MedStar Health

Outpatient Diagnosis and Management of Venous Thromboembolic Disease

Clinical Practice Guideline
MedStar Health

"*These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations."*

Introduction:

Deep vein thrombosis (DVT) and pulmonary embolism (PE) affect 350,000 to 600,000 people per year and results in 100,000 deaths per year (NHLBI (National Heart, Lung, and Blood Institute); 2008). There are multiple risk factors for having a DVT as listed below (Table 1).

Table 1:

Risk factors (causes) for the development of venous thrombosis

Inherited thrombophilia
Factor V Leiden mutation
Prothrombin G20210A mutation
Protein S deficiency
Protein C deficiency
Antithrombin deficiency
Other disorders and risk factors
Presence of a central venous catheter
Malignancy
Surgery, especially orthopedic
Trauma
Immobilization
Pregnancy
Oral contraceptives
Hormone replacement therapy
Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide, asparaginase)
Heart failure
Congenital heart disease
Antiphospholipid syndrome
Older age (≥65 years)
Obesity
Severe liver disease
Myeloproliferative neoplasms
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome

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Diagnosis of Deep Venous Thrombosis:

DVT may not present with classic symptoms of pain and swelling or physical findings including warmth, erythema, or tenderness. For patients in whom a first DVT is suspected, a diagnostic approach that incorporates clinical assessment with estimation of pretest probability by gestalt and/or the Wells score, D-dimer measurement and, when necessary, compression ultrasonography (CUS) with Doppler of the lower extremities. Wells scoring system is a widely available tool with its modified version (*UpToDate*, n.d.) (Table 2)

Table 2: Pretest probability of DVT (Wells Criteria) copied from UpToDate.

Clinical feature	Score
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than three days or major surgery, within four weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg	1
Pitting edema greater in the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
SCORE	
High probability (50-75% Prob of DVT)	3 or greater
Moderate probability (17% prob of DVT)	1 or 2
Low probability (3% Prob of DVT)	0 or less
Modification: additional factor; previously documented DVT	
DVT likely	2 or greater
DVT unlikely	1 or less

MD Cal Calculator: https://www.mdcalc.com/calc/362/wells-criteria-dvt#next-steps (Refer Table 3)

Table 3

Pre-test probability	**D-Dimer Results**	**Action**
Low	Negative	No DVT—pursue alternative diagnosis
Low	Positive	Proximal US–if positive, treat; if negative, no DVT Whole leg US—if positive for proximal DVT, treat; if positive for distal DVT, individualize; if negative, no DVT
Moderate	Negative	No DVT—pursue alternative diagnosis
Moderate	Positive	Proximal US—if positive, treat; if negative, repeat in 1 week and treat if positive and consider no DVT if negative Whole leg US—if positive for proximal DVT, treat; if positive for distal DVT, individualize; if negative, no DVT
High	NA	Ultrasound—treat if positive

Patients can proceed directly to ultrasonography if the D-dimer is expected to be positive due to another condition. (Table 4)

Table 4.

Causes of high plasma D-dimer

Condition	Mechanism

Thromboembolism:
▪ Arterial
  ▪ Myocardial infarction
  ▪ Stroke
  ▪ Acute limb ischemia
  ▪ Intracardiac thrombus
▪ Venous
  ▪ Deep vein thrombosis
  ▪ Pulmonary embolism
▪ Disseminated intravascular coagulation (DIC)
	Intravascular thrombosis and fibrinolysis

Inflammation: ▪ COVID-19 ▪ Other severe infections ▪ Sepsis ▪ DIC	Activation of the acute inflammatory response and coagulation pathway, intravascular thrombosis and fibrinolysis
Surgery/trauma	Tissue ischemia, tissue necrosis
Liver disease	Reduced clearance of fibrin degradation products
Kidney disease	Multiple, including renal vein thrombosis and nephrotic syndrome
Vascular disorders: ▪ Vascular malformations ▪ Sickle cell disease vaso-occlusion	Intravascular thrombosis and fibrinolysis
Malignancy	Multiple, including vascular abnormalities, cancer procoagulant, and microvascular thrombosis
Thrombolytic therapy	Fibrin breakdown
Pregnancy: ▪ Normal pregnancy ▪ Preeclampsia and eclampsia	Physiologic changes in the coagulation system Microvascular thrombosis and fibrin deposition

Plasma D-dimer is a product of clot breakdown, released upon degradation of polymerized, crosslinked fibrin (if non-crosslinked fibrinogen was degraded, D-monomers would be released). Elevated plasma D-dimer levels indicate that coagulation has been activated, fibrin clot has formed, and clot degradation by plasmin has occurred. There are many causes of elevated D-dimer; identification of the underlying cause requires correlation with other findings, including the clinical picture and other laboratory results. Refer to UpToDate for further explanation of fibrinogen domain structure and pathophysiology of the disorders listed here.

COVID-19: coronavirus disease 2019; DIC: disseminated intravascular coagulation.

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Alternative imaging – For patients with suspected DVT, contrast-enhanced computed tomographic venography (CTV) and magnetic resonance venography (MRV) are rarely used diagnostically, unless there is uncertainty about iliac vein or inferior vena cava thrombosis after ultrasonography.

Recurrence: In addition, diagnosis of recurrent DVT in the ipsilateral leg can be challenging since residual thrombus can persist for months-years. Comparison to prior ultrasound, if available, can be very helpful. Criteria for diagnosing a new acute DVT in this situation include non-compressibility in a previously uninvolved segment, significant extension of thrombus in the involved venous segment, and an increase in compressed venous diameter ≥ 4 mm.

Nomenclature and Duration of therapy:

Treatment durations for acute DVT (Kearon et al., 2012), (*UpToDate*, n.d.):

- Initiation or initial phase anticoagulation: This phase is up to 5-21 days.

- Anticoagulation following the initial phase (treatment phase): This phase is up to 3 months
- Extended anticoagulation phase: It is 3 months and onwards with a defined stop date (for e.g., 6-12 months).
- Indefinite anticoagulation phase: No stop date defined for anticoagulation beyond 3 months of anticoagulation therapy

Additionally, deep venous thrombosis can be provoked or unprovoked, involving the proximal or distal lower extremity. Similarly, it can have transient or persistent risk factors. The treatment of DVT has variable durations starting from initial phase to extended duration or indefinite therapy (Table 5).

Table 5:

Terms, definitions, and characterizing risk factors for indefinite anticoagulation

Term	Definition and examples
No identifiable risk factor (unprovoked)	VTE where no identifiable provoking event or risk factor is evident
Identifiable risk factor (provoked)	VTE caused by a known event or risk factor (eg, surgery, hospital admission, estrogen)
Transient risk factor	Risk factors for VTE that are reversible ▪ **Major risk factors (ie, transient factors that favor limited-duration anticoagulation):** • Major surgery >30 minutes, hospitalization or confined to bed with "bathroom privileges" for ≥3 days due to acute illness, CS, trauma with fractures, estrogen therapy, pregnancy or puerperium ▪ **Minor risk factors (ie, transient factors that favor continuing anticoagulation):** • Minor surgery <30 minutes, hospitalization <3 days, reduced mobility at home ≥3 days due to acute illness, lower extremity injury without fracture with reduced mobility ≥3 days, long-haul flight
Persistent risk factor	Risk factors that persist over a prolonged period of time ▪ Examples include irreversible conditions such as active malignancy, obesity, active inflammatory bowel disease, active autoimmune disease, continued hormonal therapy, nephrotic syndrome, recurrent long-haul flights
Proximal DVT of lower extremity	VTE that is in the popliteal, femoral, or iliac veins
Distal DVT of lower extremity	VTE that is without a proximal component and confined to the calf veins (peroneal, posterior, anterior tibial, and muscular veins)
Pulmonary embolism	Thrombus in the main, segmental, or subsegmental branches of the pulmonary artery
Initial anticoagulation	Anticoagulant therapy that is administered immediately following a diagnosis of VTE
Anticoagulation following initial phase	Anticoagulant therapy that is typically administered for a finite time period (ie, scheduled stop date, typically 3 months)
Extended anticoagulation	Anticoagulant therapy that is administered beyond the typical 3 months but with a scheduled stop date (eg, 6 to 12 months)
Indefinite anticoagulation	Anticoagulant therapy that is administered beyond the typical 3 months but without a scheduled stop date
DOACs	Also known as newer/novel oral anticoagulants (NOAs), non-vitamin K antagonist oral anticoagulants (NOACs), and target-specific oral anticoagulants (TOACs, TSOACs)

VTE: venous thromboembolism; CS: cesarian section; DVT: deep venous thrombosis; DOACs: direct oral anticoagulants.

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D-dimer could also be performed in females with VTE (venous thromboembolism) if guidance is required related to the extent of anticoagulation duration. If they have a negative D-dimer the recurrent VTE risk is estimated to be three percent per year and may aid in the decision to stop the anticoagulation. Of note, in this situation the D-dimer is of little value in males and has low specificity (Kearon et al., 2019).

General Principles of Therapy

Source: Updated CHEST guidelines 2021; (Kearon et al., 2012)

1. In patients with *acute isolated distal DVT* of the leg and (i) without severe symptoms or risk factors for extension, serial imaging of the deep veins for 2 weeks over anticoagulation is recommended (weak recommendation, moderate-certainty evidence); or (ii) with severe symptoms or risk factors for extension, anticoagulation is recommended over serial imaging of the deep veins (weak recommendation, low-certainty evidence).
2. In patients with *acute isolated distal DVT* of the leg who are treated with serial imaging, it is (i) recommend no anticoagulation if the thrombus does not extend (strong recommendation, moderate-certainty evidence), (ii) suggested anticoagulation if the thrombus extends but remains confined to the distal veins (weak recommendation, very low-certainty evidence), and (iii) recommend anticoagulation if the thrombus extends into the proximal veins (strong recommendation, moderate-certainty evidence).
3. In patients with subsegmental pulmonary embolism (PE) (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, we suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) or (ii) high risk for recurrent VTE, anticoagulation is recommended over clinical surveillance (weak recommendation, low-certainty evidence).
4. In patients with *acute VTE who have no contraindication to anticoagulation*, the recommended duration is three months (Strong recommendation, moderate-certainty evidence). Upon completion of the 3-month treatment phase of therapy, all patients should be assessed for extended-phase therapy.
5. In patients with *VTE diagnosed in the setting of a minor or major transient risk factor* (Table 5), it is recommended against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence).
6. In patients with *VTE diagnosed without a transient risk factor* (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, extended-phase anticoagulation with a VKA is recommended (weak recommendation, moderate-certainty evidence).
7. When deciding *the duration of anticoagulation*, especially for unprovoked VTE, patient preference and predicted risk of recurrent VTE or bleeding should be considered.
8. *Extended-phase anticoagulation* does not have a pre-defined stop date. Risks and benefits should be considered when continuing extended anticoagulation therapy and review annually.
9. In patients with *acute DVT* of the leg, anticoagulation therapy alone over interventional (thrombolytic, mechanical, or pharmacochemical) therapy is recommended. (Weak recommendation, moderate-certainty evidence).
10. In patients with *acute VTE* (DVT of the leg or PE) apixaban, dabigatran, edoxaban, or rivaroxaban is recommended over VKA as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence).
11. In patients with *acute VTE in the setting of cancer* ("cancer-associated thrombosis") an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) is recommended over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence). Apixaban or LMWH may be preferred in patients with luminal GI malignancies and catheter-associated thrombosis (CAT) due to the increased risk of GI bleeding associated with edoxaban and rivaroxaban.
12. In patients with *confirmed antiphospholipid syndrome*, the target INR of 2.5 with warfarin is recommended over DOAC therapy (weak recommendation, low-certainty evidence). Initiating VKA therapy should include an overlapping period of parenteral anticoagulation.
13. In patients with *superficial venous thrombosis*, (SVT) of the lower limb who are at increased risk of clot progression to DVT or PE, anticoagulation for 45 days is recommended over no anticoagulation (weak recommendation, moderate-certainty evidence). Fondaparinux 2.5 mg daily is preferred over other anticoagulants. However, patients who refuse or will not use fondaparinux can take rivaroxaban 10 mg

daily as a reasonable alternative (weak recommendation, low-certainty evidence).

14. In patients where *extended-phase anticoagulation* is offered, a reduced dose of apixaban or rivaroxaban is recommended over the full dose. Reduced dose refers to apixaban 2.5mg twice daily and rivaroxaban 10mg once daily. Several other DOACs (Direct Oral Anticoagulants), and warfarin, are also acceptable for secondary prevention (extended-phase therapy) after VTE.
15. For *initial treatment of DVT*, dabigatran and edoxaban require 5-10 days of parenteral anticoagulation (LMWH, fondaparinux); warfarin requires overlap of at least 5 days with parenteral anticoagulants, (LMWH, fondaparinux); rivaroxaban and apixaban can be used alone.
16. For patients who receive *extended therapy* (more than three months), there is no need to change anticoagulant.
17. In patients with *acute proximal DVT* of the leg and contraindication to anticoagulation, an IVC filter is recommended. However, IVC filter is not recommended in addition to the anticoagulation (strong recommendation, moderate-certainty evidence).
18. In patients with low-risk for PE, outpatient treatment is recommended over hospitalization provided access to medications, ability to access outpatient care, and home circumstances are adequate (strong recommendation, low-certainty evidence)
19. LMWHs (Low Molecular Weight Heparin) are not fully reversible with protamine because of the differing chain lengths of the LMWH molecule.
20. Reversal agents for the Directing Acting Oral Anticoagulants (DOACS) exist and may be indicated in severe, life-threatening hemorrhage (usually managed inpatient). The reversal agent for Dabigatran is idarucizumab. The reversal agent for the factor Xa inhibitors is andexanet alpha.
21. Early ambulation is recommended over initial bed rest. There is evidence that compression stockings are no longer recommended for this purpose.

Treatment Options:

Anticoagulation:

There are many different types of anticoagulants available both in parenteral and enteral forms. Depending on the patient's characteristics, an agent can be selected. Please refer to Table 6 for details. IVC filters are also discussed as a treatment option below.

Table 6: Selection criteria

Factor	Preferred anticoagulant	- Comments
Active Cancer (cancer-associated thrombosis)	DOAC (apixaban, edoxaban, rivaroxaban over LMWH	Edoxaban and rivaroxaban are associated with higher risk of GI bleeding than LMWH, therefore in luminal gastrointestinal cancer apixaban or LMWH are the preferred agents.
Parenteral therapy	Not required for rivaroxaban and apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy
Once daily oral therapy preferred	Rivaroxaban, edoxaban, VKA	
Liver disease and coagulopathy	LMWH or UFH	NOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR hard to interpret
Renal disease and CrCl < 30 ml/min	Vitamin K antagonist (VKA) used with UFH bridge	LMWH contraindicated with severe renal impairment. Each NOAC has unique dosing recommendations based on the level of renal impairment

CAD	VKA, rivaroxaban, apixaban, edoxaban	Mixed evidence about CAD events with dabigatran (Javed et al., 2021)
Dyspepsia or prior GI Bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may have increased GI bleeding than VKA
Poor compliance	DOAC	INR monitoring can help detect problems with compliance. Some patients may be more compliant with DOACs since regimen is less complex
Concurrent use of thrombolytics	Unfractionated heparin (UFH) infusion	Titration and controlled use
Available Reversal agents	VKA, UFH, Dabigatran, apixaban and rivaroxaban	Idarucizumab for direct thrombin inhibitor (Dabigatran) & andexanet alfa for direct FXa inhibitors (apixaban and rivaroxaban)
Pregnancy or pregnancy risk	LMWH	Other agents may cross the placenta
Cost, coverage licensing	Individualize	

Specific Agents:
Low Molecular Weight Heparin:

Enoxaparin (Lovenox®) 1 mg/kg subcutaneously every 12 hours (preferred) or 1.5 mg/kg subcutaneously every 24 hrs. (alternative). If using with a Vitamin K antagonist, enoxaparin should be continued for a minimum of 5 days *and* until a therapeutic oral anticoagulant effect has been achieved (INR > 2.0 for at least 2 measurements). The dosing interval should be modified for renal impairment (1 mg/kg daily for ClCr <30) and monitoring anti-Xa level is recommended.

Alternate sites with every administration. Do not mix with other injections and do not rub the injection site. Do not expel air bubble from syringe before injecting to avoid losing drug from prefilled syringes.

While weight-based dosing is recommended, and blood testing is not usually recommended when treating a patient with LMWHs, there are some circumstances when monitoring is appropriate:

- Patients who weigh less than 60 kg.
- Patients who weigh more than 150 kg.
- Therapy lasting more than 14 days
- Patients who have a creatinine clearance less than 30 ml/min
- During pregnancy

Monitoring LMWH is NOT done by measuring PTT. You must measure the anti-Xa level in the blood. The target range for the anti-Xa level is 0.5-1.0 IU/mL when administering the dose twice daily. The sample should be drawn about 4 hours after administration of the LMWH. Major hemorrhage can occur in 1-2% of patients treated with LMWH like unfractionated heparin.

Thrombocytopenia can occur with LMWH. A platelet count should be checked at baseline and on days 3 and 5 of therapy. Platelets should be checked twice weekly for patients on a prolonged course of LMWH. Patients with a history of antibody induced thrombocytopenia on unfractionated heparin should not be treated with LMWH.

Cost of enoxaparin ranges from $7-40/syringe for Lovenox and $13 for generic.

Dalteparin (Fragmin®) usual dose is 200 units/kg subcutaneously once per day or 100 units/kg twice daily. Overlap with a Vitamin K antagonist. There are no specific guidelines for dose adjustment for renal impairment. Monitoring anti-Xa level is recommended. Alternatively use enoxaparin.

Cost of Dalteparin: price per syringe is $31-224 depending on dose (brand only)

Parenteral (Direct Oral Anticoagulant) Factor Xa Inhibitor:

Fondaparinux (Arixtra)- weight based dosing (under 50kg: 5mg subcutaneously once per day; 50-100kg: 7.5mg SQ once per day; over 100kg: 10mg SQ once per day). Overlap with a Vitamin K antagonist. Fondaparinux should be continued for at least 5 days *and* until INR of greater than 2.0 for two consecutive measurements is achieved. Use is contraindicated if ClCr <30.
Cost for fondaparinux is $157/syringe for Arixtra and $60/syringe for generic.

Oral Direct Oral Anticoagulants (DOAC): It consists of oral Factor Xa inhibitors including apixaban, rivaroxaban, and endoxaban and Direct Thrombin Inhibitor dabigatran. Please refer to Table 7 and 8 for details.

Table 7: Direct Oral anticoagulants (DOAC's)

	Apixaban (Eliquis)	**Rivaroxaban (Xarelto)**	**Edoxaban (Savaysa)**	**Dabigatran (Pradaxa)**
Usual Dose	10 mg BID for 7 days, then 5 mg BID ***No parenteral therapy needed***	15 mg BID for 21 days, then 20 mg ***daily with food to improve absorption.*** ***No parenteral therapy is needed***.	Following 5+ days treatment with a parenteral anticoagulant: 60 mg once daily; 30 mg one daily if body weight < 60 kg.	Following 5+ days treatment with a parenteral anticoagulant: 150 mg BID (Start 0-2 hrs. before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip).

Conversion	***From warfarin:*** discontinue warfarin and start apixaban once INR < 2 ***To warfarin:*** discontinue apixaban and start warfarin and a parenteral agent when the next apixaban dose is due (note: apixaban may affect INR of patients also on warfarin). ***To/from apixaban and non-warfarin agents***: discontinue original medication and start new medication when the next dose of the original medication is due.	***From warfarin:*** discontinue warfarin and start rivaroxaban when INR <3 ***To warfarin:*** stop rivaroxaban and start warfarin and a parenteral anticoagulant at the time of the next rivaroxaban dose. ***From anticoagulants other than warfarin:*** stop anticoagulant and start rivaroxaban at 2 hrs. or less before the next regularly scheduled evening dose of the original anticoagulant. ***To anticoagulants other than warfarin:*** stop rivaroxaban and start new anticoagulant at the time of the next dose.	***From warfarin:*** discontinue warfarin and initiate edoxaban when INR is ≤ 2.5 ***To warfarin:*** If taking 60 mg dose, reduce dose to 30 mg once daily and begin warfarin. If taking 30 mg dose, reduce dose to15 mg daily and begin warfarin. Stop edoxaban when INR is ≥ 2; measure INR weekly or more often just before the daily dose of edoxaban is taken. ***To/from edoxaban*** and non-warfarin agents: discontinue original agent and initiate new agent at the time of the next dose of the original medication.	***From warfarin:*** discontinue warfarin and start dabigatran when INR < 2.0 ***To warfarin:*** Initiate warfarin, then stop dabigatran (per renal function; see below)—first INR 2 or more days after stopping dabigatran as it elevates INR. -eGFR > 50 mL/min—initiate warfarin 3 days before discontinuing dabigatran -eGFR 30-50 mL/min initiate warfarin 2 days before discontinuing dabigatran -eGFR 15-30 mL/min initiate warfarin 1 day before discontinuing dabigatran ***To/from anticoagulants other than warfarin:*** discontinue original agent and initiate new agent at the time of the next dose of the original medication
Renal Dosing	No adjustment recommended	Avoid if CrCl < 30 ml/min	30 mg daily for CrCl 15-50 ml/min Not recommended if CrCl < 15 ml/min	Avoid if CrCl < 30 ml/min
Clinical Benefit	Comparable to warfarin in effectiveness; less bleeding	Comparable to warfarin in effectiveness and bleeding risk	About as effective as warfarin with less bleeding	Comparable to warfarin in effectiveness or major bleeding
Therapeutic Considerations	Requires bid dosing. Severe liver impairment: not recommended. May be taken without regards to meals Tablets may be split or crushed.	Bioavailability of the 15 mg and 20mg tablets is increased by 39% when taken with food. Avoid in patients with moderate or severe liver	Not recommended in moderate or severe hepatic impairment. Administer without regard to food. No reversal agent available	Requires bid dosing. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years of age or older, poor renal function, or underweight. Do not break or chew—must be swallowed whole

	Reversal agent available – Andexanet alfa (Andexxa) – see below table for dosing ($6600/vial)	impairment or liver disease with bleeding risk. May be crushed and mixed with applesauce for immediate administration; still follow with food. Reversal agent available – Andexanet alfa (Andexxa) – see below table for dosing ($6600/vial)		without regard to meals. Reversal agent available—Idarucizumab (Praxbind)—2 iv doses administered no more than 15 minutes apart and lasting approximately 24 hrs. ($4200 total)
Select Drug-Drug Interaction	Reduce dose by 50% with strong inhibitors of BOTH CY3A4 and p-glycoprotein (e.g., itraconazole, ketoconazole, ritonavir, etc.). Avoid concomitant use in patients already taking 2.5 mg bid Avoid strong inducers of BOTH CYP3A4 and p-glycoprotein (e.g., carbamazepine, phenytoin, Phenobarbital, St. John's wort, rifampin). Caution with antiplatelets and anticoagulants	Avoid use with drugs that are BOTH p-glycoprotein and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, Posaconazole, ritonavir). Caution with clarithromycin and fluconazole. Avoid drugs that are strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) that may decrease efficacy. Antiplatelets increase bleeding risk; co-administer with caution.	Caution with antiplatelets Avoid rifampin (p-glycoprotein inducer) Reduce dose to 30 mg once daily in patients taking azithromycin, clarithromycin, dronedarone, erythromycin, itraconazole (oral), ketoconazole (oral), quinidine, or verapamil (p-glycoprotein inhibitors).	p-glycoprotein inhibitors may increase dabigatran levels; amiodarone, clarithromycin, dronedarone, quinidine, ketoconazole and other strong p-glycoprotein inhibitors should be avoided if CrCl< 50 mL/min. p-glycoprotein inducers may decrease efficacy (e.g., rifampin, carbamazepine, St. John's wort). Caution with antiplatelets. Avoid ticagrelor. Use with aspirin 100 mg or less can be considered. Co-administration with aspirin or clopidogrel about doubles bleeding risk. Drugs that increase gastric pH could reduce efficacy. Take at least 2 hrs. before antacids.
Cost of 30-day supply	2.5 mg bid or 5 mg bid: $674 (Brand only)	15mg BID x 21 days $911. 20 mg $651 (Brand only)	60 mg, 30 mg, or 15mg once daily: $467	150 mg bid: -$536

Table 8: Reversal agents

Medication Name	**Medications Reversed**	**Typical Dosing**	**Price**

Andexanet Alfa (Andexxa®)	Apixaban Rivaroxaban Edoxaban (off-label)	**Low dose**: 400mg IV bolus at a rate of 30mg/min followed by IV infusion of 4mg/min for up to 120min within 2 mins of bolus. **High dose**: 800mg IV bolus at a rate of 30mg/min followed by IV infusion of 8mg/min for up to 120min within 2 mins of bolus. For **Apixaban**: If last dose >5mg or unknown and timing of last dose <8 hours or unknown, use high dose. If last dose 5mg or less and timing of last dose <8 hours or unknown, use low dose. If the last dose is at least 8 hours ago, use low dose. For **Rivaroxaban**: If last dose >10mg or unknown and timing of last dose <8 hours or unknown, use high dose. If last dose 10mg or less and timing of last dose <8 hours or unknown use low dose. If last dose at least 8 hours ago, use low dose. For **Edoxaban**: use high dose	$3000/200mg dose (brand only)
Idarucizumab (Praxbind®)	Dabigatran	Two 2.5g doses administered up to 15 minutes apart. May consider one more dose if bleeding does not stop.	$57/2.5g dose (brand only)
Prothrombin Complex Concentrate (Kcentra®)	Warfarin	**Weight-based dosing:** For INR 2 - <4: 25 units/kg IV; up to 2500 units For INR 4-6: 35 units/kg IV; up to 3500 units For INR >6: 50 units/kg IV; up to 5000 units **Fixed dosing:** 1000-2000 units once or 1500-2000 units for intracranial hemorrhage	$4/vial of 500 or 1000 units
Vitamin K/Phytonadione (Mephyton®)	Warfarin	2.5-10 mg PO or IV For PO: recheck INR in 12-48 hours to determine if a repeat dose is needed. For IV: recheck INR in 6-12 hours to determine if a repeat dose is needed	$1 for capsules $52/10 mg vial

Inferior Vena Cava Filters:

As per the updated CHEST guidelines 2021; an IVC filter is recommended when anticoagulation cannot be used. However, it is not recommended in addition to the anticoagulation (strong recommendation, moderate-certainty evidence). Removable IVC filters should be preferred. In general, IVC filters will decrease but not

eliminate the risk of pulmonary embolism but increase the risk for recurrent DVT. Patients should be aware of the need for filter removal, and clinicians should place an appropriate reminder in the patient's medical record.

Duration of treatment

Table 9.

No treatment	Minimum 3 months (anticoagulation following initial phase)	Indefinite (no stopping date)
Distal LE DVT, asymptomatic and if does not extend when followed with serial imaging at 1 and 2 weeks. (Treat if extends.)	Distal LE DVT, symptomatic (regardless of cause), or extending or at high risk for extension (positive D-Dimer, prior VTE, > 5 cm in length or > 7 mm in diameter, involving multiple veins, close to proximal veins, active cancer, no reversible provoking factor, inpatient, prolonged immobility status)	Unprovoked proximal LE DVT (if low or moderate bleeding risk)
	Surgery or transient risk-factor associated Proximal LE DVT (regardless of symptoms)	
	Unprovoked proximal LE DVT if high bleeding risk	Cancer-associated DVT or PE
	Recurrent, unprovoked LE DVT or PE (high bleeding risk)	

The risks and benefits of continued anticoagulation in patients receiving extended duration therapy should be reassessed annually or more frequently as the patient's condition warrants.

Estimating the risk of recurrent VTE:

A meta-analysis done by American College of Chest Physicians estimated the risk of recurrent DVT as follows (Kearon et al., 2012):

- Risk of recurrent VTE after first unprovoked event: 10% during the first year, 5% per year thereafter.
- Risk of recurrent VTE after the second unprovoked event: 15% during the first year, 7.5% per year thereafter.
- Risk of recurrent VTE after an initial episode by a non-surgical provoked event: 5% for the first year; 2.5 percent/year thereafter.
- Risk of recurrent VTE after an initial VTE episode by a surgical event: 1% for the first year; 0.5%/year thereafter.

The Risk can also be classified as follows *UpToDate*, n.d.):

- Low – Less than 3 percent per year (<14 percent over 5 years)
- Intermediate – Between 3 and 5 percent per year (between 14 and 30 percent over 5 years)
- High – Greater than 5 percent per year (>30 percent over 5 years)

Estimating the patient's risk of bleeding:

Assessing the patient's bleeding risk can be done using several models. Among them, the American Collage of Chest physician (ACCP) model (Kearon et al., 2012), and VTE-BLEED (Klok et al., 2016) is widely used and most externally validated (*UpToDate*, n.d.)

Table 10: ACCP Model

Risk Factors for Bleeding (one point each)		
Age > 65		
Age >75		
Previous bleeding		
Cancer		
Metastatic Cancer		
Renal Failure		
Liver Failure		
Thrombocytopenia		
Previous Stroke		
Diabetes		
Anemia		
Antiplatelet therapy		
Poor anticoagulation control		
Comorbidity and reduced functional capacity		
Recent surgery		
Falls		
Alcohol abuse		
NSAID use		
Risk of bleeding after the first 3 months of anticoagulation		
Low risk	0 risk factors	0.8%/yr.
Moderate risk	1 risk factor	1.6%/yr.
High risk	2 or more risk factors	≥6.5%/yr.

CHEST 2016; 149 (2): 315-352.

VTE-BLEED

This score is used for extended anticoagulation. The data used to generate this score is from randomized controlled trials involving anticoagulation treatment for VTE including dabigatran for VTE treatment when compared to warfarin (Klok et al., 2016b). It involves six variables (table 10). A score of less than 2 indicates low bleeding risk of 2.8% and a score of 2 or more is suggestive of high bleeding risk of 12.6% *(UpToDate*, n.d.)

Table 11: VTE-BLEED

Risk Factor	Points
Active cancer	2
Male with uncontrolled HTN	1
Anemia	1.5
History of bleeding	1.5
CrCl 30-60 ml/min	1.5
Age ≥ 60 yrs.	1.5

HAS-BLED score:

It predicts an absolute bleeding rate and was first studied in patients with atrial fibrillation, but later it was validated for VTE treatment in the first six months of treatment. It has not been validated for treatment duration

beyond 6 months (Brown et al., 2018). (Table 12)

Table 12: HAS-BLED score from UpToDate

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years¶
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarin. Refer to UpToDate topics on anticoagulation in patients with atrial fibrillation and on specific anticoagulants for further information and other bleeding risk scores and their performance relative to clinical judgment.

INR: international normalized ratio; NSAIDs: nonsteroidal antiinflammatory drugs.

* Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal renal function is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than 2 times the upper limit of normal, plus 1 or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than 3 times the upper limit of normal). Bleeding predisposition includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion. Labile INRs for a patient on warfarin include unstable INRs, excessively high INRs, or <60% time in therapeutic range.

¶ Based on initial validation cohort from Pisters R. A novel-user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093. Actual rates of bleeding in contemporary cohorts may vary from these estimates.

Original figure modified for this publication. Lip GY. Implications of the CHA2DS2-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. Am J Med 2011; 124:111. Table used with the permission of Elsevier Inc. All rights reserved.

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A shared decision-making discussion with the patient, reviewing the risk of recurrent VTE, the risk of major bleeding and considering the patient's values and preferences is appropriate.

Testing for hypercoagulable states:

Which patients need testing for hypercoagulable states (inherited or acquired) remains a subject of some controversy, since initial management and outcomes may not be affected by the results. Testing should be considered in patients with an unprovoked clot who are young (less than age 45-50), have a FH of a first degree

relative with a clot at an early age or have a clot at an unusual site. Testing should ideally be performed after the course of anticoagulation is completed (as results will not be accurate when there is an acute clot). Hematology consultation should be strongly considered so that the most cost-effective testing strategy can be chosen.

Superficial vein thrombosis

Superficial vein thrombosis (SVT) is a common condition associated with varicose veins in 90% of cases. Other risk factors include pregnancy, estrogen therapy, prior DVT or SVT, malignancy, and hypercoagulable states. Typical presentation includes pain, tenderness, induration, and erythema along a superficial vein. DVT may co-exist (either from contiguous spread or synchronous thrombosis) and is more common in men, those over age 60, absence of varicose veins, and when bilateral SVT is present. Duplex ultrasound should be performed to confirm the diagnosis of SVT and exclude concomitant DVT. Treatment depends on the specific findings and the concomitant risk for DVT (Table-13) *(UpToDate*. (n.d.).

Table 13

Finding	**Treatment**
Low Risk for VTE: The affected vein segment is remote from saphenofemoral or saphenopopliteal junction, e.g., below knee great saphenous vein SVT	Supportive: elevation of the extremity, warm or cool compresses, NSAIDS for 2 weeks and compression therapy.
Intermediate Risk for VTE: SVT in proximity to the deep venous system 3- 5 cm from saphenofemoral/saphenopopliteal junction, or the affected vein segment is ≥5 cm.	Supportive therapy plus anticoagulation for 45 days instead of NSAIDS • Fondaparinux 2.5 mg daily (SC)or • Enoxaparin 40 mg daily (SC) • Rivaroxaban 10 mg daily • Vitamin K antagonist (warfarin)
High Risk for VTE: SVT with medical risk factors for DVT, thrombosis within 3 cm of saphenofemoral or saphenopopliteal junction, or recurrent SVT	Therapeutic anticoagulation with dose and duration like that selected for DVT
SVT with concomitant DVT or PE	Manage as DVT or PE
SVT after radiofrequency or laser vein ablation	Supportive care

Patients should be re-examined in 7-10 days to confirm improvement/resolution or identify progression.

Outpatient Treatment

The safety and efficacy of outpatient treatment of carefully screened patients with deep vein thrombosis (DVT) is supported by ACCP (American College of Chest Physicians) guidelines, which recommend initial treatment of DVT at home over treatment in the hospital in appropriately screened patients. Patients should be screened for pain control, adequacy of home circumstances including support from family/friends, telephone service, and ability to return to hospital.

- Obtain Baseline CBC (Complete Blood Count), Platelet Count, PT/INR, and a PTT
- Start Warfarin 5 mg daily or 2.5 mg daily if frail, elderly, or liver impairment; subsequent doses based on INR
- Discontinue parenteral agent once INR is within therapeutic range (2-3) for 2 consecutive days
- Warfarin therapy should be continued for at least 3-6 months
- Monitor INR regularly while patient remains on warfarin
- For DOAC dosing refer to table 6 above.
- Home health services can be used both for medical management and INR draws.

Perioperative anticoagulant bridging

Management of anticoagulation in the perioperative period requires careful balancing of the risks of recurrent clotting and perioperative bleeding. Please refer to the MedStar Guideline: **Perioperative Management of Antithrombotic Agents for** further guidance. MedStar-Perioperative Management of Antithrombotic Agents

Patient Education

Patient Education and follow-up:

- Warfarin education: signs and symptoms of bleeding and drug and food precautions
- DOAC: Teach patient or caregiver proper oral dosing, signs and symptoms of bleeding, risk of bleeding associated with these agents.
- Symptoms of DVT: increased redness, warmth, or swelling of area, pain, decreased sensitivity of extremity.
- Care instruction for DVT: elevate leg, avoid sitting or standing for extended periods.
- Symptoms of PE: shortness of breath, chest pain, hypotension, lightheadedness, rapid heartbeat.

Referrals for outpatient anti-coagulation:

- Patients can be referred to hospital based MedStar Anticoagulation Clinics where available.
- At MedStar Union Memorial or MedStar Good Samaritan Hospital med-management clinics patients can be referred for both DOAC management and warfarin dosing, bridging and follow up.
- Type “Anticoagulation” in the order section and select from one of the two referrals specified as “DOAC” or “warfarin". Once completed, it will be routed to the pool; patient will be contacted by one of the pharmacists.

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