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 is a common condition, affecting one in 1,000 persons per year[1]. Physical exam findings are neither sensitive nor specific for diagnosis, which is best established by appropriate use of an estimation of pre-test probability (by gestalt or using a scoring system) along with diagnostic testing. The most commonly used tool to estimate the pre-test probability of DVT is the Wells scoring system.

Well's Criteria

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 (nonvaricose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
SCORE	
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less

In a practice environment where moderate or high sensitivity D-Dimer testing is readily available, it can be used in the low and moderate pre-test probability patients to rule out DVT without the need for ultrasound imaging. Note that in high pre-test probability patients, ultrasound imaging (either proximal or whole leg) is needed to evaluate for DVT. If D-Dimer testing is not available or practical, the diagnostic modality of choice is compression ultrasound of the proximal leg or whole leg. Note that proximal leg US will not image calf vein clots, and in the moderate pre-test probability patient may need to be repeated in 1 week if initially negative to exclude extension of a calf vein DVT proximally.

Initial Approval Date and Reviews: August 2015, July 2017

Most Recent Revision and Approval Date: July 2017

Next Scheduled Review Date: July 2019

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

General Principles of Therapy: **Key Points**

1. For patients with proximal DVT (or distal DVT being treated with anticoagulants) and no cancer, anticoagulant therapy with dabigatran, rivaroxaban, apixaban or edoxaban is preferred over treatment with warfarin.
2. If these agents are not used, warfarin therapy is preferred over LMWH with target INR 2-3.
3. For patients with cancer associated thrombosis, LMWH is the preferred long term anticoagulant.
4. For initial treatment of DVT, dabigatran and edoxaaban require 5-10 days of parenteral anticoagulation (LMWH, fondaparinux); warfarin requires overlap of at least 5 days with parenteral anticoagulants, (LMWH, fondaparinus); rivaroxaban and apixaban can be used alone.
5. For patients who receive extended therapy (more than three months), there is no need to change anticoagulant.
6. For patients who stop extended anticoagulant therapy, aspirin can be prescribed to prevent recurrence if there is no contraindication.
7. LMWHs are not fully reversible with protamine because of the differing chain lengths of the LMWH molecule.
8. Oral factor Xa inhibitors currently do not have any available reversal agents. Dabigatran does have a reversal agent (idarucizumab).
9. Early ambulation is recommended over initial bed rest.
10. There is no evidence that compression stockings prevent post thrombotic syndrome and are no longer recommended for this purpose.

TREATMENT OPTIONS:

Treatment of acute DVT is generally divided into three phases: initial (up to 10 days), long term (10 days to 3 months) and extended (3 months onward without a defined stopping time).

Options for therapy are the following:

1. Rivaroxaban or apixaban as monotherapy
2. LMWH or fondaparinux for 5-10 days followed by dabigatran or edoxaban
3. LMWH or fondaparinux with warfarin overlap for at least five days
4. LMWH or fondaparinux continued

Factors important in selecting a specific regimen include the following:

Factor	Preferred anticoagulant	Reasoning
Cancer	LMWH	More so if just diagnosed, extensive VTE, metastatic cancer, very symptomatic, vomiting, on chemotherapy
Parenteral therapy to be avoided	Rivaroxaban, apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy
Once daily oral therapy preferred	Rivaroxaban, edoxaban, VKA	
Liver disease and coagulopathy	LMWH	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	VKA	NOACs and LMWH contraindicated with severe renal impairment. Each NOAC has unique dosing recommendations per level of renal impairment
CAD	VKA, rivaroxaban, apixaban, edoxaban	More CAD events with dabigatran than with VKA. Avoid antiplatelets if possible due to increased bleeding
Dyspepsia or prior GI Bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may have increased GI bleeding than VKA
Poor compliance	VKA	INR monitoring can help detect problems with compliance. Some patients may be more compliant with NOACs since regimen is less complex
Thrombolytics used	UFH infusion	Greater experience with use
Reversal agent needed	VKA, UFH, Dabigatran	
Pregnancy or pregnancy risk	LMWH	Other agents may cross the placenta
Cost, coverage licensing	Individualize	

SPECIFIC AGENTS

Low Molecular Weight Heparin Dosing Guidelines

Enoxaparin (Lovenox®) 1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously every 24 hrs. 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 to 3.0). The dosing interval should be modified for renal impairment (1 mg/kg daily for ClCr <30) and monitoring anti- Xa level is recommended.

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 Use of LMWH during pregnancy (FDA Category B in all trimesters) is also an instance where monitoring the therapeutic response is recommended.

Monitoring LMWH is NOT done by measuring PTT. You must measure 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 which is at a rate similar to that of UFH.

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 UFH should not be treated with LMWH.

Dalteparin (Fragmin®) usual dose is 200 units IU/kg subcutaneously once per day. 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.

Tinzaparin (Innohep®) usual dose is 175 anti-Xa IU/kg of body weight, administered SC once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin (INR at least 2.0 for two consecutive days). There are no specific guidelines for dose adjustment for renal impairment. Monitoring anti-Xa level is recommended. Alternatively use enoxaparin.

Parenteral 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 5days **and** until INR of 2.0 to 3.0 is achieved.

Oral Factor Xa and Direct Thrombin Inhibitors (NOACs)

	Apixaban	**Rivaroxaban**	**Edoxaban**	**Dabigatran**
Usual Dose	10 mg BID for 7 days, then 5 mg bid **No parenteral therapy needed**	15 mg Bid for three weeks, then 20 mg daily with food to improve absorption. **No parenteral therapy is needed**.	Following 5-10 days treatment with a parenteral anticoagulant: 60 mg once daily; 30 mg one daily if body weight < 60 kg.	Following 5-10 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).

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
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 would have been 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 rivoraxaban 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. It 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	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
Renal Dosing	2.5 mg bid for patients with two or more of the following: age ≥80, wt ≤ 60 kg, Cr ≥ 1.5 mg/dL ** No dosing information for CrCl < 30 ml/min or on dialysis	Avoid if CrCl < 30 ml/min	30 mg daily for CrCl 15-50 ml/min Not recommended if Crcl < 15 ml/min	No dosing information for CrCl < 30 mL/min or dialysis

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
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 No reversal agent	Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk. May be crushed and mixed with applesauce for immediate administration; still follow with food. No reversal agent	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 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)

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Select Drug-Drug Interactions	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: $466	15mg BID x 21 days $652 20mg $466	60 mg or 30 mg once daily: $629 15 mg once daily: $377	150 mg bid: $445

**This data is extrapolated from studies in nonvalvular atrial fibrillation. No dosage adjustments have been studied for DVT treatments and no patients with Cr > 2.5, EGFR < 25 were included in trials.

Inferior Vena Cava Filters

IVC filters are indicated in patients for whom anticoagulation is contraindicated. Removable filters should be used, and anticoagulation should be resumed if and when the increased risk of bleeding resolves. In general, IVC filters will decrease but not eliminate the risk of pulmonary embolism but increase the risk for recurrent DVT.

DURATION OF TREATMENT:

No treatment	**3 months (long term)**	**Extended (no stopping date)**
Distal LE DVT, asymptomatic and IF doesn't 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, involving multiple veins, close to proximal veins, active cancer, no reversible provoking factor)	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.

Measurement of D-Dimer or ultrasound exam to look for residual clot one month after anticoagulation has been stopped may be helpful in identifying patients at high risk for recurrence and for whom anticoagulation should be continued. Data is not yet definitive.

Assessing the patient's bleeding risk can be done using the following tables

Risk Factors[b]
Age >65 y[184-193]
Age >75 y[184-188,190,192,194-202]
Previous bleeding[185,191-193,198,201-204]
Cancer[187,191,195,198,205]
Metastatic cancer[181,204]
Renal failure[185,191-193,196,199,201,206]
Liver failure[186,189,195,196]
Thrombocytopenia[195,204]
Previous stroke[185,192,195,207]
Diabetes[185,186,196,200,202]
Anaemia[185,189,195,198,202]
Antiplatelet therapy[186,195,196,202,208]
Poor anticoagulant control[189,196,203]
Comorbidity and reduced functional capacity[191,196,204]
Recent surgery[189,209,c]
Frequent falls[195]
Alcohol abuse[191,192,195,202]
Nonsteroidal anti-inflammatory drug[210]

Categorization of Risk of Bleeding[d]			
	Estimated Absolute Risk of Major Bleeding		
	Low Risk[e] (0 Risk Factors)	Moderate Risk[e] (1 Risk Factor)	High Risk[e] (≥2 Risk Factors)
Anticoagulation 0-3 mo[f]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[g]	3.2	12.8[h]
Anticoagulation after first 3 mo[f]			
Baseline risk (%/y)	0.3[i]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[j]	1.6[j]	≥6.5

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

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 a young age or have a clot at an unusual site. Testing should be ideally 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.

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.

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.

Patients who should usually be managed as inpatients or observation status

- Suspected or proven concomitant PE
- Significant cardiovascular or pulmonary comorbidity
- Complicated or recurrent DVT
- Contraindications to anticoagulation (e.g. active PUD, active or recent bleeding, high risk for potential major bleed, intracranial neoplasm, recent trauma, stroke, epidural, neurosurgical procedure)
- Severe hypertension (SBP>220 or DBP>120mmHg)
- History of heparin sensitivity or heparin induced thrombocytopenia
- Familial bleeding disorder
- Known coagulopathy, thrombotic or bleeding disorder, platelets <100,000
- Pregnancy or nursing
- Age <18 or >80
- Weight <60kg or >150kg (monitor Xa levels outside these parameters)
- Renal failure (creatinine >2mg/dL)
- Comorbid conditions or other factors that warrant in-hospital care
- Unavailable or unable to arrange close follow-up care
- Unable to follow instructions
- Homeless
- No contact telephone
- Geographic (ie too far from hospitals)

LMWH (Low Molecular Wt. Heparin) + warfarin (Coumadin) Pathway

Patient Education

- Teach patient or caregiver injection techniques
- Warfarin education: signs and symptoms of bleeding and drug and food precautions
- 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 long periods
- Instruct patient in purpose and use for TED stockings
- Symptoms of PE: shortness of breath, chest pain, hypotension, lightheadedness, rapid heartbeat. Home Healthcare Referral
- Home nurse to inject if patient or caregiver is unable
- PT/INR daily and CBC and platelet count every 3 days

Treatment

- Obtain Baseline CBC, 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

*NOAC Pathway

Patient Education

- Teach patient or caregiver proper oral dosing, signs and symptoms of bleeding, risk of bleeding associated with irreversible 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 long periods Instruct patient in purpose and use for TED stockings.
- Symptoms of PE: shortness of breath, chest pain, hypotension, lightheadedness, rapid heartbeat.

References

This guideline is based on: *CHEST 2012 Supplement: Antithrombotic Therapy for VTE Disease* which has been endorsed by the MSH Ambulatory Best Practices Committee and the update published in 2016. http://journal.publications.chestnet.org/pdfaccess.ashx?ResourceID=4725497&PDFSource=13

1. Bates, Shannon et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012(Feb): 141 (2) (Suppl):e351S-e418S.
2. Snow, V, Qaseem, A et, al. Management of Venous Thromboembolism A Clinical Practice Guideline from the *American College of Physicians* and the *American Academy of Family Physicians*. *Ann Intern Med. 2007; 146: 204-210.

3. Kearon C, Akl E, Conerota A, et.al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012 (Feb); 141 (2 Suppl): e419S-e494S
4. Holbrook A, Schulman S, Witt D, et. al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 (Feb): 141 (2 Suppl): e152S-e184S
5. Wigle P, Hein B, Bloomfield H, et. al. Updated Guidelines on Outpatient Anticoagulation. *Am Fam Physician.* 2013:87 (8); 556-566.
6. Lexi_Comp Online, Hudson, Ohio: Lexi-Comp, Inc: June 12, 2013.
7. Manufacturer's Dosing Guidelines
8. *Up to Date*, Overview of the treatment of lower extremity deep vein thrombosis (DVT), last updated Mar 4, 2015
9. National Guideline Clearinghouse; Michigan Quality Improvement Consortium; Aug 2013.
10. Antithrombotic Therapy for VTE Disease (CHEST Guideline and Expert Panel Report). Chest 2016; 149 (2): 315-352.
11. Baglin, Trevor et al. Clinical Guidelines for Testing for Heritable Thrombophilia. British Journal of Hematology 2010; 149: 209-220.

Outpatient Treatment of Deep Vein Thrombosis with Low Molecular Weight Heparin (LMWH) Clinical Practice Guideline was initiated in 2004 by the MSH Ambulatory Best Practice Committee.

Clinical Guidelines are reviewed every two years by a committee of experts in the field. Updates to guidelines occur more frequently as needed when new scientific evidence or national standards are published.