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# Treatment of Acute Venous Thromboembolism

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**KEYWORDS**

• Deep vein thrombosis • Pulmonary embolism • Anticoagulation • Thrombolytic
• Risk stratification

**KEY POINTS**

- Guidelines suggest using direct oral anticoagulants (DOAC) over traditional therapy for low-molecular-weight heparin (LMWH) and warfarin for acute deep vein thrombosis (DVT) and pulmonary embolism (PE) based on their safety profile.
- The best route, dose, or need for thrombolytic treatment of intermediate-risk PE is an active area of research, and a definitive therapeutic approach is not currently established.
- Guidelines suggest against the routine use of thrombolytics in most patients with DVT.
- The use of DOACs in patients with cancer-associated DVT and PE is emerging, and guidance is beginning to suggest their use instead of LMWH as first-line treatment.

## INTRODUCTION AND EPIDEMIOLOGY

Acute venous thromboembolism (VTE) has an annual incidence rate of 1 to 2 per 1000 persons in the United States.[1] Despite increasing efforts to prevent occurrence, rates continue to increase in hospitalized patients across the United States.[2] VTE also represents a significant source of health care expenditures—with cost estimated between $14 billion and 27 billion annually.[3] This article reviews the current evidence regarding treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as review updates in special populations (cancer, obesity, and renal disease).

## PULMONARY EMBOLISM

### *Risk Stratification*

PE has a wide spectrum of presentations and outcomes ranging from incidental imaging findings to cardiovascular collapse, thus risk stratification of PE is essential.

Patients who are hemodynamically unstable (traditionally defined as a persistent systolic blood pressure less than 90 mm/hg or requirement of vasopressors, with

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clinical or biochemical signs of hypoperfusion) are defined as those with high-risk or massive PE.[4] Hemodynamically stable patients require further stratification. The Pulmonary Embolism Severity Index (PESI) score and the simplified (sPESI) score are risk assessment models that have been incorporated into guidelines.[5,6] Multiple online risk calculators and mobile applications are available to facilitate application of these scores. Patients who have an elevated risk based on PESI/sPESI are classified as intermediate risk. Intermediate risk patients are further stratified. Those with both right heart strain on imaging, and positive troponins are classified as intermediate-high risk, those with either right heart strain or troponins are intermediate low risk. Low risk patients are defined by a low PESI/sPESI score. Patients who would otherwise have been classified as low risk by sPESI or PESI, but are found to have evidence of right heart strain or troponin elevation are known to have increased mortality and should be treated as intermediate risk.[4,7]

### *High-risk/massive pulmonary embolism*

Initial stabilization of the patient with acute high-risk PE is based on lessons from patients with acute right heart failure.[8,9] This may include an intravenous (IV) fluid bolus of no more than 500 cc, as excess preload on an overdistended ventricle may worsen shock. Vasopressors may be required to maintain systemic perfusion with norepinephrine or dobutamine (preferred). Supplemental oxygen progressing to low tidal volume, low peak pressure ventilation can be used to support oxygenation as patients with PE are particularly sensitive to increased intrathoracic pressure. Case series have demonstrated the role of venoarterial extracorporeal membrane oxygenation as a bridge to definitive therapy, which may entail thrombolysis, embolectomy, or catheter-directed methods.[10]

The cornerstone of management in high-risk or massive PE is reperfusion. Systemic thrombolysis improves mortality in patients with high-risk PE albeit with an increased incidence of major bleeding and approximately 2% rate of intracranial hemorrhage (ICH).[11] In patients who have absolute contraindications to thrombolysis, surgical thrombectomy is a viable alternative with similar mortality rates.[12] In patients who are not candidates for systemic thrombolysis or surgical embolectomy, or in patients with failed thrombolysis, catheter-based therapies (**Table 1**) can be considered.

### *Intermediate risk/submassive pulmonary embolism*

The role of thrombolysis in patients with intermediate-risk PE is not clear. The PEITHO trial randomized 1005 participants to receive placebo or weight-based (30–50 mg) tenecteplase in addition to standard of care. Results provided evidence that thrombolysis may decrease the combined endpoint of mortality or escalation of care at the cost of increased rate of ICH in patients with intermediate-risk PE.[18] There was no statistically significant difference in mortality, but there was a significant decrease in the rate of hemodynamic decompensation (1.6% vs 5%, odds ratio [OR] 0.3, $P = .002$). Thrombolytic treatment was associated with a significant increase in stroke (2.4% vs 0.2%, OR 12.1, $P = .003$) and extracranial bleed (6.3% vs 1.2%, OR 5.55, $P<.001$). Subsequent meta-analyses have yielded a significant mortality benefit in the intermediate-risk PE population and a signal toward less bleeding for patients younger than 65 years who receive thrombolysis compared with patients older than 65 years who receive thrombolysis.[19,20] However, the routine use of systemic thrombolysis in intermediate-high–risk patients has not been supported by either the European Society of Cardiology 2019 or American College of Chest Physicians 2016 guidelines.[4,21] Although available evidence for patients with intermediate-high–risk PE is unclear, patients should be closely monitored regardless of treatment choice,

**Table 1**
**Catheter-based reperfusion strategies**

| Type | Principle | Selected Examples | Selected Studies |
|---|---|---|---|
| Catheter-directed lysis | Direct, local pulmonary arterial administration of thrombolytics can potentially reduce the required dose, increase efficacy, and improve safety | • Unifuse Catheter system<br>• Cragg-McNamara system | • PERFECT[13] |
| Ultrasound-assisted thrombolysis | Local ultrasonic energy may facilitate penetration of thrombolysis into thrombi. Typically use slow infusion of 1-2 mg/min of tPA and 12–24-h dwell time of catheter in the pulmonary artery | • EKOSonic | • ULTIMA[14]<br>• SEATTLE II[15] |
| Mechanical-assisted catheters | Use of mechanical disruption, suction, or rheolytic effects to disrupt thrombi can be used without thrombolysis in patients who have contraindications | • FlowTriever—mechanical disruption<br>• Penumbra-indigo—rheolytic destruction<br>• AngioVac-Suction thrombectomy | • FLARE[16]<br>• EXTRACT-PE[17] (ongoing) |

Unifuse Catheter system (AngioDynamics, Latham NY), Cragg-McNamara system (Medtronic, Minneapolis MN), EKOSonic (Boston Scientific, Marlborough MA), FlowTriever (Inari Medical, Irvine CA), Penumbra-indigo (Penumbra Inc, Alameda CA), AngioVac (AngioDynamics, Latham NY).
*Abbreviation:* tPA, tissue plasminogen activator.

as the median time to death or decompensation was 1.8 days in the placebo group in the PETHIOS trial.[18]

Controversy also exists regarding the dose of tissue plasminogen activator (tPA), with full dose considered to be 100 mg of alteplase given over 2 hours. The MOPPET trial enrolled 121 patients with "moderate" PE (determined by clot burden of greater than 70% involvement of thrombus in 2 or more lobar or the main pulmonary arteries) and randomized them to receive either 0.5 mg/kg (max 50 mg) or placebo in addition to standard of care. There was a statistically significant decrease in the rate of pulmonary hypertension and recurrent PE at 28 months (16% vs 63%, $P<.001$), as well as hospital length of stay (2.2 days vs 4.9 days, $P<.001$) but not in mortality (1.6% vs 5%, $P = .3$).[22]However, contrary evidence has emerged comparing full- versus reduced-dose tPA, showing no clear mortality or bleeding risk benefit with a reduced dose and demonstrating increased need for escalation of care.[23]

An alternative method of reduced-dose thrombolysis is intrapulmonary arterial administration with catheter-based therapies. Numerous devices are becoming available, consisting of an intrapulmonary catheter with or without the addition of energy-assisted thrombolysis or thrombectomy (see **Table 1**). Various studies have investigated these techniques; however, the role of catheter-based therapies for intermediate-high–risk PE is still unclear. Available evidence has shown favorable reductions in right ventricular size and pulmonary arterial pressure as surrogates for efficacy and mortality with minimal bleeding complications and rates of intracranial hemorrhage of less than 1%. To date no trials have demonstrated a mortality benefit.[13–17] Given the numerous therapeutic options and modalities available, many hospitals have built Pulmonary Embolism Response Teams (PERT) to provide

management recommendations in these complex patients. The European Society of Cardiology has given a class IIa recommendation for consultation with a PERT team, although questions remain on optimal size, composition, and funding.[4]

There is no established role of thrombolysis or catheter-directed therapy for the intermediate-low–risk PE, hence the mainstay of therapy remains systemic anticoagulation.[4,21]

### *Low-risk pulmonary embolism*

Patients with low-risk PE who have no other reason for hospitalization or additional barriers to treatment adherence can be managed at home with no increase immortality. The Outpatient Treatment of Pulmonary Embolism trial randomized 344 patients with low-risk PE to inpatient or outpatient treatment and demonstrated noninferiority of outpatient therapy.[24] The Hestia criteria have been developed to standardize the selection of these patients (**Box 1**).[25] If a patient lacks any of the Hestia criteria they may be an appropriate candidate for early discharge and home treatment.

Controversy still exists regarding the management of isolated small subsegmental PE. Interobserver variability can be as high as 50%, and in the absence of proximal DVT or risk factors, patients with isolated subsegmental PE who did not receive anticoagulation have a VTE recurrence rate and mortality similar to those who were anticoagulated.[26–28] Conservative management and close follow-up may be a reasonable treatment plan if there is no DVT.

## DEEP VEIN THROMBOSIS

### *Distal Deep Vein Thrombosis*

Anticoagulation for isolated distal calf vein thrombosis is controversial because the risk of PE is low; however, extention to the popliteal vein and hence a proximal DVT is of concern. The American College of Chest Physicians (ACCP) guidelines suggest either no anticoagulation plus mandatory Doppler surveillance for extention for more than 2 weeks or anticoagulation in patients with risk of extention.[21]

**Box 1**
**The Hestia criteria for early discharge and home treatment of pulmonary embolism**

- Hemodynamically unstable
- Thrombolysis or embolectomy needed
- Active bleeding or high risk for bleeding
- PE diagnosed while on anticoagulation
- Severe liver impairment
- Renal disease with creatinine clearance less than 30 mL/min
- Pregnancy
- Documented history of heparin-induced thrombocytopenia
- Supplemental oxygen required to maintain $SaO_2$ greater than 90% for more than 24 hours
- Severe pain needing IV pain medication required for more than 24 hours
- Medical or social reason for admission more than 24 hours

*Adapted from* Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011;9(8):1501; with permission.

The CACTUS trial was reported after the publication of the ACCP guidelines and was terminated early because study drug expired and only half of the planned number of patients was enrolled. Two hundred fifty-nine outpatients with calf vein thrombosis and no history of cancer or previous DVT were randomized to low-molecular-weight heparin (LMWH) or placebo. There was no statistical difference in the composite outcome of extention to proximal veins, contralateral DVT, or PE, and there was more bleeding with LMWH versus placebo (4% vs 0%, 95% confidence interval 0.4–9.2).[29] This underpowered trial suggests more harm than benefit in treating low-risk, isolated calf vein thrombosis.

### *Catheter-Directed Thrombolysis for Acute Proximal Deep Vein Thrombosis*

Thrombolysis, either systemic or catheter–based, using a variety of techniques has been shown to improve vein patency for treatment of DVT with the hope of decreasing post-thrombotic syndrome. However, ACCP guidelines suggest anticoagulant therapy alone over catheter-directed thrombolysis.[21] A Cochrane systematic review of 1103 randomized patients in 17 trials found thrombolysis increased vein patency and reduced postthrombotic syndrome. However, this review did not include 692 patients in the ATTRACT trial.[30]

The ATTRACT trial randomized patients with acute proximal DVT to pharmacomechanical thrombolysis with tPA and thrombus aspiration or maceration with or without stenting plus anticoagulation versus anticoagulation alone with a primary outcome of postthrombotic syndrome between 6 and 24 months.[31] Pharmacomechanical thrombolysis showed no efficacy in the primary outcome (47% vs 48%), a trend in improvement in moderate-to-severe postthrombotic syndrome (18% vs 24%, $P = .04$ [<0.01 considered significant for multiple secondary outcomes]) and more major bleeding in the first 10 days (1.7% vs 0.3%, $P = .03$), but no difference in bleeding at 24-month follow-up. This trial indicates no long-term benefit and short-term harm with pharmacomechanical thrombolysis.

The ACCP guidelines suggest anticoagulation over thrombolysis for upper extremity DVT.[21] Candidates likely to benefit would have thrombus in most of the subclavian and axillary veins, symptoms of less than 14 days, good functional status, and low risk of bleeding.

### *Compression Stockings to Prevent Postthrombotic Syndrome*

Postthrombotic syndrome can affect up to half of patients with proximal DVT, and use of compression stockings is thought to prevent venous dilatation and further valve damage. ACCP guidelines suggest not using these based on the SOX trial, which is the largest trial performed to date.[21,32] The SOX trial randomized 806 patients with first symptomatic proximal DVT to 30 to 40 mm Hg graduated elastic compression stocking or placebo stockings with less than 5 mm Hg compression. Primary outcome was development of postthrombotic syndrome at 2 years. There was no difference between active and placebo stocking groups using the specific Ginsberg scale (14.2% vs 12.7%) or the sensitive Villalta scale (52.6% vs 52.3%). A subsequent meta-analysis of 5 randomized trials, with the SOX trial representing more than half the patients, shows a 38% relative reduction in postthrombotic syndrome, although there was large statistical heterogeneity ($I^2 = 80\%$).[33]

## VENOUS THROMBOEMBOLISM TREATMENT

### *Initial Anticoagulation*

Initial anticoagulation (or acute anticoagulation) refers to anticoagulation choice at time of diagnosis. ACCP guidelines suggest DOACs over warfarin, and studies have

demonstrated that DOACs have equal efficacy and improved safety.[21] The dosing of these various agents is reviewed in **Table 2**.

### *Vitamin K Antagonists*

The first trial in 1960 that compared anticoagulant therapy with no anticoagulant therapy in patients with symptomatic DVT or PE suggested that 1.5 days of heparin and 14 days of vitamin K antagonist (VKA) therapy markedly reduced recurrent PE and mortality in patients with acute PE.[41] A 1992 randomized trial compared continuous intravenous heparin plus VKA versus VKA alone and was terminated early due to excess of symptomatic events in the VKA alone group.[42] Therefore, parenteral anticoagulation must be continued for at least 5 days and an International Normalized Ratio (INR) above 2 for 2 consecutive days.[43] However, ACCP does comment that if the INR exceeds the therapeutic range prematurely, it is acceptable to stop parenteral therapy before the patient has received 5 days of treatment.[44,45]

**Table 2**
**Anticoagulation dosing for venous thromboembolsim**

| Anticoagulant | Initial Dose and Length | Maintenance Dose |
|---|---|---|
| Unfractionated Heparin[34] | • Weight Based: 80 units/kg bolus, then 18 units/kg/h (preferred) | Adjust infusion rate to maintain target laboratory values based on institutional protocol to maintain therapeutic aPTT 1.5–2.5 times the control |
| Low-Molecular-Weight Heparin (Enoxaparin)[35] | • 1 mg/kg twice daily (preferred)<br>• 1.5 mg/kg QD can be used in nonobese patients<br>• CrCl <30 mL/min: reduce to 1 mg/kg once daily | Same |
| Fondaparinux[36] | • 5 mg QD (<50 kg)<br>• 7.5 mg QD (50–100 kg)<br>• 10 mg QD (>100 kg) | Same |
| Apixaban[37] | • 10 mg BID first 7 d<br>• CrCl ≤30 mL/min: has not been studied | 5 mg BID |
| Dabigatran[38] | • 150 mg twice daily (after initial 5–10 d of parenteral anticoagulation)<br>• CrCl ≤30 mL/min: has not been studied | Same |
| Rivaroxaban[39] | • 15 mg BID for the first 3 wk<br>• CrCl <30 mL/min: avoid use | 20 mg QD |
| Edoxaban[40] | • 60 mg once daily >60 kg<br>• 30 mg once daily <60 kg or CrCl 15–50 mL/min (after initial 5–10 d of parenteral anticoagulation) | Same |

*Abbreviation:* aPTT, activated partial thromboplastin time; CrCl, creatinine clearance.

### *Heparin, Low-Molecular-Weight Heparin, or Fondaparinux*

ACCP guidelines suggest LMWH or fondaparinux over intravenous or subcutaneous unfractionated heparin (UFH).[44] A 2017 Cochrane meta-analysis of 29 randomized controlled trials comparing twice daily LMWH with UFH in patients with acute VTE demonstrated recurrence in 3.6% with LMWH versus 5.3% with UFH (OR 0.72 $P = .001$) and major bleeding rates of 1.1% LMWH versus 1.9% UFH (OR 0.58 $P = .02$).[46,47]

There are subsets of patients in whom IV UFH should still be the initial anticoagulant. Patients with renal failure creatinine clearance (CrCl) less than 30 mL/min have relative contraindications to LMWH, fondaparinux, and DOACs. Also, those who are hemodynamically unstable from massive PE and those who may need urgent discontinuation of anticoagulation should also be treated with IV UFH.[4] A weight-based dosing nomogram protocol is recommended over a non–weight-based protocol for IV UFH. A higher percentage of patients randomized to weight-adjusted dosing achieve a therapeutic activated partial thromboplastin time (aPTT) within 24 hours (97% vs 77%) without an increase in major bleeding.[34] The efficacy of IV UFH depends on achieving a critical therapeutic level within 24 hours of initiation, which is target aPTT ratio of 1.5 to 2.5 times control. A pooled analysis of 3 randomized trials showed an increased risk of recurrent VTE when a therapeutic aPTT was not achieved within 24 hours (23% vs 4%, $P = .02$).[48] Fondaparinux has been found to be comparable to LMWH for acute VTE treatment in the MATISSE trial with no difference in recurrent VTE, major bleeding, or mortality.[49] It also has the benefit of being able to be used in patients with history of heparin-induced thrombocytopenia.

### *Direct Oral Anticoagulants*

The ACCP antithrombotic guidelines give a grade 2B suggestion for a DOAC over VKA therapy.[21] This suggestion is based on less bleeding with DOACs and greater convenience for patients and health care providers. The DOAC trials are summarized in **Table 3**.

To mitigate the high recurrence rate in the first several weeks of treatment, 2 different approaches were taken by trial investigators. Dabigatran and edoxaban were studied with at least 5 days of lead in (not overlap) with parenteral anticoagulation before DOAC initiation to help mitigate the high recurrence rate in the first week or so of therapy. Dabigatran and edoxaban require at least 5 days of parenteral anticoagulation with unfractionated heparin, LMWH, or fondaparinux and then parenteral anticoagulation is stopped and they are started.[50,51,55] Rivaroxaban was studied with a 50% increase of the daily dose for 3 weeks, whereas the apixaban trial used a 2-fold increase for 1 week.[52–54]

### *Long-Term Anticoagulation*

Long-term anticoagulation refers to treatment during the initial 3 months. At 3 months the decision is made on whether to extend anticoagulation based on risk of recurrence and bleeding (**Table 4**).

A 2014 review of 6 trials including 27,023 patients with VTE compared DOACs with VKAs; recurrent VTE occurred in 2.0% of DOAC recipients versus 2.2% in VKA recipients. Treatment with a DOAC significantly reduced the risk of major bleeding (risk ratio 0.61 $P = .002$) as well as intracranial bleeding, fatal bleeding, and clinically relevant nonmajor bleeding.[56]

### *Extended Anticoagulation*

Extended anticoagulation refers to treating indefinitely past 3-month standard long-term treatment. This decision must weigh the risk of VTE recurrence versus bleeding. Several

**Table 3**
**Direct oral anticoagulant trials**

| Anticoagulant | Trial | Year | Recurrent VTE, DOAC vs Control | Safety Outcomes |
|---|---|---|---|---|
| Dabigatran | RE-COVER[50] | 2009 | Noninferiority 2.4% vs 2.1% | No significant difference in major bleeding<br>Significant reduction in any bleeding in dabigatran (16.1% vs 21.9%) |
| Dabigatran | RE-COVER II[51] | 2014 | Noninferiority 2.3% vs 2.2% | No significant difference in major bleeding<br>Significantly less any bleeding in dabigatran (15.6% vs 22.1%) |
| Rivaroxaban | EINSTEIN-DVT[52] | 2010 | Noninferiority 2.1% vs 3.0% | No significant difference in first major or clinically relevant nonmajor bleeding |
| Rivaroxaban | EINSTEIN-PE[53] | 2012 | Noninferiority 2.1% vs 1.8% | No significant difference in first major/clinically relevant nonmajor bleeding<br>Significant decrease in major bleeding (1.1% vs 2.2%) |
| Apixaban | AMPLIFY[54] | 2013 | Noninferiority 2.3% vs 2.7% | Significantly less major bleeding (0.6% vs1.8%)<br>Significantly less clinically relevant bleeding (3.8% vs 8.0%) |
| Edoxaban | Hokusai-VTE[55] | 2013 | Noninferiority 3.2% vs 3.5% | No significant difference in major bleeding<br>Significantly less clinically relevant bleeding (8.5% vs10.3%) |

scoring systems have been developed to assist in estimating VTE recurrence. The Men and HERDOO2 rule (hyperpigmentation, edema, or redness in either leg; D-dimer level $\geq$250 μg/L; obesity with body mass index $\geq$30; or Older age $\geq$65 years) estimated that women with an unprovoked VTE who have 0 of the criteria are low risk for recurrent VTE

**Table 4**
**American College of Chest Physicians guideline anticoagulation length for proximal deep vein thrombosis or pulmonary embolism**

| Type of VTE | Bleeding Risk | Suggested Length | Grade of Evidence |
|---|---|---|---|
| Provoked by surgery | All | 3 mo | 1B |
| Provoked by a nonsurgical transient risk factor | Low/Moderate | 3 mo | 2B |
| | High | 3 mo | 1B |
| Unprovoked first VTE | Low | Extended (no stop date) | 2B |
| Unprovoked first VTE | High | 3 mo | 1B |
| Unprovoked second VTE | Low | Extended (no stop date) | 1B |
| Unprovoked second VTE | Moderate | Extended (no stop date) | 2B |
| Unprovoked second VTE | High | 3 mo | 2B |
| Active cancer | Low/Moderate | Extended (no stop date) | 1B |
| Active cancer | High | 3 mo | 2B |

*Data from* Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):315-352.

and stopping anticoagulation can be considered.[57] The DASH score uses risk factors of D-dimer, age, sex, and hormonal therapy for patient with an unprovoked VTE. A score less than or equal to 1 has a low annualized recurrence risk of 3.1%; anticoagulation may be able to be discontinued in these patients.[58] ACCP guidelines use 5 risk factors (**Table 5**) to guide the decision for extended anticoagulation.

Unlike atrial fibrillation in which the HAS-BLED score has been extensively validated, there are few robust bleeding risk assessment models for VTE. The RIETE score, which uses age greater than 75 years, recent bleeding, cancer, creatinine levels greater than 1.2 mg/dL, anemia, or pulmonary embolism, may be used to estimate bleeding risk.[59] The ACCP guidelines use bleeding risk factors (**Table 6**) to guide their recommendations for extended anticoagulation.

There have been multiple trials to evaluate extended anticoagulation, including anticoagulants versus placebo, anticoagulants versus aspirin, and aspirin versus placebo. Extended treatment with lower dose warfarin (INR 1.5–2.0), aspirin, or prophylactic dose DOAC have also been studied to mitigate bleeding, and selected trials are summarized (**Table 7**).

Usual dose warfarin (INR 2–3) is more effective and as safe as lower dose; prophylactic dose apixaban has less recurrence and no significant increase in major bleeding compared with placebo, and prophylactic dose rivaroxaban is more efficacious and as safe as aspirin. The use of lower prophylactic dose DOACs with their respective lower bleeding risk questions the traditional recurrent VTE threshold and therefore we recommend considering extended treatment of most patients.

## SPECIAL POPULATIONS

### *Malignancy*

Active malignancy represents a significant risk factor for VTE; the risk of proximal DVT or PE is 4- to 7-fold higher in patients with cancer compared with those without.[68] Initiation of anticoagulation further represents a challenge in this patient population, as they are significantly more likely to experience bleeding complications as well as VTE recurrence compared with the general population. Although guidelines have previously emphasized LMWH as first-line treatment, there is increasing evidence and acceptance for use of DOACs in the treatment of cancer-associated VTE. The Hokusai VTE Cancer study found edoxaban had similar net clinical benefit of recurrence and major bleeding as dalteparin with numerically less recurrence and more major bleeding with edoxaban.[69] Similarly, in the SELECT-D trial, rivaroxaban had a similar numeric trend of less recurrence and more bleeding with rivaroxaban compared with

**Table 5**
**American College of Chest Physicians' estimated venous thromboembolism recurrence risk**

| Risk Factor | Recurrence Risk |
|---|---|
| Surgery | 3% at 5 y |
| Transient nonsurgical (estrogen therapy, pregnancy, leg injury, flight of >8 h) | 15% at 5 y |
| Unprovoked | 30% at 5 y |
| Cancer | 15% annual (not calculated at 5 y due to higher mortality) |
| Second unprovoked VTE | 45% at 5 y |

*Data from* Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):315-352.

**Table 6**
**American College of Chest Physicians' bleeding risk categories**

| | |
|---|---|
| **Age >65 y** | **Diabetes** |
| Age >75 y | Anemia |
| Previous bleeding | Antiplatelet therapy |
| Cancer | Poor anticoagulant control |
| Metastatic cancer | Comorbidity and reduced functional capacity |
| Renal failure | Recent surgery |
| Liver failure | Frequent falls |
| Thrombocytopenia | Alcohol abuse |
| Previous stroke | Nonsteroidal antiinflammatory drug |
| *Risk Factors* | |
| Low: 0 risk factors; Moderate: 1 risk factor; High: ≥2 risk factors | |

*Adapted from* Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):329; with permission.

dalteparin.[70] Both studies reported increased bleeding, mainly in patients with intact luminal gastrointestinal malignancies. More recently, the ADAM VTE trial studied the use of apixaban compared with dalteparin in patients with cancer and found lower rates of recurrent VTE with no increase in bleeding complications.[71] Given these findings, and in view of ISTH and NCCN guidelines, we recommend consideration of either of these agents for the treatment of cancer-related VTE, with very careful consideration of bleeding risk in those with gastroesophageal malignancy.[72–74]

### *Obesity*

The use of DOACs in morbid obese patients (defined as a body mass index [BMI] >40 kg/m$^2$) remains controversial due to a paucity of clinical data in this population. To date, there has been no randomized clinical trial comparing vitamin K antagonist and DOACs dedicated to patients with BMI greater than 40 kg/m$^2$ for the treatment of acute VTE. Pharmacokinetic studies have indicated the challenge in using DOACs due to higher volume of distribution and lower mean peak concentration in patients weighing greater than 120 kg. Because of these obstacles, clinical guidance favors VKA over DOACs for patients with a BMI greater than 40 kg/m$^2$ or 120 kg or greater than 35 kg/m$^2$ or 120 kg.[75,76] In contrast, there have been retrospective studies investigating clinical outcomes with use of rivaroxaban, which found no increase in recurrent VTE or bleeding.[77] Further, the Dresden NOAC registry found elevated BMI is associated with a decrease in adverse events with use of DOACs, the so-called obesity paradox.[78]

Given the lack of data to support definitive recommendations in patient with acute VTE and BMI greater than 35 to 40 kg/m$^2$, it is suggested to use vitamin K antagonists in this population. In the appropriate clinical scenario, DOACs can be considered and management guided by DOAC levels according to ISTH guidance—anti-FXa levels for edoxaban, rivaroxaban, or apixaban or dilute thrombin time for dabigatran, although they are not readily available. Mass spectrometry drug levels can alternatively be used for all DOACs.[75]

### *Renal Failure*

Chronic kidney disease represents an independent risk factor not only for VTE occurrence but also for bleeding complications during treatment. Patients with CrCl less

**Table 7**
**Extended anticoagulation trials**

| Trial | Year | Anticoagulation | Control | Recurrent VTE Efficacy | Safety Outcomes |
|---|---|---|---|---|---|
| Kearon Seminal Study[60] | 1999 | Warfarin (additional 24 mo) | Placebo | Significantly reduced, 1.3% vs 27.4% per 100 person-years | No significant difference in major bleeding |
| PREVENT[61] | 2003 | Low-intensity Warfarin (INR 1.5–1.9) | Placebo | Significantly reduced, 2.6 vs 7.2 per 100 person-years | No significant difference in major bleeding |
| ELATE[62] | 2003 | Low-intensity Warfarin (INR 1.5–1.9) | Standard Warfarin (INR 2–3) | Significantly increased, 1.9 vs 0.7 per 100 person-years | No significant difference in any or major bleeding |
| EINSTEIN CHOICE[63] | 2017 | Rivaroxaban 20 mg | Aspirin | Significantly reduced, 1.5% vs 4.4% | No significant difference clinically relevant or major bleeding |
| | 2017 | Rivaroxaban 10 mg | Aspirin | Significantly reduced, 1.2% vs 4.4% | No significant difference in clinically relevant or major bleeding |
| AMPLIFY-EXT[64] | 2013 | Apixaban 2.5 mg | Placebo | Significantly reduced, 1.7% vs 8.8 | No significant difference in major bleeding or clinically relevant nonmajor bleeding |
| | 2013 | Apixaban 5 mg | Placebo | Significantly reduced, 1.7% vs 8.8 | No significant difference in major bleeding<br>Increased clinically relevant nonmajor bleeding (1.82 RR) |
| RE-MEDY[65] | 2013 | Dabigatran | Warfarin | Noninferiority, 1.8% vs 1.3% | No significant difference in major bleeding<br>Significant decreased major or clinically relevant bleeding, 5.6% vs10.2% |
| RE-SONATE[65] | 2013 | Dabigatran | Placebo | Significantly reduced, 0.4% vs 5.6% | Significantly increased major or clinically relevant bleeding, 5.3% vs1.8% |
| ASPIRE[66] | 2012 | Aspirin | Placebo | No significant difference | No significant difference in major or clinically relevant nonmajor bleeding |
| WARFASA[67] | 2012 | Aspirin | Placebo | Significantly reduced, 6.6% vs 11.2% | No significant difference in major or clinically relevant nonmajor bleeding |

than 30 mL/min, calculated with the Cockroff-Gualt equation using actual body weight, were excluded from trials that studied DOACs in the treatment of acute VTE.[79] Given the lack of data in this patient population, vitamin K antagonists are likely preferred for the treatment of VTE in patients with a CrCl less than 30 mL/min.

## DISCLOSURE

S. Nair, N. Garza, M. George: nothing to declare. S. Kaatz: research support to institution. Consulting: Janssen, Pfizer, Portola, Roche, and Bristol Myers Squibb.

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