REVIEW

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Decision-Making in the Management of Venous Thromboembolism

Martin H. Ellis, MD,[a,b] Orly Avnery, MD[a,b]

[a]*Hematology Institute and Blood Bank, Meir Medical Center, Kfar Saba, Israel;* [b]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.*

ABSTRACT

Venous thromboembolism comprising deep venous thrombosis and pulmonary embolus is common. Patients with venous thromboembolism may present to a variety of health care providers, and while a significant proportion of patients begin treatment in the hospital, ambulatory management of both deep venous thrombosis and pulmonary embolus is feasible and becoming more common. Initial anticoagulant management, investigation of venous thromboembolism etiology, and decisions about extended anticoagulation require coordinated care by physicians from multiple specialties. Comprehensive management of venous thromboembolism requires coordinated care from the time of presentation in order to expedite diagnosis, initiate timely anticoagulant treatment, determine the need for extended anticoagulation based on risk of bleeding and recurrent thrombosis, and advise on thromboprophylaxis during future high-risk periods for venous thromboembolism. In this review we use case scenarios to provide an operational framework, based on current evidence-based recommendations, for informed decision-making about a number of clinical practice issues that are frequently encountered in the management of venous thromboembolism patients.

KEYWORDS: Clinical decision-making; Management; Venous thromboembolism

Venous thromboembolism comprising deep venous thrombosis and pulmonary embolus is common, with an annual incidence of 1:1000.[1] While the clinical presentations of deep venous thrombosis and pulmonary embolus vary greatly, the pathogenesis and approach to anticoagulant management is similar in both. There are also common features in the approach to diagnosis in that clinical probability scores may be used to either safely exclude a diagnosis of venous thromboembolism or to trigger further investigation, which may include D-dimer measurement while imaging confirms the diagnosis.[2,3]

Patients with venous thromboembolism may present to a variety of providers, and although a significant proportion begin treatment in the hospital, deep venous thrombosis and pulmonary embolus may be managed in the community, and published guidance informs safe ambulatory management.[4,5] Investigation of etiology, decisions about extended anticoagulation, and long-term management require coordinated care provided by physicians from different specialties, thus, overall management of venous thromboembolism requires successful interfacing among multiple caregivers.

In this paper we use case vignettes upon which to base evidence- or guideline-based recommendations to assist with venous thromboembolism clinical decision-making.

CASE #1: DIAGNOSIS

A 66-year-old woman has 3 days of worsening pain in her left calf. She denies trauma or fever. She smokes heavily, and 2 weeks earlier had been in the hospital with an exacerbation of chronic obstructive pulmonary disease. She has been house-bound since discharge because of dyspnea. Examination of her legs reveals varicose veins with skin changes reflecting chronic venous hypertension and left leg swelling to the mid-thigh.

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Requests for reprints should be addressed to Martin Ellis, MD, Hematology Institute, Meir Medical Center, 59 Tchernichovsky St, Kfar Saba 44281, Israel.

E-mail address: martinel@clalit.org.il

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The diagnosis of venous thromboembolism is confirmed when a thrombus is demonstrated on an imaging test: Doppler ultrasound, computed tomography (CT) venography, or magnetic resonance imaging of the veins in the case of deep venous thrombosis, and CT angiography or ventilation perfusion scanning for pulmonary embolus. However, these tests are labor intensive, inaccessible in many clinical settings, expensive, and may involve exposure to ionizing radiation, thus, they are not recommended as first-line tests in patients with suspected venous thromboembolism.

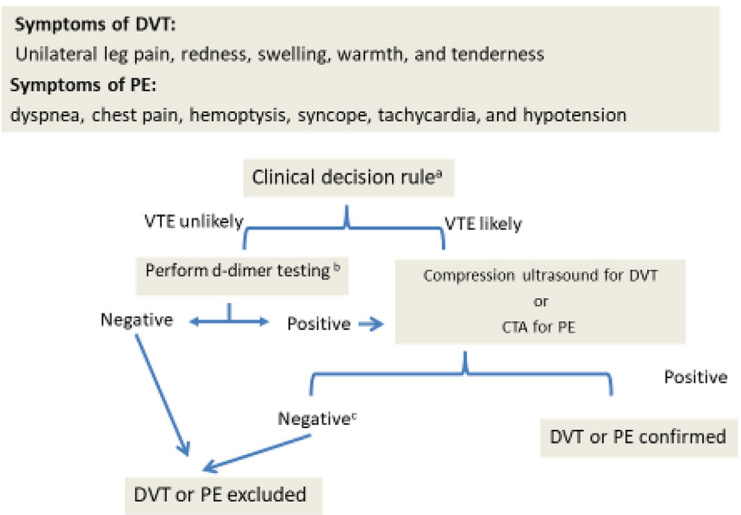
Numerous studies have shown that venous thromboembolism can be excluded in most patients with a low clinical probability score in whom the diagnosis is initially considered because of common symptoms, for example, leg swelling or cough and chest pain.[2,3,6] These scoring systems include features of deep venous thrombosis or pulmonary embolus that have been shown to predict diagnosis, and the items in the score are weighted according to their strength of association. In patients with an intermediate probability score, D-dimer levels should be measured, and when elevated, increase the probability of venous thromboembolism. In such patients and in patients with a high clinical probability score, imaging is then performed to confirm or exclude venous thromboembolism. A diagnostic algorithm based on these principles is shown in Figure 1.[7]

CLINICAL SIGNIFICANCE

- Venous thromboembolism (VTE) is a common clinical condition with significant clinical sequelae.
- Accurate diagnosis is achieved by adhering to well-defined algorithms.
- Duration of anticoagulant treatment is determined by the presence of coexisting risk factors for thrombosis and the risk of bleeding.
- Identifying inherited and acquired thrombophilias following VTE may be relevant in certain cases for family counseling and for determining the choice of anticoagulant.

A number of diagnostic probability tools using different scores and D-dimer cutoffs have been published and their performance has recently been compared. They are all able to safely avoid the necessity for imaging in nearly all appropriately selected patients.[6] The components of 2 commonly used clinical tools, the Wells and the revised Geneva scores, are shown in Tables 1 and 2.[8,9]

This patient has an intermediate probability for deep venous thrombosis using both the Wells (1 point) and revised Geneva (4 points) scores. She should have a D-dimer level measured immediately, and if this is elevated after adjustment for



a. Wells score for suspected DVT and Wells score or revised Geneva score for suspected DVT
b. Age-adjusted D-dimer threshold, calculated as the patient's age multiplied by 10 ng/mL (fibrinogen-equivalent units) for patients older than 50 years with suspected PE
c. Repeat compression ultrasound 1 week after normal finding

Figure 1 Diagnostic algorithm for the diagnosis of venous thromboembolism.
DVT = deep vein thrombosis; PE = pulmonary embolus; VTE = venous thromboembolism.

Table 1 Wells Clinical Probability Score for the Diagnosis of Deep Venous Thrombosis[8]

Clinical Feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden longer than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 mc below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	−2
Pretest probability	0 = low 1 or 2 = intermediate ≥3 = high
Clinical feature	Score

age, a Doppler ultrasound of the veins of her lower extremities should be performed. If the D-dimer level is normal, deep vein thrombosis can be excluded with 97% certainty.

In addition to demonstrating clinical decision methodology for venous thromboembolism diagnosis, this case emphasizes the necessity for venous thromboembolism prophylaxis in medical inpatients. A meta-analysis of randomized clinical trials of unfractionated heparin or low-molecular-weight heparin (LMWH) published more than a decade ago demonstrated the clinical benefit of venous thromboembolism prophylaxis in these patients[10] and has been accepted as a standard of care for patients at high risk for venous thromboembolism defined as immobilization and the presence of at least one venous thromboembolism risk factor (Table 3). However, a recent analysis of the ability of 3 risk-assessment models to identify noncritically ill medical patients at high risk for hospital-acquired venous thromboembolism found that their discriminatory power was limited and were no better than risk assessment based on age >70 years alone.[11] Thus, further studies are required to more accurately identify hospitalized medical patients at risk for venous thromboembolism in whom prophylaxis is warranted. Regarding the drug of choice when prophylaxis is offered, studies using direct-acting oral anticoagulants (DOACs) for venous thromboembolism prevention in medical patients have been performed, and a recent meta-analysis concludes that LMWH and DOACs have the same net clinical benefit, thus, the use of a drug in either class is acceptable.[12] By contrast, extending prophylaxis to the home setting after discharge in medical patients cannot be uniformly recommended because although venous thromboembolism may be prevented in these patients who remain at risk for venous thromboembolism even after discharge from the hospital, the effect on overall mortality is uncertain, and clinically relevant bleeding events are increased.[12,13]

Table 2 Revised Geneva Clinical Probability Score for the Diagnosis of Deep Venous Thrombosis[9]

Clinical Feature	Score
Age ≥65 years	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75-94 beats per minute	3
Heart rate ≥95 beats per minute	5
Pain on palpation of lower limb and unilateral edema	4
Pretest probability	0-3 = low 4-10 = intermediate ≥11 = high

DVT = deep vein thrombosis; PE = pulmonary embolism.

Table 3 Padua Scoring System for Venous Thromboembolism Risk and Prophylaxis in Hospitalized Medical Patients*

Clinical Feature	Score
Active cancer	3
Previous VTE	3
Reduced mobility	3
Known thrombophilic condition	3
Recent trauma or surgery	2
Age ≥70 y	1
Heart or respiratory failure	1
Acute MI or ischemic stroke	1
Acute infection or rheumatologic disorder	1
Obesity	1
Ongoing hormonal treatment	1
Total	<4 points = low risk ≥4 points = high risk

MI = myocardial infarction; VTE = venous thromboembolism.
*Pharmacologic prophylaxis is indicated. If high risk for bleeding, use mechanical prophylaxis.

CASE #2: INITIAL ANTICOAGULATION

A 42-year-old man presents to the Emergency Department with acute onset of dyspnea, pleuritic chest pain, and intermittent hemoptysis over a 36-hour period. His past medical history is significant for systemic lupus erythematosus, for

Table 4 Randomized Clinical Trials of Direct Oral Anticoagulants for Acute Treatment of Venous Thromboembolism

	HOKUSAI-VTE	AMPLIFY	EINSTEIN-DVT EINSTEIN-PE	RE-COVER I RE-COVER II
Drug	Edoxaban	Apixaban	Rivaroxaban	Dabigatran
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	60 mg qd 30 mg qd* (CrCI, bw, P-gp)	10 mg bid × 7 days then 5 mg bid	15 mg bid × 3 wk then 20 mg od	150 mg bid
Treatment duration	Flexible 3 to 12 mo	6 mo	Prespecified 3, 6, or 12 mo	6 mo
VTE recurrence rate compared with VKA (HR, CI)	0.89 (0.70-1.13)	0.84 (0.60-1.18)	0.89 (0.66-1.19)	1.09 (0.76-1.57)
Major bleeding rate compared with VKA (HR, CI)	0.84 (0.59-1.21)	0.31 (0.17-0.55)	0.54 (0.37-0.79)	0.73 (0.48-1.11)

bid = twice daily; bw = body weight, CI = confidence interval; CrCl = creatinine clearance; DVT= deep vein thrombosis; HR = hazard ratio; P-gp = P glycoprotein; PE = pulmonary embolism; qd = daily; VKA = vitamin K antagonist; VTE = venous thromboembolism.

*Dose modified in cases of renal dysfunction, low body weight, or concomitant use of drugs with marked P-glycoprotein inhibitor effect.

which he receives hydroxychloroquine. He reported a 10-hour airplane trip 3 weeks prior to presentation. On examination his blood pressure was 140/85 mm Hg, pulse rate was 110 beats per minute, and oxygen saturation while breathing room air was 90%. A CT angiography demonstrated bilateral segmental filling defects. Pulmonary embolism was diagnosed.

Anticoagulant treatment should be initiated immediately upon diagnosis of venous thromboembolism, absent an absolute contraindication such as active bleeding. When systemic thrombolysis for massive PE with cardiogenic shock, or local thrombolysis for extensive proximal deep venous thrombosis is considered, anticoagulation is delayed until after lytic treatment has been administered. Apart from these cases, treatment with a DOAC is currently recommended and should be administered upon diagnosis. Current terminology refers to the first 1-3 weeks of treatment as the "initial" anticoagulation period, the following 3-6 months as "acute" treatment, and thereafter, treatment is defined as "extended." DOACs have demonstrated equivalent efficacy, and for rivaroxaban and apixaban improved safety, compared with the previous standard of care, LMWH followed by a vitamin K antagonist in randomized controlled trials (RCTs).[14] With rivaroxaban and apixaban, treatment begins with a loading dose in order to overcome the high thrombin burden at the time of diagnosis of venous thromboembolism. If dabigatran or edoxaban are used, initial treatment is with LMWH for 5 days followed by the DOAC, consistent with the study design upon which the drugs were approved for use (Table 4).

An important exception is venous thromboembolism occurring in patients with the antiphospholipid syndrome in whom positive lupus anticoagulant tests, cardiolipin, and beta-2 glycoprotein 1 antibodies are all present—"triple positive" antiphospholipid syndrome. These patients carry a threefold risk of recurrent thrombosis, both venous and arterial when receiving rivaroxaban vs a vitamin K antagonist (VKA). Thus, DOACs are not recommended in triple-positive antiphospholipid syndrome.[15,16]

The decision to hospitalize venous thromboembolism patients depends upon the patient's clinical condition, access to ongoing medical care, and social support. Recent studies of deep vein thrombosis patients have shown that most can be safely treated in the community.[4,5] Appropriate patient selection is important for the success of ambulatory treatment.

Patients with pulmonary embolus who are at low risk for cardiorespiratory decompensation may be considered for ambulatory treatment. The Pulmonary Embolism Severity Index (PESI) score and the simplified PESI score (Table 5) were developed and validated for this purpose and patients with a very low (PESI class 1) or low (PESI class 2) score may safely be considered for home therapy.[17-19] Only 6.2% of these patients returned to the hospital within 5 days for a pulmonary embolus-related event.

This patient has an intermediate PESI score and should thus be admitted to the hospital. His history of systemic lupus erythematosus increases the likelihood of the presence of antiphospholipid antibodies, therefore, initial treatment with LMWH (eg, enoxaparin at a dose of 1.5 mg/kg/d) followed by a VKA should be considered in preference to a DOAC. If antiphospholipid syndrome is subsequently excluded, treatment using a DOAC would be appropriate.

CASE #3: INVESTIGATION

A 28-year-old woman presents with a swollen left leg. She is generally well and has been on a combined oral contraceptive pill (OCP) for 5 years. She had 2 first trimester pregnancy losses. An aunt had a postpartum pulmonary embolus. Doppler ultrasound examination reveals a femoral vein thrombosis and treatment with a DOAC is begun. After 3 months of treatment she is referred to a hematologist for consultation.

After initiation of anticoagulation, monitoring and counseling are essential to ensure symptomatic improvement and compliance with treatment. Once these short-term goals have been achieved, consideration should be given to determining the etiology of the venous thromboembolism. This is important, not only for patients who understandably seek an explanation for the event, but also for determining long-term management.

Table 5 Pulmonary Embolism Severity Index

Parameter	Original Version	Simplified Version
Age	Age in years	1 point (if age >80 y)
Male sex	points +10	—
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	1 point
Pulse rate ≥110 per minute	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	—
Temperature <36°C	+20 points	—
Altered mental status	+60 points	—
Arterial oxygen saturation <90%	+20 points	1 point
Risk stratification	Class I: ≤65 points Very low mortality risk (0-1.6%) Class II: 66-85 points Low mortality risk (1.7%-3.5%) Class III: 86-105 points Moderate mortality risk (3.2%-7.1%) Class IV: 106-125 points High mortality risk (4.0%-11.4%)	0 points = 30-day mortality risk 1.0% ≥1 point(s) = 30-day mortality risk 10.9%

Venous thromboembolism etiology may be sought based on the pathophysiologic determinants comprising Virchow's triad: alterations in blood flow (stasis), vessel damage, and blood hypercoagulability (thrombophilia).[20] Thrombogenic factors such as trauma, surgery, immobilization, recent onset use of an OCP, pregnancy, or malignancy may be obvious at presentation, in which case the venous thromboembolism is classified as provoked either by a minor or major, transient or permanent, risk factor.[21] Further evaluation may uncover an occult malignancy (in up to 10% of patients, particularly among older individuals) and the event is then classified as a cancer-associated thrombosis. Diagnosing occult malignancy has not been shown to improve overall survival because of lead-time bias.[22] Current recommendations support the performance of a thorough history and physical examination and age- and sex-appropriate cancer screening in patients with unprovoked venous thromboembolism.[23] Such patients may also benefit from testing for hereditary or acquired thrombophilia (Table 6). These tests are not indicated in provoked or cancer-associated thrombosis.[24] Hereditary thrombophilia should be suspected in patients with a family history of thrombosis, venous thromboembolism at age <40 years, or recurrent thrombosis. Diagnosing thrombophilia may have implications for patients' understanding of their condition, for long-term venous thromboembolism management, and for genetic screening of unaffected family members. While guidelines recommend against routine screening for hereditary thrombophilias in family members,[25] there are circumstances where this may be indicated, for example, in first-degree relatives prior to OCP prescription or pregnancy.[26]

Table 6 Hereditary and Acquired Thrombophilias Associated with Venous Thromboembolism

Hereditary	Acquired
Antithrombin deficiency Protein C deficiency Factor V Leiden (activated protein C resistance) Protein S deficiency Prothrombin 20210A mutation Elevated Factor VIII activity Hyperhomocysteinemia	Antiphospholipid antibodies (Lupus anticoagulant, cardiolipin antibodies, β2 glycoprotein 1 antibodies)

This patient has a history of pregnancy losses, which may be associated with both hereditary and acquired thrombophilias[27] and a family history of venous thromboembolism, albeit in a second-degree relative. She also has prolonged OCP exposure. None of these features alone are highly correlated with thrombophilia but their combined presence raises the clinical suspicion for such a tendency. Testing may influence the duration of anticoagulation in this patient because the OCP use is not of recent (<1 year) onset and may be considered a minor persistent risk factor for thrombosis. Testing would not influence decisions about prophylaxis during high-risk exposures in the future such as pregnancy or surgery, because thromboprophylaxis is already indicated because of a previous deep venous thrombosis. Results of hereditary thrombophilia tests may be important for counseling other first-degree female relatives in her family about OCP use and pregnancy, while the presence of antiphospholipid antibodies would determine the choice of anticoagulant.

Table 7 Clinical Scoring Systems Predictive of Recurrent Venous Thromboembolism

HERDOO2 Score	
Predictor	Scoring
H — Hyperpigmentation	1 point total, if any one of these criteria present
E — Edema	
R — Redness of either leg	
D — D-dimer ≥250 μg/L while anticoagulated	1
O — Obesity with BMI ≥30 kg/m^2	1
O — Older age (≥65 y)	1
Decision-making	
Women: 0-1 Discontinue anticoagulation	
Women: ≥2 Continue anticoagulation	
All men Continue long-term anticoagulation	
DASH (D-dimer, age, sex, hormone use) score	
Characteristic	Score
D-dimer abnormal 30 days after stopping anticoagulant therapy	+2
Age ≤50 y	+1
Sex: male	+1
Hormone-use provoked venous thromboembolism	−2
Final score	Annual risk of recurrence (95% CI)
≤1	3.1% (2.3-3.9)
2	6.4% (4.8-7.9)
≥3	12.3% (9.9-14.7)

BMI = body mass index.

CASE #4: EXTENDED ANTICOAGULATION

A 56-year-old woman with metastatic breast cancer is referred for consultation about ongoing anticoagulation management. She received a diagnosis of pulmonary embolism 6 months earlier and was treated with LMWH for 5 days and then transitioned to a DOAC, which she is currently taking. She is also using low-dose aspirin because of a strong family history of cardiovascular disease. She complains of easy bruising but has no abnormal bleeding.

After completion of the acute phase of treatment (3-6 months), the need for long-term or extended anticoagulation must be considered. This is based on the estimated risk of a recurrent venous thromboembolism if therapy is stopped, vs the risk of major hemorrhage if anticoagulation is continued.[7] If the venous thromboembolism was related to a major transient risk factor such as major surgery or trauma, the risk of recurrence after initial anticoagulation is low at 1%-3% within 10 years. This is the basis for recommending time-limited treatment in such cases, as well as in most cases involving a minor transient risk factor such as travel or minor surgery, which have a recurrence risk of 3%-5%, although some patients in this group could be considered for extended therapy.[28] However, if no etiology for the venous thromboembolism is determinable and the event is defined as being unprovoked, the recurrence rate increases significantly and reaches as much as 25% over a 10-year period.[29] Such patients should be considered for long-term treatment. Clinical decision-making tools have been derived from the retrospective analysis of factors associated with recurrent venous thromboembolism,[30-32] and one has been validated prospectively.[33] Two of these are shown in Table 7. Recurrence of unprovoked venous thromboembolism in men is twice that in women; thus, extended anticoagulation is frequently recommended in men. A biomarker for recurrence is D-dimer concentration measured 4 weeks after discontinuing anticoagulation. Elevated levels are associated with recurrence of >10%, while normal values predict recurrence of <5%.[34]

An important next step after assessing recurrence risk is to estimate bleeding risk, and scores have been developed for this purpose (Table 8). Notably, prospective validation of these scores is lacking; therefore, decision-making requires discussion with the patient and determination of preferences and acceptance of risk.

RCTs of extended anticoagulation with reduced-dose DOACs compared with placebo have largely simplified decision-making in this regard.[35-37] These studies demonstrate a low recurrence among patients receiving reduced-dose DOAC treatment, without a significant increase in major hemorrhage. A recent meta-analysis of 16 studies of extended treatment showed that DOACs and VKAs were associated with a significant relative risk reduction in overall and venous thromboembolism-related mortality of 52% and 64%, respectively, without an increase in major bleeding among patients receiving DOACs.[38] Guidelines support the administration of reduced-dose DOAC for extended therapy in patients with unprovoked venous thromboembolism.[39] An algorithm for clinical decision-making about extended therapy is shown in Figure 2.

Patients with cancer-associated thrombosis have a high risk of venous thromboembolism recurrence. The treatment approach in this setting is to continue anticoagulation while

Table 8 Prediction Scores for Anticoagulant-Related Bleeding in Venous Thromboembolism Patients

Variable	ACCP	VTE-BLEED	Hokusai
Age	X	X	
Anemia	X	X	X
History of bleeding	X	X	
Abnormal renal function	X	X	
History of stroke	X		
Hypertension		X	X
Antiplatelet agents	X		X
Cancer	X	X	
Abnormal liver function	X		
Alcohol abuse	X		
Sex			X (Female)
Diabetes	X		
Labile INRs	X		
Poor anticoagulant control	X		
Thrombocytopenia	X		
Increased fall risk	X		
Nonsteroidal anti-inflammatory drugs	X		

ACCP = American College of Chest Physicians; INR = international normalized ratio; VTE = venous thromboembolism.

the malignancy is active or cancer treatment, particularly chemotherapy, is ongoing.[40] Four trials have shown noninferiority of DOACs (edoxaban, rivaroxaban, and apixaban) compared with LMWH for this indication, and despite increased clinically relevant nonmajor bleeding, particularly gastrointestinal and genitourinary in DOAC-treated patients, oral agents significantly improve quality of life in cancer patients requiring anticoagulation.[41-44]

This patient should be counseled about the high risk of venous thromboembolism recurrence in the context of metastatic breast cancer. Given this risk, she should continue therapeutic-dose DOAC, which is the current recommendation for extended anticoagulation for cancer-associated thrombosis. She should be advised to stop taking aspirin, which is not indicated and which significantly increases bleeding risk.[45]

Like all patients on anticoagulation, she should be advised to seek medical attention for unusual or unexplained bleeding, she should have renal function monitored periodically, and have an annual assessment of the benefits vs risks of continued treatment.[46]

CASE #5: PREVENTION OF RECURRENCE IN HIGH-RISK SITUATIONS

A 48-year-old man is referred for consultation about venous thromboembolism prophylaxis prior to knee arthroscopy following a sports injury. Ten years earlier he had a pulmonary embolus while in the hospital for shoulder trauma after a skiing accident.

A history of venous thromboembolism, particularly unprovoked or related to a minor transient risk factor, should trigger the administration of thromboprophylaxis during future periods of increased venous thromboembolism risk such as surgery, immobilization, or pregnancy.[47] The situation is less clear if the previous event was provoked by a major transient factor and individualized decision-making is necessary, taking into account the venous thromboembolism

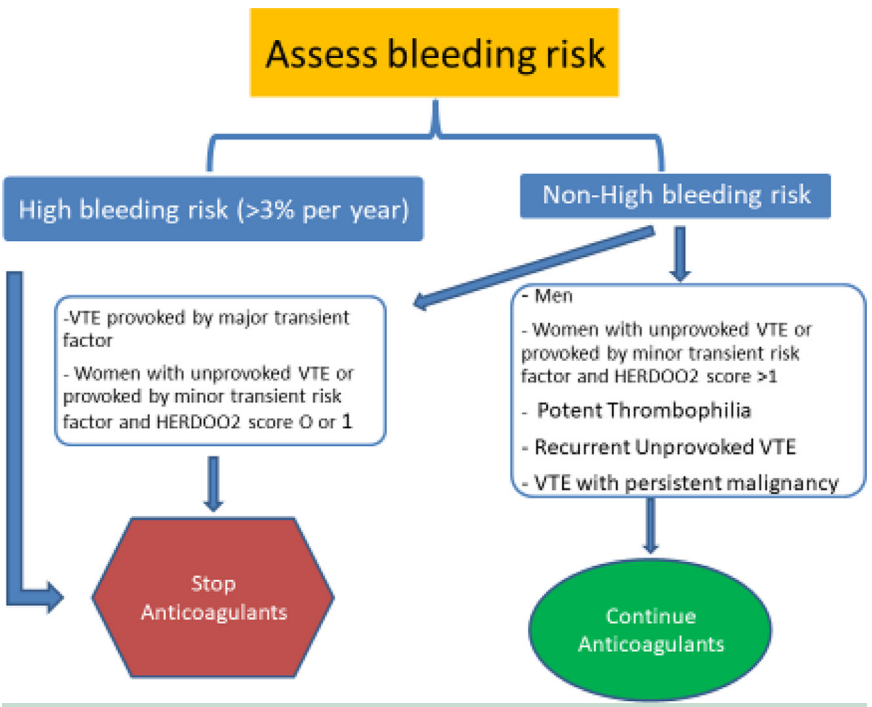


Figure 2 An algorithm for decision-making concerning extended anticoagulation. VTE = venous thromboembolism.

risk, the risk of major or clinically relevant nonmajor bleeding such as wound hematoma, and cost. Both DOACs and LMWH are appropriate drugs for use in this setting, and in cases where there is a contraindication to their use, such as active bleeding or renal failure, intermittent pneumatic devices applied to the legs are an alternative, providing a comparable degree of prophylaxis.[48]

This patient will undergo a procedure with a thrombosis risk of ~1%.[49] There is equipoise regarding the necessity for venous thromboembolism prophylaxis for knee arthroscopy,[50] but in a patient with previous pulmonary embolism related to a minor transient risk factor, prophylaxis using a DOAC or LMWH would be appropriate.

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