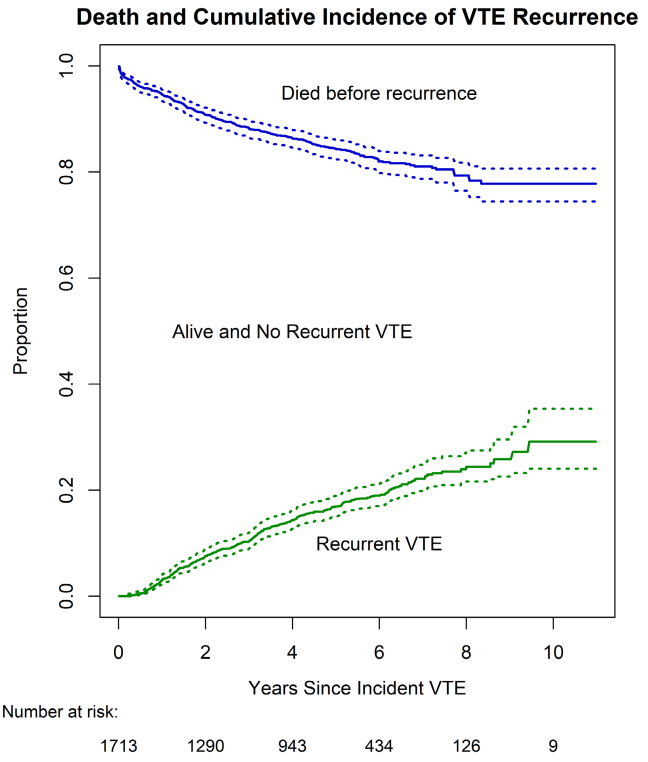

FIGURE 1 Death without recurrence and cumulative incidence of recurrence over time. The vertical distance above the blue line represents the proportion of individuals who died before a recurrent VTE, the vertical distance below the green line represents the proportion of individuals who experienced a recurrent VTE, and the vertical distance between the blue and green lines represents the proportion of individuals who remained alive with no recurrent VTE at that number of years since the incident VTE. Dotted lines give limits of 95% pointwise confidence intervals. VTE, venous thromboembolism

Figure 1 shows the cumulative proportions over time of those having experienced VTE recurrence, those having died without recurrence, and those still alive without recurrence. Cumulative incidence graphs for VTE recurrence without recurrence are shown stratified by etiology (Figure 2A) and thrombus location (Figure 2B).

Table 2 provides cumulative incidence at 1 and 5 years overall and by stratification variables. Among all participants, the cumulative incidence of recurrence was 3.0% at 1 year and 16.9% at 5 years (Table 2). At 1 year, cumulative incidence of recurrence ranged from 1.7% for distal DVTs to 7.5% for unknown DVT location; at 5 years, it ranged from 9.7% for distal DVTs to 24.1% for iliofemoral DVTs. Cumulative incidence varied by etiology subgroups and was highest at 5 years in those with an unprovoked event.

Relative to those with an incident iliofemoral DVT without PE (Table 3), those with incident thrombi in a popliteal location had a similar incidence of recurrence (adjusted subdistribution hazard ratio [aSHR], 0.82 [95% confidence interval [CI], 0.57-1.2]) and those with incident thrombi in a distal location had lower risk of recurrence (aSHR, 0.34 [95% CI, 0.20-0.57]); for those with incident PE, the relative risk was also lower (aSHR, 0.58 [95% CI, 0.45-0.76]). Secondary analyses following subjects immediately after their incident event produced similar aSHR estimates to the primary analysis (Table S3).

In subgroups (Table 4, upper), the aSHR estimates by location compared with the reference group of iliofemoral DVT without PE were similar across the three etiology strata (*P* value for interaction = 0.946). Data are also shown using unprovoked iliofemoral DVT without PE as a single reference group (Table 4, lower) for this cross classification. With either presentation, there was little evidence that etiology of incident event modified aSHR estimates; however, CIs were wide due to small counts in many of the cells.

4 | DISCUSSION

Our analyses used data from a prospectively documented, population-based cohort to evaluate the relationship between incident thrombus location and cumulative incidence of VTE recurrence. Compared with participants with an incident iliofemoral DVT without PE, we observed similar recurrent VTE risks in participants with an incident popliteal DVT without PE, but markedly decreased risks in participants with a distal DVT without PE and in participants with PE. These estimates were similar when follow-up was restricted to those discontinuing anticoagulation and when not restricted. Overall, the 5-year cumulative incidence of VTE recurrence was 22% to 24% after a proximal DVT (iliofemoral or popliteal) without PE, 10% after a distal DVT, and 14% after a PE.

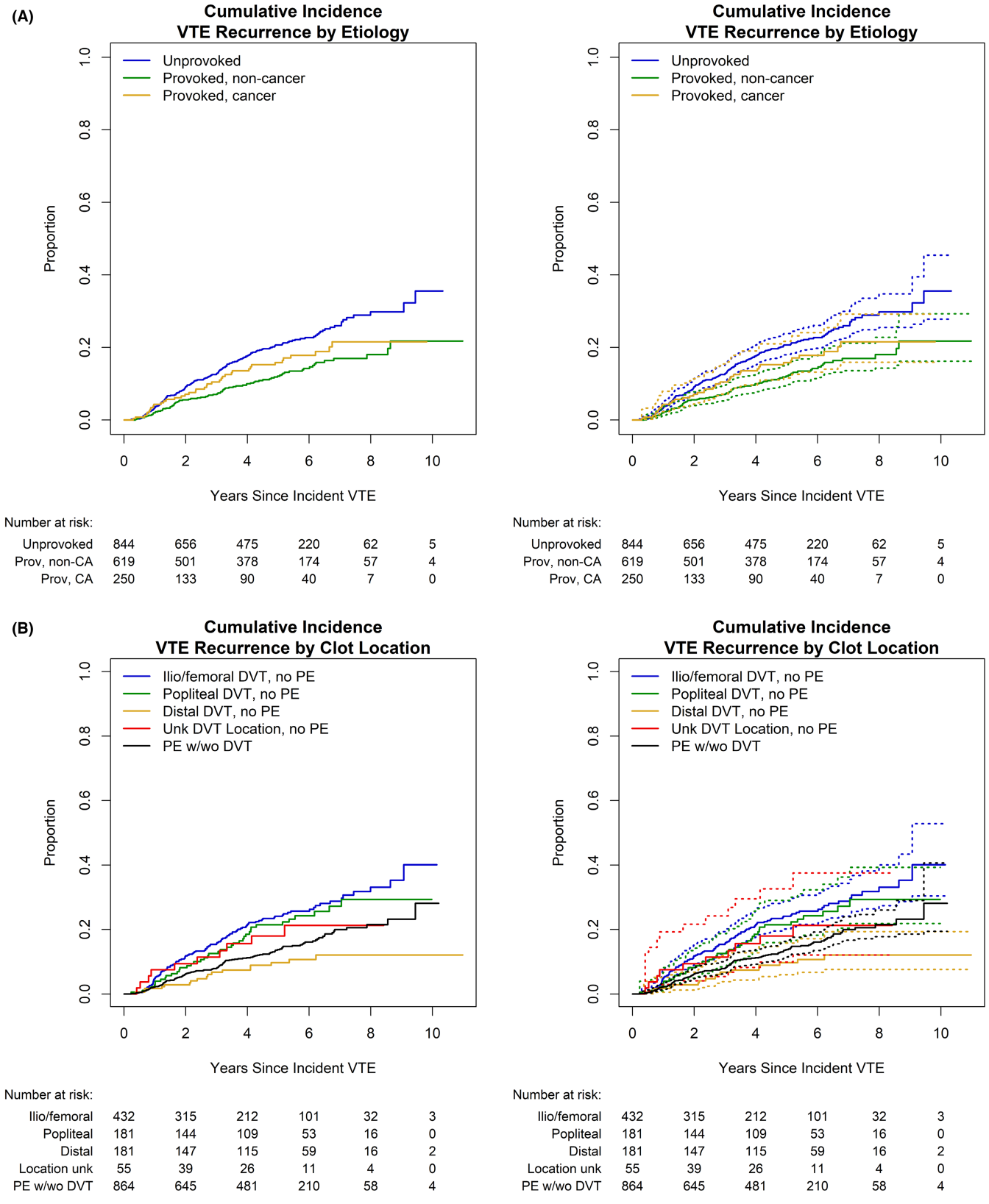

FIGURE 2 Cumulative incidence of recurrence stratified by etiology (A) and thrombus location (B), without (left) and with (right) 95% pointwise confidence intervals (dotted lines). CA, cancer; DVT, deep vein thrombosis; VTE, venous thromboembolism

TABLE 2 Cumulative incidence of recurrence following anticoagulation discontinuation by participant characteristic

	Person-years of follow-up	Events	Cumulative incidence (%) of VTE recurrence at 1 year	Cumulative incidence (%) of VTE recurrence at 5 years
Participants after anticoagulation	5748	301	3.0	16.9
Location of incident thrombus				
Iliofemoral DVT	1368	108	4.7	24.1
Popliteal DVT	680	40	2.8	21.5
Distal DVT	736	17	1.7	9.7
Unknown location of DVT	154	10	7.5	18.0
Pulmonary embolism	2811	126	2.1	13.8
Sex				
Male	2497	157	3.7	20.8
Female	3251	144	2.4	13.9
Age groups, y				
<50	1064	39	1.0	13.5
50-65	1830	98	4.0	18.8
≥65	2855	164	3.1	16.8
Incident VTE etiology				
Unprovoked	2901	181	3.4	20.7
Provoked, noncancer	2293	81	2.0	12.1
Provoked, cancer related	554	39	4.3	15.8

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism.

4.1 | Strengths and limitations

Our study benefitted from high-quality, objective data prospectively documented by medical professionals and later extracted from the electronic health record. Our aSHRs were estimated with good precision for our primary hypotheses, and missing data were limited. A strength of this study is the population-based design. Indeed, our cohort included essentially all GHC members diagnosed with an incident VTE event during the inception period, including VTEs that were cancer related and VTEs that were both unprovoked and provoked, with very few exclusions. This contrasts with most of the published literature for VTE recurrence and its risk factors, which have reported studies based primarily on patients from specialty or tertiary centers.[5,6,15] This study is best generalized to other population-based estimates. This is a natural history study of VTE recurrence. All diagnoses and decisions about treatment duration were made by the health care providers. Although GHC has guidelines for DVT and PE care—including duration of treatment, the care delivered in this study was heterogenous and reflects real-world practice but also introduces variability. We acknowledge a potential for misclassification for the concomitance of DVT in case of incident PE and of asymptomatic PE in case of incident DVT, which is not investigated systematically. However, symptoms of PE in presence of proximal DVT are likely to have led to physician diagnoses of concomitant DVT and PE, even in the absence of lung imaging, and have been categorized so in our cohort. Further, the initiation and duration of anticoagulant treatment—a key predictor of recurrence risk—was not randomized and may have been influenced by the VTE severity and comorbidities. However, the fact that our analysis including time both before and after discontinuing anticoagulation yielded similar results to those found after discontinuation suggests that confounding factors associated with treatment duration did not greatly bias our estimates. Our cohort follow-up does not include time when direct oral anticoagulants were widely adopted, which is a limitation if these newer drugs are prescribed differently from vitamin K antagonists. Also, follow-up for surviving patients who did not experience an event was continued only until their last clinical contact with GHC. Removing these subjects from risk a little early may have resulted in slight overestimates of cumulative incidence of recurrence and death.

4.2 | Current literature

Our data build on prior research and confirm the lower risk of recurrence after an incident distal DVT, compared with a proximal location,[16,17,18] Our analysis of proximal DVT comparing popliteal to iliofemoral locations is novel in a contemporary setting. The similar observed risks of recurrent VTE demonstrate that the current clinical standard of care is appropriate, by treating popliteal, femoral, and/or iliac DVT similarly.

We found that participants whose initial event included a nonfatal PE, with or without a diagnosed DVT, were at lower risk of recurrence than those with an initial iliofemoral DVT. This association persisted when stratifying by etiology. This signal has already been observed in

TABLE 3 Unadjusted and adjusted subdistribution hazard ratios of VTE recurrence in subjects following anticoagulation discontinuation

Primary categorization	Ilio/femoral DVT without PE (n = 432)	Popliteal DVT without PE (n = 181)	Distal DVT without PE (n = 181)	Unknown DVT Location without PE (n = 55)	PE with or without DVT (n = 864)
Recurrent events	108	40	17	10	126
Unadjusted SHR (95% CI)	1.00 (ref)	0.83 (0.58-1.2)	0.33 (0.20-0.55)	0.70 (0.36-1.4)	0.57 (0.44-0.73)
Adjusted[a] SHR (95% CI)	1.00 (ref)	0.82 (0.57-1.2)	0.34 (0.20-0.57)	0.67 (0.34-1.3)	0.58 (0.45-0.76)

[a]Adjusted for race, sex, body mass index, smoking status, menopausal status, recent minor transient risk factors, recent major transient risk factors, and recent cancer at time of the index event; and age at time anticoagulation use ceased.

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; SHR, subdistribution hazard ratio.

TABLE 4 Adjusted subdistribution hazard ratios of VTE recurrence by incident thrombus location and etiology in subjects following anticoagulation discontinuation

	Ilio/femoral DVT without PE	Popliteal DVT without PE	Distal DVT without PE	Unknown DVT Location without PE	PE with or without DVT
Unprovoked incident VTE, n = 844	68/225	28/108	7/85	5/28	73/398
aSHR (95% CI)	1.00 (ref)	0.81 (0.52-1.25)	0.24 (0.11-0.54)	0.53 (0.20-1.42)	0.62 (0.44-0.86)
Provoked, noncancer incident VTE, n = 619	22/135	9/54	7/70	3/17	40/343
aSHR (95% CI)	1.00 (ref)	0.91 (0.39-2.12)	0.45 (0.19-1.06)	0.83 (0.25-2.80)	0.61 (0.35-1.04)
Provoked, cancer-related incident VTE, n = 250	18/72	3/19	3/26	2/10	13/123
aSHR (95% CI)	1.00 (ref)	0.55 (0.16-1.85)	0.47 (0.14-1.58)	0.66 (0.14-3.12)	0.46 (0.22-0.97)
Overall *P* value for interaction: thrombus location and etiology interaction 0.946					
Single reference group					
Unprovoked incident VTE, n = 844	68/1713	28/1713	7/1713	5/1713	73/1713
aSHR (95% CI)	1.00 (ref)	0.82 (0.53-1.28)	0.26 (0.12-0.56)	0.54 (0.21-1.44)	0.61 (0.44-0.85)
Provoked, noncancer incident VTE, n = 619	22/1713	9/1713	7/1713	3/1713	40/1713
aSHR (95% CI)	0.60 (0.37-0.99)	0.56 (0.27-1.16)	0.28 (0.13-0.62)	0.57 (0.18-1.80)	0.37 (0.25-0.56)
Provoked, cancer-related incident VTE, n = 250	18/1713	3/1713	3/1713	2/1713	13/1713
aSHR (95% CI)	0.92 (0.54-1.57)	0.55 (0.18-1.70)	0.39 (0.13-1.20)	0.61 (0.15-2.49)	0.39 (0.21-0.72)

Note: Adjusted for race, sex, body mass index, smoking status, and menopausal status at time of the index event and age at the time of anticoagulation discontinuation.

Abbreviations: aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism.

a recent meta-analysis of mostly interventional trials, where the risk of incident proximal DVT was associated with a 40% increased risk of recurrent VTE, compared with incident isolated PE, among patients with a first unprovoked VTE event after cessation of anticoagulation.[3] Our data suggest that, among all VTE patients, proximal DVT carries a greater risk of recurrent VTE than PE, has potentially important clinical implications, and should be evaluated in other population-based settings.

5 | SUMMARY

Our analyses showing differential risks of recurrent VTE between distal and proximal DVT and similar risks between popliteal and more proximal thrombus location are consistent with current clinical practice, which treats nondistal DVTs more aggressively. The differential risk of recurrence between DVT and PE is meaningful and should be further evaluated.

AUTHOR CONTRIBUTIONS

SCL was responsible for study design, preliminary analyses, and drafting the manuscript. KLW was responsible for study design, finalized analyses, and drafting the manuscript. LBH, BM, and MB were responsible for study design, interpretation of results, and scientific review of the final manuscript. NLS was responsible for study funding, study design, interpretation of results, and the finalized version of the manuscript.

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RELATIONSHIP DISCLOSURE

There are no real or potential conflicts of interest for each author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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