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Predicting the Risk of Venous Thromboembolism Recurrence

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Abstract

Venous thromboembolism (VTE) is a chronic disease with a 30% ten-year recurrence rate. The highest incidence of recurrence is in the first 6 months. Active cancer significantly increases the hazard of early recurrence, and the proportions of time on standard heparin (APTT≥0.2 anti-X_a U/mL) and warfarin (INR≥2.0) treatment, significantly reduce the hazard. The acute treatment duration does not affect recurrence risk after treatment is stopped. Independent predictors of late recurrence include increasing patient age and body mass index, leg paresis, active cancer and other persistent VTE risk factors, idiopathic VTE, antiphospholipid antibody syndrome, antithrombin, protein C or protein S deficiency, hyperhomocysteinemia and a persistently increased plasma fibrin D-dimer. A recommendation for secondary prophylaxis should be individualized based on the risk for recurrent VTE (especially fatal pulmonary embolism) and bleeding. The appropriateness of secondary prophylaxis should be continuously re-evaluated, and the prophylaxis stopped if the benefit no longer exceeds the risk.

Keywords

thrombophlebitis; venous thromboembolism; deep vein thrombosis; pulmonary embolism; epidemiology

Introduction

Venous thromboembolism consists of deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE). Venous thromboembolism is a major health problem. The average annual incidence of VTE among persons of European ancestry is 108 per 100,000 person-years, with about 250,000 incident cases occurring per year among US whites.[1] The incidence appears to be similar or higher among African-Americans, and lower among Asian- and Native-Americans.[2,3] Adjusting for the different age- and sex-distribution of African-Americans, the VTE incidence is about 78 per 100,000, suggesting that about 27,000 incident VTE cases occur annually among US Blacks.[1] Venous thromboembolism is predominantly a disease of older age; incidence rates increase exponentially with age for both men and women, and for both DVT and PE.[1] Although the overall age-adjusted VTE incidence rate is higher for men (114 per 100,000) then women (105 per 100,000; male:female sex ratio 1.2:1), incidence rates are higher in women during the childbearing years. The higher VTE incidence at a younger age in women has important implications for interpreting the risk of VTE recurrence by sex. Pulmonary embolism accounts for an increasing proportion of VTE with increasing age for both men and women.[1] Given the

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markedly worse survival after PE compared to DVT alone,[1] the number of annual deaths due to PE likely will increase as the average US population age increases over time.

Estimating the risk of recurrent VTE is complex and imprecise, and requires consideration of demographic characteristics as well as multiple baseline and time-dependent clinical and laboratory characteristics.[4,5] These characteristics can be used to estimate the risk of early (i.e., within six months) and late recurrence. The duration of acute treatment and secondary prophylaxis can be based on these recurrence estimates as well as estimates of anticoagulant-related bleeding. Prevention of any VTE recurrence is important, but avoiding fatal PE usually is the most patient-important outcome. Consequently, an assessment of patient cardiopulmonary functional reserve is another important factor when considering a recommendation for secondary prophylaxis.

Predictors of Early Venous Thromboembolism Recurrence

The cumulative proportions of incident VTE patients with recurrence at 14-, 90- and 180-days are 2.0%, 6.4% and 8%, respectively, with corresponding recurrence incidence rates of 55.4, 30.0 and 17.7 per 100 person-years, respectively (Figure 1A).[6] Thus, the rate of VTE recurrence is highest during heparin therapy and the transition to warfarin. The two-week case fatality rates for recurrent PE (with or without [±] DVT) and recurrent DVT alone are 11% and 2%, respectively.[6] Among demographic and several baseline clinical characteristics, only active cancer is an independent predictor of early VTE recurrence, with about a three-fold increased hazard rate (Table 1).[6] About 16% of active cancer patients develop recurrence within six months. Idiopathic incident VTE is not a predictor of early VTE recurrence; only about 4% of idiopathic VTE patients develop recurrence within six months.[6,7] Among several time-dependent characteristics, the proportions of time on standard heparin with an activated partial thromboplastin time (APTT) ≥ a time (seconds) corresponding to a plasma heparin level ≥ 0.2 anti-X_a U/mL, and on warfarin with an INR≥2.0, significantly reduce the hazard of recurrence by about 10% and 17%, respectively.[6,8] The time from VTE onset to start of heparin and the duration of heparin/warfarin overlap are not independent predictors of early VTE recurrence. Failure to rapidly achieve an APTT≥0.3 anti-X_a U/mL despite an adequate heparin dose is a predictor of early recurrence and likely reflects relative heparin resistance, possibly due to high factor VIII activity.[6,9] Inferior vena cava filter placement may increase the risk of early VTE recurrence by about 50%; almost one-third of early recurrences after IVC filter placement are PE.[6]

The cumulative proportions of incident VTE patients with major bleeding at 14-, 90- and 180-days are 0.6%, 1.0% and 1.1%, respectively, with corresponding major bleeding incidence rates of 16.4, 4.4 and 2.5 per 100 person-years, respectively (Figure 1B).[6,10] The 14- and 30-day case fatality rates after major bleeding are 8% and 25%, respectively. The hazard of major bleeding is significantly increased for a higher daily mean INR while on warfarin.[6]

Predictor of Late Recurrence after Venous Thromboembolism

Although the hazard of VTE recurrence is highest within the first 6 months, the hazard never returns to baseline; patients with incident VTE are always at risk for recurrence, regardless of the time since the incident VTE event.[11,12] However, the hazard of recurrence does decrease with increasing time since the incident VTE event. The cumulative proportions of incident VTE patients with recurrence at one, two, five and ten years are about 13%, 17%, 23% and 30%, respectively (Figure 2).[11,13–18]

Demographic and baseline clinical characteristics that independently increase the hazard for late VTE recurrence are shown in Table 2.[11] Although increasing patient age at the incident

VTE date is an independent predictor of recurrence,[11] age does not appear to be a predictor of recurrence among patients with idiopathic incident VTE.[19] Studies of patient sex as a predictor of VTE recurrence after stopping acute treatment have reported conflicting results.[12,20–26] The risk of recurrence may be increased for males with idiopathic incident VTE,[20,21,23,24,26] although this was not confirmed in all studies[22] and Hispanic women may have a recurrence that is similar to whites with idiopathic VTE.[25] Since women have a higher incidence of VTE at a younger age (i.e., during childbearing years), studies that adjusted for age at incident VTE, hormonal contraceptive exposure, and pregnancy or the postpartum period found that patient sex was not an independent predictor of VTE recurrence.[11,27] Increasing patient BMI at the incident VTE event is a predictor of recurrence,[11,28] but studies of the recurrence risk by VTE event type (PE ± DVT vs. DVT alone) report conflicting results, with either no increased risk by VTE event type,[11] or an increased risk for patients with incident PE[29] or proximal DVT.[30] A family history of VTE does not appear to affect the recurrence risk.[31]

Persistent baseline clinical characteristics such as active cancer,[11,13,14,32,33]} neurological disease with leg paresis[11] and inflammatory bowel disease[34] significantly increase the risk of recurrence. Limited data suggest that metastatic cancer, adenocarcinoma and lung cancer confer a higher risk of VTE recurrence compared to patients with localized cancer, non adenocarcinoma or breast cancer.[35] Cancer patients diagnosed and treated for incidentally-discovered PE appear to have similarly high rates of recurrent VTE as cancer patients with symptomatic PE.[36]

Transient baseline clinical characteristics such as major surgery, hospitalization for acute medical illness and trauma or fracture appear to have no effect on recurrence risk.[7,11,37–39] Women with incident VTE related to hormonal contraceptive exposure or pregnancy/postpartum period may have a lower risk of recurrence compared to women with VTE in the absence of these exposures,[11,40,41] although this has not been confirmed in all studies.[42] Idiopathic VTE also appears to be a predictor of VTE recurrence.[12,43–45]

Baseline and time-dependent laboratory characteristics that increase the risk of VTE recurrence include an abnormally shortened APTT,[46,47] increased procoagulant factor VIII[48] and factor IX[49] activities, deficiency of antithrombin, protein C or protein S,[50–52] hyperhomocysteinemia,[53] and antiphospholipid antibodies.[43,54] Idiopathic VTE patients with high plasma levels of apolipoprotein AI and HDL may have a decreased risk of recurrent VTE.[55] The risk of recurrence is modestly increased for carriers of the Factor V Leiden and prothrombin G20210A mutations,[56] but there is no association between the *MTHFR* 677C→T polymorphism and VTE.[57]

Idiopathic VTE patients with a persistently increased plasma D-dimer level have a 2.6-fold increased hazard of recurrence.[30,58–60] Idiopathic VTE patients with a D-dimer level that is normal at one month after stopping treatment but becomes persistently abnormal two months later also are at increased risk of recurrence.[61] Consequently, repeated D-dimer testing after stopping treatment may be helpful in stratifying VTE recurrence risk among patients with idiopathic VTE. Residual vein thrombosis (**RVT**) after completing acute treatment for proximal DVT has also been suggested as a predictor of VTE recurrence.[45,62–64] A systematic review and meta-analysis found a positive relationship between RVT and recurrent VTE during follow-up although there was significant study heterogeneity due to differences in study populations and in the timing and methods of measuring RVT.[65] A change in thrombus length of up to nine centimeters is within the bounds of measurement error using venous duplex ultrasound.[66] Moreover, it is unclear whether RVT adds further useful information over and above the plasma D-dimer in predicting recurrence after an idiopathic DVT.[59] Consequently, the utility of RVT as an

independent predictor of recurrent VTE is uncertain. Nevertheless, repeat venous duplex ultrasound imaging of the affected leg about 12 months later[67] is useful in establishing a new baseline image for the purposes of future comparison should the patient develop new symptoms or signs of a possible recurrent DVT in the same leg.

Patients with incident VTE who develop recurrence are significantly more likely to recur with the same VTE event type as the incident event type[29,68] Because the case fatality rate is significantly higher for recurrent PE compared to recurrent DVT alone,[6,29] secondary prophylaxis should be considered for incident PE, especially for patients with chronically reduced cardiopulmonary functional reserve as it is these patients who are most likely to develop recurrent fatal PE.

It is important to make a distinction between acute therapy and secondary prophylaxis. Acute therapy aims to prevent extension or embolism of an acute thrombosis, and needs to continue for a sufficient duration of time and intensity to insure that the acute thrombus has either recanalized or organized, and the "activated" acute inflammatory/innate immunity system has returned to baseline.[69] The most appropriate duration of acute therapy varies among individual patients but probably is between three and six months (Figure 3).[15,30,37,43,44,70–75] Beyond three to six months, the aim of continued anticoagulation is not to prevent acute thrombus extension or embolism, but instead, to prevent recurrent thrombosis (e.g., secondary prophylaxis). Venous thromboembolism is now viewed as a chronic disease (likely because all such patients have an underlying, if not recognized, thrombophilia), with episodic recurrence.[1,4] All randomized clinical trials that tested different durations of anticoagulation showed that as soon as anticoagulation is stopped, VTE begins to recur. Thus, anticoagulation treatment does not "cure" VTE.[16,30]

The decision regarding a recommendation for secondary prophylaxis also depends on estimates of the risk of anticoagulant-related bleeding and the patient's individual preference.[76] The relative risk of major bleeding is increased about 1.5-fold for every 10-year increase in age,[73,77–80] and about 2-fold for patients with active cancer.[32,73,78,79,81,82] Additional risk factors for bleeding include a history of prior gastrointestinal bleeding or stroke, or one or more comorbid conditions, including recent myocardial infarction, anemia (hematocrit <30%), or impaired renal function (serum creatinine > 1.5 mg/dL) [83,84] impaired liver function and thrombocytopenia. Moreover, the ability to perform activities of daily living should be considered because of the increased risk of bleeding associated with falls. The patient's prior anticoagulation experience during acute therapy should also be considered; patients with unexplained wide variation in the INR or noncompliant patients likely should not receive secondary prophylaxis. Finally, the mechanism(s) by which the INR will be monitored and the warfarin dose adjusted should be considered; the efficacy and safety of such care when rendered through an "anticoagulation clinic" or when "self-managed" at home is superior to usual medical care.[85–87] With appropriate patient selection and management, the risk of major bleeding can be reduced to 1% per year, or less.[74,88,89]

Because the hazard of VTE recurrence decreases with time since the incident event,[11] and because the risk of anticoagulant-related bleeding also may vary over time,[80] the need for secondary prophylaxis must be continually re-evaluated and the prophylaxis should be stopped if the benefit no longer exceeds the risk. It is inappropriate to simply recommend "life-long" or "indefinite" anticoagulation therapy.

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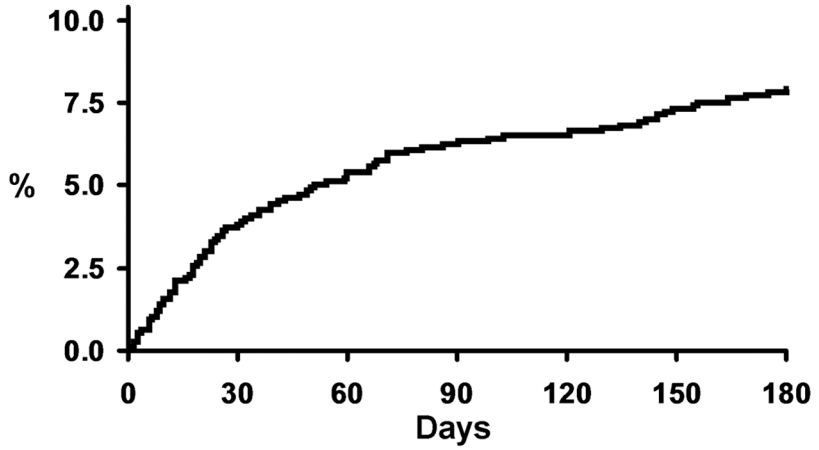
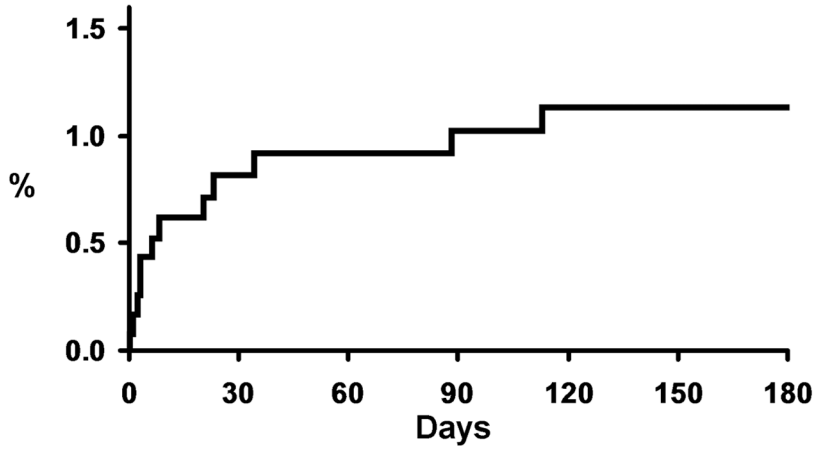
A



Variable	14 day	90 day	180 day	15-180 day
At risk (no.)	1,166	1,166	1,166	1,073
Events (no.)	23	69	85	62
Cumulative incidence (%)	2.0	6.4	8.0	6.1
Person-years (no.)	41.5	229.9	478.9	436.1
Incidence/100 person-years	55.4	30.0	17.7	14.2

B



Variable	14 day	90 day	180 day	15-180 day
At risk (no.)	1,166	1,166	1,166	1,066
Events (no.)	7	11	12	5
Cumulative incidence (%)	0.6	1.0	1.1	0.5
Person-years (no.)	42.6	249.0	475.9	433.3
Incidence/100 person-years	16.4	4.4	2.5	1.2

Figure 1.
Cumulative 180-Day Venous Thromboembolism Recurrence (1A) and Major Bleeding (1B) by Day from Incident Venous Thromboembolism Event.

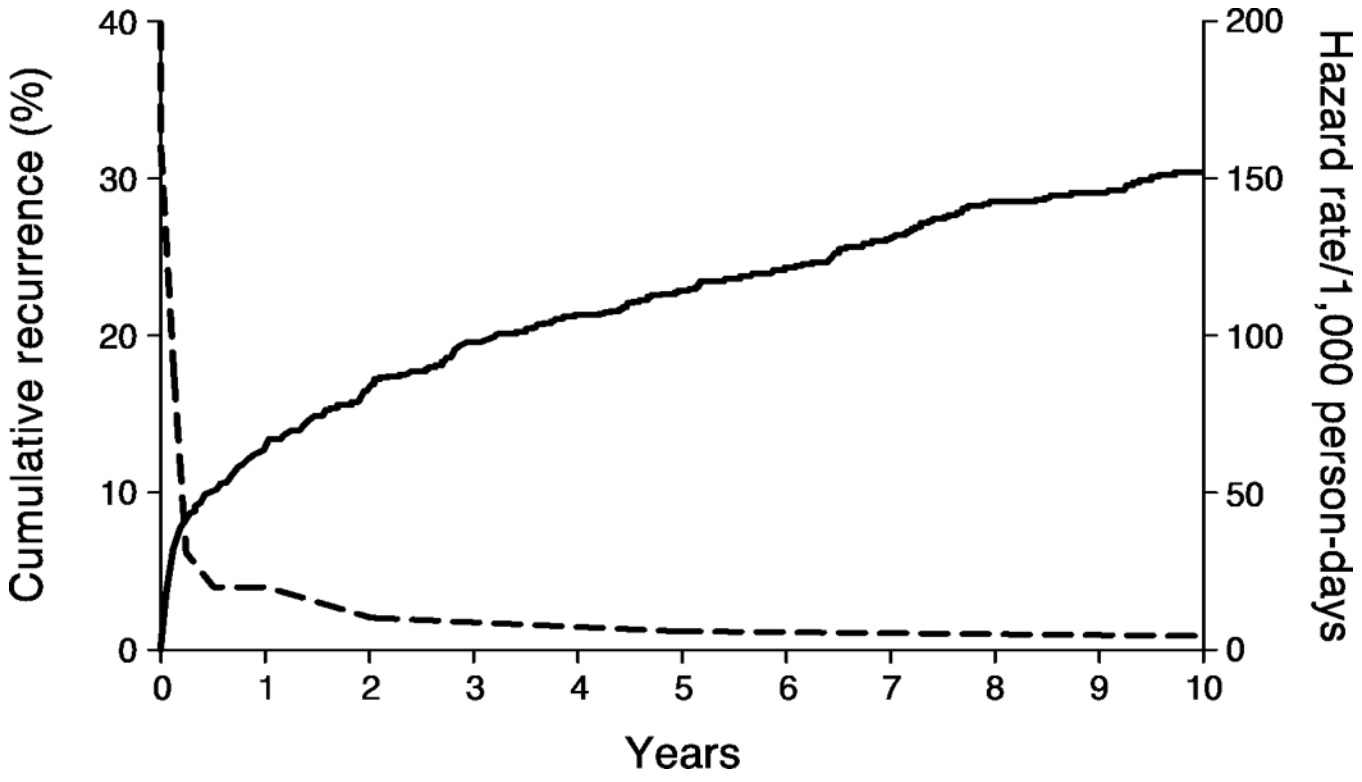


Figure 2.
Cumulative incidence of first venous thromboembolism recurrence (—), and the hazard of first recurrence per 1000 person-days (- - -).

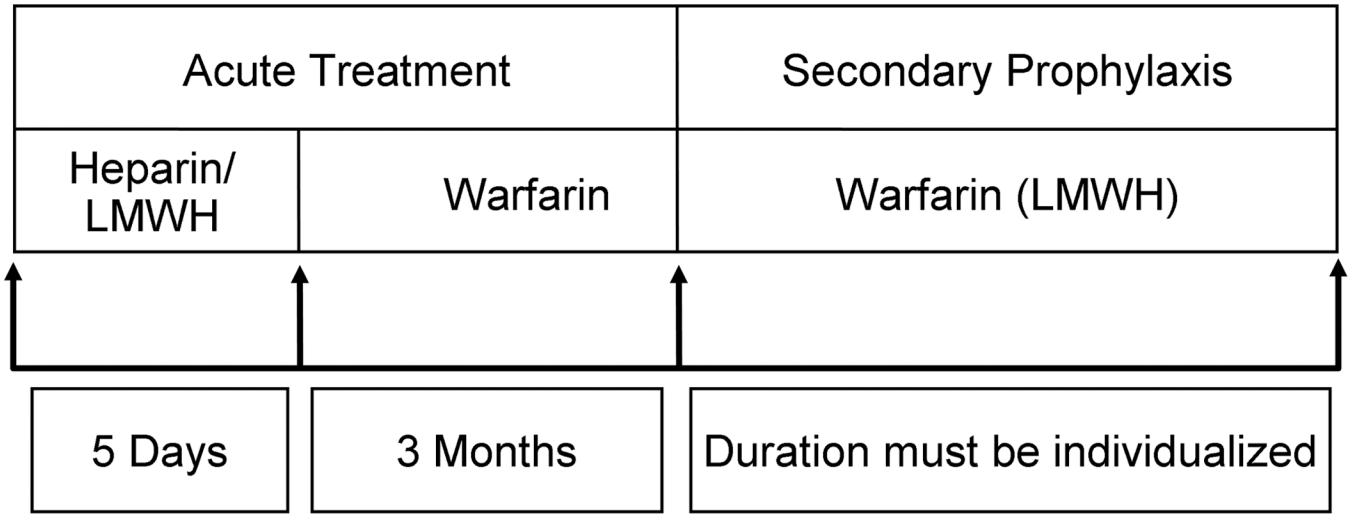


Figure 3.
Venous thromboembolism management; acute therapy vs. secondary prophylaxis.

Table 1

Independent Predictors of 180-Day Venous Thromboembolism Recurrence by Activated Partial Thromboplastin Time (APTT) Therapeutic "Threshold"6.

Variable		Hazard Ratio (95% CI) [P-value] with APTT Threshold ≥40 seconds†		Hazard Ratio (95% CI) [P-value] with APTT Threshold≥58 seconds‡	
BMI	< 20 kg/m^2	0.17 (0.02, 1.27)		0.19 (0.02, 1.38)	
	20–25 kg/m^2	Referent	[0.08]	Referent	[0.14]
	25–30 kg/m^2	1.13 (0.65, 1.96)		1.04 (0.60, 1.81)	
	> 30 kg/m^2	0.83 (0.44, 1.56)		0.82 (0.44, 1.54)	
Active cancer		2.93 (1.82, 4.74) [<.001]		2.82 (1.74, 4.55) [<.001]	
APTT≥ indicated seconds within 24 ± 4 hours of starting heparin		0.87 (0.40, 1.91) [0.73]		0.57 (0.34, 0.97) [0.04]	
Proportion of time on heparin with APTT≥ indicated seconds (per 10% increase)		0.90 (0.83, 0.97) [<.01]		0.96 (0.89, 1.04) [0.33]	
Proportion of time on warfarin with 1.5≤INR≤2.0 (per 10% increase)		0.98 (0.84, 1.14) [0.76]		0.97 (0.83, 1.13) [0.71]	
Proportion of time on warfarin with INR≥2.0 (per 10% increase)		0.83 (0.77, 0.90) [<.001]		0.83 (0.77, 0.90) [<.001]	
Inferior vena cava filter placement		1.54 (0.76, 3.11) [0.23]		1.66 (0.82, 3.37) [0.16]	

† Corresponding to plasma heparin level=0.2 anti-X_a U/mL

‡ Corresponding to plasma heparin level=0.3 anti-X_a U/mL

Table 2

Independent Predictors of Late Venous Thromboembolism Recurrence[11]

Characteristic	Hazard Ratio	95% C. I.
Patient age *	1.17	1.11, 1.24
Body mass index †	1.24	1.04, 1.47
Neurologic disease with leg paresis	1.87	1.28, 2.73
Active cancer		
Cancer with chemotherapy	4.24	2.58, 6.95
Cancer without chemotherapy	2.21	1.60, 3.06

* per decade increase in age.

† per 10 kg/m^2 increase in body mass index.