Venous Thromboembolism Guideline Team

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Special Topics in Venous Thromboembolism

Patient population: Non-pregnant patients of ages ≥18 years with suspected or diagnosed venous thromboembolism (VTE), especially those with severe disease, or those with less common clinical scenarios. This document focuses primarily but not exclusively on inpatient, observation, and emergency department services for patients with suspected or diagnosed VTE. Note: In-depth coverage of the standard diagnosis and management of VTE is provided in the ambulatory venous thromboembolism guideline.

Objectives: To provide evidence-based recommendations to address special clinical scenarios related to VTE not covered in the related ambulatory guideline. This guideline covers VTE-related scenarios such as the extremes of severity (eg. incidentally discovered asymptomatic pulmonary embolism (PE); massive PE; obstructive, proximal deep venous thromboembolism (DVT), or scenarios that are less common and, therefore, more likely to involve difficult or nuanced decision-making (eg. calf vein, portal vein, or mesenteric vein thrombosis). The document also addresses upper extremity and catheter-associated VTE, and criteria for admitting and discharging patients with PE.

Key points:

Upper extremity DVT

Compression ultrasonography is the first-line imaging modality for the diagnosis. *[I-B]*
For acute DVT involving the axillary or more proximal veins treat with anticoagulation for 3 months. *[I-A]*
For central venous catheter-associated upper extremity DVT:
- when the catheter is no longer needed or is not functioning, remove the catheter and provide 3 months of anticoagulation. *[I-C]*
- when the catheter is still needed and remains functional, continue anticoagulation treatment for either 3 months, or as long as the catheter is in place, whichever is longer. *[I-C]*
- consult vascular surgery and interventional radiology for cases of suspected Paget-Schroetter syndrome, and for cases involving severe symptoms.

Lower extremity DVT (Figure 1 and Figure 2, Table 1 and Table 2)

Distal (calf) DVT **(**Table 2 for definition)

Two approaches are possible for patients with distal lower extremity (LE) DVT (Table 1):
- treat with anticoagulation therapy (for 3 months), or
- surveillance with serial compression Doppler ultrasound examinations (weekly for 2 weeks), withholding treatment unless these studies demonstrate extension of the thrombus (Table 1). *[II-C]*

Severe obstructive proximal DVT

Manage femoropopliteal DVTs with anticoagulation rather than thrombus removal. *[II-C]*
Refer iliofemoral DVTs to vascular surgery or interventional radiology to assess for the appropriateness of early thrombus removal. (See indications and contraindications for catheter-directed thrombolysis in Table 3 and Table 4.)
Early thrombus removal is the preferred treatment in patients with limb-threatening venous ischemia (phlegmasia cerulea dolens or venous gangrene) due to iliofemoral venous thrombosis with or without associated femoropopliteal venous thrombosis.[1-3] *[II-B]* Consult vascular surgery urgently in these cases.

Pulmonary Embolism (PE)

Incidentally discovered asymptomatic PE

Incidentally discovered asymptomatic PEs are clinically relevant. Consider treatment with the same systemic anticoagulation given to patients with symptomatic PE. *[II-C]*
Avoid anticoagulation in patients with a high bleeding risk. *[II-E]*

*** Strength of recommendation:**
I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Level of evidence supporting a diagnostic method or an intervention:
A = systematic reviews of randomized controlled trials with or without meta-analysis, B = randomized controlled trials, C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control), D = individual observation studies (case study/case series), E = expert opinion regarding benefits and harm

Pulmonary Embolism (PE) (Continued)

Massive PE

Massive PE is an acute PE with sustained hypotension (despite adequate fluid resuscitation with either a systolic blood pressure < 90 mm Hg for more than 15 minutes or requiring vasopressor support).

Emergent consultation to medical and interventional experts in PE is advised to determine the thrombolytic strategy (i.e. systemic thrombolytics vs catheter-directed thrombolysis). At Michigan Medicine, this can be achieved at any time by activating the PE Response Team (PERT) via page. This service includes pulmonologists, cardiologists, hospitalists, and interventional radiologists.

Indications and contraindications for systemic thrombolytic therapy for PE are listed in Table 6.

Submassive PE

Submassive PE is an acute PE without hypotension but with right ventricular (RV) dysfunction and/or myocardial necrosis (i.e. RV strain evidenced on imaging, or elevation of biomarkers such as troponin or BNP).

Treat with immediate initiation of anticoagulation with IV unfractionated heparin or low molecular weight heparin (LMWH). Urgent consultation to medical and interventional experts in PE is advised to determine if thrombolytic therapy is indicated. At Michigan Medicine, the PE Response Team (PERT) can be paged at any time for urgent evaluation of massive and submassive PE cases.

Indications and contraindications for systemic thrombolytic therapy for higher-risk acute PE are shown in Table 6. *[II-E]*

Admitting and discharging a patient with an acute PE

Patients with a Pulmonary Embolism Severity Index (PESI) score $\leq$ 85 (Table 7) and no other criteria that require hospital admission (Table 8), can be treated as an outpatient without hospital admission (Figure 3). *[II-B]*

Other sites of venous thrombosis

Portal vein thrombosis (PVT)

Portal vein thromboses typically require systemic anticoagulation. *[I-C]* Management depends on the acuity and chronicity of the thrombosis, and whether or not the patient has cirrhosis Figure 4, Figure 5 and Figure 6). *[II-C]*

Mesenteric vein thrombosis (MVT)

Mesenteric vein thrombosis treatment typically requires a multidisciplinary team approach, which may include medicine, gastroenterology, surgery, and interventional radiology (Figure 7). *[II-E]*

For acute MVT, perform systemic anticoagulation (Figure 7). *[I-D]*

For chronic MVT, the decision for anticoagulation is determined on a case-by-case basis. *[II-E]*

Special Considerations in Venous Thromboembolism

Thrombophilia workup, recurrent VTE events, treatment failure, and referral to hematology

Thrombophilia evaluation should not be performed in the setting of acute VTE. Although testing may be useful in some cases (eg. recurrent VTE, treatment failure, unusual VTE sites, etc.), it is generally deferred to the outpatient setting, often via hematology consultation.

Table 1. Management of Acute Distal* Lower Extremity (Calf) DVT with Anticoagulation and Serial Compression Ultrasound Examinations

Consider anticoagulation if:	Use serial compression ultrasound (without anticoagulation) if:
One or more of the following symptoms or risk factors for extension: active cancer history of prior VTE event thrombosis was not provoked** significant calf pain immobility	None of the symptoms or factors listed for considering anticoagulation.
Anticoagulation was initially withheld, but thrombosis extension is later visualized on compression ultrasound, particularly into a proximal deep vein	High risk of bleeding from anticoagulation
Patient is more concerned with avoiding DVT extension, PE, and DVT recurrence than the risk of bleeding	Patient is more concerned with avoiding bleeding than the risk of DVT extension, PE, and DVT recurrence

* See Table 2 for listing of distal deep veins

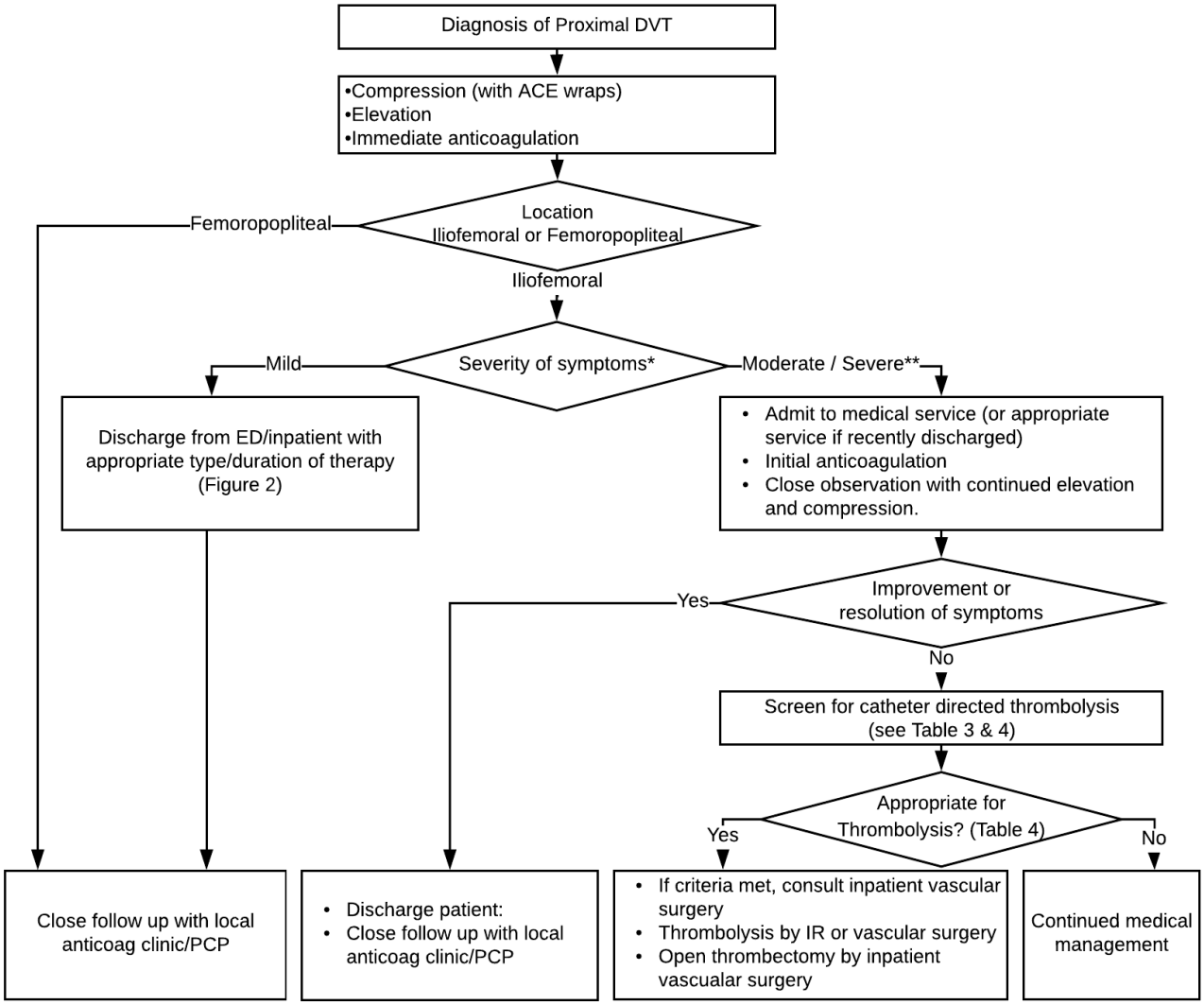
** Examples of provoked VTE events include: active cancer, current or recent hospitalization, diagnosis of a genetic or acquired thrombophilia, exposure to oral contraceptive pills or hormone replacement therapy, immobility, postoperative status, pregnancy, presence of central venous catheters. See Table 5 for a more comprehensive list of hypercoagulable states.

Table 2. Management of VTE of the Lower Extremity (including distal and superficial veins)

VTE Location	Management Approach
Proximal Deep Veins Iliac (common, external, internal) Femoral Popliteal	Anticoagulation is required. (Page 15)
Distal Deep Veins Anterior tibial Posterior tibial Peroneal	Anticoagulation or surveillance is acceptable.* (Page 14.)
Gastrocnemius Soleus	Surveillance* is preferred. DVT in these locations usually do not require anticoagulation.
Superficial veins Great saphenous vein	If clot is > 5 cm long and > 3 cm from the SFJ, consider treatment with fondaparinux 2.5 mg daily or enoxaparin 40 mg daily x 45 days. If clot is ≤ 3 cm from the SFJ, management should be similar to an acute proximal DVT. (See anticoagulation, page 15.)
Small saphenous vein	If clot is > 5 cm long and < 3 cm from the SPJ, consider treatment with fondaparinux 2.5 mg daily or enoxaparin 40 mg daily x 45 days If clot is ≤ 5 cm long and > 3 cm from the SPJ, anticoagulation is generally not recommended

*surveillance: serial compression Doppler ultrasound weekly for 2 weeks
SFJ: saphenofemoral junction; SPJ: saphenopopliteal junction; SVT: superficial venous thrombosis

Figure 1. Management of Acute Proximal Lower Extremity DVT

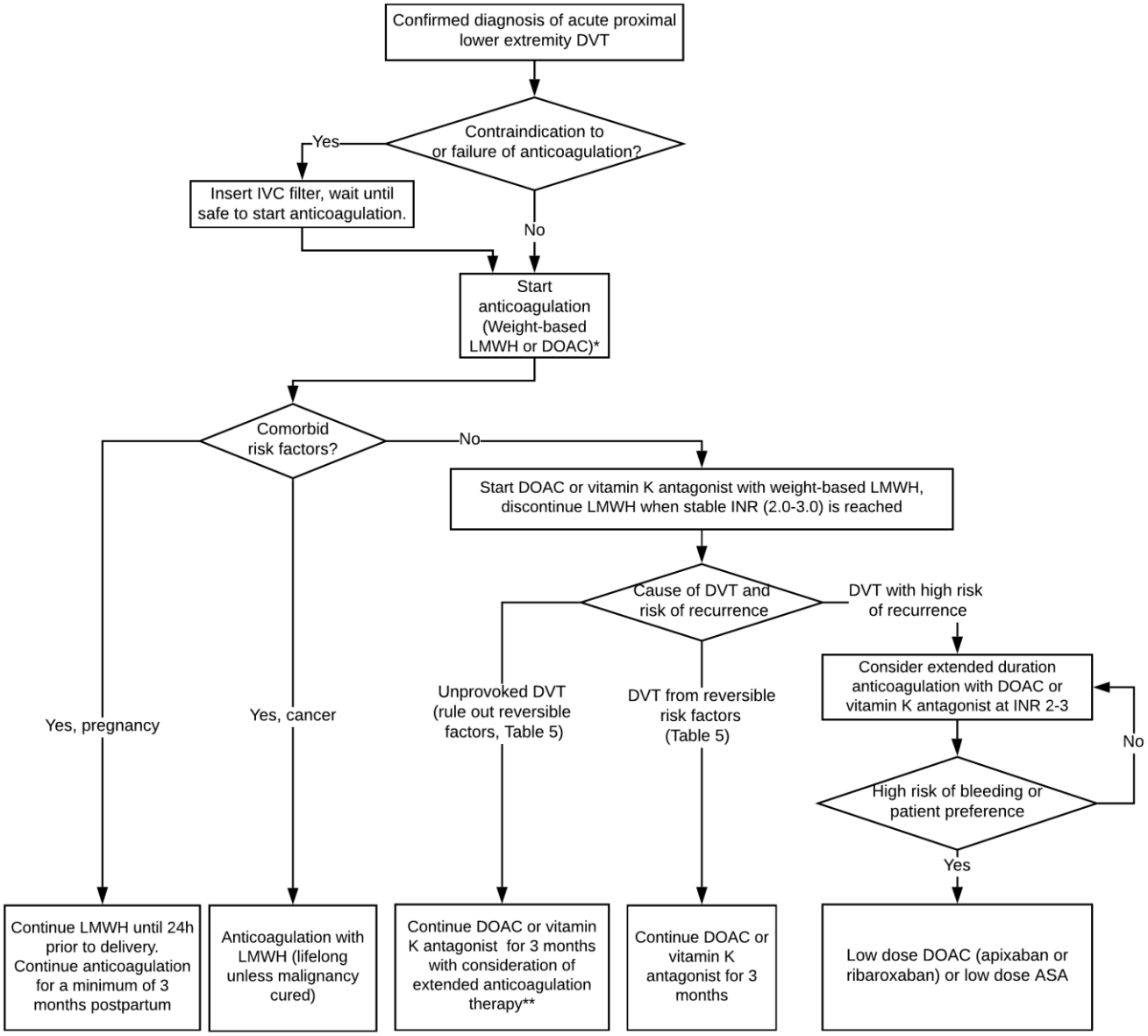


* For assessment of severity, use Villalta score. (See Table 9.)

** When phlegmasia (alba or cerulea dolens) or venous gangrene is present (rare):

- urgent vascular surgery consultation AND
- initiate anticoagulation

Figure 2. Anticoagulation Management of Acute Proximal Lower Extremity DVT



*Some DOACs (dabigatran and edoxaban) first require 5-10 days of a parenteral anticoagulant while other DOACs (rivaroxaban and apixaban) do not. Use IV unfractionated heparin for patients with significantly reduced renal function, or patients expected to undergo an urgent procedure.

**The decision for extended anticoagulation therapy requires a risk/benefit assessment that takes into consideration factors such as: persistent thrombotic risk, bleeding risk, and patient preference.

DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; INR: international normalized ratio; IVC filter: inferior vena cava filter; LMWH: low-molecular-weight heparin.

Table 3. Contraindications to Catheter-Directed Thrombolysis for DVT & PE*

Allergies
- Alteplase (recombinant tissue plasminogen activator)
- Heparin
- Iodinated contrast

Anatomic criteria
- DVT not involving the iliac system (i.e. distal DVT, isolated femoral-popliteal DVT)
- Symptoms lasting > 28 days

Bleeding risk
- Active bleeding
- Bleeding diathesis
- Recent (< 10 days) history of surgery, CPR, trauma, obstetrical delivery, cataract surgery, major invasive procedure
- Recent (< 3 months) internal eye surgery, hemorrhagic retinopathy, gastrointestinal bleed
- Recent history of stroke or intracranial lesion
- Severe liver dysfunction

Co-morbidities
- Active cancer (except non-melanoma primary skin cancer)
- Pregnancy
- Severe hypertension
- Severe renal impairment

Functional status
- Chronic non-ambulatory status
- Inability to provide consent
- Inability to tolerate catheter directed therapy (strict bedrest 24-72 hours)
- Life-expectancy < 2 years

* Final decision depends on patient characteristics and technology used (aspiration or other mechanical technique, infusion of alteplase or other thrombolytic agent, etc.) based on discussion with the appropriate consultants including vascular surgery and/or interventional radiology for DVT, and the Pulmonary Embolism Response Team (PERT) for PE.

CPR: cardiopulmonary resuscitation

Table 4. Indications for Catheter Directed Thrombolysis for Acute DVT to Prevent Post Thrombotic Syndrome

Functional status
Ambulatory
Life expectancy > 2 years
Anatomic criteria
Must involve iliac veins
Must be an acute DVT (acute thrombus on ultrasound and symptoms < 4 weeks)
1st time episode of DVT
Patient values
Patient places high quality of life value on prevention of post-thrombotic syndrome; potential benefits outweigh bleeding risks

Table 5. Hypercoagulable States

Irreversible Hypercoagulable States	Transient Hypercoagulable States
Active connective tissue disorder or vasculitis Active malignancy, especially with chemotherapy Antiphospholipid antibody syndrome* Hyperhomocysteinemia Inherited thrombophilias: Strong: Protein C, protein S, or antithrombin deficiency Weak: Factor V Leiden, prothrombin gene polymorphism, sickle cell trait Myeloproliferative neoplasms (essential thrombocytosis, *JAK2* gene mutation, myelofibrosis, polycythemia vera) Nephrotic syndrome Paroxysmal nocturnal hemoglobinuria (PNH)	Central venous catheters or lines Heparin induced thrombocytopenia (HIT) Hormones (hormone replacement therapy, oral contraceptive pills, pregnancy, testosterone) Immobility Local inflammation** Recent hospitalization (within 90 days) Recent travel >4-6 hour duration Surgery Systemic infection Trauma

* A diagnosis of antiphospholipid antibody syndrome requires confirmation with positive repeat testing in 12 weeks

** For mesenteric venous thrombosis, causes of local inflammation may include active inflammatory bowel disease, acute pancreatitis, appendicitis, diverticulitis, peritonitis.

JAK2: Janus kinase 2 gene mutation

Table 6. Indications and Contraindications for Systemic Thrombolytic Therapy with Alteplase in Higher-Risk Acute PE

Indications

Consider systemic thrombolytic therapy with alteplase in adults with acute PE if any of the following factors are present:

- Massive PE and acceptable risk of bleeding complications
- Submassive PE in selected patients (See section on submassive PE.)
- New hemodynamic instability
- Worsening respiratory insufficiency
- Severe RV dysfunction by chest CT scan (RV:LV ratio > 0.9)
- Severe RV dysfunction by transthoracic echocardiography on apical 4-chamber view (RV:LV ratio > 0.9)
- Newly elevated BNP, or BNP significantly above baseline
- New or increasing myocardial necrosis with elevated serum troponin level

Major contraindications

Avoid systemic thrombolytic therapy with alteplase in adults with acute PE if any of the following criteria are present:

- Structural intracranial disease (i.e. arteriovenous malformation or aneurysm)
- Intracranial neoplasm
- Previous history of intracranial hemorrhage
- Ischemic stroke or CVA within 3 months
- Recent brain or spinal surgery within 3 months
- Recent head trauma with fracture or brain injury within 3 months
- Any known bleeding diathesis or internal bleeding

Minor contraindications

Systemic thrombolytic therapy with alteplase is generally **not recommended** in adults with acute PE when any of the following criteria are present:

- Prolonged cardiopulmonary resuscitation (CPR)
- Systolic BP > 180 mm Hg
- Diastolic BP > 110 mm Hg
- Recent non-intracranial bleeding (within 2-4 weeks)
- Recent surgery within 2 weeks
- Recent invasive procedure within 1 week
- Ischemic stroke or CVA > 3 months ago
- Currently therapeutic on an oral anticoagulant
- Age > 75 years or < 18 years
- Pregnancy

Warnings and precautions

The following additional factors have been associated with an increased risk for intracranial hemorrhage following systemic thrombolysis with alteplase:

- Black race
- Diabetic retinopathy
- Female gender
- Low body weight (< 60 kg)
- Pericarditis or pericardial effusion

BNP: brain natriuretic peptide; CVA: cerebrovascular accident; LV: left ventricular; RV: right ventricular

Figure 3. Acute PE: Determining Candidates for Outpatient Treatment

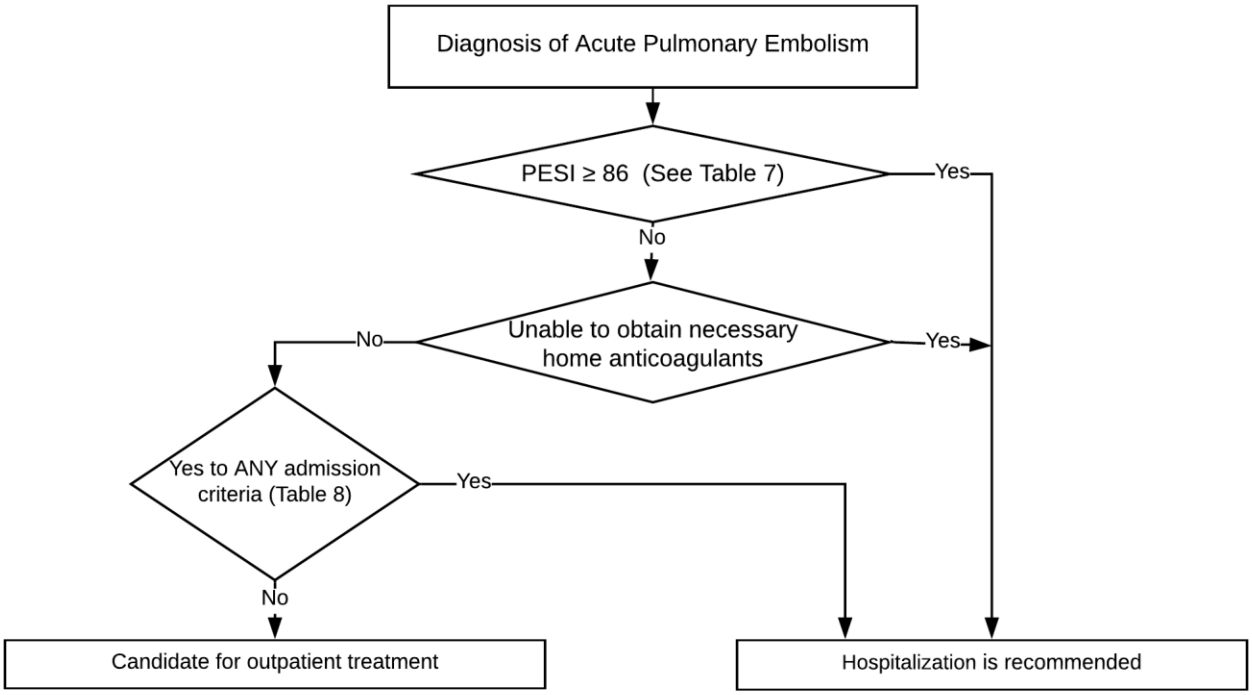


Table 7. Pulmonary Embolism Severity Index (PESI) Score

Criteria	Points
Age	+ 1 for each year of age
Male	+ 10
History of malignancy*	+ 30
History of heart failure	+ 10
History of chronic lung disease	+ 10
Triage heart rate ≥ 110	+ 20
Triage systolic blood pressure < 100	+ 30
Triage temperature < 36° C	+ 20
Triage respiratory rate ≥ 30/minute	+ 20
Triage oxygen saturation < 90%	+ 20
Altered mental status	+ 60

* Any diagnosis of cancer other than basal-cell or squamous-cell carcinoma of the skin, within the prior 6 months, any treatment for cancer in the previous 6 months, or recurrent or metastatic cancer.

Scoring**: Add the points for each of the criteria that applies to the patient. The total number of points is the PESI score. Scores can be divided into the following five risk classes:

Class I, very low risk (score ≤65)
Class II, low risk (66-85)
Class III, intermediate risk (86-105)
Class IV, high risk (106-125)
Class V, very high risk (>125)

**The PESI score can also be calculated using an on-line calculator, such as:
https://www.mdcalc.com/pulmonary-embolism-severity-index-pesi

Adapted from: Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172: 1041–1046.

Table 8. Admission Criteria for Patients with Acute PE*

Patient history at the time of VTE

Requires admission for reasons other than acute PE

Not appropriate for long term anticoagulation (fall risk, unreliable, unable to comply with treatment or follow-up)

Therapeutic on anticoagulation at the time of diagnosis of acute PE:

- INR > 2 on warfarin *OR*
- Compliant with LMWH or DOAC

Active bleeding

Bleeding disorder

Gastrointestinal bleed within the past 2 weeks

CVA within the past 6 weeks

Brain, spinal, or ophthalmological surgery within the past 6 weeks

Noncutaneous surgery within the past 2 weeks

Patient physical exam at the time of VTE

Hypoxia (oxygen saturation < 90% on room air) at any time in the emergency department

Hypotension (systolic blood pressure < 100 mm Hg) at any time in the emergency department

Pregnancy

Weight > 150 kg

Location of VTE

Presence of a proximal DVT

Centrally located PE (main pulmonary artery)

Intracardiac thrombus or central vein thrombus

Test results

Right ventricular strain noted on CT-angiogram of chest or echocardiogram (if obtained)

Positive troponin or BNP

Thrombocytopenia (platelets < 75,000 per microliter)

Creatinine clearance < 30 mL/min

* Patients that meet any of the criteria listed will likely require hospital admission. Note that patients with a pulmonary embolism severity index (PESI) score greater than 85 will also likely require hospital admission.

BNP: brain natriuretic peptide; CVA: cerebrovascular accident; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; INR: international normalized ratio; LMWH: low-molecular-weight heparin; PE: pulmonary embolism

Table 9. Villalta Score for Diagnosis of Post Thrombotic Syndrome

Symptoms/clinical signs	None	Mild	Moderate	Severe
Venous ulcer	Absent			Present
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points

Calculations:

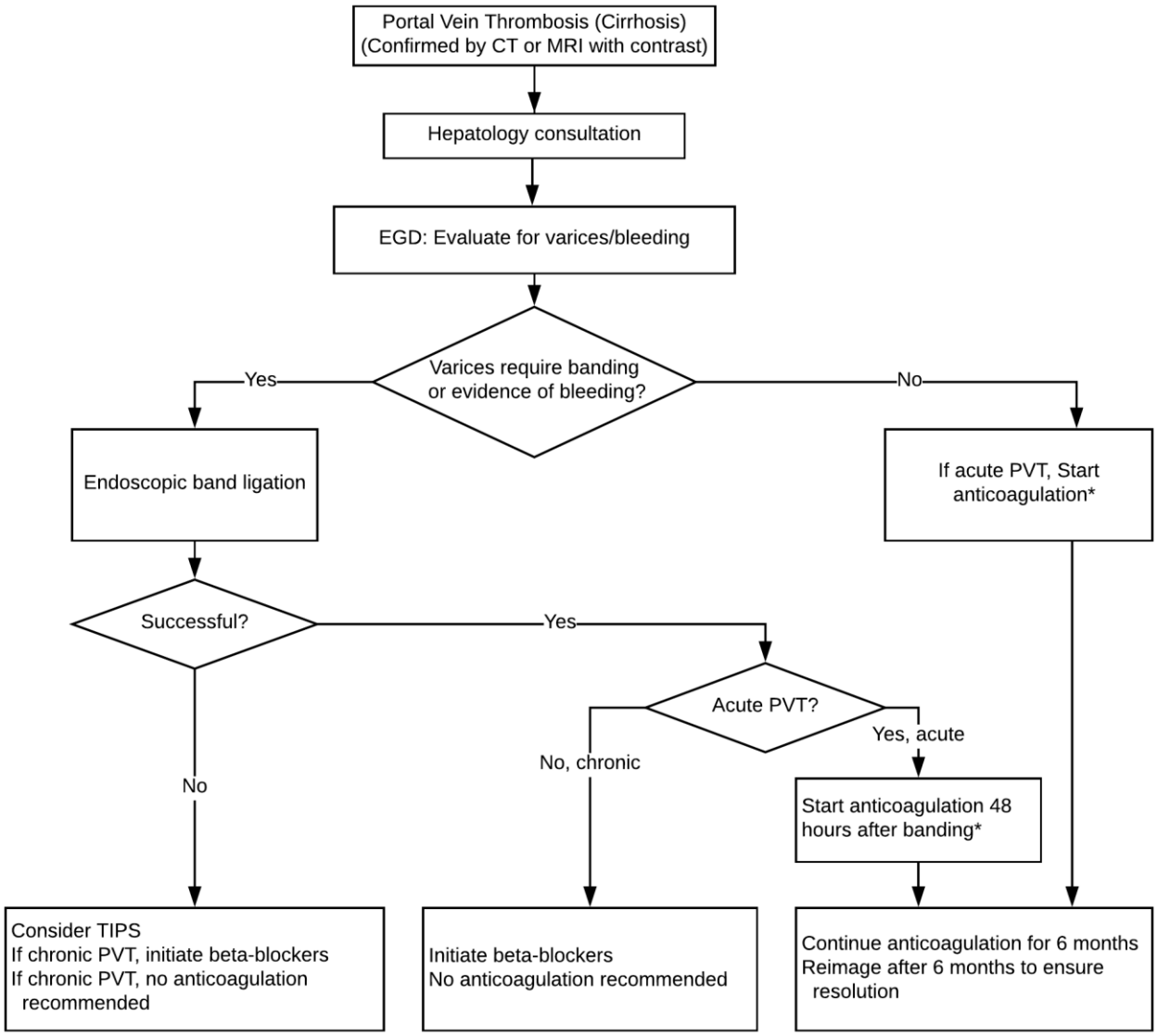
- If a venous ulcer was present, the severity of the condition was classified as severe, regardless of the presence or absence of other signs or symptoms.
- Sum points for all signs and symptoms.
- If the Villalta score is ≥5 or if a venous ulcer is present, the patient is diagnosed as having post thrombotic syndrome.

Scoring:

Mild disease	Moderate disease	Severe disease
5-9 pts	10-15pts	>15 or ulcer present

Adapted from: Arany Soosainathan, Hayley M. Moore, Manjit S. Gohel, Alun H. Davies, Scoring systems for the post-thrombotic syndrome, In Journal of Vascular Surgery, Volume 57, Issue 1, 2013, Pages 254-261, ISSN 0741-5214, https://doi.org/10.1016/j.jvs.2012.09.011.

Figure 4. Management of Portal Vein Thrombosis in Cirrhotic Patients*

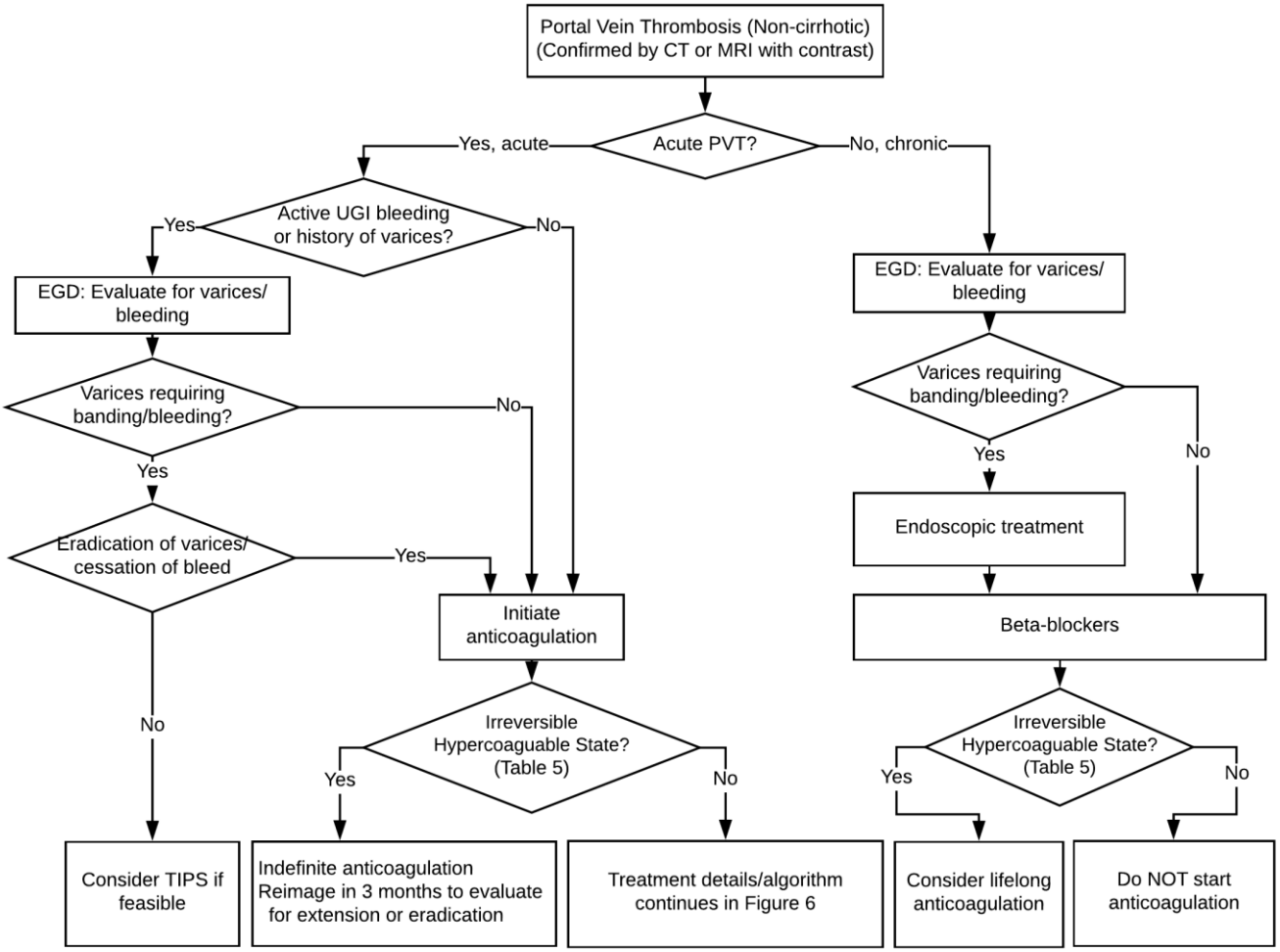


*Decision to anticoagulate is individualized and patient specific dependent upon:

- Severity of liver failure: Those with higher MELD/Child-Turcotte-Pugh scores have lower life expectancy and less benefit to anticoagulation
- Risk: Patients with encephalopathy/debility are higher risk for falls and bleeding with anticoagulation
- Symptoms: More benefit to anticoagulation if there is pain, new onset ascites, evidence of worsening portal hypertension, or mesenteric ischemia

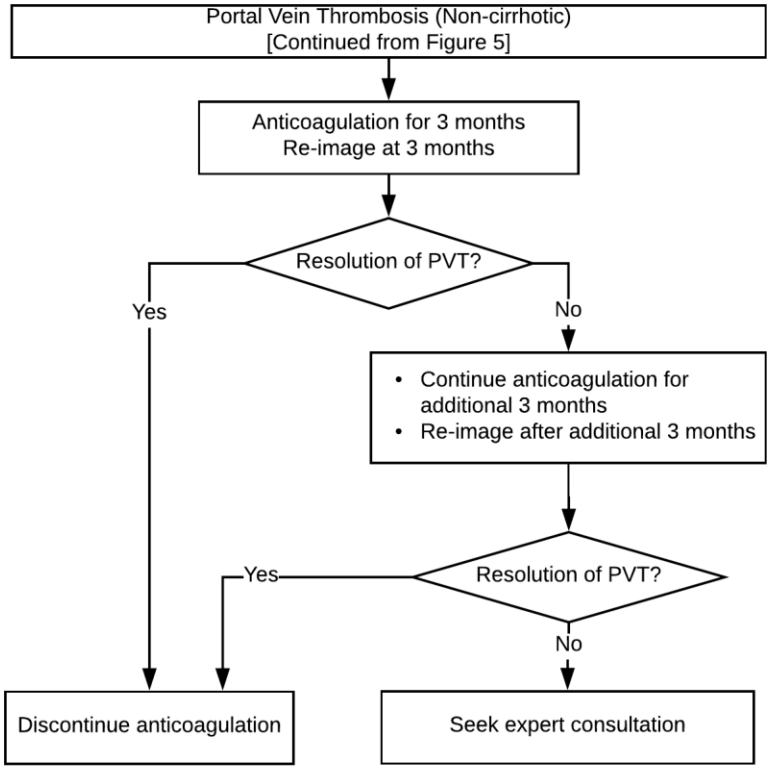
*Consultation with gastroenterology and interventional radiology is recommended
EGD: upper endoscopy (esophagogastroduodenoscopy); TIPS: transjugular intrahepatic portosystemic shunt

Figure 5. Management of Portal Vein Thrombosis in Non-cirrhotic Patients*



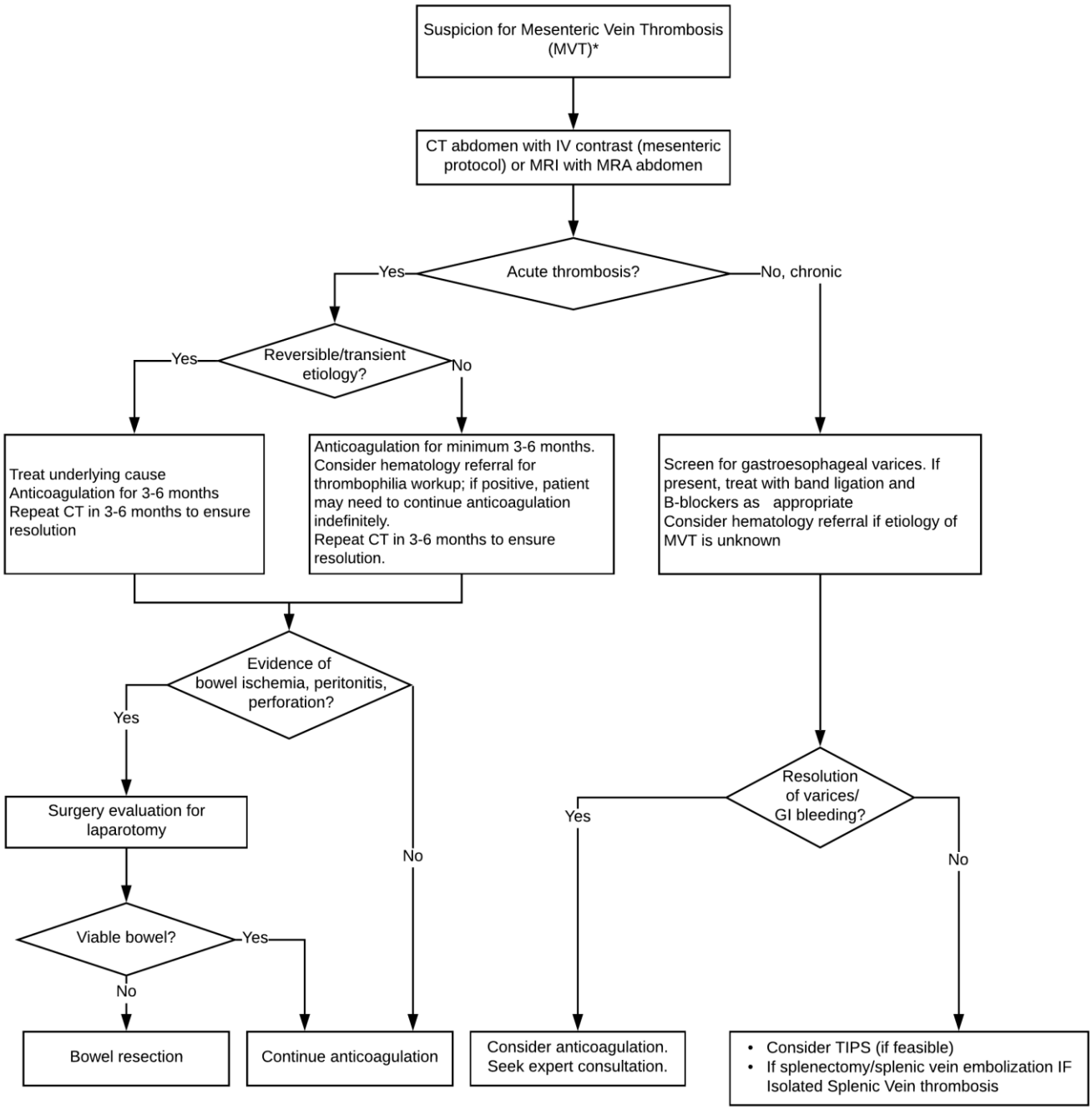
* Consultation with gastroenterology and interventional radiology is recommended in most cases.
EGD: upper endoscopy (esophagogastroduodenoscopy) PVT: portal vein thrombosis; TIPS: transjugular intrahepatic portosystemic shunt; UGI: upper gastroenterology

Figure 6. Portal Vein Thrombosis in Non-Cirrhotic Patients Confirmed by CT/MRI



PVT: portal vein thrombosis

Figure 7. Management of Mesenteric Vein Thrombosis



Clinical Background

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). While VTE is a common diagnosis, the approach to management varies based on several factors, including the severity and location of the thrombosis and the patient's underlying risk factors for developing a VTE. Given these complexities, the published literature often lacks adequate evidence to guide the management of all VTE scenarios. Treatment decisions are problematic because they typically include anticoagulants which are among the highest risk-class of medications.

Rationale for Recommendations

This guideline is intended to supplement the existing information available for managing VTE in the ambulatory setting (Michigan Medicine Ambulatory Venous Thromboembolism Guideline). In contrast to that document, this guideline provides diagnostic and management recommendations for special topics in VTE that often arise in the hospital or the emergency department including general thrombosis issues. As such, the scope of this guideline is limited to a discrete set of conditions:

1 Upper extremity DVT
2 Lower extremity DVT
  2.1 Distal (calf) DVT
  2.2 Proximal (iliofemoral and femoropopliteal) DVT
  2.3 Acute lower extremity DVT with chronic large central vein thrombosis
3 Pulmonary embolism (PE)
  3.1 Incidentally found PE
  3.2 Massive PE
  3.3 Submassive PE
  3.4 Discharge considerations for patients with PE
4 Other sites of DVT
  4.1 Portal Vein Thrombosis (PVT)
  4.2 Mesenteric Vein Thrombosis (MVT)
5 Special topics in DVT
  5.1 Thrombophilia workup
  5.2 Recurrent VTE
  5.3 Treatment failure
  5.4 Referral to hematology

1. Upper Extremity DVT (UEDVT)

Recommendations:

- Compression ultrasonography is the first-line imaging modality for the diagnosis of UEDVT. *[I-B]*
- Treat with anticoagulation for 3 months for acute UEDVT involving the axillary or more proximal veins (see list below). *[I-A]*
- D-dimer testing is not helpful in the diagnosis of UEDVT. [*III-C*]
- For central venous catheter-associated UEDVT:
  - when the catheter is no longer needed or is not functioning, remove the catheter and provide 3 months of anticoagulation. *[I-C]*
  - when the catheter is still needed and remains functional, continue to treat with anticoagulation for either 3 months, or as long as the catheter is in place (whichever is longer). *[I-C]*
- Consult vascular surgery and interventional radiology for cases of suspected Paget-Schroetter syndrome, and for cases involving severe symptoms.

1.1 Background

Approximately 10% of all DVTs involve an upper extremity.[4] The incidence of UEDVT is rising due to the increased use of central venous catheters, pacemakers, and implantable cardioverter-defibrillators. The adverse outcomes of UEDVT are similar to those of lower extremity DVT, and can include PE, recurrent DVT, and post-thrombotic syndrome.

UEDVT requires systemic anticoagulation similar to treatment of lower extremity DVTs. Indwelling venous catheters and active cancer increase risk for UEDVT, specific recommendations are provided for each of these patient populations.

Recognizing which veins of the upper extremity are classified as "deep" is important. Superficial thrombophlebitis (involving the superficial veins) is a common, but separate entity with different treatment recommendations. Furthermore, treatment differs for deep veins of the arm that are proximal and distal.

Veins of the Upper Extremity

Deep veins	
Proximal:	Brachiocephalic vein
	Internal jugular vein
	Subclavian vein
	Axillary vein
	Brachial veins
Distal:	Radial vein
	Ulnar vein
Superficial veins	External jugular vein
	Cephalic vein
	Basilic vein

1.2 Primary UEDVT

Primary (or spontaneous) UEDVT accounts for approximately 20% of cases of UEDVT and may be associated with the following:

Thoracic outlet syndrome.

Risk for UEDVT increases in thoracic outlet syndrome. The subclavian vein is compressed by one of the following: first rib, a cervical rib, clavicle, subclavian muscle, or anterior scalene muscle. This is typically seen in athletes with hypertrophied muscles who perform heavy lifting and overhead movements.

Paget-Schroetter syndrome.

Paget-Schroetter syndrome (often referred to as effort-related thrombosis) is typically caused by microtrauma to the subclavian vein from repetitive arm movements. This subcategory of thoracic outlet syndrome leads to primary thrombosis of the subclavian vein at the costoclavicular junction. Typical cases include sporting activities such as pitching, swimming, or rowing, and occupations such as painting or automotive mechanics. If Paget-Schroetter syndrome is suspected, consult vascular surgery for consideration of thrombolytic therapy in addition to surgical intervention.5

Idiopathic (unprovoked).

The specific etiology is unknown; consider an underlying hypercoagulable state.

1.3 Secondary UEDVT

Secondary (or provoked) UEDVT account for approximately 80% of cases of UEDVT. The most common causes include:

- catheter-associated, including central venous catheters, peripherally inserted central catheters (PICC), and pacemaker leads. Half of all UEDVTs are associated with a catheter.
- malignancy
- surgery or trauma to the arm
- others including hospitalization, presence of hormonal therapy, thrombophilia, and systemic infection.

1.4 Clinical presentation

The clinical signs and symptoms of UEDVT are similar to those of lower extremity DVTs. Edema is the most common presenting finding (present in approximately 80% of cases) followed by pain, and erythema.

1.5 Imaging

Compression ultrasonography is the first-line imaging modality for the diagnosis of UEDVT. *[I-B]* In a systematic review that included 9 studies, compression ultrasonography had a sensitivity of 97% and a specificity of 96% in diagnosing UEDVT.[6] However, bony structures can interfere with visualizing some vessels including the proximal subclavian and brachiocephalic veins. In these cases, computed tomography (CT) venography or magnetic resonance (MR) venography may be indicated. Although contrast venography may be the "gold standard" for UEDVT diagnosis, it is seldom employed given the invasive nature of the study as well as the exposure to IV contrast agents and radiation.

D-dimer testing is not helpful in the diagnosis of UEDVT. *[III-C]* The underlying causes of most UEDVTs (e.g. cancer, indwelling catheters) can themselves also elevate D-dimer levels. In one small study that evaluated the accuracy of D-dimer in 52 consecutive patients, the sensitivity was 100%, but the specificity was only 14%.[7]

1.6 Anticoagulant options

Anticoagulation is the primary treatment for acute DVT of the upper extremity involving the axillary vein and more proximal veins. *[I-A]* Several anticoagulant options exist for treatment of acute UEDVT. Traditionally, the first-line agent has been low-molecular-weight heparin (LMWH) (with IV unfractionated heparin or fondaparinux as alternatives), followed by a transition to warfarin. However, large randomized trials support the use of the direct oral anticoagulants (DOACs) for treatment of proximal *lower* extremity DVT,[8-11] which suggests their likely benefit for treatment of UEDVT as well. These agents include the direct Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, as well as the direct thrombin inhibitor, dabigatran. Edoxaban and dabigatran require a minimum of 5 days of parenteral anticoagulation (eg. enoxaparin) prior to their use. In contrast, parenteral anticoagulation is not required with rivaroxaban and apixaban making them a more favorable option if using a DOAC.

DOACs have not been adequately studied in patients with cancer. Patients with cancer and acute VTE are preferentially treated with a LMWH (eg. enoxaparin), at least for the first 3-6 months.

1.7 Anticoagulation Duration

In most patients with an UEDVT, the recommended duration of anticoagulation therapy is 3 months. For patients with active malignancy, treatment with anticoagulation is

typically continued as long as the cancer is active. In many cases, this means continuing anticoagulant treatment indefinitely.

For central venous catheter-associated UEDVT:

- If the catheter is still needed and remains functional, the catheter should remain in place and anticoagulation treatment initiated. Anticoagulation should be continued for 3 months or as long as the catheter is present, whichever is longer.
- If the catheter is non-functional or no longer needed, the catheter should be removed and anticoagulation given for 3 months.

These treatment recommendations are consistent with the 2012 American College of Physicians guidelines.[12]

1.8 Thrombolysis

In rare instances a patient with an acute UEDVT should be considered for catheter directed thrombolysis (CDT). For patients with all the following criteria, consider CDT with consultation to vascular surgery and interventional radiology:

- severe symptoms (eg. pain)
- large thrombus involving most of the subclavian and axillary veins
- good functional status with a life expectancy of greater than 1 year
- low bleeding risk

If CDT is administered, systemic anticoagulation should be given with the same intensity and duration as described in the "Anticoagulant options" and "Anticoagulation duration" sections above.

2. Lower Extremity DVT

2.1 Distal (calf) DVT

Recommendations:

The two approaches to patients with distal (calf) DVT are (see Table 1):

- Treatment with anticoagulation therapy (for 3 months), or
- Surveillance with serial compression Doppler ultrasound examinations (weekly for 2 weeks), withholding treatment unless these studies demonstrate extension of the thrombus *[II-C]*

Background.

The need for treatment of calf-level DVT remains controversial, with clinical recommendations both for and against anticoagulant treatment.[13,14] Outpatient studies report that the proportion of all DVTs that are "distal" is as high as 60% to 70%, demonstrating the magnitude of the problem.[14,15] Calf DVT is more commonly associated with transient risk factors, and has lower mortality than proximal DVT (4.4% vs. 8.0%, $p < 0.01$).[16] The important clinical consequences of calf DVT include proximal extension, VTE recurrence, pulmonary embolism (PE), and post-thrombotic syndrome (PTS). The limited available evidence for the natural history of calf level DVT suggests that complications, including PE and PTS, are significantly decreased with distal versus proximal DVT, although these rates still remain somewhat high.[17] The studies are highly heterogeneous, and rates vary widely between earlier and more recent cohorts.

Diagnosis.

Compression ultrasonography is the first-line imaging modality for the diagnosis of distal DVT. The performance of the D-dimer to evaluate symptomatic distal DVT is controversial, with not all assays found to be reliable for this purpose.[18] Therefore, we do not recommend the routine use of the D-dimer for diagnosis.

Treatment.

Two recommended options for the management of distal (calf) DVT:

- weekly serial compression ultrasound for 2 weeks to assess for clot propagation, or
- anticoagulation therapy using the same strategy as for patients with acute proximal DVT.

Although both of these options are acceptable, Table 1 provides information to help individualize the treatment decision. Calf DVTs such as the gastrocnemius and soleus vein usually do not require anticoagulation therapy (Table 2), but should still undergo serial compression ultrasound surveillance.

Extension of distal blood clots to proximal veins is a known risk of proximal DVT. In a review of the literature, the rate of proximal extension was highly variable, ranging from 0% to 23% in patients without anticoagulation, and 0% to 44% in patients with anticoagulation.[19] The studies are too heterogeneous for meaningful comparisons between untreated and treated patients, but in studies following untreated patients with serial ultrasound, the rate of proximal extension ranges from 0.9% to 5.7%.[19]

The CALTHRO study[20] assessed the clinical consequence of untreated calf DVT in 431 symptomatic outpatients with initial negative ultrasound for proximal vein DVT and an abnormal D-dimer. At the 3-month follow-up, adverse outcomes occurred in three patients: 1 with proximal vein extension, 1 with PE, and 1 with worsening symptoms.[20] In contrast, limited randomized studies have shown recurrent thrombotic events in up to 29% of patients with inadequately treated calf vein thrombosis.[21] In prospective cohorts of

patients with isolated calf-level DVT largely treated with anticoagulation, VTE recurrence rates at 3 months are 2% to 2.2%, which includes 0.7% to 1.1% rates of PE.[16,22]

The most recent randomized controlled trial on this controversy, called the CACTUS Trial,[23] found no advantage for LMWH in reducing the risk of proximal extension or venous thromboembolic events in low-risk outpatients with symptomatic calf DVT; it did increase the risk of bleeding. However, this study was underpowered for its endpoints. Widely accepted management studies suggest that withholding anticoagulation is safe in outpatients with suspected DVT if serial compression ultrasound is negative for proximal DVT at baseline and at 1 week.[24-29] The pooled estimate of the 3-month thromboembolic risk in untreated patients in studies using only serial proximal vein ultrasound is 0.6% (95% CI 0.4%-0.9%).[13] This strategy is based on the premise that calf-level DVT does not need to be treated with anticoagulation, but does require surveillance.

Regarding post-thrombotic syndrome, Meissner and colleagues followed a prospective cohort of patients with acute DVT and noted that at 12 months, symptoms of post-thrombotic syndrome occurred in 23% of limbs with calf DVT (3/13) and 54% of limbs with proximal DVT (51/95).[30] In various studies the proportion of patients treated with anticoagulation has varied from 51% to 72%, and varied in the length of time of anticoagulation.[31-33]

The 2016 American College of Chest Physicians guidelines for venous thromboembolism[34] recommends that patients with isolated distal DVT of the leg without severe symptoms or risk factors for extension receive weekly serial imaging of the deep veins for 2 weeks over anticoagulation. *[I-C]* Conversely, if significant calf pain or risk factors for extension are present (Table 1), anticoagulation for 3 months is recommended over serial imaging.

In patients with acute isolated distal DVT who are managed with anticoagulation, recommended treatment is the same as for patients with acute proximal DVT. Anticoagulation options include a DOAC (i.e. rivaroxaban, apixaban, edoxaban, or dabigatran) or warfarin. Initial treatment with LMWH is required if transitioning to edoxaban, dabigatran, or warfarin, while rivaroxaban and apixaban do not require initial treatment with heparin.

Finally, in patients with an acute isolated distal DVT who are managed with serial imaging, switching to anticoagulation is recommended when the thrombus extends but remains confined to the distal veins, or extends into a proximal vein.

For patients with distal DVT, the patient's bleeding risk may influence the decision to prescribe anticoagulation or prescribe serial compression ultrasonography. Furthermore, patient preferences with respect to proximal DVT or PE risk versus bleeding risk need to be taken into consideration.

2.2 Severe, Obstructive Proximal (Iliofemoral and Femoropopliteal) DVT

Recommendations:

- Manage femoropopliteal DVTs with anticoagulation rather than thrombus removal. *[I-C]*Refer iliofemoral DVTs to vascular surgery or interventional radiology to assess for the appropriateness of early thrombus removal (see indications and contraindications for catheter-directed thrombolysis in Table 3 and Table 4).
- Perform early thrombus removal in patients with limb-threatening venous ischemia (phlegmasia ceruea dolens or venous gangrene) due to iliofemoral venous thrombosis with or without associated femoropopliteal venous thrombosis. *[I-B]*[1-3] Vascular surgery should be urgently consulted in these cases.
- For DVT limited to the femoropopliteal region without extension into the iliac system, treat with anticoagulation alone.

Background.

Proximal DVT is usually manifested by unilateral calf swelling, pitting edema, and pain of the affected leg. Proximal DVT includes thrombosis of the iliac, femoral, and popliteal segments (Table 2). Severe obstructive iliofemoral DVT sometimes manifests with severe swelling and pain. In all cases, the mainstay of therapy involves compression, elevation, and prompt initiation of anticoagulation (Figure 1). If an absolute contraindication to anticoagulation exists, consider inferior vena cava filter placement to prevent pulmonary emboli (Figure 2).

Diagnosis.

The gold standard for imaging is duplex ultrasonography. If iliofemoral venous thrombosis is suspected, but not confirmed using standard diagnostic modalities such as venous duplex ultrasound imaging, use adjunctive imaging modalities such as computerized tomography venography (CTV) or magnetic resonance venography (MRV) to characterize the most proximal extent.[35,36] *[I-B]*

CTV and MRV evaluate the inferior vena cava and veins of the pelvis better than ultrasound or contrast venography. Pooled analysis of studies comparing CTV to ultrasound or venography demonstrate a sensitivity and specificity of >95%.[37] MRV has also been found to be accurate in the diagnosis of DVT. In a large meta-analysis, compared to venography or ultrasound imaging, sensitivity and specificity of 92% (94% for proximal DVT) and 95% was found,[38] and MRV is accurate in the diagnosis of pelvic vein thrombosis.[39]

Treatment.

For proximal DVT treatment, the goals are three-fold:
- To prevent extension or recurrence of DVT
- To prevent pulmonary embolism
- To minimize the late sequelae of thrombosis, chronic venous insufficiency called post-thrombotic syndrome

Standard anticoagulants accomplish the first two goals but do not always accomplish the third goal. Post-thrombotic syndrome occurs in up to 30% of patients after DVT, and that number is even higher in patients with iliofemoral-level DVT.[40] In select ambulatory patients who have a reasonable life expectancy and a favorable risk profile, more aggressive therapies for extensive thrombosis are indicated. For DVT limited to the femoropopliteal region, and without extension into the iliac system, anticoagulation alone is recommended. Phlegmasia is an exceedingly rare condition associated with massive iliofemoral DVT.

Anticoagulation.

Anticoagulation is indicated for all patients with proximal LEDVT. The 2016 ACCP guidelines emphasize anticoagulant therapy over catheter directed thrombolysis. The exception is in patients who attach a high value to the prevention of post thrombotic syndrome for quality of life considerations, and a lower value to the initial complexity, cost, and risk for bleeding of aggressive therapies as compared to anticoagulation alone.[34]

Anticoagulation alone is recommended over early thrombus removal for isolated femoropopliteal DVT. Evidence insufficient to recommend early thrombus removal instead of a thrombolytic agent.[35,41] Patients with femoropopliteal DVT show a lower risk of thrombosis recurrence (11.8% iliofemoral vs. 5.3% femoropopliteal),[42] a lower risk of the development of post-thrombotic syndrome,[43] fewer symptoms on presentation, and inferior outcomes with thrombolysis. Most patients with femoropopliteal DVT do not need aggressive pharmacomechanical thrombolysis.

Thrombus removal.

Some patients with proximal LEDVT may also be candidates for thrombus removal, if they meet specific criteria, or if they have venous ischemia, as described below.

Early thrombus removal may be performed[1,44-50] for patients with <u>all</u> of the following:
- First episode of acute iliofemoral DVT
- Symptoms less than 14 days in duration (although may be considered up to 28 days)
- Low risk of bleeding
- Patient is ambulatory with a good functional capacity and acceptable life expectancy
- Moderate to severe symptoms (which can be determined by a Villalta score ≥ 10 after a trial of anticoagulation). (Table 9).

Patients meeting all of these criteria should be referred to vascular surgery. Thrombolysis may be performed by interventional radiology or vascular surgery.

<u>Catheter directed thrombolysis (CDT).</u> While not currently endorsed by major society guidelines, CDT has been shown to decrease symptoms of pain and swelling at 30 days and may decrease development of post thrombotic syndrome in highly select groups of patients (acute iliofemoral DVT, Villalta score ≥ 10 after a trial of anticoagulation) (Table 3 and Table 4). Following initial symptoms, CDT is ideally performed within 2 weeks but may be performed up to 4 weeks. At Michigan Medicine, outpatients may be seen in the Venous Health Program clinic for consideration of CDT, or if hospitalized, in consultation by the vascular surgery service and/or interventional radiology for a discussion of risks and benefits of such a procedure (Figure 1).

CDT has been employed in many non-randomized studies and, in small randomized trials, was more effective than standard therapy in patients with acute proximal lower extremity DVT. Quality of life was improved with thrombolysis. Results are optimized by combining CDT with mechanical devices.[46,51] These devices hasten thrombolysis, decrease the amount of thrombolytic agent needed, and thus decrease bleeding potential.

<u>Phlegmasia and venous gangrene</u>. This is rare clinical phenomena that places the affected limb at risk of ischemia. Phlegmasia cerulea dolens (PCD) is an uncommon form of DVT characterized by severe pain, swelling, cyanosis, and edema. This is preceded by phlegmasia alba dolens, which is characterized by the same clinical signs except the limb is pale and white due to early ischemia, and not yet cyanotic. Venous gangrene is defined as skin necrosis, discoloration, and documented VTE.

Initial treatment for PCD or venous gangrene is the same as for proximal DVT with an emphasis on immediate anticoagulation and vascular surgical consultation. Early thrombus removal is the treatment of choice in patients with limb-threatening venous ischemia due to iliofemoral venous thrombosis, with or without associated femoro-popliteal venous thrombosis. [1-3] These patients require thrombolysis when characterized by all of the following:
- Massive painful limb swelling, with or without cyanosis
- Skin blisters or necrosis
- Loss of or diminished arterial pulses

Aggressive therapies for phlegmasia include both venous thrombectomy and thrombolysis. If the patient does not respond to initial extremity elevation, fluid resuscitation, and aggressive systemic anticoagulation (usually within the first 6 hours), then CDT with pharmacomechanical assist should be first-line therapy. Surgical venous thrombectomy is reserved for patients who have contraindications to thrombolysis (Table 3).[52]

2.3 Acute Lower Extremity DVT with Chronic Large Central Vein Thrombosis

Recommendations:

- Treat the acute thrombus to restore the patient to baseline status. Then address the chronic occlusion at a later date after the inflammatory state has abated.
- Recanalize the chronically occluded segment with stenting. *[II-C]*

Background.

Extensive lower extremity acute DVT frequently occurs in the setting of chronic thrombosis of large central veins, such as the inferior vena cava or common iliac veins.

Treatment.

Treat the acute thrombus to restore the patient to baseline status. Then address the chronic occlusion at a later date after the inflammatory state has abated. Occasionally, restoring flow also requires treatment of the chronic occlusion. In these cases, the chronically occluded segment can be recanalized with stenting.[53] *[II-C]* At Michigan Medicine, patients needing to be recanalized with stenting should be referred to the outpatient Venous Health Program within 72 hours of discharge.

3. Pulmonary Embolism (PE)

See the Michigan Medicine Ambulatory Venous Thromboembolism Guideline for general information, risk factors, and a diagnostic testing algorithm regarding pulmonary embolism.

3.1 Incidentally Discovered Asymptomatic Pulmonary Embolism

Recommendations:

- Incidental/asymptomatic PEs are clinically relevant. Consider treating with systemic anticoagulation as for patients with symptomatic PE. *[II-C]*
- Avoiding anticoagulation is reasonable in patients with a high bleeding risk. *[II-E]*

Diagnosis.

Incidentally discovered asymptomatic PE includes PEs that are found as a result of testing not intended to diagnose PE.

Treatment.

Incidentally discovered asymptomatic PEs are clinically relevant based on observational data. Treatment with systemic anticoagulation should be considered just as for patients with symptomatic PE. *[II-C]* In patients with contraindications to anticoagulation, deciding not to treat PE with systemic anticoagulation is reasonable.

Most incidentally discovered asymptomatic PEs are found during CT imaging performed for oncologic staging in patients with active cancer.[54] Decisions on treating these findings are clinically challenging. Among patients with asymptomatic PE, no randomized trials compare outcomes for treatment with anticoagulation versus surveillance without anticoagulation. Evidence is limited to small observational and retrospective cohort studies. Most of these studies included patients with a malignancy diagnosis.

Evidence is mixed as to whether patients with asymptomatic PE have increased mortality. A retrospective cohort study of lung cancer patients who were incidentally found to have a PE, but were not treated with anticoagulation showed increased mortality.[55] Another retrospective cohort study found no statistical difference in mortality, recurrent pulmonary embolism, or bleeding complications among patients treated with anticoagulation for both symptomatic and asymptomatic PE.[56]

3.2 Massive PE

Recommendations:

- Massive PE is defined as an acute PE with sustained hypotension (despite adequate fluid resuscitation, with either a systolic blood pressure < 90 mmHg for more than 15 minutes or requiring vasopressor support).
- Treatment of massive PE includes emergent initiation of IV unfractionated heparin, and emergent consultation with medical and interventional experts in PE to determine thrombolytic strategy (i.e. systemic thrombolytics vs catheter-directed thrombolysis). At Michigan Medicine, emergent consultation from these specialties can be achieved at any time by activating the PE Response Team (PERT) via page.
- Table 6 shows indications and contraindications for systemic thrombolytic therapy for PE.

Massive PE is an acute PE with resultant sustained hypotension despite adequate fluid resuscitation, with either a systolic blood pressure (SBP) < 90 mmHg for more than 15 minutes or hypotension requiring vasopressor support. A decrease in systolic blood pressure of more than 40 mmHg from baseline can also be used to define hypotension. The cause of hypotension should not be due to other causes (i.e. septic shock, hypovolemia, known left ventricular systolic dysfunction, or bradycardia). Radiographic criteria such as a "saddle embolism" should not be used to define massive PE.

While no definition of massive PE is universally accepted, two large international registries of acute pulmonary embolism report excess attributable mortality with PE

associated sustained systemic hypotension. The registries are the International Cooperative Pulmonary Embolism Registry (ICOPER) and the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET). The ICOPER registry demonstrated a 52.4% 90-day mortality in patients presenting with an SBP < 90 mm Hg vs. 14.7% in those with a SBP > 90 mm Hg.[57] The MAPPET registry showed an 8.1% in-hospital mortality for hemodynamically stable patients with acute PE vs. 25% in-hospital mortality in those with cardiogenic shock, and 65% in those presenting with cardiac arrest.[58]

Treatment.

All patients with massive PE should have emergent consultation from medical and interventional experts in PE. Michigan Medicine has instituted a PE Response Team (PERT) that includes pulmonologists, cardiologists, hospitalists, and interventional radiologists who can provide expert opinion in the management of acute PE. PERT can be activated by the paging system and is available 24 hours a day, 7 days a week.

National guidelines[12,34] endorse administering systemic thrombolytics for patients with hemodynamic decompensation, shock, or cardiac arrest unless a contraindication exists (Table 6). Although few trials have evaluated systemic thrombolytics in patients with massive PE, a meta-analysis that included a subgroup of these patients demonstrated a decrease in the composite endpoint of death and recurrent thromboembolism compared to heparin alone.[59] If there are contraindications to systemic thrombolysis (i.e. patients with a high bleeding risk), catheter-directed thrombolysis may be considered but only upon consultation with a multidisciplinary team such as the PERT (described above). It should be emphasized that while evolving, the data on catheter-directed thrombolytic therapy at the present time is limited. Temporary placement of an inferior vena cava (IVC) filter is reasonable if a proximal DVT is also present.

If hemodynamic collapse is imminent or compelling contraindications exists for all thrombolytic therapies (systemic and catheter-directed therapy), thoracic surgery should be urgently consulted for consideration of an open pulmonary artery embolectomy or extracorporeal membrane oxygenation (ECMO). Alternatively, interventional radiology may consider an emergent suction embolectomy.

For blood pressure support, an initial IV crystalloid fluid bolus of no more than 500 mL can be administered. Excessive IV fluids may result in right ventricular (RV) overload and worsening RV failure. For persistent hypotension, initiate IV vasopressor therapy; norepinephrine is the drug of choice and is preferred over both dopamine and dobutamine.

IV unfractionated heparin (UFH) is the anticoagulant of choice for massive PE. Avoid intubation and positive pressure ventilation whenever possible.

Systemic thrombolysis alteplase (tPA): dosing, preparation, administration and monitoring (see also Table 6).

Prior to systemic thrombolytic therapy, obtain a baseline CBC, PT/INR and activated partial thromboplastin (aPTT). Dose alteplase at 100 mg IV infused over 2 hours. IV heparin must be stopped prior to initiating the alteplase infusion. Alternatively, give alteplase more quickly with the first 50 mg given over 15 minutes in patients exhibiting rapid deterioration.[12] There are no head-to-head studies comparing these two alteplase dosing regimens.

After the alteplase infusion has been completed, check the aPTT time every 1-hour post-infusion. When the aPTT decreases to twice the upper normal level or less (<80 seconds), resume IV heparin infusion at the previous dose.

Before, during, and after the alteplase infusion, obtain blood pressure measurements frequently and monitor the patient for signs of bleeding. Post-infusion blood pressures and neuro checks should be performed every 15 minutes for 2 hours, every 30 minutes for the next 6 hours, and hourly for the next 16 hours. Monitoring should take place in an ICU or moderate care area but the alteplase infusion may be initiated on a general care floor prior to patient transfer.

3.3 Submassive PE

Recommendations:

- Submassive PE is defined as an acute PE without hypotension but with RV dysfunction and/or myocardial necrosis (i.e., RV strain evidenced on imaging, or elevation of biomarkers such as troponin or BNP).
- Treatment of submassive PE includes immediate initiation of anticoagulation with IV unfractionated heparin or LMWH, and consultation with medical and interventional experts in PE to determine if thrombolytic therapy is indicated. At Michigan Medicine, urgent consultation from these specialties can be achieved at any time by activating the PE Response Team (PERT) via page.
- Table 6 shows indications and contraindications for systemic thrombolytic therapy for PE.

Although no high quality studies definitively define submassive PE, this guideline defines it as an acute PE without hypotension, but with right ventricular (RV) dysfunction and/or myocardial necrosis (i.e. elevated troponins).

While registries and clinical scoring tools for PE support the concept that patients with advanced age and comorbidities are at increased risk of poor outcomes, these do *not* predict adverse outcomes independent of imaging findings (i.e. from chest CT or transthoracic echocardiogram) or biomarker results (i.e. elevated troponin or BNP). While submassive PE

is not consistently defined, cohort studies reliably show an increased risk of adverse outcomes in subgroups of patients with acute PE. These risk groups include patients with abnormal biomarkers or abnormal chest imaging that suggest RV strain. Such criteria have recently been accepted by other society guidelines including the American Heart Association (AHA) and the American College of Chest Physicians (ACCP).

Diagnosis of submassive PE.

Clinicians need to rely on clinical judgement as to whether a patient may have a submassive PE. Concerning findings may include transient hypotension unexplained by other findings, arrhythmia, patient appearance (i.e. altered mental status, cool extremities, diaphoresis, elevated lactate, or poor urine output), or clinical trajectory. In these settings, the clinician should obtain additional data. Any of the following findings are diagnostic of a submassive PE:

- Elevated BNP (either above the laboratory reference range or higher than a patient's baseline, if known)
- Elevated troponin
- CT imaging evidence of RV strain (CT findings of an RV:LV ratio of $\geq$ 0.9). If this information is not present in the radiology report, it can be obtained by conferring with the radiologist.
- Transthoracic echocardiogram evidence of RV strain (RV size > LV size; RV pressure overload with flattening of the interventricular septum in both systole and diastole; reduced tricuspid annular plane systolic excursion (TAPSE) of < 16 mm). Of note, the RV systolic pressure (RVSP) may only be modestly elevated in submassive PE.

Treatment.

As with massive PE, patients with submassive PE require urgent systemic anticoagulation. IV UFH or LMWH are both reasonable anticoagulation options, depending on the patient's specific circumstances (i.e. patients with poor renal function or who are anticipated to undergo a procedure should be treated with UFH).

Urgent consultation from medical and interventional experts in PE is advised for all patients with suspected submassive PE. At Michigan Medicine, this can be achieved at any time by activating the PE Response Team (PERT) by page.

IV crystalloid fluids can be administered, but should generally be limited to a fluid bolus of no more than 500 mL. If persistent hypotension develops, initiate IV vasopressor therapy; norepinephrine is the drug of choice (preferred over both dopamine and dobutamine). Persistent hypotension should prompt consideration of the diagnosis of massive PE. Due to right ventricular dysfunction commonly seen in massive and submassive PE, avoid intubation and positive pressure ventilation whenever possible.

The effectiveness of systemic thrombolytic therapy for patients with submassive PE is not clear. The PEITHO trial is the largest randomized controlled trial to assess the role of thrombolytic therapy in patients with submassive PE (n=1006).[60] The primary endpoint of death or hemodynamic decompensation occurred in significantly fewer patients randomized to tenecteplase (2.6% vs 5.6%) while major bleeding (including hemorrhagic stroke) was more common (11.5% vs 2.4%). The TOPCOAT trial was a randomized trial of 83 patients with submassive PE that demonstrated a favorable composite outcome including improved quality of life, RV function, exercise capacity, and perception of physical wellness in patients randomized to LMWH and tenecteplase versus LMWH alone.[61] A meta-analysis showed thrombolysis was associated with lower mortality in submassive PE vs anticoagulation alone (NNT=65) but with significantly more major bleeding (NNH=18).[62] Importantly, this analysis also found that major bleeding was *not* significantly increased in patients 65 years of age and younger.

In higher risk patients (eg. age > 65 years or medical frailty) or those with a higher risk of bleeding complications from systemic thrombolytic therapy, half-dose thrombolytic therapy or catheter-directed thrombolysis are potential treatment options. Although published data are limited, half-dose thrombolytics have shown favorable outcomes in specific outcomes (i.e. less clot burden and pulmonary hypertension)[63] in addition to demonstrating a lower bleeding risk when compared to full-dose thrombolytic.[64] At Michigan Medicine, activation of the PERT pager will provide expert multidisciplinary consultation recommendations regarding these potential therapeutic options.

Indications for systemic thrombolytic therapy are outlined in Table 6. Systemic thrombolytic therapy (eg. IV alteplase) is not recommended for patients with either non-sustained hypotension or minor RV dysfunction (i.e. mildly elevated BNP or troponin and insignificant RV strain by either chest CT or transthoracic echocardiogram). However, if clinical evidence indicates an adverse prognosis, systemic thrombolytic therapy can be considered.

Registries have been the largest source of data on adverse outcomes in submassive PE. In addition to the ICOPER[57] and MAPPET[58] registries, the EMPEROR registry reported a 30-day attributable mortality rate due to PE of 0.9%.[65] The subset of these patients considered to have submassive PE treated with heparin alone was estimated to be < 3%. As a result, it is very unlikely that thrombolytic therapy would show a statistically significant reduction in mortality. However, several cohort studies have reported improved outcomes for secondary end-points such as RV dysfunction, chronic thromboembolic pulmonary hypertension (CTEPH) and exertional dyspnea.[66-68]

3.4 Discharge Considerations for Patients with PE

Recommendation:

If patients meet criteria contained in the Pulmonary Embolism Severity Index (PESI) score (Table 7) in addition to other criteria (Table 8), treat them entirely as outpatients without hospital admission (see Figure 3). *[II-B]*

Outpatient treatment of pulmonary embolism.

Patients diagnosed with PE in the emergency department or as outpatients who meet select criteria may be safely treated entirely in the outpatient setting. Although high quality evidence is lacking, a randomized controlled trial used the Pulmonary Embolism Severity Index (PESI) (Table 7) to risk stratify patients and determine if discharge from the ED was safe.[63] This multi-center international trial randomized to inpatient vs outpatient treatment 344 patients who presented to the emergency department with acute, symptomatic PE and a PESI score of less than 86. Results demonstrated no difference in recurrent VTE events or major bleeding at 90 days. Numerous cohort studies and retrospective studies show that the risk of treating acute PE as an outpatient can be relatively low when patients are appropriately selected. Most studies use one of several existing risk stratification tools, but none of the currently available scoring systems is reliable enough to supplant clinical judgment.

Even when employing one of the many risk stratification tools, some low risk patients may still have features that make inpatient treatment preferable (Table 8). A meta-analysis[69] included 40 studies reporting 11 clinical prediction rules. PESI, sPESI (simplified PESI) and the European Society of Cardiology (ESC) score were the most sensitive tools. The sPESI is the easiest to use, but it may be too restrictive, leading to unnecessary admissions. PESI has received the most attention and has the most evidence supporting its use. The PESI score has multiple data points (Table 7) and yields a score that relates to a risk category of I-IV. Patients with PESI scores > 105 (category III), or > 125 (category IV) should probably be admitted to the hospital for initiation of anticoagulation, but there may still be some in this group (based on some idiosyncrasies of the scoring) who are safe for discharge (i.e. a 60-year-old patient with a history of malignancy will be a PESI category III).

Patients with low-risk PESI scores (categories I and II, which include scores ≤ 85) may be considered for treatment as an outpatient if none of the exclusion criteria are met. Multiple retrospective studies corroborate the safety of outpatient treatment in this group. However, a single smaller retrospective analysis showed an unacceptably high percentage of patients (14%) that had significant in-hospital complications even though the patients were in PESI categories of I or II.[70]

Biomarkers (troponin or BNP) might be used to help better risk stratify such patients. An elevated troponin[71] or an elevated BNP (or N-terminal-pro-BNP)[72] is associated with higher risk of adverse outcomes, but it is unclear how these factors should be incorporated into risk stratification.

Admit patients with structural evidence of RV dysfunction on chest CT scan or echocardiogram. Also admit patients with acute PE and a proximal lower extremity DVT by Doppler ultrasound, as this is an independent predictor of death. The risk of death was two times higher and risk from PE-specific death was four times higher in patients with this finding.[73]

When is it safe to discharge a hospitalized patient with an acute PE?

The recommended length of time to monitor and treat hospitalized patients with an acute PE has not been extensively studied. Thus, a safe timeframe from diagnosis to discharge is not clear. A strategy including reassessment of the PESI score (Table 7) in addition to observing clinical improvement of the patient is recommended.

Patients at low risk (PESI ≤ 85) and demonstrated clinical improvement (i.e. significantly improved or resolved symptoms, stable vital signs, no hypoxia), can be safely discharged from the hospital. Meta-analyses have shown that in low risk patients, the risk of recurrent VTE, major bleeding, and death, were comparable between outpatients, early discharged patients, and inpatients.[74]

If a patient's PESI score has increased to the intermediate risk-category (≥ 86) after reassessment, then continued monitoring in the hospital for another 24-48 hours is reasonable. However, given the lack of published data on this issue, the decision to discharge should largely be determined on clinical grounds and at the discretion of the primary service.

In patients admitted with an initial PESI score ≥ 86, a repeat assessment of the PESI score at 24-48 hours after admission can be helpful. If the repeat score is ≤ 85, and the patient has demonstrated clinical improvement, hospital discharge is reasonable. If the patient's PESI score continues to remain ≥ 86 but the patient is clinically stable (i.e. improved symptoms, stable vital signs, no hypoxia), discharge should be at the discretion of the primary service.

A retrospective cohort study of 304 patients analyzed changes in the PESI score to predict 30-day mortality in intermediate risk patients.[75] Patients classified at the time of admission into PESI class III (PESI score 86 – 105) were reclassified 48 hours after admission. Eighty-three patients (27%) were reclassified from intermediate risk (PESI Class III) on admission to low-risk (Classes I and II, PESI score ≤ 85). Thirty-day mortality in these patients was 1.2% as opposed to 11.3% in those patients remaining at higher risk. Reclassifying patients using a second PESI score at 48 hours from admission increased correctly identifying low risk

patients that survived, as well as correctly identifying high-risk non-survivors. Thus, reclassifying patients by PESI risk score is a useful method to determine when patients are safe to discharge after an acute PE diagnosis.

4. Other Sites of Venous Thrombosis

4.1 Portal Vein Thrombosis

Recommendations:

- For newly identified portal vein thrombosis, hepatology/gastroenterology consultation is recommended to identify the safest and most effective management strategy
- In non-cirrhotic patients, acute portal vein thrombosis is usually treated with anticoagulation upon discussion with IR and GI services (see Figure 5 and Figure 6). *[I-C]*
- In cirrhotic patients, the risk of anti-coagulation for PVT is higher and benefit is lower. Therefore, management of PVT is individualized depending upon the acuity/chronicity of the thrombosis, severity of liver disease, presence of varices, and other clinical features (Figure 4).

Background.

The risk of developing a portal vein thrombosis (PVT) increases with more advanced cirrhosis and portal hypertension. PVT can also be associated with non-cirrhotic and non-hepatocellular cancer patients such as those with intra-abdominal infection, trauma, other malignancies, and myeloproliferative disorders. PVT is often incidentally diagnosed on imaging performed for other clinical indications, although patients with PVT can present symptomatically with acute colicky abdominal pain, ileus, and even upper gastrointestinal bleeding secondary to varices and portal hypertensive gastropathy. A partially obstructing PVT is less likely to be symptomatic. Extension of a portal vein thrombosis into the superior mesenteric vein can lead to bowel ischemia, with increased morbidity and mortality.

PVT is classified as either acute or chronic, and as either related to a diagnosis of liver cirrhosis or not.

Acute PVT in a cirrhotic patient (Figure 4).

Screen patients for gastroesophageal varices with upper endoscopy prior to initiating anticoagulation.

If no large varices are present, start patients on anticoagulation immediately if no contraindications exist. Possible contraindications include limited life span due to advanced liver failure (Child-Turcotte-Pugh part C (CTP C) or MELD > 30), unresectable/ metastatic hepatocellular carcinoma (HCC) and excessive risk of bleeding due to frailty, encephalopathy, and medical co-morbidities. These recommendations are based on systematic reviews of observational studies.[76]

If varices are present, the risk of bleeding is higher. Consult the hepatology service to consider the optimal treatment strategy, including the role of anticoagulation. The decision to initiate anticoagulation for acute PVT in a cirrhotic patient is on a case-by-case basis and should take into account the severity of underlying liver disease, risk of anti-coagulation, and presence of underlying thrombophilia. Up to 45% of patients with cirrhosis and non-malignant partial PV thromboses will have spontaneous recanalization without anticoagulation[77-79] and natural history studies have demonstrated conflicting results on the impact of spontaneous PVT on liver disease progression and survival. *[II-C]* After endoscopic band ligation of varices, anticoagulation should be held for 48 hours to prevent post ligation ulcerative bleeding.[76]

Management of PVT is important to prevent thrombosis-related complications, including portal hypertension, gastrointestinal bleeding secondary to gastroesophageal varices, ischemic hepatitis, and intestinal ischemia from extension of clot to the superior mesenteric vein. The goal of anticoagulation is to allow recanalization of the portal vein.

No consensus exists for the optimal choice of anticoagulant for PVT.[80] Warfarin and LMWH are the mainstays of therapy. In patients with a baseline INR > 2 (as is common in advanced liver disease), LMWH is preferred.[76] In addition, LMWH is preferred in patients with refractory ascites requiring frequent paracentesis and patients with moderate to severe liver insufficiency with jaundice or those receiving antibiotics at risk for vitamin K deficiency. There are also evolving data on the use of direct acting oral anticoagulants in highly selected patients, but further studies of are needed.[81-83] Six months of anticoagulation therapy has a higher rate of recanalization, but no specific duration has been established.

Chronic PVT in a cirrhotic patient (Figure 4).

Systemic anticoagulation is not recommended for cirrhotic patients found to have a chronic PVT, *[III-C]* because little data exists for any benefit of anticoagulation in this patient population.[84] Perform non-urgent evaluation with upper endoscopy to assess for esophageal varices or gastrointestinal bleeding, along with standard primary and secondary treatments of varices with esophageal banding and nonselective beta blockers. If beta-blockers and endoscopic therapy are unsuccessful for bleeding, consider transjugular intrahepatic portosystemic shunt (TIPS).

Acute PVT in a non-cirrhotic patient (Figure 5).

If no active gastrointestinal bleeding is present, initiate anticoagulation as early as possible (Figure 5). *[I-C]* If active bleeding is present, perform upper endoscopy to evaluate for variceal bleeding.

Continue anticoagulation for at least 3 months, followed by re-imaging. If the portal vein is recanalized, anticoagulation can be discontinued. If the portal vein is not recanalized, continue anticoagulation for another 3 months. *[I-C]* If the patient has an irreversible hypercoagulable state (Table 5), continue anticoagulation indefinitely (Figure 6). *[I-C]*

Chronic PVT in a non-cirrhotic patient (Figure 5 and Figure 6).

For non-cirrhotic patients found to have a chronic portal vein thrombosis, screen for gastroesophageal varices with upper endoscopy. If present, treat. Systemic anticoagulation in non-cirrhotic patients should only be considered if they have a permanent risk factor for venous thrombosis or if the thrombus has extended (or has risk of extension) into the superior mesenteric vein.[76]

4.2 Mesenteric Vein Thrombosis (MVT)

Recommendations:

- Mesenteric vein thromboses typically require a multidisciplinary team approach, which may include medicine, gastroenterology, surgery, and interventional radiology (Figure 7). *[II-E]*
- For acute MVT, systemic anticoagulation is recommended (Figure 7). *[I-D]*
- For chronic MVT, anticoagulation is determined on a case-by-case basis. *[II-E]*

Acute Mesenteric Vein Thrombosis (MVT).

MVT is the cause of mesenteric ischemia in approximately 5-15% of cases.[85-87] It can be associated with hypercoagulable states, malignancy, inflammatory bowel disease, intra-abdominal infections, and surgery. Presenting symptoms for acute MVT can include abdominal pain, nausea, vomiting, and even hematemesis, hematochezia, and melena. The imaging modality of choice to diagnose this condition is contrast-enhanced CT of the abdomen and pelvis. Chronic MVT is usually detected incidentally on imaging and is differentiated from an acute MVT by the presence of extensive collateral circulation.

Management of acute MVT.

For acute MVT without evidence of bowel ischemia or peritonitis and a reversible condition, provide a minimum of 3-6 months of anticoagulation (Figure 7). Repeat CT after 3-6 months to ensure resolution. Patients with a known thrombophilia or unexplained acute MVT may need to continue anticoagulation indefinitely. *[II-B]*

Anticoagulation.

The goals of therapy in acute symptomatic MVT include preventing extension of thrombus and preventing intestinal infarction by recanalizing thrombosed mesenteric veins.

- For patients with reversible or transient conditions associated with acute MVT such as pancreatitis, infection or trauma, no evidence of bowel ischemia, peritonitis, or perforation, initiate early anticoagulation for at least 3-6 months (Figure 7).
- For patients with long-term hypercoagulable state or an unknown etiology for their acute MVT, indefinite duration of anticoagulation is indicated.[88]
- Incidentally discovered asymptomatic acute MVT can be treated with anticoagulation in a patient at low risk of bleeding, with the understanding that no studies have been performed to assess the role of anticoagulation versus watchful waiting in this setting.

Warfarin (with a goal INR of 2-3) or LMWH have been the mainstays of therapy, but a recent systematic review suggests that DOACs may be another option.[89] However, DOACs have not been specifically studied in patients with acute MVT.

Surveillance imaging should be obtained at 3-6 months to ensure it is appropriate to discontinue anticoagulation in patients with transient risk factors.

Surgical evaluation.

For patients with evidence of bowel ischemia, infarction, or peritonitis, obtain urgent evaluation by general surgery in addition to anticoagulation. *[I-A]*

Even if a potential surgical abdomen is a concern, anticoagulation treatment should begin with IV unfractionated heparin. For patients with evidence of bowel infarction, development of peritonitis, or other systemic signs of intra-abdominal sepsis, obtain a general surgical evaluation for laparotomy and possible bowel resection. Anticoagulation should be continued post-operatively as soon as adequate hemostasis has been achieved (as determined by the surgeon).

Operative thrombectomy is not recommended for acute MVT.

Chronic Mesenteric Vein Thrombosis (MVT).

Management of chronic MVT.

Chronic MVT is usually detected incidentally on imaging and is differentiated from acute MVT by the presence of extensive collateral circulation. Management of chronic MVT requires a multidisciplinary approach that may include, but is not limited to, surgery, gastroenterology, and interventional radiology.

Anticoagulation.

Consider anticoagulation for patients with chronic MVT only after evaluation for and treatment of esophageal and gastric varices. Anticoagulation may be of particular benefit

in patients with thrombophilia. In addition, weigh the risks of bleeding against the benefits of anticoagulation.[88] *[II-C]*

Esophageal band ligation.

Patients with chronic MVT should undergo non-urgent evaluation with an upper endoscopy. If esophageal varices are present, they should undergo esophageal band ligation to decrease the risk of variceal bleeding.[88] *[I-B]*

Beta blockers.

For patients with chronic MVT and evidence of portal hypertension (including varices), initiate non-selective beta blockers when feasible to decrease the risk of variceal bleeding. *[II-B]*

TIPS.

Consider transjugular intrahepatic portosystemic shunt (TIPS) for patients with variceal bleeding complications that are not amenable to endoscopic or pharmacologic therapies.[88] *[II-C]*

5. Special Considerations in Venous Thromboembolism

5.1 Thrombophilia Workup

Recommendations:

- Thrombophilia testing should generally be deferred to the outpatient setting.
- Thrombophilia testing is unreliable in the inpatient setting, with results uninterpretable in the setting of either acute thrombosis or exposure to anticoagulation.

Thrombophilia testing should generally be deferred to the outpatient setting. The only likely indication for inpatient testing is for an inpatient with a new thrombosis. If the clinical likelihood of a heparin induced thrombocytopenia (HIT) is moderate to high, perform thrombophilia testing. (At Michigan Medicine, See Michigan Medicine clinical guideline on HIT.)

In general, thrombophilia testing is indicated only when it would change management, and inpatient thrombophilia testing would not alter the inpatient management strategy of starting anticoagulation. Moreover, thrombophilia testing is unreliable in the inpatient setting, with results uninterpretable in the setting of either acute thrombosis or exposure to anticoagulation. Limiting thrombophilia testing is a key element of ongoing "choosing wisely" campaigns.[90]

Although not recommended, if inpatient thrombophilia testing is strongly desired, genetic testing (i.e. factor V Leiden, prothrombin gene polymorphism) will remain accurate in the acute setting. In patients who have had recurrent VTE events or treatment failure, specific thrombophilia testing may be of use, as discussed below. In patients who develop a blood clot in an unusual site (i.e. mesenteric thrombosis), testing for a myeloproliferative neoplasm (JAK2 mutation), or paroxysmal nocturnal hemoglobinuria (PNH) may provide some additional guidance; however, testing can still be deferred to the outpatient setting if it can be performed expeditiously.

5.2 Recurrent VTE Events

Recommendations:

- Patients with a history of VTE who develop a new event while off anticoagulation should be started on a new anticoagulant regimen as appropriate.
- Patients with recurrent VTE events should be referred for outpatient hematology consultation to discuss the possibility of an underlying hypercoagulable state and review options for extended maintenance anticoagulation therapy.

Patients with a history of VTE who develop a new event while off anticoagulation should be started on a new anticoagulant regimen as appropriate. (See below for the management of patients with anticoagulant failure.) Patients with recurrent VTE events should be referred for outpatient hematology consultation to discuss the possibility of an underlying hypercoagulable state and review options for extended maintenance anticoagulation therapy.

Certain acquired hypercoagulable states (i.e. antiphospholipid antibody syndrome [APLAS], cancer, vasculitis) may be associated with both recurrent VTE events and treatment failure. In these cases, assess patients for any concerning constitutional symptoms with subsequent testing for a systemic condition as indicated. While age appropriate cancer screening should be updated, studies have found no benefit for more extensive screening for cancer.[91]

Testing for antiphospholipid antibody syndrome is appropriate in recurrent VTE. Testing is not practical in the inpatient setting. Lupus anticoagulant (LAC) testing should not be performed while taking most anticoagulants (heparin, LMWH, DOACs). Additionally, some antibodies (i.e. anti-cardiolipin IgM antibodies) may be non-specific in acute thrombosis. All APLAS testing needs to be repeated in 12 weeks to confirm the diagnosis.

Numerous studies have failed to demonstrate an association between VTE recurrence and weak inherited thrombophilias (i.e. Factor V Leiden and Prothrombin gene polymorphism) and only modest associations with more severe thrombophilias (i.e. protein C, protein S, antithrombin deficiency).[1] ACCP guidelines conclude that inherited thrombophilias may "predict risk of recurrence, but not

strongly or consistently enough to influence recommendations on duration of therapy."[12]

5.3 Treatment Failure

Recommendations:

- Checked anticoagulant levels in patients presenting with acute VTE who are prescribed anticoagulation
- For patients who develop a VTE event:
  – while on warfarin or a DOAC: switch to LMWH (for at least ~1 month while assessing for cancer)
  – while on LMWH: increase dose of LMWH by about one-quarter to one-third.[34] *[II-C]*
- If anticoagulation cannot be increased due to risk of bleeding and no reversible risk factors have been identified, consider insertion of a temporary IVC filter as a last option.

No randomized controlled trials or prospective cohort studies guide us on the management of patients who develop a recurrent VTE while on therapeutic anticoagulant therapy (ie, anticoagulation failures). True anticoagulation failure is unusual. The first step is to verify the development of a recurrent acute VTE event. Obtaining a D-dimer level and carefully comparing new imaging to prior radiological studies may be useful. Consider thrombophilia testing (see section on recurrent VTE events), with a particular focus on screening for an undiagnosed cancer or APLAS.

The most significant cause of "treatment failure" is medication non–compliance, which should be carefully assessed in all patients presenting with potential anticoagulant treatment failure. Anticoagulant levels should be checked in patients presenting with acute VTE who are prescribed anticoagulation (i.e. INR for warfarin; random or trough levels for dabigatran, rivaroxaban, and apixaban; anti-Xa LMWH levels 4 hours after an enoxaparin dose; anti-Xa levels 3 hours after a fondaparinux dose). Random LMWH and fondaparinux levels are generally not helpful outside the recommended time frame.

Query patients regarding taking their anticoagulant as prescribed, and starting any new medications that may interfere with anticoagulant efficacy. Most recurrent VTE events occur shortly (within 30 days) after the initial event. For patients on DOACs, remember that dabigatran and edoxaban require a parenteral bridge after an acute VTE, and that rivaroxaban and apixaban require higher initial doses prior to beginning maintenance therapy dosing.

For any patient presenting with an acute clot while on anticoagulation, the simplest initial treatment strategy is to begin weight-based LMWH or therapeutic IV UFH. If HIT is suspected, consider anticoagulation with IV argatroban. Inpatients presenting with anticoagulation failure should have a hematology consultation to help guide therapy. For patients on warfarin, options include raising the INR goal (i.e. to 2.5-3.5) or switching to a different anticoagulant agent. Patients on DOACs should be switched to a different anticoagulant. For patients on LWMH, options include increasing the LMWH dose or switching to a different agent.

Patients on once-daily LMWH dosing are generally switched to a twice daily regimen.[34] A retrospective observational study in 47 cancer patients who failed LMWH found an acceptable 3-month VTE recurrence rate (8.6%, 95% CI 4.0-17.5%) when the LMWH dose was increased by 20-25%, with few bleeding complications.[92] This finding led to the most recent ACCP recommendation that patients who develop a VTE event while on warfarin or a DOAC should be switched to LMWH (at least for ~1 month while assessing for cancer) and that patients on LMWH should have a dose increase by about one-quarter to one-third.[34] *[II-C]* In patients who have failed anticoagulation, other acceptable anticoagulant agents may include those whose levels can be monitored and adjusted as needed (warfarin, LMWH, fondaparinux). If anticoagulation cannot be increased due to risk of bleeding, and no reversible risk factors have been identified, consider insertion of a temporary IVC filter as a last option.

5.4 Referral to Hematology

Recommendations:

- Consult inpatient hematology for patients with significant anticoagulation concerns.
- Refer patients with recurrent VTE events for outpatient hematology consultation.
- Refer patients with idiopathic (unprovoked) clots in unusual sites (i.e. mesenteric, retinal) to hematology for thrombophilia testing.

Patients with significant anticoagulation concerns should have an inpatient hematology consult requested to help guide anticoagulant choice and management. Refer patients with recurrent VTE events for outpatient hematology consultation to discuss a possible underlying hypercoagulable state and review options for extended maintenance anticoagulation therapy. In addition, refer patients with idiopathic clots in unusual sites (i.e. mesenteric, retinal) to hematology for thrombophilia testing.

Guideline Creation Process and Considerations

Related National Guidelines

This guideline is generally consistent with the:

- GOLD 2017 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.[93]

- The COPD Pocket Consultant: COPD Foundation Guide for Management of COPD (2017).[94]
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD (2015).[95]
- US Preventive Services Task Force (USPSTF). Screening for chronic obstructive pulmonary disease (2016).[96]
- VA/DOD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2014).[97]

Related National Performance Measures

The Michigan Medicine Clinical Guideline on VTE is generally consistent with other guidelines published nationally and internationally, including:

- The Joint Commission: Venous Thromboembolism Warfarin Therapy Discharge Instructions: This measure assesses the number of patients diagnosed with confirmed VTE that are discharged on warfarin to home, home with home health or home hospice with written discharge instructions that address all four criteria: compliance issues, dietary advice, follow-up monitoring, and information about the potential for adverse drug reactions/interactions
- The Joint Commission: Incidence of Potentially Preventable Venous Thromboembolism: This measure assesses the number of patients with confirmed venous thromboembolism (VTE) during hospitalization (not present at admission) who did not receive VTE prophylaxis between hospital admission and the day before the VTE diagnostic testing order date.

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Guideline Development Team and Disclosures

The multidisciplinary guideline development team consisted of:

- Internal medicine physicians: Paul J Grant, MD, Hospital Medicine; Mark S Kolbe, MD, Hospital Medicine; Steven L Kronick, MD, Emergency Medicine.
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- Literature search services were provided by informationists at the Taubman Health Sciences Library, University of Michigan Medical School.

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used for most of the search topics. The search below is identified as Main in the search strategies document. The appropriate indexing terms either do not exist or were applied inconsistently, so the main search uses keywords in addition to MeSH terms to arrive at the following main strategy.

1. *venous thromboembolism/ or exp *venous thrombosis/
2. limit 1 to (english language and yr="1/2010 -3/2015")
3. limit 2 to pregnancy
4. 2 not 3
5. (child* or infant* or newborn* or neonat* or adolescen* or pediatric* or paediatric* or baby or babies or boy$1 or girl$1).ti.
6. 4 not 5
7. 6 not exp *neoplasms/

Results were limited to adults, English language and January 2010 to March 2015. The Main search retrieved 6,291 references. This includes duplicate references, which cannot be excluded from this size result set. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added and duplicate references removed, the base results are as follows:

VTE etc. -Guidelines, total results were 197
VTE etc. -Clinical Trials, total results were 733
VTE etc. -Cohort Studies, total results were 1344

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Level of evidence supporting a diagnostic method or an intervention:

A = systematic reviews of randomized controlled trials with or without meta-analysis
B = randomized controlled trials
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Search details are available at http://www.uofmhealth.org/provider/clinical-care-guidelines.

Recommendations

Guideline recommendations were based on prospective randomized controlled trials (RCTs)if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

The strength of recommendations regarding care were categorized as:
I = Generally should be performed
II = May be reasonable to perform
III = Generally should not be performed

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Cardiac Surgery, Cardiovascular Medicine, Emergency Medicine, Family medicine, General Medicine, Hematology, Internal Medicine, Pharmacy Division(s), Radiology, Vascular Surgery. The final version of this guideline was endorsed by the Clinical Practice Committee of the University of Michigan Medical Group and by the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

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