



# VENOUS THROMBOEMBOLISM TREATMENT IMPLEMENTATION GUIDE

IMPROVED TREATMENT, TRANSITIONS  
AND ENGAGEMENT OF PATIENTS

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# Introduction

Recent advances in the number of available anticoagulants, in-diagnostic algorithms, and in-risk stratification and prognostication tools have rapidly transformed the care of venous thromboembolism (VTE) patients over the past several years. New developments include easier and safer treatment options, cost-effective diagnostic strategies and tools that help triage pulmonary embolism (PE) patients with “large clots” toward thrombolysis and “small clots” toward outpatient management without the need for prolonged hospitalization. Additionally, effective strategies for the prevention of long-term consequences of VTE, including recurrence and post-thrombotic syndrome, have become clearer. This *Guide* provides a quick overview of VTE to support clinicians in delivering high-value care to their patients.

In 1960, Barritt and Jordan performed the first randomized trial of anticoagulation in pulmonary embolism. Their dramatic results, which were extrapolated to patients with deep vein thrombosis, ushered in the era of anticoagulation treatment for acute VTE. For decades, inpatient care with unfractionated heparin infusion followed by a vitamin K antagonist (warfarin in the United States) was the standard of care. In the 1990s, low-molecular-weight heparin became available and back-to-back trials published in *The New England Journal of Medicine* in 1996 showed that acute VTE could be treated in the outpatient arena. Within the past several years, four direct oral anticoagulants have been approved for acute treatment of VTE — two of these can be given without the need for initial parenteral anticoagulation, allowing for oral-only treatment.

In concert with advances in anticoagulation treatment, the diagnosis of acute VTE has also advanced while the use of venography and pulmonary angiography has virtually disappeared from clinical practice. More recent advancements in diagnostic pathways recommend using a Bayesian approach and utilizing D-dimer testing in patients with low pretest probability, where VTE is ruled out with a negative D-dimer; thus forgoing the expense, radiation exposure (for PE) and unintended consequence of detecting trivial clots.

The validation of risk stratification tools and the use of biomarkers now allow more precise triage algorithms for patients with PE, assuring that care is performed in the correct environment, such as the intensive care unit, a general inpatient unit or at home. Thrombolysis has been shown to decrease mortality in high-risk patients with PE and its use in patients with DVT is being investigated to prevent post-thrombotic syndrome.

The recurrence rate of VTE is 5 to 10 percent per year in patients with unprovoked VTE. Although the decision to extend treatment of VTE past the initial three months usually falls to outpatient care providers, hospitalists are positioned to begin the discussion for indefinite anticoagulation in appropriate patients. The utility of clinical prediction rules, D-dimer testing and thrombophilia testing is important when transitioning patients out of the hospital.

This *Implementation Guide* varies from previous Society of Hospital Medicine (SHM) *Guides* because it does not specifically address quality improvement processes. Wonderful examples of how to build a process improvement team, perform a gap analysis, gain hospital leadership support, use quality improvement tools, develop care maps and measure process improvement can be found in other SHM *Guides* and at the SHM “Quality 101” project site ([http://www.hospitalmedicine.org/Web/Quality\\_Innovation/Quality\\_101/Web/Quality\\_\\_\\_Innovation/Quality\\_101/Landing\\_Page.aspx?hkey=da9afa38-dedd-4250-bee9-dba1a4f6aea2](http://www.hospitalmedicine.org/Web/Quality_Innovation/Quality_101/Web/Quality___Innovation/Quality_101/Landing_Page.aspx?hkey=da9afa38-dedd-4250-bee9-dba1a4f6aea2)).

This *Implementation Guide* is intended to be a quick-read resource for the busy hospitalist and the sections are relatively short by design, with key references to guide further reading if needed. The aim is to complement and not replace comprehensive guidelines like the 10th edition update on Antithrombotic Therapy for VTE Disease <https://www.ncbi.nlm.nih.gov/pubmed/?term=kearon+c+and+chest+and+2016> and expert guidance documents such as those published by the [acforum.org](http://www.acforum.org).



## Section I: Cost-effective Diagnosis of Acute VTE

# Section I. Cost-effective Diagnosis of Acute VTE

## A. VTE Diagnosis

For decades the gold-standard test for acute deep vein thrombosis (DVT) has been venography. This test is now rarely performed due to several serious limitations, including its invasive nature, need for contrast and attendant risk of acute kidney injury, and cost. Several advances in noninvasive diagnostic modalities and studies examining the combined use of these modalities allow for the diagnosis to be made promptly, safely and in a cost-effective manner for most patients. The diagnosis of venous thromboembolism (VTE) is best made using a combination of clinical findings, laboratory testing for markers of active thrombosis and radiologic studies. For both DVT and pulmonary embolism (PE), elicitation of relevant aspects of the past medical history, the nature and course of current symptoms, and pertinent components of the physical exam are essential in the evaluation. A careful and evidence-based assessment helps provide for a timely diagnosis and prompt administration of effective treatment.

### 1. The Clinical Exam

The classic signs and symptoms of DVT include unilateral lower extremity pain, warmth and swelling. Clinicians need to consider alternative diagnoses that can produce similar symptoms, including cellulitis, superficial thrombophlebitis, ruptured Baker's cyst or acute musculoskeletal injury, such as a tear of the gastrocnemius muscle. The cardinal signs and symptoms of acute PE include dyspnea, pleuritic chest pain, cough and hemoptysis. When sub-massive or massive, PE may present with pre-syncope, syncope, respiratory distress, hypotension, shock or sudden death.

**Key elements of the patient's medical history that should be assessed include:**

- Past medical history focusing on conditions that can lead to hypercoagulability, including active cancer (defined as evidence of current disease or treatment within the prior six months) or systemic lupus erythematosus
- Prior history of VTE
- Recent surgery, fracture or immobilization
- Lower extremity trauma
- Prolonged travel by land or air
- Pregnancy history, including the trimester of any miscarriages and the number of live births
- Current medications, including oral contraceptives and hormone replacement therapy, and anticoagulants and anti-platelet agents
- Family history of VTE

Specific findings on physical exam that suggest the presence of an acute DVT include swelling below the calf that is 3 cm larger than the contralateral side. Calf circumference is best measured at a standardized point 10 cm below the tibial tuberosity. Dilated non-varicose veins may be present. Though mild erythema and a low-grade fever may be present, these findings are nonspecific and also commonly seen in cellulitis. Tenderness of the calf or medial thigh or pain on dorsiflexion of the foot (Homan's sign) is also nonspecific and thus its presence does not increase the likelihood of the presence of a DVT.



When examining a patient with suspected PE, clinicians should assess for the presence or absence of tachycardia, tachypnea and hypoxia as these findings have diagnostic and prognostic value. The signs of DVT should also be evaluated as the presence of a DVT in the setting of a patient with suspected PE suggests that a PE is present and can simplify the diagnostic process. For example, a patient with suspected PE who has a unilateral swollen painful leg, for whom computed tomography angiography (CTA) is relatively contraindicated due to chronic kidney disease, can have ultrasonography of the leg, potentially obviating the need for further testing if positive.<sup>1</sup>

Though the overall clinical exam is valuable in diagnosing VTE, each item is of limited diagnostic utility. The value of the exam can be increased through incorporation of specific elements into a clinical prediction rule.

### **2. Clinical Prediction Rules (CPRs)**

Several clinical prediction rules have been shown to help increase the accuracy of the diagnosis of VTE. The Wells DVT rule has been the most extensively studied.<sup>2</sup> This CPR consists of aspects of the medical history and findings on the physical exam combined with the absence of an alternative diagnosis that is at least as likely as DVT (**Table 1** in *Lancet*). The CPR categorizes patients as being low (–2 to 0 points), moderate (1 or 2 points) or high (>3 points) pretest probability for DVT. A meta-analysis identified 14 studies examining the accuracy of the Wells DVT score in more than 8,000 patients and found a prevalence of DVT of 5.0 percent, 17 percent and 53 percent for the low-, moderate- and high-risk groups, respectively.<sup>3</sup>

[Click here](#) to view the Clinical feature Table 1: Clinical Model for predicting pretest probability for deep-vein thrombosis in the *Lancet* article

Both the Geneva and Wells PE CPRs have been shown to have utility in categorizing patients as low, moderate and high probability for PE (**Table 1** in *American Journal of Medicine*). The original Geneva score is not widely used because its calculation requires an arterial blood gas test and a chest x-ray. The revised Geneva score, which does not require these additional tests, has shown diagnostic utility and has been validated in three European emergency departments.<sup>4</sup> The prevalence of PE in the low-, moderate- and high-risk groups based on this score was 8 percent, 28 percent and 74 percent, respectively. The Wells score has shown similar discriminative ability; the original study found a prevalence of 3 percent, 28 percent and 78 percent for the low-, moderate- and high-risk groups, respectively,<sup>5</sup> and has since been shown to be able to dichotomize patients into low- and high-risk groups.<sup>6</sup> Chagnon and colleagues compared the Geneva and Wells scores and found similar accuracy for diagnosing acute PE.<sup>7</sup> Penalzoza and colleagues compared the revised Geneva and Wells scores to each other and to clinical gestalt and found overall better performance by clinical gestalt, primarily due to an increased proportion of patients categorized as either low or high probability for PE.<sup>8</sup> The use of clinical gestalt rather than a structured rule is limited as gestalt is more subjective and dependent on the experience of the examiner.<sup>9</sup>

[Click here](#) to view Table 1. within the article Prediction Rules for Suspected Pulmonary Embolism in the *American Journal of Medicine* written by Chagnon.<sup>7</sup>

### **3. D-dimer Measurement**

D-dimers are breakdown products of cross-linked fibrin, and are typically elevated during an acute thromboembolic event. The test is nonspecific, however, and is elevated in numerous other conditions, including cancer, trauma and infection. D-dimers are also elevated in the elderly, which has led to investigation of age-specific cut-off values. Despite the low specificity, the test has a prominent role in diagnosis. A normal level is a powerful predictor of the absence of an acute VTE. Despite the high negative predictive value, the test remains insufficient as an isolated test to rule out an acute event and is best utilized when combined with clinical assessment.

Several types of D-dimer assays are available, including the quantitative enzyme-linked immunosorbent assay (ELISA), the quantitative latex-derived assay and the whole blood agglutination assay. Of these, the ELISA has been shown to be the most highly sensitive. All three assays have been shown to be able to safely exclude the diagnosis of PE for patients felt to be clinically unlikely to have a PE.<sup>10</sup> The modest specificity of the ELISA assay can limit its utility, as many patients without PE may have an elevated result, including older patients and patients with active infection, trauma, cancer and other conditions. Investigators have assessed the accuracy of age-based cut-offs in efforts to decrease the number of false positives while maintaining the high sensitivity. These studies have shown that using a cut-off of 10 times the age for patients greater than 50 years of age increased specificity from 34 to 46 percent without decreasing sensitivity.<sup>11</sup>

### **4. Combination of CPR and D-dimer Measurement**

As both the clinical exam and D-dimer testing can help identify patients who are unlikely to have had an acute VTE, the combination of these tests would be expected to be particularly powerful clinically. Wells and colleagues examined the combined use of the Wells DVT CPR and D-dimer measurement to determine whether ultrasonography can be safely avoided for select patients.<sup>12</sup> Subjects deemed unlikely to have DVT based on the dichotomous Wells score were randomized to usual care where an ultrasound was performed or to a D-dimer strategy. For the D-dimer group, patients who were at low (unlikely) likelihood for DVT and had a negative D-dimer result had no further testing and were not anticoagulated. The incidence of VTE during the three-month follow-up period was 0.4 percent vs. 1.4 percent ( $P=0.16$ ) for the D-dimer and usual care groups, respectively. *The American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Guidelines, 9th edition (AT9)* extended the utility of the combination of CPR and D-dimer by suggesting that patients at moderate risk who have a negative result for a highly sensitive D-dimer assay can also be considered to be negative for DVT without requiring an ultrasound.<sup>13</sup>

The Christopher trial also evaluated the safety of omitting radiographic testing for patients with suspected acute PE who were at low pretest probability (unlikely) for PE based on the dichotomized Wells score and had a negative D-dimer test.<sup>14</sup> Only one of 437 patients who were at low probability and had a negative D-dimer result was noted to develop a VTE on three-month follow-up (negative predictive value 99.5%).

### **B. Deep Vein Thrombosis**

#### ***1. Compression Ultrasonography***

B-mode ultrasonography can include both visualization of vein architecture and thrombi as well as compression ultrasonography. Duplex ultrasonography is the combination of B-mode ultrasound plus Doppler waveform analysis. Color flow can be added for further examination of thrombi through detection of obstruction to flow. Though several modalities are available, studies have found that compression ultrasonography as a stand-alone test is a highly accurate means of diagnosing acute DVT.<sup>15</sup> Proximal compression ultrasound consists of sequential compression of the deep veins of the leg to assess for venous blood flow. The common femoral, superficial femoral, deep femoral and popliteal veins are typically assessed. The criterion for a positive test is lack of full compressibility of any vein segment by gentle probe pressure. The 2-point compression ultrasound is limited to compression of the common femoral vein at the groin and the popliteal vein proximal to the popliteal fossa and has proven to be accurate and less time-consuming than more extensive ultrasound testing of the lower extremity.<sup>16,17</sup>

Whole-leg ultrasound testing can be performed in an effort to identify calf vein thrombi. Concerns regarding this strategy are that the component examining the calf is unnecessary if a proximal thrombus has been detected, the sensitivity and specificity are decreased compared to detection of proximal thrombi, and there is potential for treatment of isolated calf vein thrombi that would not have propagated proximally. An alternative strategy to whole-leg testing is to perform serial proximal compression ultrasonography, which entails repeating the test in one week for patients for whom the clinician has a high pretest probability for DVT and have a negative initial study. Serial testing can be performed for patients for whom the initial test was technically inadequate or equivocal, such as patients with morbid obesity or who have difficulty complying with the initial exam due to discomfort. Bernardi and colleagues performed a large randomized trial comparing whole-leg and 2-point ultrasonography.<sup>16</sup> Patients in the 2-point ultrasonography group with a negative initial test underwent D-dimer testing. If the D-dimer result was negative, DVT was considered excluded. Patients with a positive D-dimer result underwent repeat ultrasound testing. Of 256 patients with an initial negative ultrasound and a positive D-dimer result, 14 (5.5 percent) were diagnosed with an acute DVT by serial ultrasonography. This study suggests that serial testing should be considered for patients who do not have a low pretest probability who have a positive D-dimer test. Repeat testing is unnecessary for patients who are at low or moderate pretest probability and have a negative D-dimer result.

#### ***2. DVT Diagnosis – Recommendation***

Several efficient and cost-effective approaches are possible when evaluating patients for acute DVT.<sup>13</sup> Pretest probability should be assessed for all patients with suspected DVT. Use of a validated CPR, such as the Wells score, is preferable though clinical gestalt can be utilized. Patients at low or moderate (or unlikely) pretest probability should have D-dimer testing; DVT can be considered excluded for patients with a negative result. A highly sensitive D-dimer assay should be used in patients with moderate pretest probability given the increased prevalence of DVT relative to patients with low pretest probability. If the sensitivity of the assay is unknown, compression ultrasonography should be performed rather than a D-dimer testing strategy for the moderate-probability patients. Patients at high pretest probability should have compression ultrasonography and if negative, should either have D-dimer testing using a highly sensitive assay or repeat ultrasound testing in one week.

## Section I. Cost-effective Diagnosis of Acute VTE (continued)

- [Click here to view the Diagnosis of DVT tables from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, specifically the figures listed below:](#)
  - Recommendations for evaluation of suspected first lower extremity DVT patients with moderate pretest probability (PTP) for DVT – Figure 2
  - Recommendations for evaluation of suspected first lower extremity DVT patients with high pretest probability (PTP) for DVT – Figure 3
  - Use of Whole-leg US – Figure 5

For all patient groups, patients who have DVT excluded should be followed closely for at least one week and further testing performed (e.g., repeat compression ultrasonography or whole-leg ultrasound) if symptoms worsen and an alternative diagnosis has not been identified.

### C. Pulmonary Embolism

#### 1. Ventilation-Perfusion (V/Q) Scanning

V/Q scanning was the primary means for diagnosing PE prior to the widespread availability of computed tomography angiography (CTA). V/Q scanning entails comparing the uptake of an inhaled radioisotope tracer, such as technetium or xenon, by the lung with vascular uptake of an injected technetium radioisotope. Areas of mismatch where lung uptake is normal and vascular uptake is diminished suggest the presence of a thrombus. The utility of V/Q scanning is primarily limited by conditions impacting lung uptake of the tracer, including pneumonia and heart failure, which decrease the accuracy and lead to few reports being interpreted as “normal” or “high probability” for PE. In the PIOPED study, only 14.1 percent and 13.3 percent of scans were read as “normal or near normal” and “high probability,” respectively.<sup>18</sup> The remainder were classified as “low” or “intermediate” probability. The prevalence of PE for the low-, intermediate- and high-probability V/Q scan results was 16 percent, 33 percent and 88 percent, respectively. All interpretations require clinicians to place the result in the context of the patient’s clinical probability to determine whether treatment or further testing is indicated. For example, though the prevalence of PE in patients with “low probability” results is not low enough to omit further testing, the incidence was 4 percent when limited to patients whose pretest probability was 0–19 percent by the treating clinicians.

Though V/Q scanning remains limited as a diagnostic modality, it remains a useful tool for diagnosis for select patients. One patient group who may benefit are patients with severe renal insufficiency for whom the contrast dye load necessary for CTA testing might worsen renal failure.

#### 2. Computed Tomography Angiography

CTA has supplanted V/Q scanning as the test of choice for PE. CTA has the added advantage of being able to assess the pulmonary parenchyma and therefore can identify alternative diagnoses, including pneumonia and malignancy. The PIOPED II study demonstrated that CTA has high sensitivity and specificity for acute PE compared to V/Q scanning.<sup>19</sup>

Anderson and colleagues directly compared CTA and V/Q scanning in the diagnosis of PE.<sup>20</sup> Patients with suspected PE were randomized to either CTA or V/Q scanning. Patients with a negative evaluation were not anticoagulated and followed for three months. Significantly more patients who underwent CTA were diagnosed with PE (19 percent vs. 14 percent). On follow-up, the incidence of PE for patients who had PE excluded was 0.4 percent for the CTA group and 1.0 percent for the V/Q group. This study demonstrated that CTA is highly sensitive for the diagnosis and is an adequate diagnostic strategy. The clinical significance of the additional PE identified by CTA relative to V/Q scanning was uncertain. These PEs were treated and there was a lower incidence of PE on follow-up, suggesting that CTA detected clinically important thromboemboli. The possibility of false-positive tests or the identification of small, subsegmental PE (SSPE) of limited clinical significance by CTA was also raised.

Given the enhanced ability to detect small abnormalities, Carrier and colleagues performed a systematic review of CTA to investigate the potential for the overdiagnosis of PE.<sup>21</sup> They found that trials utilizing multiple-detector CTA identified a greater number of patients with PE compared to single-detector CTA, though the rate of clinically relevant PE without treatment was low and similar for both groups. The authors concluded that multiple-detector CTA likely identifies small PE that may not be clinically significant. Further support for the possibility of overdiagnosis comes from data showing that the incidence of PE in the U.S. markedly increased after the introduction of CTA, though overall mortality from PE has not correspondingly increased.<sup>22</sup> These data suggest that small thromboemboli of questionable clinical importance are being identified.

Goy and colleagues examined the outcomes of patients with SSPE identified at three hospitals in Canada.<sup>23</sup> They found that 82 of 550 positive CTA tests were categorized as isolated SSPE. Of these, 55 of 82 (67.1 percent) were noted to have an alternative diagnosis identified. Anticoagulation was administered to 52.4 percent of patients with SSPE. No patients with isolated SSPE who were treated or untreated developed a PE on follow-up. A Cochrane review found no randomized trials assessing the efficacy of treatment for SSPE.<sup>24</sup> Overall, the significance of these emboli remains controversial and is being evaluated in a cohort management study by withholding anticoagulation for patients with SSPE and negative bilateral serial lower extremity ultrasound.<sup>25</sup> Management is discussed further in the “Treatment” section.

### ***3. Magnetic Resonance Angiography***

Magnetic resonance angiography (MRA) has been proposed as a potential modality for the diagnosis of PE. The PIOPED III study compared gadolinium-enhanced MRA with CTA.<sup>26</sup> The study revealed the technical difficulties of MRA testing for PE; 25 percent of all MRA results were technically inadequate to assess whether a PE was present. Of interpretable results, sensitivity and specificity were 78 percent and 99 percent, respectively. Due to the technical limitations, moderate sensitivity and high cost, MRA should be reserved for centers with expertise and experience and for patients who have contraindications to CTA.

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## Section II: Outpatient Management of VTE



## Section II: Outpatient Management of VTE

A sea change in the management of uncomplicated DVT occurred in the 1990s with the approval of subcutaneous low-molecular-weight heparins (LMWH) that allowed bridging to an oral vitamin K antagonist (VKA) in the outpatient setting. At first, providers were sufficiently hindered by inertia, protocols and clinical insecurity that they would consider sending patients with DVT home only for the final day or two of bridging; but over time, enough clinical experience accumulated that short stays, observation unit stays or even direct discharge home from the ED for selected patients became the norm. This approach, while appealing on the surface to patients, was still encumbered by the need to teach patients injection techniques, the need to rely on self-injection after discharge, the ready availability of (and insurance coverage for) outpatient LMWH and the need for daily INR monitoring during bridging. Practice gradually moved in the direction of outpatient management for DVT because of declining reimbursement for inpatient care.

The clinical environment was therefore “ripe” for the adoption of mostly to wholly outpatient management of DVT when direct oral anticoagulants (DOACs) gained approval for treatment of DVT starting in late 2012. While insurance coverage issues persist, the need for injection therapy, for bridging and for ongoing management and monitoring of warfarin and other VKA therapy were suddenly rendered obsolete. The remaining clinical issues in management of VTE include (1) risk stratification of DVT (whom should I admit?), (2) the disposition decision between observation unit or direct discharge in those patients who do not need inpatient care choice of agents (how quickly can I send them home?), (3) the choice among approved DOAC agents and (4) the possibility of outpatient management of the higher-risk manifestation of VTE, pulmonary embolism.

### A. Risk Stratification

There are many ways of classifying DVT, such as proximal vs. distal, provoked vs. unprovoked, symptomatic vs. asymptomatic. In general, proximal DVT (in the lower extremity, popliteal and proximal) carries a higher risk of both embolization and recurrence compared to isolated calf DVT.<sup>1</sup> Pelvic DVTs and those clots extending into the inferior vena cava generally are managed, at least at first, in the inpatient setting. Outpatient therapy is generally not deemed appropriate for DVT that is (a) iliofemoral or higher, (b) already associated with diagnosed PE, (c) a high risk of bleeding on anticoagulation therapy (such as the patient on concomitant antiplatelet therapy or the patient with known GI, GU or other bleeding issues), or (d) a comorbidity that itself requires admission.<sup>2</sup>

The differentiation of provoked vs. unprovoked DVT is pertinent to the decision of how long a patient should remain anticoagulated. It generally does not enter into the disposition decision, except perhaps in patients with unprovoked VTE that is recurrent and has previously resulted in PE.

Likewise, presence of symptoms does not have much impact on site of care. The anatomic location of the DVT is more important, although it should also be noted that asymptomatic DVT is more often diagnosed in the inpatient setting. Asymptomatic PE may well be detected in the outpatient setting during the evaluation of other pulmonary disease or of malignancy.

Current clinical practice in the U.S. is that pulmonary embolism is generally managed, at least at the time of diagnosis, in the inpatient setting. See below for further information on how that practice may be evolving.

### **B. When is an Observation Stay Appropriate?**

If the patient does not meet one of the four criteria for inpatient management previously mentioned, the indications for an observation stay are limited and include both clinical and social concerns. An observation stay is appropriate prior to outpatient management of DVT (a) in patients who have significant comorbidities that require stabilization and observation unit management, (b) for patients (or caregivers) requiring extended education and/or compliance assessments, (c) for patients requiring financial assistance, (d) to arrange follow-up for required dose transitions on rivaroxaban or apixaban, or (e) for instruction or logistical planning for patients who are being managed on LMWH as a bridge to VKA, or when being discharged on LMWH with transition to dabigatran or edoxaban.

### **C. Which Agent Should I Choose?**

There are, and it is unlikely there ever will be, no studies that directly compare one DOAC to another. All four (in the order in which they were approved: rivaroxaban, apixaban, dabigatran and edoxaban) came to market in the U.S. based on studies in which the new oral anticoagulant (NOAC) was compared to a bridge-to-warfarin strategy. It is not scientifically valid to compare these trials in an effort to argue for either the safety or the efficacy of one DOAC over another for the management of VTE in the outpatient setting. There is, however, an obvious distinction in the requirement for parenteral lead-in therapy prior to use of a DOAC. Because of the way their Phase 3 studies were designed, rivaroxaban and apixaban may be started immediately upon VTE diagnosis. Those studies allowed up to 48 hours of treatment with a parenteral anticoagulant before randomized therapy began, but patients so treated had outcomes that were no different from those who received no pre-randomization therapy.<sup>3,4,5</sup> On the other hand, dabigatran and edoxaban were compared to bridging therapy only after an initial five or more days of parenteral therapy with a LMWH, and their labels concordantly require such “lead-in” therapy (note: this is not bridging, as LMWH therapy and DOAC therapy do not overlap). For that reason, dabigatran and edoxaban are less reasonable options for a direct-to-outpatient (including observation) strategy. For those patients who were initially triaged to inpatient management, these drugs may have appeal over VKA therapy after the patient leaves the hospital.

### **D. What About PE (Pulmonary Embolism)?**

In Canada and Western Europe, it is not uncommon for patients diagnosed in the outpatient setting with PE who are hemodynamically stable to be treated as outpatients, after initial anticoagulation is administered in the healthcare setting. This practice has not developed to any robust extent in the U.S. to date, owing to — again — clinical inertia, provider insecurity and medicolegal concerns. A notable exception has been the management of patients with active non-pulmonary malignancy who have asymptomatic and incidentally identified subsegmental PE. While such patients in the past have often been managed with long-term LMWH (especially dalteparin), experience seems to be growing with the use of DOACs in this setting.<sup>6</sup> However, an outpatient disposition decision in such cases should be made by the patient’s oncologist.

A number of small trials and others expected to start in 2015 and 2016 may ultimately further expand both the use of DOACs and predominately outpatient treatment settings for hemodynamically stable PE.<sup>7</sup> There is no thought that patients who have hemodynamic instability at presentation will be triaged to outpatient therapy, although in otherwise healthy patients, those who respond quickly to supportive therapy and anticoagulation and do not require thrombolysis may one day be deemed suitable for initial management and observation in observation units.

## Section II: Outpatient Management of VTE (continued)

In the meantime, a to-home disposition (whether direct or via observation) for PE must be grounded in the context of the patient's overall clinical status (especially cardiac and pulmonary comorbidities), the patient's (and caregiver's) level of comfort with the outpatient approach (until the standard of care changes, specific documentation of informed consent might be advisable), and clear assessment of the individual patient's risk-benefit balance vis-à-vis chronic oral anticoagulation in any setting.

Pending specific, randomized, U.S.-based studies and/or registries of outpatient PE management, the suitable candidate for outpatient (or expedited discharge from inpatient) management will have (a) a low risk of mortality (probably best and most easily indicated by a sPESI<sup>8</sup> score of 0 or PESI<sup>9</sup> Class I or II), (b) hemodynamic stability, (c) oxygen saturation >95 percent on room air, (d) no requirement for narcotic analgesia, (e) a stable home situation (including unfettered access to medications, follow-up and emergency care) and (f) other comorbidities that carry their own independent indication for admission.<sup>10,11</sup> In addition, as noted earlier in the discussion of DVT, it is likely unwise to move too quickly to outpatient management of patients with concomitant DVT and PE.

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## Section III: Thrombolysis and Pharmacomechanical Treatment of DVT

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The usual medical management of acute DVT changed little over the past 50 years,<sup>1</sup> with a parenteral bridge to a vitamin K antagonist, until the availability of a single-drug approach with the DOACs. The anticoagulation approach, however, provides minimal fibrinolytic activity, focusing instead on prevention of clot propagation and embolization and relying on the body's fibrinolytic defenses (mostly native urokinase) to “break down” the clot. With high proximal (in the lower extremity, that is iliofemoral and pelvic) DVT, the clot burden can be so large, and the risk of pulmonary embolism so high, that clinicians are not comfortable with just the “anticoagulate and wait” approach.<sup>2</sup> A fully occluded iliac vein system in a patient with poor venous collaterals impeding the venous drainage of the entire leg<sup>2,3</sup> increases the risk of subsequent post-thrombotic syndrome (PTS), which itself can be debilitating.<sup>4</sup> Attempts to decrease the risk of PTS include systemic fibrinolysis, local catheter-directed fibrinolysis and — most recently — pharmacomechanical clot removal.

Systemic fibrinolysis for proximal DVT with tissue plasminogen activator (TPA) results in greater than 50 percent clot lysis more often than using heparin alone, but does not significantly reduce PTS.<sup>5</sup> A meta-analysis of randomized trials in patients with proximal DVT showed similar lysis success for streptokinase.<sup>5</sup> Major bleeding, however, is greater with systemic lysis than with anticoagulation alone, which leads to the idea of “local” catheter-directed lysis (CDL). CDL is a fluoroscopically guided invasive procedure in which an infusion catheter delivers lytic agents directly into the clot. CDL of acute proximal DVT has been shown to prevent valvular damage, reduce the likelihood of PTS and prevent recurrent DVT,<sup>6</sup> and the reduced dose with local direct infusion reduces the risk of bleeding complications compared to systemic venous lysis. For example, Comerota et al. compared 68 patients with iliofemoral DVT treated with CDL to 30 similar patients treated with anticoagulation alone and the patients who received CDL had less PTS, fewer DVT recurrences and significantly better quality of life.<sup>7</sup>

In another study, Enden et al. reported improved long-term outcomes in patients with proximal DVT treated with CDL vs. anticoagulation alone (n=118)<sup>8</sup> and venous patency at six months was increased with CDL (64 percent vs. 36 percent, p=0.004). Major bleeding was similar in this study, with 2 percent in CDL (using TPA) and 1.7 percent in anticoagulated patients. Of particular interest to hospitalists, the initial anticoagulation dosage before CDL is not different from usual anticoagulation treatment doses; however, it is preferable to obtain vascular access before anticoagulation, so an early consult to Interventional Radiology may be advisable. It should also be noted that the typical duration of a CDL procedure exceeds 48 hours.

A more efficient and intuitively appealing option is the “pharmacomechanical (PM) clot dissociation” approach, which is already available but is still being evaluated in a large National Heart, Lung, and Blood Institute (NHLBI)-funded trial comparing PM CDL to CDL alone.<sup>9</sup> In the PM approach, endovascular lysis is augmented with local mechanical thrombus fragmentation, with or without aspiration, during the CDL procedure. In retrospective comparisons of PM CDL versus CDL alone, the rates of thrombolysis (70 percent to 80 percent) and of major bleeding (5 percent to 8 percent) were similar, but PM CDL was associated with shorter treatment times, lower lytic doses, shorter ICU and hospital stays, and reduced costs.<sup>10,11,12</sup>

The latest refinements in PM treatment use single-use disposable catheters, which allow the combination of catheter-directed thrombolysis and mechanical thrombus fragmentation and aspiration to be completed in a single treatment session, often eliminating the need for post-procedural ICU monitoring. These devices include proximal and distal balloons that, when inflated after passing the catheter through the targeted clot, isolate the clot to minimize the likelihood of either systemic lytic agent exposure or proximal embolization of clot fragments. The two devices currently approved by the Food and Drug Administration (FDA) are the AngioJet Rheolytic Thrombectomy System (Possis Medical, Minneapolis, MN) and the Trellis Peripheral Infusion System (Covidien, Mansfield, MA), and pertinent details about their use have been published.<sup>4</sup> After clot removal, some patients may require iliofemoral venous angioplasty and stenting.<sup>2</sup> An algorithm for the management of iliofemoral clot has been proposed.<sup>13</sup>

# Section III: Thrombolysis and Pharmacomechanical Treatment of DVT

(continued)

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## Section IV: Risk Assessment and Thrombolysis in Acute Pulmonary Embolism

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The severity of clinical presentation predicts the short-term mortality risk in patients with acute PE. The development of acute right ventricular dysfunction (RVD) is a crucial determinant of worse outcomes. Severe RVD manifesting with hemodynamic instability is seen in about 12 percent of patients and their risk of in-hospital or 30-day PE-related mortality is greater than 15 percent.<sup>1,2</sup> These high-risk patients may benefit from timely aggressive interventions to restore pulmonary perfusion; thus, prompt recognition is critical and treatment options must be explored even while diagnostic confirmation is still in progress. The European Society of Cardiology (ESC) guidelines describe hemodynamically unstable patients as those who present with either shock or persistent systemic hypotension, which is defined as a systolic blood pressure (SBP) <90 mmHg or a drop in SBP  $\geq$ 40 mmHg for >15 minutes that is not due to new-onset arrhythmia, hypovolemia or sepsis.<sup>3</sup>

Among those who are hemodynamically stable at presentation, the ESC guidelines recommend the use of validated clinical prediction rules to differentiate between low-risk patients who may be appropriate for outpatient management and intermediate-risk patients who require further monitoring and risk stratification (Figure 1).<sup>3</sup> These prediction tools incorporate acute clinical findings with the patient's premorbid condition in estimating the risk of death. They are generally efficient at identifying those who are at low risk of death, with pooled mortality rates of 0.7 percent at 14 days, 1.7 percent at 30 days and 2.2 percent at 90 days.<sup>4</sup>

The most extensively validated clinical prediction model is the Pulmonary Embolism Severity Index (PESI). The original PESI includes 11 clinical variables that are readily available or obtainable at the time of presentation (Table 1). It is most reliable at identifying those who are least likely to die within 30 days. In the derivation cohort, the 41 percent who were classified to be very low to low risk (Class I and II) had a 2 percent mortality risk, while the rest who were intermediate to very high risk (Class III to V) had a 14 percent risk of death within 30 days.<sup>5</sup> In a subsequent validation study, low-risk PESI (Class I and II) had an overall mortality risk of 1.2 percent and a PE-specific mortality risk of 0.7 percent.<sup>6</sup> Another study showed a 90-day risk of death of only 1 percent for this category, with no recurrent thromboembolic or major bleeding events.<sup>7</sup>

The sPESI is a simplified version of the original PESI that includes only seven clinical variables with equal weights, which makes the score easier to calculate. However, a comparative analysis found that the original PESI classified more patients as low risk and it had a greater discriminatory power compared to sPESI.<sup>8</sup>

The Geneva risk score incorporates six variables that independently predict a composite of adverse outcomes of acute PE, specifically recurrent VTE, major bleeding and death. In the derivation study, 67.2 percent of patients were identified as low risk while 32.8 percent were high risk; the rates of adverse outcomes at 90 days for each group were 2.2 percent and 26.1 percent, respectively.<sup>9</sup> However, when the Geneva score was compared to PESI, the latter performed better at identifying patients who have a low risk of death at 30 days.<sup>10</sup>

Hemodynamically stable patients who are classified as non-low-risk based on these clinical prediction tools are considered intermediate risk, and can be further stratified using imaging and laboratory markers of acute RVD and myocardial injury. However, the American College of Chest Physicians (ACCP) recommends against routinely performing these tests in all patients with PE, even those with non-low-risk PESI.<sup>11</sup> Generally, these imaging and laboratory tests have low positive predictive values for early mortality; and positive results do not have clear therapeutic implications. The performance of these tests is more useful at identifying patients who are at low risk of death.

Acute RVD can be detected using any of the following widely available diagnostic tools: echocardiography, CTA, brain natriuretic peptide (BNP) and NT-proBNP. PE-related acute myocardial injury manifests with elevations in levels of cardiac troponin I or T, or heart-type fatty acid-binding protein (H-FABP). The presence of both acute RVD and myocardial injury defines an intermediate-high category, which may necessitate close monitoring to detect hemodynamic decompensation early and promptly initiate rescue reperfusion when indicated. If there is no evidence of either RVD or myocardial injury, the patient is classified as intermediate-low risk. If both RVD and myocardial injury are absent, the risk of early mortality is low. Negative findings on imaging and laboratory tests are associated with a low likelihood of PE-related in-hospital or 30-day mortality.<sup>3</sup>



### A. Primary Pulmonary Reperfusion for Acute Pulmonary Embolism

Primary pulmonary reperfusion can significantly reduce the risk of death for hemodynamically unstable patients with acute PE. Systemic thrombolysis is the treatment of choice,<sup>11</sup> with more than 90 percent of patients showing signs of clinical and echocardiographic improvement within 36 hours.<sup>12</sup> It is most effective if administered within 48 hours of symptom onset, but it is still beneficial to those who have symptoms for six to 14 days.<sup>13</sup> FDA-approved regimens for systemic thrombolysis of PE are shown in Table 2 and the contraindications to thrombolysis are listed in Table 3.

If systemic thrombolysis is contraindicated or if it has failed to result in hemodynamic improvement, surgical embolectomy or percutaneous catheter-directed interventions are the recommended alternatives.<sup>3,11</sup>

For hemodynamically stable patients with acute PE, primary pulmonary reperfusion with thrombolytics may be considered for those who are at intermediate risk of short-term mortality. The Pulmonary Embolism Thrombolysis (PEITHO) trial was a randomized double-blind study that compared tenecteplase, a recombinant tissue plasminogen activator (r-tPA), against placebo in normotensive patients with intermediate-risk pulmonary embolism, and found that fibrinolytic therapy was associated with less hemodynamic decompensation with a number needed to treat (NNT) of 29. However, there was increased risk of major hemorrhage with a number needed to harm (NNH) of 11. Both seven-day and 30-day mortality were unchanged.<sup>14</sup> The Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial used a lower dose of the thrombolytic drug and found it to be effective at reducing the risk of pulmonary hypertension and recurrent PE (NNT, 2) without increasing the risk of bleeding.<sup>15</sup> A subsequent meta-analysis on intermediate-risk patients with RVD, which included results from both the PEITHO and MOPETT trials, showed an increased risk of major bleeding with thrombolytics compared to anticoagulation alone (NNH, 18) but there was a significant reduction in all-cause mortality (NNT, 65).<sup>16</sup> When only the results from trials with an average patient age of  $\leq 65$  years were included, there was no significant difference in the rate of major bleeding.

The most recent ACCP Guidelines suggest that PE patients who are not hypotensive are best initially managed with aggressive anticoagulation and other supportive measures alone; thrombolytic therapy should be reserved for those who become hypotensive or who exhibit other signs of clinical deterioration.<sup>11</sup>

### B. Early Discharge or Outpatient Management for Low-Risk Patients

Patients with acute PE are considered low risk for early mortality if they are hemodynamically stable and if they have a PESI score  $\leq 85$  or a sPESI score of 0.<sup>3</sup> They may be managed safely in the outpatient setting either completely or after a brief period of hospitalization. LMWH, administered subcutaneously, can provide immediate anticoagulation. Alternatively, the new DOACs, which have emerged in the past decade, have broadened the choices for both immediate and extended anticoagulation. Patients considered for outpatient management must have access to any of these anticoagulant options and must not have any contraindications for their use.

Multiple studies have demonstrated the safety of managing carefully selected patients with low-risk acute PE in the outpatient setting.<sup>17,18,19,20</sup> An international trial randomly assigned patients with low-risk PE (PESI Class I and II) to either outpatient or inpatient treatment, and found that outpatient care is non-inferior to hospitalization with respect to recurrent VTE and death within 90 days.<sup>18</sup>

## C. Subsegmental Pulmonary Embolism

Subsegmental PE (SSPE) may present in a symptomatic patient or may be found incidentally during imaging evaluation for other pulmonary conditions. Advances in technology, particularly with increasing resolution of computed tomography scanners, has been associated with increased diagnosis of SSPE.<sup>21,22,23</sup> However, there is only fair inter-observer agreement ( $\kappa = 0.38$ ) among radiologists for emboli in the subsegmental vessels.<sup>24</sup> In one study, 59.4 percent of SSPE diagnosed on computed tomography pulmonary angiography (CTPA) were considered negative upon retrospective review by experienced chest radiologists.<sup>25</sup>

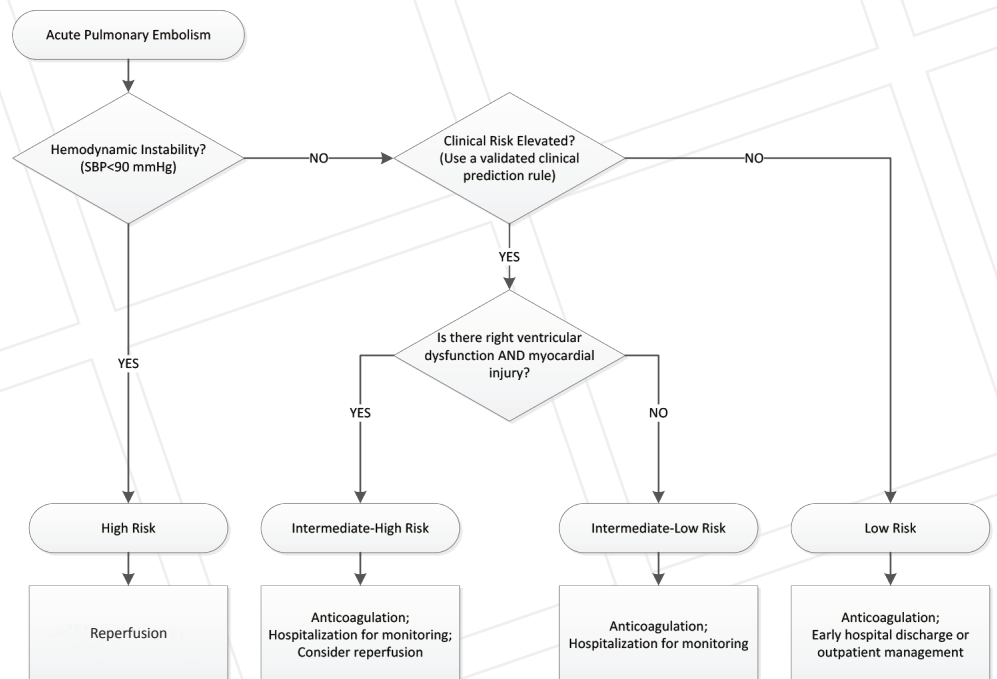
In a cohort study of patients who underwent CTPA at three Canadian teaching hospitals, 15 percent of those with PE had SSPE, about 52 percent of whom received anticoagulation.<sup>26</sup> There were no documented recurrent VTE events in any of the patients with SSPE, regardless of anticoagulation treatment. But two of the 43 (5 percent) patients on anticoagulation experienced life-threatening bleeding complications.

In another study, which combined data from two prospective outcome studies, 16 percent of patients with PE had SSPE and they had the same prevalence of VTE risk factors and three-month risks of recurrent VTE and of mortality as those patients with more proximally located PE.<sup>27</sup> The proportion of patients with signs and symptoms related to DVT was also similar in both groups.

Thus, the clinical relevance of SSPE currently remains unclear. Most experts suggest that when a patient is diagnosed with SSPE, a compression ultrasonography of both legs must be performed to determine if the SSPE is an isolated finding. If the leg compression ultrasonography is negative for proximal VTE, the decision to treat with anticoagulation must be individualized based on patient-specific risks and benefits.<sup>11</sup>

In summary, acute PE can manifest with varying degrees of severity. Patients who present with shock or persistent systemic hypotension should be considered for immediate systemic thrombolysis. Hemodynamically stable patients should be risk-stratified based on acute clinical findings and underlying comorbidities. Low-risk patients may be treated safely in the outpatient setting. Patients with isolated SSPE may not require anticoagulation, and treatment decisions must be individualized based on patient-specific factors.

**Figure 1. Risk Stratification Algorithm for Acute Pulmonary Embolism<sup>3</sup>**



## Section IV: Risk Assessment and Thrombolysis in Acute Pulmonary Embolism (continued)

**Table 1. Pulmonary Embolism Severity Index<sup>5,28</sup>**

Clinical Variable	Points	
	Original	Simplified
Age >80 years old	Age in years	1
Male sex	10	
History of cancer	30	1
History of heart failure	10	1
History of chronic lung disease	10	
Pulse $\geq$ 110 beats/minute	20	1
Systolic blood pressure <100 mmHg	30	1
Respiratory rate $\geq$ 30 breaths/minute	20	
Temperature <36°C	20	
Altered mental status	60	
Arterial oxyhemoglobin saturation <90%	20	1
Risk Class	Total Point Score	
Low	$\leq$ 85 <sup>a</sup>	0
High	$>$ 85 <sup>b</sup>	$\geq$ 1

<sup>a</sup>Class I and II <sup>b</sup>Class III, IV and V

**Table 2. Systemic Thrombolysis for Acute Pulmonary Embolism<sup>a</sup>**

Thrombolytic Agent	Administration	Precautions
Tissue Plasminogen Activator (tPA) (Alteplase)	100 mg IV over two hrs; follow with heparin infusion once PTT or thrombin time returns to twice normal or less	Extravasation can cause ecchymosis and/or inflammation
Streptokinase (SK)	250,000 IU IV over the first 30 mins, then 100,000 IU/hour for 24 hrs (72 hrs if concurrent DVT is suspected)	hypotension, anaphylaxis, asthma, allergic reaction (if mild, reduce infusion rate)
Recombinant Human Urokinase (UK)	4,400 IU/kg IV over the first 10 mins, then 4,400 IU/kg per hour for 12 hrs	

<sup>a</sup>Source: FDA-approved prescribing information.

## Section IV: Risk Assessment and Thrombolysis in Acute Pulmonary Embolism (continued)

**Table 3. Contraindications to Systemic Thrombolysis<sup>a</sup>**

Thrombolytic Agent	Contraindications
Tissue Plasminogen Activator (tPA)(Alteplase)	<ul style="list-style-type: none"> <li>active internal bleeding</li> <li>history of cerebrovascular accident</li> <li>recent intracranial or intraspinal surgery or trauma</li> <li>intracranial neoplasm, arteriovenous malformation or aneurysm</li> <li>known bleeding diathesis</li> <li>severe uncontrolled hypertension</li> </ul>
Streptokinase (SK)	<ul style="list-style-type: none"> <li>active internal bleeding</li> <li>recent (within two months) cerebrovascular accident, intracranial or intraspinal surgery</li> <li>intracranial neoplasm</li> <li>severe uncontrolled hypertension</li> <li>severe allergic reaction to streptokinase</li> </ul>
Recombinant Human Urokinase (UK)	<ul style="list-style-type: none"> <li>active internal bleeding</li> <li>recent (within two months) cerebrovascular accident</li> <li>recent (within two months) intracranial or intraspinal surgery</li> <li>recent trauma including cardiopulmonary resuscitation</li> <li>intracranial neoplasm, arteriovenous malformation or aneurysm</li> <li>known bleeding diatheses</li> <li>severe uncontrolled arterial hypertension</li> </ul>

<sup>a</sup>Source: FDA-approved prescribing information.

# Section IV: Risk Assessment and Thrombolysis in Acute Pulmonary Embolism (continued)

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## Section V: Selection of Anticoagulants

## Section V: Selection of Anticoagulants

Acute venous thromboembolism (VTE) has conventionally been treated with a dual-drug approach consisting of a parenteral anticoagulant overlapped with warfarin until attainment of a therapeutic INR. However, given their proven safety and efficacy, direct oral anticoagulants (DOACs) are now given preference over conventional approaches for VTE treatment in recently updated guidelines.<sup>1</sup> It is important to emphasize that not all patients are appropriate DOAC candidates. Thus, practical anticoagulant selection that takes into consideration patient preferences, clinical characteristics and drug properties is essential.

### A. Conventional vs. DOAC Approaches

VTE treatment is divided into three phases: acute (first 5–10 days), long-term (first three months) and extended (>three months). In the acute phase, the risk for adverse events such as DVT extension, VTE recurrence, bleeding and death is extremely high. Rapid attainment of therapeutic levels of anticoagulation with evidence-based approaches is imperative to minimize short- and long-term morbidity and mortality.<sup>1</sup>

Because of warfarin's slow onset (**Table 1**), conventional dosing strategies involving use of rapid-acting parenteral anticoagulants overlapped with warfarin have evolved and been shown to be extremely effective.<sup>1,2</sup> The chosen parenteral anticoagulant must be overlapped with warfarin for a minimum of five days and until the INR is >2 for two consecutive measurements to ensure adequate anticoagulation (**Figure 1**).

The DOACs represent a significant shift in the therapeutic landscape of VTE treatment. The pharmacokinetics of these drugs, as a class, dramatically differ from those of warfarin and more closely approximate those of LMWH (**Table 1**). The short half-life and rapid onset of action of DOACs precludes the need for parenteral overlap therapy. When using edoxaban or dabigatran for treatment of acute VTE, a lead-in period with a parenteral agent is required, and the patient is then switched to the dabigatran or edoxaban (**Figure 1; Table 1**). When using apixaban or rivaroxaban, a single-drug approach is employed, with higher dosing in the initial period and subsequent dose de-escalations at a specified time (**Figure 1; Table 1**). Less than 2 percent of patients in the rivaroxaban and apixaban trials received >two days of parenteral anticoagulation before randomization, proving that these agents are a viable single-drug strategy for acute VTE treatment in select patients.<sup>3,4,5</sup>

### B. Selection of Anticoagulant(s)

All patients with acute VTE should receive prompt, assertive anticoagulation unless contraindications (e.g., active bleeding) exist. When deciding on initial anticoagulation, the severity of presentation, potential need for invasive procedures, eligibility for outpatient treatment and the patient's clinical characteristics, as well as their preferences, must all be considered (**Figure 2**).

The DOACs represent an attractive alternative to the labor-intensive conventional approach, as they have more predictable pharmacokinetics and pharmacodynamics, fewer drug and dietary interactions, and can thus be given in fixed doses without need for routine monitoring. Further, apixaban and rivaroxaban avoid the inconvenience of parenteral therapy via use of a single-drug approach (**Table 1, Figure 1**). In clinical trials, DOACs have been proven equally efficacious (non-inferior) and often safer than conventional anticoagulation strategies in VTE patients.<sup>6</sup> However, it is important to emphasize that not all patients are appropriate DOAC candidates due to presence of contraindications or lack of evidence in certain populations. All of the DOACs are renally eliminated to some degree, and this must be considered when developing an anticoagulant regimen. While DOACs have fewer drug interactions

than warfarin, they are all substrates of the P-glycoprotein (p-gp) efflux transporter system, and the anti-Xa inhibitors rivaroxaban and apixaban undergo metabolism via the CYP3A4 hepatic isoenzyme. Inhibition or induction of these enzymatic pathways will alter the patient's exposure to the DOAC. DOACs in general do not have dietary implications, except rivaroxaban, which should be taken with the largest meal of the day to optimize absorption and dabigatran, which should be taken with a full glass of water to avoid dyspepsia (**Table 1**).

When use of a DOAC is not feasible and a conventional approach is pursued, ACCP guidelines (9th ed. 2012) suggest either LMWH or fondaparinux over UFH for initial management of VTE due to better safety and efficacy.<sup>2</sup> Unfractionated heparin should be reserved for use in specific clinical situations, such as patients with potential need for invasive procedures, potential for thrombolysis or with increased bleeding risk, given its short-half life and complete reversibility with protamine sulfate. For VTE patients with severe renal impairment, UFH is preferred, as it is less reliant on renal elimination as compared to LMWHs, fondaparinux and the DOACs<sup>1,2</sup> (**Table 1**).

### C. Special Populations

#### *Pregnancy and Breastfeeding*

Warfarin is a known teratogen and the DOACs have not been studied in pregnant patients.<sup>1,7</sup> Therefore, these agents should be avoided in pregnant patients with VTE. The exception to this is pregnant women with mechanical cardiac valves, in whom warfarin therapy may be considered during pregnancy. Fondaparinux is pregnancy category B and has been used successfully in pregnant patients with a contraindication to heparins. However, due to its extensively proven safety and efficacy, the drug of choice for VTE in pregnancy is LMWH. If a pregnant patient has significant renal impairment, long-term SQ UFH therapy may be employed.<sup>7</sup>

For breastfeeding, warfarin or LMWH are preferred therapies. The safety of DOACs has not been established in breastfeeding women, and they should be avoided (**Figure 2**).

#### *Cancer*

Among patients with active malignancy and acute VTE, LMWH monotherapy for the first three to six months is preferred based on data from clinical trials showing superior efficacy and safety.<sup>2</sup> Meta-analyses suggest DOACs are as efficacious as warfarin in preventing VTE recurrence,<sup>8</sup> however the number of patients with active cancer who were treated with DOACs in the clinical trials is small and it is unknown if they are comparable to LMWH for this indication. If a patient adamantly refuses long-term LMWH injections, use of either DOACs or warfarin may be considered<sup>1</sup> (**Figure 2**).

#### *Thrombophilias*

The DOACS have not been specifically studied in inherited or acquired thrombophilia. It is likely that a number of patients with an undiagnosed thrombophilia were enrolled in the DOAC VTE trials, suggesting these agents may be a viable option in this population. Until more robust data is available, a conventional approach with LMWH plus warfarin titrated to an INR of 2-3 is recommended.<sup>1,2</sup>



### ***Extremes of Weight***

The DOAC VTE trial populations did not adequately represent patients at extremes of weight (<40 kg or >120 kg). It is unknown if fixed-dose DOACs might lead to over- or under-treatment in these patients. In patients weighing  $\leq 60$  kg, the usual 60 mg daily dose of edoxaban is decreased to 30 mg daily and the usual 5 mg dose of apixaban is decreased to 2.5 mg twice daily if a patient has either a serum creatinine  $\geq 1.5$  mg/dL and/or is  $\geq 80$  years of age. A conventional approach with LMWH (without dose capping in obesity) and warfarin is currently recommended until more data and experience are available<sup>3</sup> **(Figure 2)**.

### ***Renal Impairment***

The LMWHs, fondaparinux and the DOACs are all renally eliminated to an appreciable degree, and thus should be avoided in severe renal impairment (estimated CrCl <30 mL/min).<sup>9</sup> Preferred therapies in this population include UFH for acute management, with transition to warfarin for longer-term therapy<sup>9</sup> **(Figure 2)**.

In conclusion, clinicians now have several anticoagulants in the armamentarium of options for VTE treatment. Consideration of patient preferences and clinical characteristics, along with properties and dosing strategies of each of the agents, is imperative for optimal anticoagulation therapy **(Figure 2)**.

# Section V: Selection of Anticoagulants (continued)

**Table 1. Anticoagulants for Treatment of VTE**

Drug	Pharmacokinetics	Drug interactions	Routine measurement(s)	Reversal	Dosage adjustments	Dosing	
						Acute phase	Long-term
Parenteral agents							
Unfractionated heparin	Half-life (hrs) <sup>a</sup> : ~1.5 Peak effect (hrs): IV: immediate SQ: 1-2 hours Renal clearance: Minimal	Concomitant antithrombotics	IV: Lab-specific aPTT equivalent to an anti-Factor Xa level of 0.3-0.7 IU/mL SQ: Consider aPTT 6 hours after injection on 3rd day to confirm therapeutic level Platelet count q3 days for first few weeks	Protamine 1 mg for each 100 units of UFH administered within the last 2-3 hours  Alternative: Protamine 50 mg IV over 10 minutes	Use weight-based dosing algorithm to maintain therapeutic aPTT or anti-Xa	80 units/kg bolus followed by continuous infusion of 18 units/kg/hr or 333 U/kg SQ first dose then 250 U/kg SQ q12h <sup>a,c</sup>	N/A
	LMWHs						
	Enoxaparin Dalteparin	Half-life (hrs) <sup>a</sup> : 3-7 Peak effect (hrs): 3-5 Renal clearance: >50%	Concomitant antithrombotics	Routine measurement of anticoagulant activity not routinely needed May consider anti-Factor Xa level if: - changing/impaired renal function - extremes of weight - pregnant Platelet count q3 days for first few weeks	Protamine 1 mg for each 1 mg or 100 anti-Xa units of LMWH given in previous 8 hours  Alternative: Protamine 50 mg IV over 10 minutes  Only provides ~60% reversal of LMWH activity	Estimated CrCl 15-29 mL/min: 1 mg/kg SQ q24h  Estimated CrCl <15 mL/min: Avoid use  Estimated CrCl <30 mL/min: No specific dose adjustments provided	1 mg/kg SQ q12h or 1.5 mg/kg SQ q24h <sup>a,b,d</sup>  200 IU/kg SQ q24h or 100 IU/kg SQ q12h <sup>a,b,d</sup>
Fondaparinux	Half-life (hrs) <sup>a</sup> : 17-21 Peak effect (hrs): 2-3 Renal clearance: >80%	Concomitant antithrombotics	Routine measurement of anticoagulant activity not routinely needed Serum creatinine	None currently May consider recombinant factor VIIa	Estimated CrCl 30-50 mL/min: Use with caution Estimated CrCl <30 mL/min: Avoid use	Administer 1 dose SQ q24 h based on weight: <sup>a,b,d</sup> 5 mg (<50 kg) 7.5 mg (50-100 kg) 10 mg (>100 kg)	N/A

# Section V: Selection of Anticoagulants (continued)

**Table 1. Anticoagulants for Treatment of VTE (continued)**

Drug	Pharmacokinetics	Drug interactions	Routine measurement(s)	Reversal	Dosage adjustments	Dosing		
						Acute phase	Maintenance	Extended
Oral agents								
Warfarin	Half-life (hrs): 40 Peak effect (hrs): 120-180 Renal clearance: N/A	Numerous Concomitant antithrombotics	INR	Vitamin K, prothrombin concentrate (PCC) or fresh frozen plasma (FFP)	Should be performed using a validated dosing nomogram in conjunction with clinical judgment	5-10 mg PO daily and adjust via initiation dosing nomogram	Varies and is based on routine INR monitoring & use of maintenance dosing nomogram	
Apixaban	Half-life (hrs) <sup>e</sup> : ~12 Peak effect (hrs): 3-4 Renal clearance: 25%	Combined P-gp and strong CYP3A4 inhibitors and inducers  Concomitant antithrombotics	Not routinely needed	None currently May consider prothrombin complex concentrate (PCC)	No dosage adjustments provided for renal impairment <sup>f</sup> Dual strong CYP3A4 and P-gp inhibitors: If dose >2.5 mg BID, decrease by 50% If already taking 2.5 mg BID and dual strong CYP3A4 and P-gp inhibitor: Avoid use	10 mg PO BID x 7 days	5 mg PO BID	2.5 mg PO BID <sup>g</sup>
Rivaroxaban	Half-life (hrs) <sup>e</sup> : 5-9 Peak effect (hrs): 2-4 Renal clearance: 36%				Estimated CrCl <30 mL/min: Avoid use Dual strong CYP3A4 and P-gp inhibitors: Avoid use	15 mg PO BID x 21 days with largest meal of the day		20 mg PO daily with largest meal of the day
Edoxaban	Half-life (hrs) <sup>e</sup> : 10-14 Peak effect (hrs): 1-2 Renal clearance: 50%	P-gp inhibitors or inducers  Concomitant antithrombotics			Estimated CrCl <15 mL/min: Avoid use Weight ≤60 kg OR Estimated CrCl 15-50 mL/min OR Concomitant therapy with P-gp inhibitors: 30 mg PO daily <sup>c, d</sup>	60 mg PO daily <sup>c, d</sup>		Not studied
Dabigatran	Half-life (hrs) <sup>e</sup> : 12-17 Peak effect (hrs): 1-3 Renal clearance: 80%				Estimated CrCl <50 mL/min and concomitant P-gp inhibitor: Avoid use Estimated CrCl <30 mL/min: No dosage adjustments provided <sup>h</sup> Any P-gp inducer: Avoid use			150 mg PO BID with a full glass of water <sup>c, d</sup>

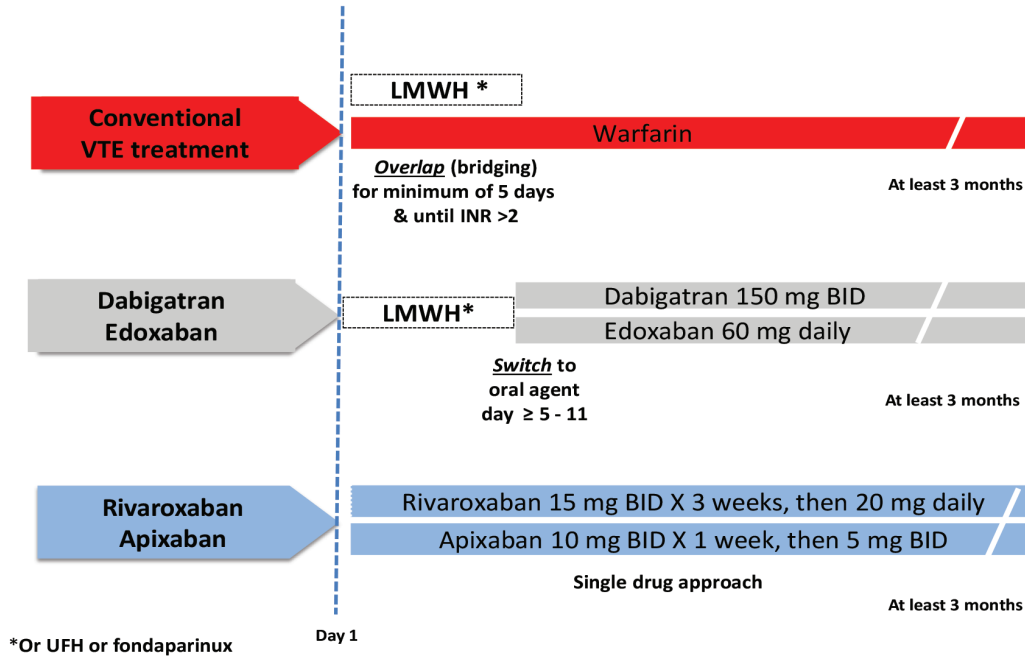
<sup>a</sup>Warfarin should be started as soon as feasible and *overlapped* with parenteral agent for minimum of 5 days and until INR >2; <sup>b</sup>May be used as monotherapy in acute phase in VTE patients with active malignancy or pregnancy; <sup>c</sup>When used with dabigatran or edoxaban for VTE, a minimum of 5 days IV UFH monotherapy, then *switch* to dabigatran or edoxaban immediately once UFH infusion stopped. DO NOT overlap IV UFH and dabigatran or edoxaban; <sup>d</sup>When used with dabigatran or edoxaban for VTE, a minimum of 5 days LMWH or fondaparinux monotherapy, then *switch* to dabigatran or edoxaban at the time the next dose of LMWH/fondaparinux would be due. DO NOT overlap IV UFH and dabigatran or edoxaban; <sup>e</sup>Normal renal function; <sup>f</sup>Patients with serum creatinine >2.5 mg/dL or estimated CrCl <25 mL/min (by Cockcroft-Gault) excluded from clinical trials; <sup>g</sup>After at least 6 months of anticoagulation; <sup>h</sup>Patients with CrCl <30 mL/minute were excluded from clinical trials.

## Section V: Selection of Anticoagulants (continued)

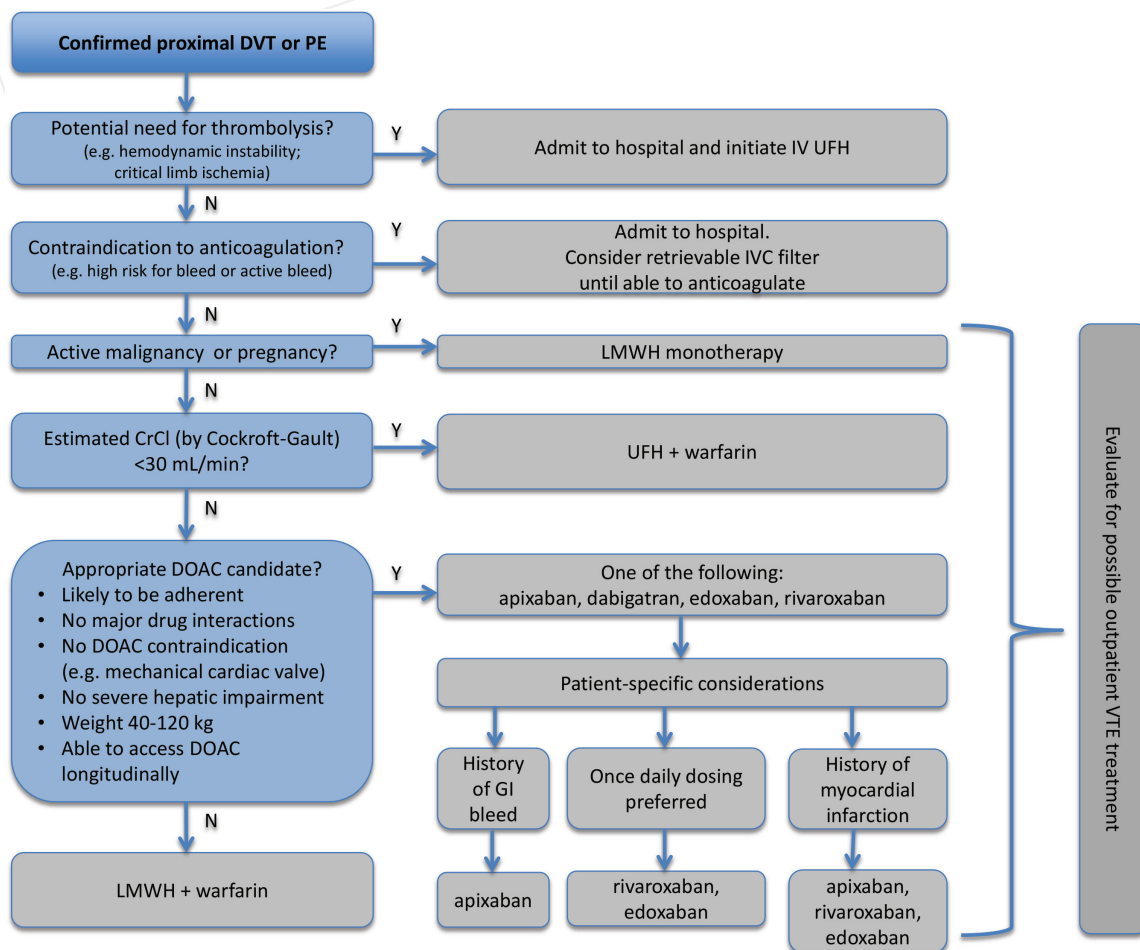
**Table 2. Patient Selection Criteria for DOAC Use<sup>7,9</sup>**

Criteria for optimal DOAC use	Comment(s)
Patient preference for and willingness to take DOAC	Patients should be presented with all therapeutic options and their individual advantages and disadvantages.
Highly likely to be adherent with DOAC therapy and follow-up plan	Short half-lives of DOACs place patients who miss doses at increased risk of thromboembolic event.
No contraindication to DOAC therapy	<ul style="list-style-type: none"> <li>-Active bleeding</li> <li>-Age &lt;18 years</li> <li>-Extremes of weight (&lt;40 kg or &gt;120 kg)</li> <li>-Pregnancy</li> <li>-Breastfeeding</li> <li>-Mechanical heart valve</li> <li>-Need for dual antiplatelet therapy</li> <li>-Thrombophilia (acquired or inherited)</li> <li>- Severe renal impairment (estimated CrCl &lt;30 mL/min)</li> <li>-Active cancer</li> <li>-Unusual site thrombosis (cerebral, splanchnic, etc.)</li> </ul>
Confirmed ability to obtain DOAC on a longitudinal basis from a financial, insurance coverage and retail availability standpoint	<p>DOACs may be cost prohibitive for some patients, as compared with warfarin plus laboratory monitoring.</p> <p>Patient assistance programs are available via the pharmaceutical companies, and this should be arranged prior to prescribing.</p>
Adequate renal function	Clinicians should regularly monitor renal function, particularly for DOACs with greater reliance on renal elimination and for any concomitant factors that may contribute to DOAC accumulation (e.g., age, unavoidable use of concomitant p-gp/CYP3A4 inhibitors).
No significant drug-drug interactions	<p>All DOACs are substrates of the P-glycoprotein (P-gp) efflux transport system. Inhibition or induction of this system will alter DOAC exposure.</p> <p>The anti-Xa inhibitors apixaban and rivaroxaban are substrates of the hepatic CYP3A4 isoenzyme. Inhibition or induction of this enzyme will alter exposure to the anti-Xa inhibitor.</p> <p>Patients taking any anticoagulant with antiplatelet agents or NSAIDs have a significantly higher risk of bleeding. To minimize bleeding, avoid these drug combinations when possible.</p>
No significant disease state interactions	Patients with a history of GI bleeding or at risk for GI bleeding may be better candidates for warfarin or apixaban, as there may be a higher risk of GI bleeding with dabigatran, edoxaban and rivaroxaban.

**Figure 1. Initiation of Anticoagulation for Acute VTE**



**Figure 2. Anticoagulant Selection Algorithm**



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## Section VI: Reversal of Anticoagulants

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A key consideration when reversing anticoagulation is the risk of thrombosis. As expected, the use of prothrombotic agents is associated with an increased risk of thromboembolic events.<sup>1,2</sup> Because the risk of recurrent VTE is highest in the first several weeks and months after an acute event,<sup>3</sup> prothrombotic agents should be used judiciously during this time frame.

Intravenous unfractionated heparin has a half-life of approximately one hour, and discontinuation is usually all that is needed to reverse its effect when bleeding occurs. If bleeding is serious enough to require immediate reversal, protamine sulfate can completely and immediately normalize the aPTT. One milligram of protamine sulfate neutralizes 100 units of heparin. Since the half-life of heparin is 60 to 90 minutes, only the amount of heparin given in the preceding couple of hours needs to be reversed. It is also important to remember that protamine sulfate should be administered by slow IV infusion to avoid inducing hypotension or bradycardia.<sup>4</sup>

LMWHs have half-lives of approximately three to five hours, and there is little data on the efficacy of reversal agents. Nevertheless, protamine sulfate has been recommended at a dose of 1 mg per 1 mg of enoxaparin or 100 anti-Xa units of other LMWHs.<sup>4</sup> Fondaparinux has a half-life of 17 hours, which is increased dramatically with renal failure; recombinant factor VIIa (rVIIa) has been suggested to reverse it based on a small study in human volunteers.<sup>4</sup>

Warfarin and other vitamin K antagonists (VKAs) inhibit the liver's production of vitamin K-dependent clotting factors. Their effect can be reversed by administering vitamin K to allow the liver to increase coagulation factor production or by transfusing extraneous clotting factors using either fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs). Without reversal, warfarin's anticoagulant effect lasts approximately five days; thus, most bleeding events that require hospitalization will also require the use of a reversal agent. Vitamin K should be given when reversing warfarin. Since normalization of the INR with vitamin K alone can take 12 to 24 hours, PCCs should be administered when bleeding requires more immediate reversal.

The American College of Chest Physicians (ACCP) recommends the use of 4-factor PCC over FFP for VKA-related bleeding.<sup>5</sup> A randomized clinical trial found a 4-factor non-activated PCC to be non-inferior to FFP for adequate hemostasis at 24 hours in patients with VKA-related bleeding, and the INR was more rapidly corrected with PCC compared to FFP.<sup>6</sup> Another trial in patients receiving VKA who required emergent surgery compared 4-factor PCC with FFP in addition to vitamin K and found improved hemostasis at the end of surgery, more rapid correction of the INR to <1.3 and earlier time to surgery with PCC.<sup>7</sup>

The new oral anticoagulants have many different acronyms including new/novel oral anticoagulants (NOACs), non-vitamin K oral anticoagulants (NOACs), target-specific oral anticoagulants (TSOACs), specific oral direct anticoagulants (SODAs) and direct oral anticoagulants (DOACs). We will use the term DOAC to be consistent with the International Society of Thrombosis and Hemostasis (ISTH) nomenclature recommendation.<sup>8</sup> The four currently available DOACs all have relatively (compared to warfarin) short onset and offset of action with half-lives of approximately 12 hours. All four undergo some amount of renal excretion but the increase in half-life is most pronounced with dabigatran when the creatinine clearance is <30 mL/min.<sup>9</sup> On the other hand, with normal renal function, most of the anticoagulant effect of the DOACs will be gone in 24 to 48 hours. Thus, in most cases, time is the primary therapy for most bleeding patients with these medications. Several specific antidotes for the DOACs are in phase II or III studies and may become available in the near future.

Idarucizumab is a monoclonal antibody designed specifically for dabigatran. It causes immediate reversal of the anticoagulant effect as measured by the dilute thrombin time.<sup>10</sup> In a study of 90 patients treated with dabigatran who required reversal because of bleeding or emergent surgery, the anticoagulant effect of dabigatran was immediately reversed as measured by the dilute thrombin time and the ecarin clotting time.<sup>10</sup> Idarucizumab was approved by the FDA in November 2015.



## Section VI: Reversal of Anticoagulants (continued)

Andexanet alfa is a factor Xa decoy that retains its binding site for factor Xa inhibitors (rivaroxaban, apixaban, edoxaban and betrixaban) but the catalytic site that converts factor II (prothrombin) to IIa (thrombin) has been altered so that the molecule cannot act as an anticoagulant. The factor Xa inhibitor DOACs bind to the decoy instead of factor Xa, thus keeping them from exerting their anticoagulant effect. The effect of andexanet alfa is immediate but short-lived and requires a bolus followed by continuous infusion. The anti-Xa activity of rivaroxaban and apixaban were reversed with andexanet alfa in human volunteers<sup>11</sup> and an ongoing study is evaluating efficacy and safety in bleeding patients.<sup>12</sup>

Ciraparantag (PER977 or Aripazine) binds to many anticoagulants including DOACs by a non-covalent electrostatic mechanism and has shown an immediate normalization of the whole blood clotting time in normal healthy volunteers pre-treated with edoxaban.<sup>13</sup>

Until specific antidotes for DOACs become available, PCCs either as 3-factor, 4-factor, activated or recombinant factor VIIa should be considered when bleeding is severe enough to require immediate reversal or if emergent surgery is required. Most of these agents are suggested by the FDA for this purpose. However, studies on reversing DOACs using different strategies show that there is poor correlation between the normalization of clotting assays and bleeding observed in animals. Therefore, the normalization of the prothrombin time, partial thromboplastin time or other clotting assays in healthy human volunteers may not necessarily translate to cessation of bleeding in actual patients.<sup>14</sup>

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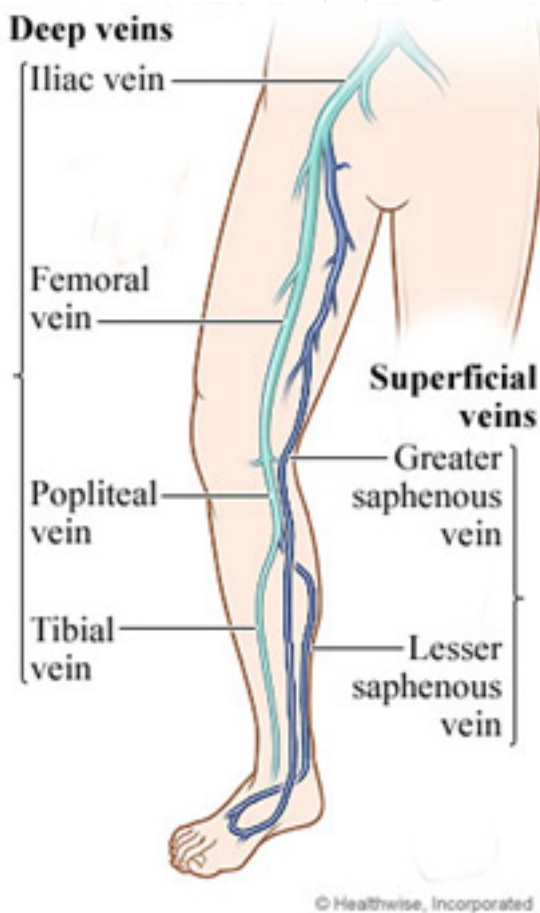


## Section VII: Superficial Venous Thrombosis of the Lower Extremity

## Section VII: Superficial Venous Thrombosis of the Lower Extremity

Superficial venous thrombosis (SVT), also known as superficial thrombophlebitis, appears to have an annual incidence of 0.64 percent (~6 per 1,000 patients/year), a six-fold greater incidence than DVT and PE, which comprise VTE (1 per 1,000 patients/year).<sup>1</sup> It occurs most commonly in the greater saphenous vein of the leg (60–80 percent of cases), but can affect other superficial veins (**Figure 1**). It should be noted that the misnomered superficial femoral vein is a deep vein (distal portion of femoral vein), and this nomenclature should be avoided, as it may lead to lack of appropriate treatment. SVT shares many common risk factors with DVT, and these are shown in **Table 1**.<sup>2</sup>

**Figure 1.**<sup>9</sup>



**Table 1**<sup>2</sup>

Risk factors for SVT
Advanced age
Autoimmune disease
Cancer
History of SVT or VTE
Hormone therapy
Immobility
Inherited thrombophilia
Obesity
Pregnancy or puerperium
Surgery
Trauma
Varicose veins

In prior decades, SVT was considered a benign, self-limiting disease. Contemporary data highlighting SVT as a potentially more severe entity is changing our perception of this condition, as well as its management.<sup>3</sup>

### A. Diagnosis

Traditionally, SVT was diagnosed clinically based on the presence of warmth, tenderness and swelling of the affected vein segment, often with a palpable cord. Treatment consisted of local therapies such as warm compresses and topical anticoagulants, such as heparin gel, along with non-steroidal anti-inflammatory drugs (NSAIDs) to alleviate symptoms.

However, isolated SVT (without concomitant DVT or PE at diagnosis) has the potential to migrate into the deep venous system via the saphenofemoral junction (SFJ). Studies have shown that concomitant DVT or PE is present in up to 36 percent of SVT patients. Given the frequent association of SVT and VTE, clinical diagnosis alone is no longer considered sufficient. Compression ultrasonography is recommended to confirm presence and extent of SVT, as well as evaluate for concomitant VTE, the presence of which affects therapeutic decisions.<sup>4,5</sup>

### B. Management

To date, no consensus on optimal management of SVT has been achieved. However, recent clinical trials and systematic reviews have suggested that anticoagulation is the treatment of choice for those with isolated SVT of the lower extremity at increased risk for extension or migration into the deep venous system.<sup>2,3</sup>

The best evidence is provided by the CALISTO study.<sup>6</sup> In this randomized, controlled trial comparing fondaparinux 2.5 mg subcutaneously once daily to placebo, the composite primary efficacy outcome of all-cause mortality, symptomatic VTE or symptomatic extension or recurrence of SVT occurred in 5.9 percent and 6.3 percent of placebo patients by day 47 and day 77, respectively. This provides convincing evidence that SVT is indeed not a benign disease. Prophylactic fondaparinux for 45 days resulted in an absolute risk reduction of 5 percent in the incidence of the composite primary outcome (0.9 percent vs. 5.9 percent; RR 0.15; 95% CI 0.08-0.26;  $p < 0.001$ ; number needed to treat=20) compared to placebo, with no difference in bleeding. Similarly, fondaparinux therapy provided an 85 percent risk reduction for the composite outcome of symptomatic DVT or PE at day 47 (0.2 percent vs. 1.3 percent;  $p < 0.001$ ; number needed to treat=88), which was maintained at day 77.

Based on these results, prophylactic dose fondaparinux for 45 days is recommended for isolated lower extremity SVT of at least 5 cm in length but  $>3$  cm from the SFJ.<sup>2</sup> Alternatively, prophylactic LMWH for 45 days may be employed, although the evidence for this approach is weaker than that for fondaparinux.<sup>3</sup> However, fondaparinux (and LMWH) is expensive with an estimated cost of \$42 per day (\$1,890 for a course of treatment) and this therapy was found not to be cost effective, with an estimated incremental cost-effectiveness ratio of \$500,000 per quality adjusted life year (traditional thresholds \$50,000 – \$100,000).<sup>7</sup> If fondaparinux or LMWH prove to be cost-prohibitive for the patient, it is reasonable to alternatively use traditional therapies of NSAIDs, compression stockings and topical agents. The patient should be followed closely for signs and symptoms of VTE development.

The CALISTO trial, like many previous studies of SVT, excluded patients with SVT within 3 cm of the SFJ, as this is often considered very high risk for extension. Some experts and organizations, including the British Committee for Standards in Haematology, recommend that confirmed SVT within 3 cm of the SFJ be considered equivalent to DVT, warranting therapeutic anticoagulation. However, no recommendations for duration of therapy are provided.<sup>5,8</sup>

For patients with SVT at lower risk for extension, NSAIDs, compression devices or topical therapies may be considered to alleviate symptoms.<sup>4,5</sup>

A proposed management approach that stratifies patients into low-, intermediate- and high-risk SVT is shown in **Figure 2**.

## C. Surgical Intervention

Anticoagulation therapy has been shown to be more effective than surgical intervention, including ligation of the SFJ and ligation and stripping of the phlebotic veins, in treating SVT. Additionally, data suggest that surgical intervention may provoke formation or migration of thrombosis. Thus, surgery is not recommended as first-line therapy for SVT.<sup>2,3,5</sup>

## D. Upper Extremity SVT

Upper extremity SVT (UESVT) is most commonly caused by peripheral vein infusion and occurs in 25–35 percent of hospitalized patients with peripheral IV catheters. Unfortunately, optimal therapeutic approaches for UESVT are unknown. The data for use of anticoagulation for UESVT are severely lacking. General approaches include cessation of infusion, removal of the peripheral IV catheter and use of local or systemic anti-inflammatory medications to alleviate symptoms.<sup>3,5</sup>

**Figure 2. Therapies for SVT of the Lower Extremity<sup>2,3</sup>**

Suggested Therapies for SVT of the Lower Extremity		
Risk Category	Definition	Therapy
High	Thrombus <3 cm from SFJ	<ul style="list-style-type: none"> <li>• May consider therapeutic anticoagulation. However no recommendations for duration of therapy provided</li> </ul>
Intermediate	Thrombus ≥5 cm in length and >3 cm from SFJ	<ul style="list-style-type: none"> <li>• Prophylactic fondaparinux (preferred) or LMWH for 45 days</li> <li>• If fondaparinux and LMWH cost-prohibitive, use NSAIDs, compression devices and/or topical therapies</li> </ul>
Low	Thrombus <5 cm in length and >3 cm from the SFJ	<ul style="list-style-type: none"> <li>• NSAIDs</li> <li>• Compression devices</li> <li>• Topical therapies</li> </ul>

### Summary

Preferred guideline-based therapy for SVT with increased risk for extension is prophylactic dose fondaparinux for 45 days. However, this treatment is expensive (approximately \$1,800 for fondaparinux) and is not cost-effective. Prophylactic dose LMWH is an option based on insurance coverage and co-pay considerations. If neither treatment option is available, then traditional treatment with NSAIDs, compression stockings and topical therapies should be used and the patient should be followed closely for the development of DVT and PE.

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## Section VIII: Management of Isolated Calf Vein Thrombosis

## A. Doppler Surveillance vs. Immediate Anticoagulation

The distal veins of the lower extremity include the paired veins (peroneal, anterior tibial and posterior tibial) and the calf muscle veins (gastrocnemius and soleal) (**Figure 1**). Among hospitalized patients, approximately 80 percent of diagnosed DVTs are proximal (popliteal vein or higher) and 20 percent are distal. While anticoagulation is well-established as the standard of care for patients with proximal DVT (symptomatic or asymptomatic) to reduce death from PE, controversy persists regarding the management of a first isolated distal DVT (IDDVT), primarily due to its unknown clinical significance.

The reported risk of IDDVT propagation varies considerably, from approximately 25 percent in early studies to as low as 3 percent in more recent analyses. Additionally, IDDVT has been shown to have a very low risk of recurrence compared to proximal DVT or PE. However, some IDDVT may be potentially concerning and treatment may be warranted in patients at higher risk of developing complications (**Table 1**).<sup>1</sup>

There are two possible management approaches when IDDVT is diagnosed. The first is treating all IDDVTs with therapeutic anticoagulation, an approach that is supported by an international consensus statement on prevention and treatment of VTE.<sup>2</sup>

The second approach, endorsed by the American College of Chest Physicians (ACCP),<sup>1</sup> involves selective anticoagulation. In patients with a relatively mild presentation and low risk for proximal extension (**see Table 1**), it is suggested to withhold anticoagulation, perform serial ultrasound for two weeks and anticoagulate if the thrombus extends into the popliteal vein. If the patient is severely symptomatic from the IDDVT, is at high risk for proximal extension (**Table 1**) or is unlikely or unable to comply with a follow-up ultrasound examination, it is suggested to start anticoagulation therapy at the initial exam. For patients who are to undergo conservative management, it is reasonable to prescribe anti-inflammatory medications and/or compression stockings to minimize discomfort.

**Table 1. Risk Factors for Distal Lower Extremity Thrombus Propagation<sup>1</sup>**

Risk Factors for Distal Thrombus Propagation
Active cancer
History of VTE
Inpatient status
Unprovoked VTE
D-dimer >500 mg/mL
Extensive thrombosis (>5 cm in length, >7 mm in diameter)
Involvement of multiple vessels (e.g., BOTH peroneal or tibial veins of one leg)
Thrombosis near proximal veins
Prolonged immobility



## B. Anticoagulation Duration for IDDVT

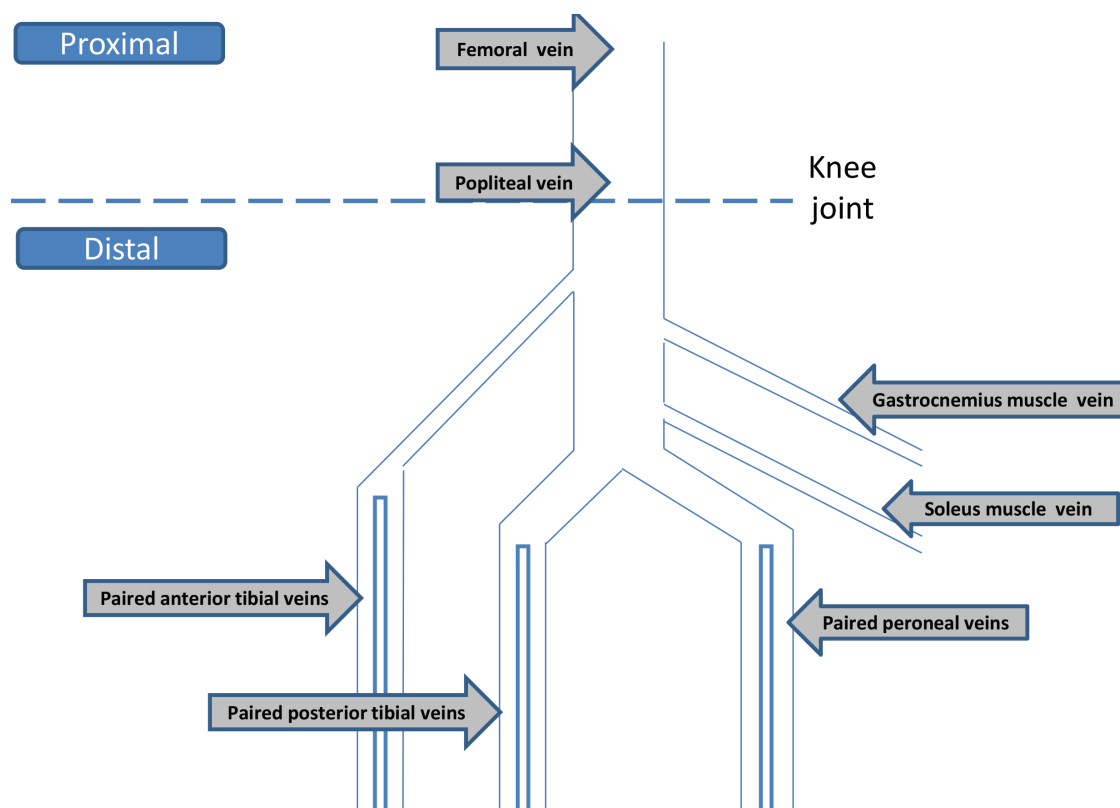
Clinical trials and meta-analyses comparing shorter durations of anticoagulation (four to six weeks) to longer durations (three to six months) among patients with a first proximal lower extremity DVT have shown an increase in recurrent VTE with no appreciable reduction in hemorrhagic events with abbreviated therapy. Conversely, one meta-analysis suggests that an IDDVT provoked by a transient risk factor (surgery, travel, hormone therapy) has an extremely low risk of recurrence and may be treated with a shorter duration (e.g., four to six weeks) of anticoagulation rather than three months.

The ACCP guidelines acknowledge that not all patients with IDDVT will be treated with anticoagulants. Among those patients in whom anticoagulation is pursued, they recommend three months of therapy for unprovoked IDDVT, and suggest the same duration of therapy for provoked IDDVT. However, if a patient is unable to tolerate a full three months of therapy, it is not unreasonable to consider an abbreviated course, particularly in the setting of provoked IDDVT.<sup>1</sup>

## C. Asymptomatic Surveillance Screening

Hospitalists should be aware that no major organizations or societies advocate surveillance screening for DVT in asymptomatic high-risk patients, including medicine, surgical or trauma patients. Rather, it is recommended to employ evidence-based VTE prevention strategies, whenever possible, in these high-risk populations and investigate for VTE only if a patient becomes symptomatic.<sup>3</sup>

**Figure 1. Distal Deep Veins of the Lower Extremity<sup>4</sup>**



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## Section IX: Management of Upper Extremity DVT

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## Epidemiology and Etiology

Upper extremity DVT (UEDVT) involves the brachial, axillary or subclavian veins. More proximal disease may include the brachiocephalic, superior vena cava or internal jugular vein. UEDVT accounts for approximately 5–10 percent of all DVT and constitutes 30–40 percent of hospital-acquired DVTs. UEDVT is categorized as primary (20 percent of cases) or secondary (80 percent of cases).<sup>1,2</sup> Risk factors for UEDVT are shown in **Table 1**.

**Table 1. Risk Factors or Conditions Associated with UEDVT<sup>2</sup>**

Category	Risk Factor(s) or Condition(s)
Primary (20%)	Venous thoracic outlet syndrome (VTOS)
	Effort-related thrombosis (Paget-Schroetter syndrome)
	Idiopathic
Secondary (80%)	Catheter or cardiac device (pacemaker, defibrillator)
	Cancer
	Hospitalization
	Upper extremity surgery or trauma
	Hormones (pregnancy/peurperium, oral contraceptives, hormone replacement, ovarian hyperstimulation syndrome)

Primary UEDVT is most commonly a result of anatomic anomalies at the thoracic outlet (thoracic outlet syndrome) and/or repetitive effort of the limb resulting in injury to the axillosubclavian vein (Paget-Schroetter syndrome). This is commonly seen in otherwise healthy young males, two-thirds of whom report vigorous repetitive or overhead arm motion just prior to symptom onset.<sup>2</sup> The majority of UEDVT is secondary to a provoking event such as a presence of a central venous catheter (CVC) (45–62 percent of patients), malignancy (38 percent of patients) or hospitalization (50–75 percent).<sup>1</sup>

## A. Clinical Presentation

Patients with UEDVT may be asymptomatic or present with complaints of limb heaviness, pain, swelling, paresthesias or functional impairment or have dilated collateral veins of the shoulder girdle.<sup>2</sup>

## B. Complications

Potential complications of UEDVT include PE, recurrent VTE, post-thrombotic syndrome (PTS) and mortality. While the incidence of symptomatic PE at diagnosis is significantly lower in UEDVT (9 percent) compared to LEDVT (29 percent),<sup>3,4</sup> the incidence becomes equivalent at 30 days. Data from prospective registries suggest that the risk of recurrent VTE is ~1.7x times higher in the first six months among patients with UEDVT compared to lower extremity DVT (LEDVT), with no statistically significant difference in mortality at one, three, six or 12 months.<sup>3,4</sup> PTS occurs in approximately 5 percent of UEDVT patients at 12 months compared to 56 percent of patients with LEDVT.<sup>2</sup>

### C. Management

Based on similarities in prognosis, antithrombosis guidelines from ACCP recommend that UEDVT be treated in the same manner as LEDVT<sup>1</sup> (see **Figure 1**). Therapeutic approaches include anticoagulation therapy, thrombolysis, surgery or mechanical interventions.

If the UEDVT is provoked by a CVC, removal of the CVC with new site insertion is not recommended if the device is still needed, not infected and functioning. Small studies have shown it is feasible to treat the UEDVT with anticoagulation while the CVC remains in place, without unacceptable risk of line failure or clot extension. Importantly, recurrent thrombosis has been shown to occur in up to 86 percent of new catheter placement sites. If the CVC is no longer needed, non-functioning or potentially infected, prompt removal is recommended.<sup>1,2</sup>

Anticoagulation is the mainstay of UEDVT management, even though no randomized controlled trials of anticoagulation therapy for UEDVT have been conducted. Data from randomized trials of LEDVT, as well as observational studies in patients with UEDVT, are used to guide management. Small prospective studies of three months of therapeutic anticoagulation with either a parenteral heparin followed by warfarin or with low-molecular-weight heparin (LMWH) alone have shown low rates of both VTE recurrence and bleeding in patients with UEDVT. Data from prospective registries and community studies also support these therapeutic anticoagulation strategies.<sup>1</sup>

Given their proven efficacy and safety, updated guidelines from ACCP now suggest DOACs (as a class) over conventional anticoagulant therapies for treatment of proximal LEDVT and PE.<sup>1</sup> Consideration for their use in UEDVT is not unreasonable if the patient cannot tolerate or refuses conventional therapies and as long as the patient meets appropriate patient selection criteria. (See **Section V on Selection of Anticoagulants**)

For patients who are not DOAC candidates, conventional approaches should be employed. For the acute phase of conventional anticoagulation, LMWH is recommended over IV unfractionated heparin (UFH) whenever possible due to better efficacy and safety shown in LEDVT randomized trials. However, for patients with severe renal impairment or potential need for invasive procedures, IV UFH is preferred. Patients should be bridged to warfarin for longer-term therapy, except for patients with active malignancy who should receive LMWH monotherapy.

Due to lack of data pertaining to clinical outcomes and a real potential to cause harm, other interventions such as thrombolysis, surgical removal of the first rib to alleviate thoracic outlet obstruction or insertion of a superior vena cava filter should be reserved for severely symptomatic patients and/or exceptional circumstances (e.g., contraindication to anticoagulation) and should only be performed in medical centers adequately equipped and trained to care for these patients.

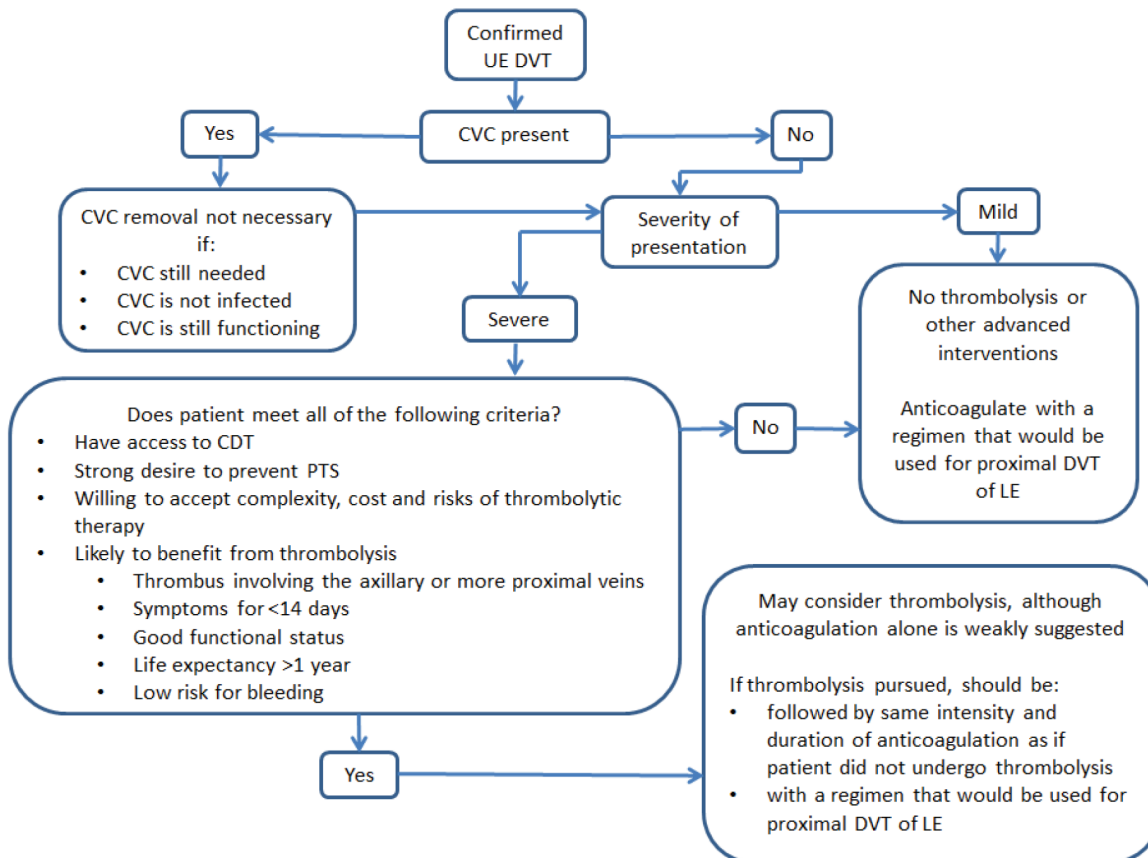
### D. Anticoagulation Duration for UEDVT

The cumulative incidence of VTE recurrence is lower in UEDVT than LEDVT<sup>5,6,7</sup> for both provoked and idiopathic events, suggesting that extending anticoagulation beyond three months is not needed in most patients. **Table 2** summarizes ACCP-recommended durations of anticoagulation for UEDVT.<sup>1</sup>

**Table 2. ACCP-recommended Durations of Anticoagulation for UEDVT<sup>1</sup>**

Patient Population	Duration of Anticoagulation	Comment
All UEDVT	Suggested minimum of 3 months	Grade 2B
CVC-provoked UEDVT <i>with</i> removal of CVC	No longer than 3 months	<i>Recommended for non-cancer patients</i> (Grade 1B) Suggested for active cancer patients (Grade 2C)
CVC-provoked UEDVT <i>without</i> removal of CVC	As long as CVC remains in place	<i>Recommended for active cancer patients</i> (Grade 1C) Suggested for non-cancer patients (Grade 2C)
UEDVT not associated with CVC or active cancer	Recommend no longer than 3 months	Grade 1B

**Figure 1. Management of UEDVT<sup>2</sup>**



CDT= catheter-directed thrombolysis; DVT= deep vein thrombosis; LE= lower extremity; PTS= post-thrombotic syndrome; UE= upper extremity

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## Section X: Management of Unusual Site Thrombosis



## Section X: Management of Unusual Site Thrombosis

Cerebral vein thrombosis (CVT) and splanchnic vein thrombosis are the most frequent manifestations of unusual site VTE and will be reviewed here. For information on retinal, vena caval and genitourinary venous thrombosis, readers are referred to the guideline by Tait et al.<sup>1</sup>

Lack of robust evidence, along with heterogeneity of underlying cause, clinical presentation and individual risk of thrombosis and bleeding, renders management of CVT and splanchnic vein thrombosis particularly challenging. When these unusual site thromboses occur, a multidisciplinary approach (hematology, gastroenterology, neurology, surgery, interventional radiology, antithrombosis expert, clinical pharmacist, etc.) is clearly indicated.

### A. Splanchnic Vein Thrombosis

Splanchnic vein thrombosis collectively comprises blood clots within the portal, mesenteric and splenic veins, as well as within the supra-hepatic vein (Budd-Chiari syndrome).<sup>2</sup> Incidence of splanchnic vein thrombosis is low, ranging from 0.5–1 case/million persons/year for Budd-Chiari syndrome to 0.7–2.7/100,000 persons/year for portal vein thrombosis and mesenteric vein thrombosis.<sup>1</sup>

Heterogeneity in presentation among symptomatic patients varies based on the rapidity of development of thrombus, degree of splanchnic obstruction and presence of comorbidities. Those with acute splanchnic vein thrombosis commonly present with abdominal pain, increased abdominal girth, nausea, vomiting, jaundice or lower gastrointestinal bleeding. Patients with sub-acute or chronic splanchnic vein thrombosis may have no symptoms or present with milder, vague or more intermittent symptoms due to development of collateral venous circulation.<sup>1</sup>

Up to 29 percent of all splanchnic vein thrombi are asymptomatic and detected incidentally upon routine investigations, such as evaluation for liver cirrhosis or cancer staging.<sup>1</sup>

Recognition of and investigation for provoking risk factors associated with splanchnic vein thrombosis is important as this will aid in determining appropriate therapeutic interventions. Identification of a growing number of risk factors has reduced the incidence of true idiopathic splanchnic vein thrombosis to 15–27 percent.<sup>1</sup> Risk factors for splanchnic vein thrombosis are listed in **Table 1**.

## Section X: Management of Unusual Site Thrombosis (continued)

**Table 1. Potential Risk Factors for Splanchnic Vein Thrombosis<sup>3</sup>**

Risk factor	
<b>Abdominal</b>	
<b>Acute</b>	Diverticulitis
	Hydatidosis
	Inflammatory bowel disease
	Pancreatitis
	Peritonitis
	Surgery (general abdominal, splenectomy)
	Trauma
	Variceal sclerotherapy
<b>Chronic</b>	Abdominal cancer
	Liver disease (cirrhosis, portal hypertension)
<b>Autoimmune disease</b>	Behcet's syndrome
	Hypereosinophilic syndrome
<b>Biologic markers</b>	CD55 and CD59
	JAK2 mutation
<b>Blood disorders</b>	Essential thrombocythemia
	Idiopathic myelofibrosis
	Myeloproliferative neoplasm (MPN)
	Paroxysmal nocturnal hemoglobinuria (PNH)
	Polycythemia vera
<b>Cytomegalovirus</b>	
<b>Hormone-related</b>	Oral contraception
	Hormone replacement therapy
	Pregnancy/puerperium
<b>Thrombophilia (acquired or inherited)</b>	Antithrombin, Protein C or Protein S deficiency
	FVL or Prothrombin mutation
	Antiphospholipid antibody syndrome
<b>Membranous web within inferior vena cava</b>	

Impaired or obstructed splanchnic blood flow places patients at short- and long-term risk of adverse events such as intestinal or splenic infarction, portal hypertension, hepatic necrosis, liver failure and possibly death. As with other types of VTE, these patients are at risk of recurrent VTE, particularly if the index event is inadequately treated.<sup>2,3</sup> Thus, resolution of thrombus and restoration of blood flow is a primary goal of therapy. Unfortunately, these patients are often at extremely high risk of bleeding or may present with active bleeding due to comorbidities (e.g., cirrhosis, gastroesophageal varices, malignancy, thrombocytopenia) making optimal management of splanchnic vein thrombosis difficult.<sup>3</sup> All aspects of the clinical situation, including patient characteristics, baseline laboratory values, severity of presentation and thrombus burden, should be considered when weighing the risks and benefits of anticoagulation therapy. If the bleed risk is deemed to be unacceptably high or clinical benefit unacceptably low, antithrombotic therapy may be avoided or postponed. In these cases, periodic reassessment is imperative. In general, due to lack of evidence and extremely high risk of bleeding, thrombolytic therapy should be limited to very select patients who are at low risk of bleeding and would otherwise suffer a devastating outcome as a result of the splanchnic thrombosis extension.

Given the lack of strong evidence, recommendations regarding anticoagulation therapy for splanchnic vein thrombosis set forth by the American College of Chest Physicians<sup>4</sup> guidelines on antithrombotic therapy are largely based on expert opinion<sup>1,2,3,4,5</sup> and are listed in **Table 2**.

**Table 2. Recommendations for Treatment of Splanchnic Vein Thrombosis<sup>4</sup>**

Condition	Recommendation	Grade of Evidence	Comment
<b>Symptomatic</b> splanchnic vein thrombosis	<b>Recommend anticoagulation</b> over no anticoagulation	1B	Unless major contraindication(s) to anticoagulation present
<b>Incidentally detected</b> splanchnic vein thrombosis	<b>Suggest no anticoagulation</b> over anticoagulation	2C	Factors that might warrant anticoagulation: <ul style="list-style-type: none"> <li>• New, acute extensive thrombosis</li> <li>• Extension of thrombus on repeat imaging</li> <li>• Active chemotherapy</li> </ul>

It is recommended to initiate anticoagulation, in the absence of major contraindications, with full-dose low molecular weight heparin (LMWH) for the acute phase of symptomatic splanchnic vein thrombosis treatment. If the patient has significant renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault estimation), has had a recent bleed or is expected to undergo an invasive procedure, unfractionated heparin (UFH) is preferred over LMWH because of its reversibility and shorter half-life. In the setting of concomitant significant thrombocytopenia (<50,000/mm<sup>3</sup>), clinicians may consider avoidance of anticoagulation or use of prophylactic doses of anticoagulation until platelet counts improve. For patients with cirrhosis, additional therapies, such as beta blockers for portal hypertension or surgical intervention for varices, should be employed to mitigate bleed risk.<sup>4</sup>

Patients presenting with symptomatic splanchnic vein thrombosis should eventually be bridged to warfarin for longer-term therapy, unless they have active cancer, in which case long-term LMWH monotherapy is recommended.<sup>4</sup>

It should be noted that the direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban and edoxaban, have not been specifically studied in this population, and therefore cannot currently be recommended as first-line therapy. Durations of therapy for symptomatic splanchnic vein thrombosis set forth by national guidelines<sup>4,5</sup> are listed in **Table 3**.

**Table 3. Recommended Duration of Therapy for Splanchnic Vein Thrombosis<sup>1,4,5</sup>**

Splanchnic vein thrombosis population	Recommended duration of anticoagulation
<b>Provoked</b>	3 months
<b>Unprovoked</b>	≥3 months with ongoing risk-benefit assessment of continued anticoagulation therapy
<b>Provoked by persistent risk factor</b> (e.g., cirrhosis, cancer, severe thrombophilia, etc.)	
<b>Budd-Chiari syndrome</b>	

In patients with asymptomatic, incidentally diagnosed splanchnic vein thrombosis, it is not unreasonable to consider foregoing anticoagulation therapy if one or more of the following criteria are met:

- Non-occlusive thrombus
- Non-acute thrombus
- Involvement of single vein
- Absence of permanent risk factors for splanchnic vein thrombosis
- Bleeding risk is high (e.g., severe thrombocytopenia, recent bleed)
- Poor overall prognosis

If these criteria are not met, the same anticoagulation recommendations as for symptomatic patients should be employed unless contraindications exist.<sup>4</sup>

## B. Cerebral Vein Thrombosis

CVT is an extremely rare event, accounting for <1 percent of all strokes.<sup>1,4</sup> CVT most often occurs within the major dural sinuses (transverse > superior sagittal > sigmoid), and less frequently within cerebral veins<sup>6,7</sup> (**Figure 1**). Almost 80 percent of CVT occur in patients younger than 50 years of age, and it is far more common in women than men (3:1 ratio). The overwhelming majority of CVT (>85 percent) is provoked by an identifiable trigger.<sup>6</sup> Risk factors for CVT are listed in **Table 4**.

## Section X: Management of Unusual Site Thrombosis (continued)

**Table 4. Potential Risk Factors for CVT<sup>2,6,7</sup>**

Risk factor	
Blood disorder	Polycythemia vera
	Thrombocytosis
	Paroxysmal nocturnal hemoglobinuria (PNH)
Cancer	
Chronic inflammatory disorder	Inflammatory bowel disease
	Behcet's disease
Connective tissue disorder	Systemic lupus erythematosus (SLE)
	Oral contraception
	Hormone replacement therapy
	Pregnancy/peurperium
Infection	Sinusitis, mastoiditis, otitis, meningitis
Nephrotic syndrome	
Surgery	Local injury to cerebral vein or sinus
Thrombophilia (acquired or inherited)	Antithrombin, Protein C or Protein S deficiency
	FVL or Prothrombin mutation
	Antiphospholipid antibody syndrome
Trauma	Traumatic head injury
	Neurosurgical procedures
	Lumbar puncture
	Jugular venous access device

Clinical presentation of CVT depends on site and extent of the thrombus, time from onset to diagnosis and parenchymal involvement. Headache is the most common symptom, present in almost 90 percent of patients. Clinical suspicion for CVT should be elevated in any young patient presenting with headache and at least one of the risk factors listed in **Table 4**.

CVT prevents the normal outflow of blood from the intracranial space, decreases absorption of cerebrospinal fluid and may lead to increased intracranial pressure, headache, brain swelling, decreased cerebral perfusion and resultant ischemia. This may progress to vessel rupture, bleeding into the brain and stroke-like symptoms. In acutely severe cases with large parenchymal lesions, patients may experience transtentorial herniation and death. Signs and symptoms of CVT can be grouped into the three syndromes shown in **Table 5**.

**Table 5. CVT Syndromes<sup>2,6,7</sup>**

Syndrome	Signs and symptoms
Isolated intracranial hypertension	Headache ± emesis, papilledema, visual disturbances
Focal neurologic syndrome	Focal deficits, seizures
Encephalopathic syndrome	Mental status changes, stupor, coma

## Section X: Management of Unusual Site Thrombosis (continued)

Management of CVT in the acute phase should encompass consultation with neurology and neurosurgical services. Therapeutic interventions, such as anti-epileptics and decompressive surgery, may be warranted.<sup>6</sup>

Clinicians are commonly concerned about hemorrhagic conversion or exacerbation of intracranial hemorrhage (ICH) with anticoagulation therapy in CVT. In a meta-analysis of the only two randomized controlled trials comparing parenteral anticoagulation to placebo for CVT (n=79), 30–50 percent of patients had some evidence of ICH prior to initiation of anticoagulation. Results showed a non-statistically significant reduction in death or dependency and no increase in new ICH in patients who received therapeutic anticoagulation. In the absence of overt contraindications (ICH should not be considered an absolute contraindication to anticoagulation), anticoagulation is suggested for all patients with CVT to promote recanalization of the vein, alleviate venous and intracranial pressure, and avoid potential adverse sequelae.<sup>1,4,6</sup> If the patient has evidence of extensive venous infarct or parenchymal involvement, the risk of bleeding is likely higher and may offset any benefit of anticoagulation. Consultation with an anticoagulation expert is recommended and use of prophylactic doses or postponement of anticoagulation may be considered until bleed risk is diminished in these patients.

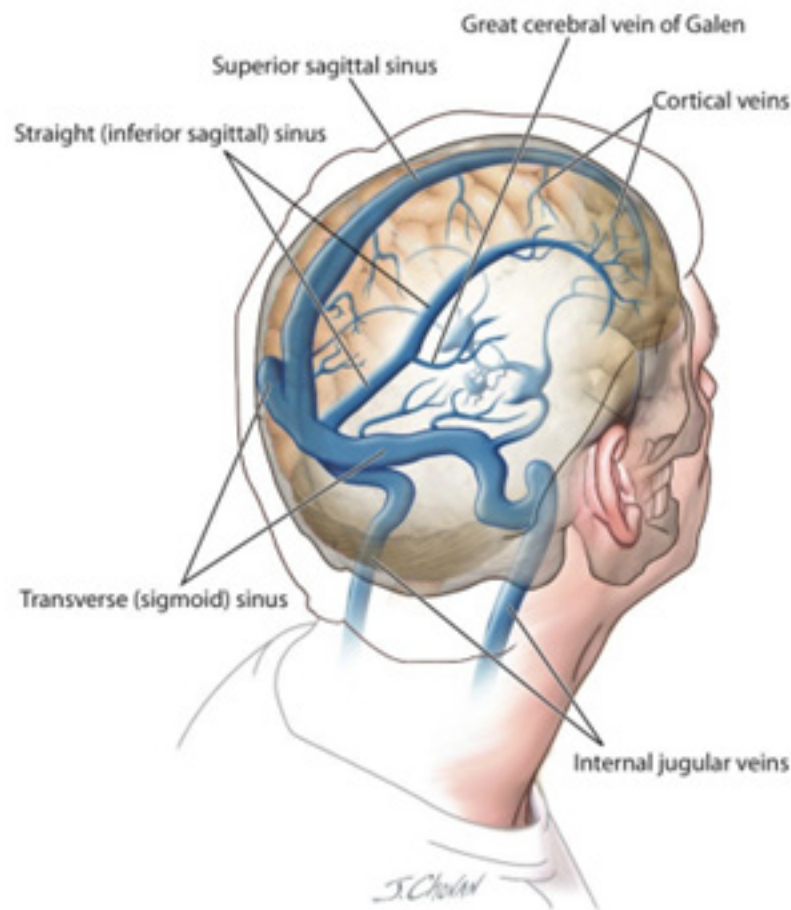
If anticoagulation is pursued, use of IV UFH for the first one to two days is reasonable given its reversibility and short half-life. If the patient tolerates this, a switch to LMWH is recommended if the patient has adequate renal function. If the patient's condition deteriorates despite anticoagulation more advanced therapies, such as thrombolysis, thrombectomy or decompressive surgery, may be indicated.

CVT patients should eventually be bridged to warfarin for longer-term therapy, unless they have active cancer, in which case long-term LMWH monotherapy is recommended.<sup>4</sup> As with splanchnic vein thrombosis, DOACs have not been specifically studied in CVT, and therefore cannot currently be recommended as first-line therapy. Recommended durations of anticoagulation for CVT are shown in **Table 6**.

**Table 6. Recommended Duration of Anticoagulation for CVT<sup>4,6</sup>**

CVT population	Recommended duration of anticoagulation
Provoked	3–6 months
Unprovoked	6–12 months
Provoked by persistent risk factor (e.g., cancer, severe thrombophilia, etc.)	Indefinite with ongoing risk-benefit assessment of continued anticoagulation therapy
Recurrent CVT, DVT or PE	

**Figure 1. Cerebral Venous Vasculature<sup>8</sup>**



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## Section XI: Duration of Anticoagulation and Thrombophilia Testing



## Section XI: Duration of Anticoagulation and Thrombophilia Testing

Although the use of extended anticoagulation beyond the initial three months of acute treatment for venous thromboembolic disease is usually made in the outpatient arena, hospitalists have the opportunity to set the stage and begin the discussion on a common patient question, “how long will I need to be treated”? The seminal paper by Prandoni<sup>1</sup> demonstrated a 30 percent recurrence rate at eight years follow-up in a cohort of patients with VTE and it changed the way we think of this disease from an isolated acute event to a chronic disease. Several years later, Baglin and his group classified VTE into surgically provoked, non-surgically provoked, pregnancy-related and unprovoked. They showed distinct rates of recurrence after two years of follow-up between these categories: 0 percent for surgically provoked, 8.8 percent with non-surgically provoked and 19.4 percent with unprovoked.<sup>2</sup> Of note, cancer-related VTE was excluded from this cohort and thrombophilia testing was not shown to predict recurrence. These two studies, in addition to other observations, shaped the current approach of risk-stratifying VTE patients to determine the optimal length of anticoagulation therapy.

### A. Provoked VTE

The American College of Chest Physicians (ACCP) guidelines recommend three months of anticoagulation for patients with surgically and non-surgically provoked VTE.<sup>3</sup> Non-surgical provoking factors, including fracture with a cast, hospitalization with bed confinement for three days, estrogen therapy, pregnancy, history of travel and others, have been inconsistently used to define “provoked” VTE in clinical trials.<sup>4</sup> For pregnancy-related VTE, ACCP guidelines recommend three months of anticoagulation and at least six weeks of anticoagulation post-partum.<sup>5</sup> Estrogen as a provoking factor has been widely debated. However, a recent cohort study demonstrated no recurrences when estrogen was thought to have “provoked” VTE, thus suggesting that three months of anticoagulation should be sufficient in this scenario.<sup>6</sup> The ACCP lists estrogen therapy, pregnancy, leg injury and airplane flight of greater than eight hours as non-surgical provoking factors.<sup>3</sup>

### B. Cancer-related VTE

Guidelines recommend extended anticoagulation in cancer-related VTE if the bleeding risk is acceptable.<sup>3</sup> Low-molecular-weight heparin is the anticoagulant of choice in this setting.<sup>3</sup>

### C. Non-provoked VTE

ACCP guidelines suggest indefinite anticoagulation in patients with non-provoked VTE who have a low to moderate bleeding risk.<sup>3</sup> Multiple strategies to further risk stratify patients have been studied, including D-dimer testing, risk assessment models, gender and thrombophilia testing. If anticoagulation is not used indefinitely, then aspirin should be considered if not contraindicated. Although aspirin is not as effective (indirect evidence) as anticoagulation, it does confer an approximate one-third reduction in recurrent VTE.<sup>7,8</sup>

## D. Gender

In a systematic review of nine randomized trials and six prospective cohort studies, men are one and a half times more likely to have a VTE recurrence compared to women, even after the effect of estrogen therapy is accounted for.<sup>9</sup> This observation was confirmed in a patient-level systematic review of seven prospective cohort studies<sup>10</sup> and in another study among patients who had negative D-dimer test results after completion of anticoagulation.<sup>6</sup> Male patients with acute VTE clearly have a higher risk of recurrence than women. Therefore, it is not unreasonable to consider indefinite anticoagulation for men with low bleeding risk.

## E. Clinical Prediction Rules and Risk Assessment Models

Several risk assessment models have been derived to guide the decision to extend anticoagulation in patients with non-provoked VTE. The MEN continue and HER DOO2,<sup>11</sup> Vienna prediction model<sup>12</sup> and the DASH score<sup>13</sup> are three examples (see Tables 1, 2 and 3). Each of these models utilizes D-dimer testing to help predict recurrence, and all account for the higher risk in men.

## F. D-dimer

D-dimer is a breakdown product of fibrin clot and is an indirect marker of continued clot formation. A randomized trial of patients who had completed at least three months of vitamin K antagonist (VKA) treatment for acute VTE had D-dimer testing one month after completion of anticoagulation. Those with a negative D-dimer remained off VKA therapy. Patients with a positive D-dimer were randomized to resume or remain off of VKA treatment. Annualized recurrence rates were 4.4 percent in patients with a negative D-dimer, 2.0 percent in patients with a positive D-dimer who were randomized to resume VKA, and 10.9 percent among those who had a positive D-dimer and remained off VKA. A systematic review showed similar annualized rates of recurrence with positive (8.9 percent) and negative (3.5 percent) D-dimer results after three months of anticoagulation.<sup>14,15</sup>

Although D-dimer testing may be useful to select which patients with non-provoked VTE should continue anticoagulation, the timing of testing and the patient's age may affect results. In a patient-level meta-analysis, patients with a positive D-dimer had rates of recurrence that were more than double regardless if testing was done <3 weeks, 3–5 weeks or >5 weeks after stopping VKA or if they were less than or greater than 65 years of age.<sup>10</sup> There are many D-dimer tests available with different cut-offs for positive and negative, which may explain differences in study results.<sup>16</sup> A prospective cohort study using a qualitative point-of-care D-dimer testing estimated recurrence rates with negative and positive tests of 8 percent and 16 percent per year, respectively, in men; and 5 percent and 10 percent per year, respectively, in women who were not on estrogen. If the bleeding risk is low and the annual risk of recurrence of either 8 percent for men or 5 percent for women is considered high enough to continue anticoagulation, then D-dimer testing has no added value in decision-making.<sup>6</sup>

## G. Thrombophilia Testing

Thrombophilia or hypercoagulability is one of the three clinical derangements that can result in venous thrombosis; the other two are injury to the vascular endothelium and venous stasis.<sup>17</sup> A hypercoagulable state can either be hereditary or acquired (**Table 4**).

There is a paucity of evidence to support the practice of routine genetic testing in patients with VTE. Experts agree that it is not indicated in those with a known provoking or triggering event, such as surgery or malignancy,<sup>18,19,20,21</sup> but there is no consensus when it comes to patients with idiopathic VTE. Some suggest that it may be useful when making a decision on the duration of anticoagulant treatment,<sup>22</sup> particularly for patients who are relatively young and those who are less committed to lifelong therapy. However, other authors argue that the occurrence of an unprovoked or idiopathic VTE is the ultimate phenotypic expression of the patient's overall thrombotic risk; performing routine genetic testing is an unnecessary expense and can potentially lead to discontinuation of treatment in some patients who are still at high risk of VTE recurrence.<sup>23</sup> Measuring the D-dimer level after three months of anticoagulation treatment may be a more suitable alternative for those patients with idiopathic VTE who are weighing the risks and benefits of continued therapy.<sup>24</sup>

Acquired thrombophilia is associated with a number of clinical conditions, and it is not uncommon for a VTE event to be the presenting complication that leads to the diagnosis of the underlying disease. Clinicians must consider the likelihood of an undiagnosed malignancy or antiphospholipid syndrome in the appropriate clinical setting. Patients over the age of 40 years who experience an unprovoked VTE must have a complete age-appropriate cancer screening.<sup>17</sup>

### Summary

We recommend that patients with clearly provoked VTE should be treated for three months and have no further work-up. Patients with cancer-related VTE should be treated indefinitely as long as the bleeding risk is low and preferably with a LMWH. Men with non-provoked VTE with low to moderate bleeding risk are candidates to be treated indefinitely and no further work-up is required. Women with non-provoked VTE should be treated indefinitely if the threshold for recurrence is at least 5 percent, otherwise, risk stratification with D-dimer testing or a risk assessment model should be performed. Women who are contemplating future pregnancy may benefit from genetic thrombophilia testing to help plan for VTE prevention during pregnancy (**see Table 5**).

If testing is performed to evaluate thrombophilia, clinicians must consider the effects of active thrombosis and of the various anticoagulant medications on the interpretation of results (**Table 6**).

# Section XI: Duration of Anticoagulation and Thrombophilia Testing (continued)

**Table 1. The “Rodger” or “MEN Continue and HER D002” Recurrent VTE Risk Assessment Model**

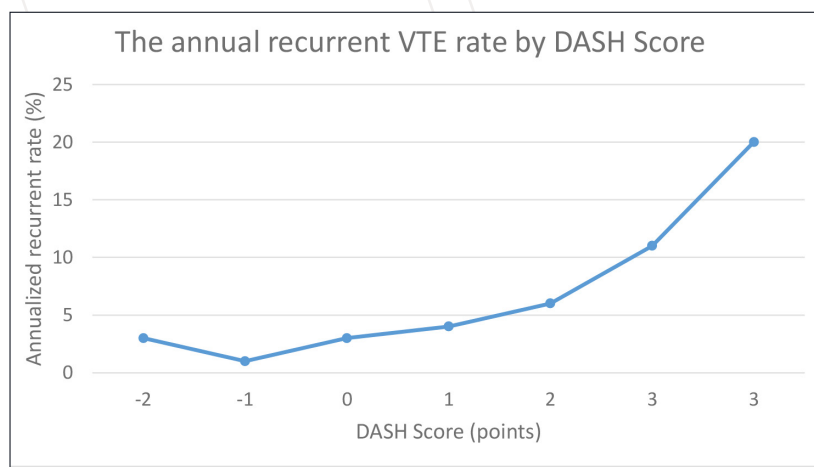
Risk Factors
Post-thrombotic syndrome signs (hyperpigmentation, edema, redness of either leg)
D-dimer $\geq 250$ mg/L (on anticoagulation)
Body mass index $\geq 30$ kg/M <sup>2</sup>
Age $\geq 65$ years
Women with 0 or 1 of these risk factors have a low annual risk for recurrence (1.6%)

**Table 2. Vienna Prediction Model for VTE**

Risk Factors
Patient sex: Male > female
Event type: Pulmonary embolism > proximal DVT > distal DVT
D-dimer: (drawn 3 weeks after discontinuation of anticoagulation) – higher value = higher risk
Vienna Prediction Model for VTE web calculator version 2.0 at <a href="http://cemsis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/recurrent-vte/">http://cemsis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/recurrent-vte/</a>

**Table 3. The “Dash” Score**

Risk Factors	Points
D-dimer abnormal <sup>a</sup>	2 points
Age <50 years	1 point
Male sex	1 point
Hormone-associated VTE	-2 points
<sup>a</sup> D-dimer drawn 3-5 weeks after discontinuation of anticoagulation	



**Table 4. Hereditary and Acquired Thrombophilia**

Thrombophilias	
Hereditary	Factor V Leiden mutation
	Prothrombin gene mutation
	Protein S deficiency
	Protein C deficiency
	Antithrombin deficiency
	Dysfibrinogenemia
Acquired	Antiphospholipid antibody syndrome
	Polycythemia vera
	Essential thrombocythemia
	Paroxysmal nocturnal hemoglobinuria
	Nephrotic syndrome

**Table 5. VTE Prevention During Pregnancy**

Category of VTE	Duration of Anticoagulation	Genetic Thrombophilia Testing
Surgical provoked	3 months	No
Pregnancy provoked	3 months and at least 6 week post-partum	No
Estrogen, leg injury and flight >8 hours provoked	3 months	No
Cancer related	Indefinite	No
Non-provoked men	Indefinite	No
Non-provoked women with positive D-dimer	Indefinite	Consider if contemplating future pregnancy
Non-provoked women with negative D-dimer Indefinite or risk stratify with D-dimer or clinical prediction rule Consider if contemplating future pregnancy		

**Table 6. Effect of Thrombosis and Medications on Thrombophilia Test Results**

Laboratory Test for:	Acute Thrombosis	Medications				
		Heparin	LMWH <sup>1</sup>	Vitamin K Antagonist	Direct IIa Inhibitor	Direct Xa Inhibitor
Factor V Leiden	No effect	No effect	No effect	No effect	No effect	No effect
Factor II gene mutation	No effect	No effect	No effect	No effect	No effect	No effect
Protein S deficiency	May be low	No effect	No effect	Don't test	No effect	No effect
Protein C deficiency	May be low	No effect	No effect	Don't test	No effect	No effect
Antithrombin deficiency	May be low	Lowered	Lowered	No effect	No effect	No effect
Antiphospholipid antibody	No effect	No effect	No effect	No effect	No effect	No effect
Lupus anticoagulant	No effect	Don't test	Don't test	Don't test	Don't test	Don't test

<sup>1</sup>LMWH, low-molecular-weight heparin

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## Section XII: Inferior Vena Cava Filter

## Section XII: Inferior Vena Cava Filter

The inferior vena cava (IVC) filter is a mesh-like, metallic endovascular device that is deployed in the infrarenal vena cava to prevent the propagation and embolization of thrombus from the lower extremities. It can be introduced through the femoral vein, the internal jugular vein or the antecubital vein under fluoroscopic guidance by either an interventional radiologist or a vascular surgeon.

When initially developed, the IVC filters were placed permanently and were used primarily as an alternative to anticoagulation. In a seminal randomized trial, the placement of a permanent IVC filter in addition to at least three months of anticoagulation in patients with proximal DVT reduced the risk of symptomatic pulmonary embolism (PE) but increased the rate of recurrent DVT at two years follow-up.<sup>1</sup> However, at eight years follow-up, the rate of recurrent VTE was similar in those who received an IVC filter compared to anticoagulation alone – and there were more DVT in patients with a filter and more PE in those without a filter.<sup>1,2</sup> There was no effect on overall survival, however the majority of deaths in the study were due to cancer, cardiac or respiratory insufficiency, or advanced age. Also, there was no difference in the rate of post-thrombotic syndrome.

Retrievable IVC filters later became available and were designed to be amenable to removal after a period of time, when the contraindication against anticoagulation is no longer present or when the risk of thrombosis has declined. A randomized trial compared the use of retrievable IVC filter plus anticoagulation with anticoagulation alone in higher-risk patients with acute PE and found no difference in the risk of recurrent PE at three months and at six months.<sup>3</sup> The rates of symptomatic DVT, major bleeding and death were also similar. These results show that there is no additional benefit in using retrievable IVC filters in patients with acute PE who can receive anticoagulation. Thus, the American College of Chest Physicians (ACCP) recommends against using an IVC filter on VTE patients who are treated with anticoagulants.<sup>4</sup> However, there is a paucity of outcome evidence on using an IVC filter alone when anticoagulation is contraindicated, which is the most common indication.<sup>5,6</sup>

When looking at current practice experience in the United States, retrievable IVC filters are generally not being removed. In a retrospective review of 679 retrievable IVC filters placed at one tertiary referral center in Boston between 2003 and 2011, removal was attempted in only 10 percent and was successful 81 percent of the time.<sup>7</sup> In comparison, retrieval was almost eight times more frequently attempted in the United Kingdom and the success rate was similar.<sup>8</sup> Failure to successfully remove the filter is directly related to its dwell time. Those that have been implanted for more than nine weeks were significantly more likely to fail retrieval attempts compared to those that have a shorter dwell time. This is usually due to any one of the following: the filter has incorporated into the IVC wall, thrombosis has developed in the IVC or the filter legs have penetrated the caval wall.<sup>8</sup>

The American Society of Hematology (ASH) recommends avoiding the routine use of IVC filters in the management of VTE as one of its five recommendations for the American Board of Internal Medicine's (ABIM) Choosing Wisely® campaign.<sup>9</sup> The only indication for IVC filter placement where there is consensus among all the major recommending bodies is to prevent PE in patients with acute VTE when anticoagulation is contraindicated.<sup>10,11,12</sup> However, when the contraindication has resolved, these patients must be started on anticoagulation and the IVC filter must be removed.<sup>10</sup>

For patients with a recent (<30 days) acute VTE and undergoing an urgent high bleeding risk procedure, placing a retrievable IVC filter may be considered.<sup>13</sup> However, if the VTE event is more than 30 days old, perioperative bridging anticoagulation may be more appropriate instead of inserting an IVC filter.<sup>14</sup>

There are other frequent justifications for placing an IVC filter, including patients who experience recurrent VTE despite being on anticoagulation, high-risk trauma patients and those undergoing surgical procedures that are known to carry a high risk of thrombosis, such as bariatric surgery. However, there is insufficient evidence to support the use of IVC filters in these settings.<sup>15,16</sup>



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## Section XIII: Prevention of Post-thrombotic Syndrome

## Section XIII: Prevention of Post-thrombotic Syndrome

Post-thrombotic syndrome (PTS) represents significant morbidity and occurs in a quarter to a half of all patients following DVT.<sup>1,2</sup> PTS is a clinical diagnosis, and several diagnostic criteria have been developed. The International Society of Thrombosis and Hemostasis recommends the use of the Villalta scale, which comprises five symptoms (pain, cramps, heaviness, paresthesia and pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia and pain on calf compression).<sup>3</sup> Each of the 11 symptoms or signs is scored with 0, 1, 2 or 3 points for none, mild, moderate or severe manifestations. PTS is classified as mild with a score of 5–9, moderate (10–14) and severe ( $\geq 15$  or for any score plus skin ulceration).<sup>3</sup>

The American College of Chest Physicians' 2012 guidelines had suggested (Grade 2B) the use of compression stockings be worn for two years after an acute DVT,<sup>4</sup> and the 2016 guidelines now suggest not using compression stockings routinely to prevent PTS.<sup>5</sup> The 2012 suggestion was based on two open-label randomized trials that demonstrated the risk of development of PTS was reduced by approximately 50 percent with use of stockings.<sup>6,7</sup> Because the definition of PTS is based heavily on patient symptoms, the lack of masking treatment allocation could have influenced outcomes. The SOX trial was reported in 2014 and designed to overcome this methodologic weakness and employed a placebo stocking that was similar in appearance but only had 5 mmHg of compression. Stockings were mailed directly to research patients, and they did not wear the stockings to follow-up visits to keep investigators blinded.<sup>8</sup> Unlike the previous two open-label trials, this randomized double-blinded trial found no difference in the development of PTS by the Ginsberg scale (a stricter definition of PTS) or the Villalta scale<sup>8</sup> in the intention to treat analysis. Similar results were found in the "on treatment" analysis in patients who self-reported good compliance with stocking use. In addition, there was no difference in pain symptoms based on a 0–10 scale at 14, 30 or 60 days after randomization.<sup>9</sup>

Compression stockings can be cumbersome to apply, hot, constricting and itchy with a cost up to \$100 a pair and patients have difficulty complying with daily applications for a couple of years.<sup>8</sup> The SOX trial is the best evidence to date, and the results have been incorporated into the 2016 ACCP guidelines. Hospitalists should not routinely prescribe compression stockings after an acute DVT.

**Table 1. Randomized Trials to Prevent Post-thrombotic Syndrome**

Author	Year	Intervention	Comparison	Post-thrombotic incidence (Villalta scale)		Follow up
				Intervention	Control	
Brandjes	1997	30-40 mm Hg made to order calf stockings	No stockings	20%	47%	2 years
Prandoni	2004	30-40 mm Hg off the rack calf stockings	No stockings	25%	49%	2 years
Kahn	2014	30-40 mm Hg off the rack calf stockings	Placebo 5 mm Hg stockings	53%	52%	2 years

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## Section XIV: Transitions of Care

## Section XIV: Transitions of Care

Transition of care among various care settings — both inpatient and outpatient — presents multiple challenges. Detailed handoff from the hospitalist to the patient's primary care physician is required for good continuity of care. Anticoagulated patients with VTE generate additional requirements for information transfer on transition to outpatient care (**Table 1**). Communication and coordination of care among outpatient, emergency, inpatient, subacute and long-term care settings are vital for patients with VTE receiving anticoagulants.

**Table 1. Elements of Good Care Transition for Patients Receiving Anticoagulation**

• Accurate and complete information exchange among transferring and receiving provider
• Medication reconciliation
• Case management with arrangement for uninterrupted medication supply and laboratory monitoring (e.g., INR for warfarin, renal function)
• Education of patient and caregiver(s) about the purpose of the medication, importance of adherence, how to take the medication, signs and symptoms of bleeding, when to seek medical attention and adverse effects
• Follow-up contact to ensure adherence and continuity of care

### A. Inpatient Care

The Society of Hospital Medicine (SHM) has launched a program designed to improve transitions in care, with an eye toward preventing readmissions. Project BOOST® (Better Outcomes by Optimizing Safe Transitions) is an evidence-based, multidisciplinary intervention that focuses on changing the culture within a hospital, rather than serving as a one-size-fits-all quick fix.<sup>1,2</sup> Specific components of the program are implemented on the basis of a hospital's current state of care, needs and resources. Hospitals that implement Project BOOST® receive help from mentors who coach the hospital staff for one year on how to integrate the components of the program into their care flow. To date, this program has been implemented in more than 200 hospitals, large and small, nationwide. Early data from six sites that have implemented this program have shown a 14 percent reduction in 30-day, all-cause readmissions.

One of the best-known programs focused on transitions in care is Project RED (Re-Engineered Discharge). Designed to prevent readmissions, Project RED started at a Massachusetts safety-net hospital, where a research group tested a transition-in-care program aimed at patients and caregivers.<sup>3</sup> During a 21-month period in 2006 and 2007, a package of services that included patient education, medication reconciliation and individualized discharge instructions for patients and their primary care providers reduced 30-day readmissions and ER visits by 30 percent. The results of this program were published in *Annals of Internal Medicine* in 2009.<sup>4</sup> The program immediately caught the attention of national healthcare leaders for its innovation and applicability to different patient populations. Within two months of the publication of the *Annals* article, more than 2,000 people had registered for an Agency for Healthcare Research and Quality (AHRQ) Web conference about Project RED.<sup>5</sup>

Today, Project RED is used by hospitals around the country.<sup>6,7,8,9</sup> Toolkits for Project RED implementation are funded by AHRQ; the National Heart, Lung, and Blood Institute; the Blue Cross Blue Shield Foundation; and the Patient-Centered Outcomes Research Institute.

### **B. Transition to Outpatient Care**

Prior to discharge, patients leaving inpatient care should be referred to the care management team to facilitate transition to at-home or long-term care. Elderly, particularly frail or debilitated patients who are transferring to long-term care need a detailed transfer of information between settings, education of the patient and caregiver, medication reconciliation and a plan for follow-up medical care that includes pending test results.<sup>10</sup> For patients who are prescribed the newer anticoagulants, their insurance coverage and ability to pay for medication should be investigated. Patients receiving warfarin who will be discharged to self-care will require handoff to a provider for INR monitoring. Referral to a formal, structured management program, such as an anticoagulation clinic, is ideal for most patients.<sup>11</sup> For highly motivated patients, self-monitoring may be an option.<sup>12</sup>

Patient education is critically important for patients receiving either warfarin or the newer anticoagulants. Persistence and adherence to medication regimens increase when patients understand why medications are prescribed and potential side effects.<sup>13</sup> Education for patients receiving warfarin should include information on drug and dietary interactions and the importance of regular INR monitoring.<sup>11</sup> Education for patients receiving the newer anticoagulants should include an explanation about the importance of taking medication as prescribed, given the short duration of anticoagulant effect compared with warfarin and the dangers of abruptly stopping medication without medical advice. Patients and their caregivers should know the signs and symptoms of bleeding and how to differentiate minor bleeding from bleeding that requires medical attention. Transition to long-term care should be similar to hospital-to-hospital transfer, with systematic methods in place to ensure a complete handoff.<sup>14</sup> Measures to ensure that anticoagulant doses are not missed or duplicated during the transition are critically important to avoid increased risk for stroke or bleeding.<sup>14</sup>

Elderly patients with VTE face several related hazards that require special consideration in anticoagulation, including an increased risk for bleeding and other adverse effects, interactions with other anticoagulants, comorbid conditions and falls. The risk of falling or advanced age should not be absolute or relative contraindications to anticoagulation; potential benefit (recurrent VTE) versus bleeding risk should be carefully considered for each patient.<sup>15</sup> Much of the total cost associated with VTE is attributed to direct and indirect hospitalization costs; clinical strategies that can reduce VTE-related hospitalizations may optimize care by improving clinical outcomes and reducing costs.

For patients transitioning to outpatient care, involvement of a care manager can ensure attention to practical issues, such as educating the patient and caregiver, securing an uninterrupted source of medication and arranging follow-up care and laboratory tests, which may decrease the risk for re-hospitalization. Inadvertent discontinuation of anticoagulant therapy and poor adherence are frequent causes of hospital readmission.<sup>16</sup>

The impact of the availability of dabigatran<sup>17</sup> and the new factor Xa inhibitors, such as rivaroxaban,<sup>18</sup> apixaban<sup>19</sup> and edoxaban,<sup>20</sup> is now being seen. However, vigilant transition of care for patients receiving anticoagulation will continue to be a key element in achieving the best patient outcomes.

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Section XV: Quality Metrics, Choosing Wisely and High-Value Care



## Section XV: Quality Metrics, Choosing Wisely and High-Value Care

The era of healthcare payment reform and the emphasis on payment based on quality rather than the quantity of service provided has brought with it the imperative to measure and report elements of the quality of care. Venous thromboembolism performance measures examine a hospital's performance in the prevention and management of acute VTE. In 2005 The Joint Commission (TJC) and the National Quality Forum (NQF) began developing measures related to VTE and other conditions impacting hospitalized patients. In 2008, six VTE measures were finalized and endorsed by NQF (**see Table**). The Centers for Medicare & Medicaid Services (CMS) aligned with these measures, harmonizing the key VTE metrics for TJC and CMS. The VTE measure set was subsequently made available for selection by hospitals to meet their core measure set accreditation requirement.

These initial six VTE performance measures focused on the rate of appropriate VTE prophylaxis for hospitalized patients and ICU patients (VTE 1, 2, 6), ensuring a minimum of five days' overlap of warfarin and parenteral heparin for patients with acute VTE (VTE-3), lab monitoring for patients on intravenous heparin (VTE-4) and discharge instructions for patients on warfarin (VTE-5). Several of these measures have been either made voluntary or proposed for removal due to high national compliance.

**Table 1. VTE Measures<sup>1</sup>**

VTE Measure	Description	Status
VTE-1 – Venous Thromboembolism Prophylaxis	Percentage of hospitalized patients who received adequate VTE prophylaxis	CMS has proposed removal 2016 due to high compliance
VTE-2 – Intensive Care Unit Venous Thromboembolism Prophylaxis	Percentage of ICU patients who received adequate VTE prophylaxis	CMS has proposed removal 2016 due to high compliance
VTE-3 – Venous Thromboembolism Patients with Anticoagulation Overlap Therapy	Percentage of patients with acute VTE who are treated with warfarin who receive $\geq 5$ days' overlap with intravenous heparin or subcutaneous low-molecular-weight heparin	CMS has proposed removal 2016 due to high compliance
VTE-4 – Venous Thromboembolism Laboratory Monitoring	Percentage of patients on intravenous heparin who receive appropriate platelet monitoring	Converted in 2015 to CMS "Voluntary only" reporting
VTE-5 – Venous Thromboembolism Warfarin Therapy Discharge Instructions	Percentage of patients discharged on warfarin who receive discharge instructions addressing warfarin management (e.g., medication interactions, anticipatory signs and symptoms, laboratory follow-up)	Current
VTE-6 – Hospital Acquired Potentially Preventable Venous Thromboembolism	Percentage of hospital-acquired VTE for which adequate VTE prophylaxis was not administered	Current

## Section XV: Quality Metrics, Choosing Wisely and High-Value Care

(continued)

The VTE performance measures utilized by CMS and TJC are primarily focused on process measures in that most assess process of care (i.e., prophylaxis rates) rather than clinical outcomes. An advantage of process measures is that expectations are uniform across disparate settings and populations. For example, a small rural community hospital and a tertiary care urban academic medical center would both be expected to have high and similar rates of providing discharge instructions for patients on warfarin. A primary limitation of process measures, however, is the possible disconnect from clinically important events. Whether excellent performance on a specific process measure translates into decreased clinical adverse events is typically unknown.

Flanders and colleagues performed a large cohort study to assess whether more aggressive VTE prophylaxis is associated with lower event rates for medical patients.<sup>2</sup> The analysis included 20,794 patients at 35 Michigan hospitals. Hospitals were categorized into tertiles of low, moderate and high performance for pharmacologic VTE prophylaxis. They found that hospitals in the low- and moderate-performance tertiles did not have higher VTE rates at 90 days than hospitals in the high-performance tertile. The conclusions did not change when controlling for use of mechanical prophylaxis or for VTE occurring after a subsequent hospitalization.

The Agency for Healthcare Research and Quality (AHRQ) has developed Patient Safety Indicators (PSIs) to examine clinically important outcomes. PSI-12 assesses the incidence of post-operative hospital-acquired VTE. The patient population includes all patients >18 years of age who have a surgical discharge diagnosis as defined by specific DRG codes undergoing an operative procedure as defined by ICD procedure codes. In addition, PSI-90 reflects the weighted average of 11 indicators that reflect patient safety, including PSI-12.

Concerns regarding VTE performance measures include the burden of measurement, distraction for other possible quality improvement initiatives related to VTE or to other important clinical conditions, and whether results accurately reflect the quality of care. One study found that hospital quality scores were correlated with VTE prophylaxis rates.<sup>3</sup> In contrast, this study found that despite high prophylaxis rates, hospitals with higher quality scores had higher hospital-acquired VTE rates. A possible mediator was an increased use of VTE imaging studies, suggesting that more thorough VTE surveillance may identify more episodes of acute VTE and lead to increased event rates at high-quality hospitals.

The Surgical Care Improvement Project (SCIP) is a partnership of multiple organizations, including TJC and CMS, developed to reduce the incidence of the most common and serious postoperative complications, including postoperative VTE. SCIP-VTE entails two performance measures: (1) whether VTE prophylaxis was ordered, and (2) whether VTE prophylaxis was administered within 24 hours prior to surgery to 24 hours following surgery. The agents and regimens that are defined as adequate are updated based on evidence and as new agents become available. Whether adherence with SCIP guidelines translates into lower event rates is uncertain. Altom and colleagues performed an administrative database review of 30,531 surgeries from 2006–2009 in the Veteran Affairs hospital system.<sup>4</sup> The overall VTE prophylaxis rate was 89.9 percent and the incidence of post-operative VTE was 1.4 percent. SCIP-VTE adherence increased annually from 73.1 percent to 96.2 percent ( $P < .0001$ ). VTE rates were similar for hospitals that had prophylaxis rates greater than and less than the average rate (1.3 percent vs. 1.4 percent, respectively).

An observational study of more than 17,000 patients undergoing joint replacement surgery at 128 New York state hospitals in 2008 examined the impact of SCIP compliance on clinical outcomes.<sup>5</sup> The investigators found that VTE prophylaxis increased from the pre-SCIP to the SCIP intervention period. There was a direct relationship between SCIP VTE compliance and post-operative infection rates; hospitals that were more compliant with SCIP had the highest rate of infection. VTE incidence was not examined. The authors suggested that an unintended consequence of aggressive VTE prophylaxis may be an increase in wound infection.

## A. High-Value Care for Patients with VTE

In an era of spiraling healthcare costs, hospitals look to hospitalists to provide high-value care, which can be defined as care of high quality delivered in a cost-effective manner. Fortunately, the needs of healthcare systems align well with the interests and expertise of hospitalists. The Core Competencies published by the Society of Hospital Medicine (SHM) state that hospitalists should be able to triage patients to appropriate hospital resources, construct cost-effective care pathways that allocate resources equitably and practice evidence-based, cost-effective care for all patients.<sup>6</sup> The management of VTE affords several opportunities for clinicians to provide outstanding care while being attentive to the cost to the patient, hospital and society. These include:

- A prompt evaluation that can obviate the need for expensive imaging and potentially harmful radiation exposure
- A thrombophilia workup that targets patients for whom testing will be of high yield, and avoids unnecessary testing
- Evidence-based determination of patients with acute DVT and acute PE who can be treated entirely at home or can be discharged safely home after a brief admission

## B. Diagnosis

In 2012, the American Board of Internal Medicine (ABIM) Foundation sponsored the *Choosing Wisely*<sup>®</sup> initiative. *Choosing Wisely* called for the major medical specialty societies to identify common strategies performed by their members that are of low value. The program focuses on tests or treatments that clinicians should stop performing as they add no benefit, may cause harm and add cost. More than 70 societies have joined the *Choosing Wisely* campaign, including SHM and the American College of Physicians (ACP). The ACP's list includes:

*In patients with low pretest probability of venous thromboembolism (VTE), obtain a high-sensitive D-dimer measurement as the initial diagnostic test; don't obtain imaging studies as the initial diagnostic test.*

This recommendation reflects the evidence that the incidence of acute VTE in this population is very low and additional testing would be of low yield and high cost.

## C. Evaluation

Numerous hereditary and acquired factors have been identified that contribute to the risk of acute VTE. The list of factors has grown and with it the ability to test. However, though there may be an association with the risk of a first or a recurrent VTE, there is often no impact on management and the routine testing of unselected patients is not recommended.<sup>7</sup> Examples of scenarios along the spectrum of risk where management is typically unchanged by the result of testing include:

- A patient with a single provoked VTE, such as after knee arthroplasty — A longer duration of anticoagulation would not be routinely recommended if positive for a thrombophilic state, such as heterozygosity for the Factor V Leiden gene.

- A patient with a second unprovoked VTE and at low risk for bleeding — Indefinite anticoagulation is recommended by national guidelines.<sup>8</sup> If this strategy is selected, the results of a thrombophilia evaluation will not impact management.
- A patient with a single unprovoked life-threatening PE for whom the patient's attending and the patient have decided to pursue lifelong anticoagulation to reduce the risk of a recurrence — A negative thrombophilia evaluation will not alter management.

The guiding principle when considering whether to order an expensive battery of tests for a hypercoagulable state is to only order tests that will change management. In many clinical situations, including the examples above, the result will not alter the treatment strategy. In addition, when testing is ordered, the specific tests that will guide future therapy should be selected rather than a comprehensive list of all available tests.

### **D. Treatment**

The outpatient treatment of acute VTE has become increasingly common since the seminal studies by Levine and Koopman in 1996.<sup>9,10</sup> The introduction of the DOACs, such as rivaroxaban and apixaban, has further facilitated the potential for home treatment. Aujuskey and colleagues have demonstrated that the spectrum of patients with acute VTE who can be safely treated at home can be extended to select patients with acute PE.<sup>11</sup>

Discharge from the Emergency Department or a prompt discharge in one to two days from the medical wards can tremendously decrease costs for the hospital and for society. However, discharge must be done with care and expertise or patient safety can be jeopardized. When considering an early discharge, a hospitalist must:

- Determine the risk of death or deterioration, such as by using the Pulmonary Embolism Severity Index (PESI) score<sup>12</sup>
- Educate the patient on their acute illness
- Educate the patient on their treatment and the need for full adherence
- Ensure the patient can access the medication, which often entails contacting the insurance company and/or pharmacy to determine coverage status and the cost to the patient

Though these tasks are complex and require time and effort, hospitalists can complete the assessment and provide for a safe discharge. Timely discharge decreases the risks of hospitalization and allows for a more rapid transition of the patient back to their home environment. Thus, ensuring a prompt and safe discharge benefits the patient and decreases costs, and affords an opportunity for the hospitalist to provide care of the highest value.

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