

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 year¹. 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 (non-varicose)	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. 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.

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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. Some literature suggests a lower risk of bleeding with apixaban and that risk of GI bleeding can be reduced by concomitant PPI use.
- 2. If these agents are not used, warfarin therapy is preferred over low molecular weight heparin (LMWH) with target INR 2-3.
- 3. For patients with cancer associated thrombosis, LMWH is the preferred long-term anticoagulant. Emerging data suggests that rivaroxaban and edoxaban may be as effective as LMWH but at the expense of increased bleeding. In patients who are unable or unwilling to use LMWH, hematology consultation should be sought.
- 4. 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.
- 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. 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.
- 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.

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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	Vitamin K antagonist (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	Unfractionated heparin (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	

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SPECIFIC AGENTS

Low Molecular Weight Heparin Dosing Guidelines

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 CICr <30) and monitoring anti- Xa level is recommended.

Alternate sites with every administration. Do not mix with other injections. Do not rub 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 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 unfractionated heparin should not be treated with LMWH.

Cost of enoxaparin ranges from \$7-40/syringe for Lovenox and \$4-27 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 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 CICr <30.

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Oral Factor Xa and Direct Thrombin Inhibitors (DOACs)

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran (Pradaxa)
	(Eliquis)	(Xarelto)	(Savaysa)	
Usual Dose	10 mg BID for 7 days, then 5 mg BID	15 mg BID for 21 days, then 20 mg daily with food to improve absorption. No parenteral	Following 5+ days treatment with a parenteral anticoagulant: 60 mg once	Following 5+ days treatment with a parenteral anticoagulant: 150 mg BID (Start 0-2 hrs before the next dose of parenteral anticoagulant
	therapy needed	therapy is needed.	daily; 30 mg one daily if body weight < 60 kg.	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	From warfarin: discontinue warfarin and start rivaroxaban when INR <3 To warfarin: stop rivaroxaban and	From warfarin: discontinue warfarin and initiate edoxaban when INR is ≤ 2.5 To warfarin: if	From warfarin: discontinue warfarin and start dabigatran when INR < 2.0 To warfarin: Initiate warfarin, then stop dabigatran (per renal
	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).	start warfarin and a parenteral anticoagulant at the time of the next rivaroxaban dose.	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	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
	To/from apixaban and non-warfarin agents: discontinue	From anticoagulants other than warfarin: stop anticoagulant and	the daily dose of edoxaban is taken. To/from	dabigatran To/from anticoagulants other than warfarin: discontinue original agent

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	original	start rivoraxaban	edoxaban and	and initiate new agent at
	medication and	at 2 hrs or less	non-warfarin	the time of the next dose
	start new	before the next	agents:	of the original medication
	medication	regularly	discontinue	or the original medication
	when the next	scheduled evening	original agent	
	dose of the	dose of the	and initiate new	
	original	original	agent at the	
	medication	anticoagulant.	time of the next	
	would have been	anticoaguiant.	dose of the	
	due.	To anticoagulants	original	
	due.	other than	medication	
		warfarin: stop	medication	
		rivaroxaban and		
		start new		
		anticoagulant at		
		the time of the		
B I B	Ni d' - i i	next dose.	20 4-11 (A -::1:1 C -: C1 + 20 -: 1/:::
Renal Dosing	No adjustment	Avoid if CrCl < 30	30 mg daily for	Avoid if CrCl < 30 ml/min
	recommended	ml/min	CrCl 15-50	
			ml/min	
			Not	
			recommended if	
			CrCl < 15 ml/min	
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Clinical Benefit	Comparable to	Comparable to	About as	Comparable to warfarin
Clinical Benefit	Comparable to warfarin in	Comparable to warfarin in	About as effective as	Comparable to warfarin in effectiveness or major
Clinical Benefit	Comparable to warfarin in effectiveness;	Comparable to warfarin in effectiveness and	About as effective as warfarin with	Comparable to warfarin
	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	Comparable to warfarin in effectiveness; less bleeding Requires bid	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients	About as effective as warfarin with less bleeding Not	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing.
	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or	About as effective as warfarin with less bleeding Not recommended in	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver	About as effective as warfarin with less bleeding Not recommended in moderate or	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal symptoms in over 10% of
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment.	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years of age or older,
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk.	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years of age or older, poor renal function, or
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk. May be crushed	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard	Comparable to warfarin in effectiveness or major bleeding Requires bid dosing. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years of age or older, poor renal function, or underweight.
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk. May be crushed and mixed with	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food	Comparable to warfarin in effectiveness or major bleeding 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—
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk. May be crushed and mixed with applesauce for	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals	Comparable to warfarin in effectiveness and bleeding risk Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk. May be crushed and mixed with applesauce for immediate	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed	Comparable to warfarin in effectiveness and bleeding risk 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;	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent	Comparable to warfarin in effectiveness and bleeding risk 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	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent available –	Comparable to warfarin in effectiveness and bleeding risk 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;	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent available – Andexanet alfa	Comparable to warfarin in effectiveness and bleeding risk 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.	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent available — Andexanet alfa (Andexxa) — see	Comparable to warfarin in effectiveness and bleeding risk 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. Reversal agent	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent available – Andexanet alfa (Andexxa) – see below table for	Comparable to warfarin in effectiveness and bleeding risk 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. Reversal agent available –	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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
Therapeutic	Comparable to warfarin in effectiveness; less bleeding Requires bid dosing Severe liver impairment: not recommended May be taken without regards to meals Tablets may be split or crushed Reversal agent available — Andexanet alfa (Andexxa) — see	Comparable to warfarin in effectiveness and bleeding risk 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. Reversal agent	About as effective as warfarin with less bleeding Not recommended in moderate or severe hepatic impairment. Administer without regard to food No reversal	Comparable to warfarin in effectiveness or major bleeding 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

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		below table for		
		dosing		
		(\$6600/vial)		
Select Drug-	Reduce dose by	Avoid use with	Caution with	p-glycoprotein inhibitors
Drug	50% with strong	drugs that are	antiplatelets	may increase dabigatran
Interactions	inhibitors of	ВОТН р-		levels; amiodarone,
	BOTH CY3A4 and	glycoprotein and	Avoid rifampin	clarithromycin,
	p-glycoprotein	strong CYP3A4	(p-glycoprotein	dronedarone, quinidine,
	(e.g.	inhibitors (e.g.,	inducer)	ketoconazole and other
	itraconazole,	ketoconazole,		strong p-glycoprotein
	ketoconazole,	itraconazole,	Reduce dose to	inhibitors should be
	ritonavir, etc).	posaconazole,	30 mg once daily	avoided if CrCl< 50
		ritonavir).	in patients	mL/min.
	Avoid		taking	
	concomitant use	Caution with	azithromycin,	p-glycoprotein inducers
	in patients	clarithromycin and	clarithromycin,	may decrease efficacy
	already taking	fluconazole.	dronedarone,	(e.g. rifampin,
	2.5 mg bid		erythromycin,	carbamazepine, St. John's
		Avoid drugs that	itraconazole	wort).
	Avoid strong	are strong CYP3A4	(oral),	Caution with
	inducers of	inducers (e.g.,	ketoconazole	antiplatelets.
	BOTH CYP3A4	rifampin,	(oral), quinidine,	A
	and p-	carbamazepine,	or verapamil (p-	Avoid ticagrelor.
	glycoprotein	phenytoin, St.	glycoprotein	11
	(e.g.	John's wort) that	inhibitors).	Use with aspirin 100 mg
	carbamazepine,	may decrease		or less can be considered.
	phenytoin,	efficacy.		C
	Phenobarbital,	Antinlatalata		Co-administration with
	St. John's wort,	Antiplatelets		aspirin or clopidogrel
	rifampin).	increase bleeding		about doubles bleeding
	Coution with	risk; co-administer with caution.		risk.
	Caution with antiplatelets and	with Caution.		Drugs that increase
	anticoagulants			gastric pH could reduce
	anticoaguidills			efficacy. Take at least 2
				hrs before antacids.
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Cost of 30 day	2.5 mg bid or 5	15mg BID x 21 days	60 mg, 30 mg, or	150 mg bid: \$572
supply	mg bid: \$599	\$827	15mg once daily:	
	(brand only)	20mg \$591	\$467	
	(112122,)	(brand only)		
	1	ios in nonvalvular atrial	<u> </u>	

^{**}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.

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Andexanet alfa (Andexxa) dosing:

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 last dose 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.

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. 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:

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 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.

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Estimating the risk of recurrent VTE:

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.

A meta-analysis done for the American College of Chest Physicians in 2012 estimated the following risk:

- Risk after first unprovoked VTE event: 10% during the first year, 5% per yr thereafter
- Risk after the second unprovoked VTE event: 15% during the first yr, 7.5% per yr thereafter

Several clinical prediction rules also exist, none in widespread use:

• DASH score: one point each for elevated D Dimer, Age less than 50, Male sex, and clot not occurring on hormone therapy in women.

Score	Annualized Recurrence Rate
≤1	3.1%
2	6.4%
≥3	12.3%

Estimating the patient's risk of bleeding:

Assessing the patient's bleeding risk can be done using several models ACCP Model¹⁰

Risk Factors for B	leeding (one point each)		
Age > 65			
Age >75			
Previous bleeding	3		
Cancer			
Metastatic Cance	r		
Renal Failure			
Liver Failure			
Thrombocytopen	ia		
Previous Stroke			
Diabetes			
Anemia			
Antiplatelet there	ару		
Poor anticoagula	tion control		
Comorbidity and	reduced functional capacity		
Recent surgery			
Falls			
Alcohol abuse			
NSAID use			
Risk of bleeding a	ifter the first 3 months of an	ticoagulation	
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	

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VTE-BLEED¹⁶

Calculates the bleeding risk for the next 6 months following the initial 30 days of stable anticoagulation

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

Score less than 2 = low risk (bleeding risk 2.8%) Score of 2 or more = high risk (bleeding risk 12.6%)

The Bleeding risk Index for Warfarin Therapy is accessible through the calculator section of MedConnect.

Bleeding Risk Index for Warfari	in Therapy
	☐ Patient 65 years old or older (1 point)
	☐ Patient has history of CVA (1 point)
	☐ Patient has history of GI bleeding (1 point)
	☐ Is there either a recent MI, anemia with HCT <30%, Creatinine >1.5 mg/dL or Diabetes present (1 point)
Total Criteria Point Count: 0	
	Reset Form Copy to Clipboard
	Include literature references: Yes ○ No ●
Risk of Major Bleeding	
	0 points: 2% at 3 months, 3% at 12 months
	1 to 2 points: 5% at 3 months, 12% at 12 months
	3 to 4 points: 23% at 3 months, 48% at 12 months

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 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

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recurrent clotting and perioperative bleeding.

Please refer to the MedStar Guideline: **Perioperative Management of Antithrombotic Agents** for further guidance.

http://starport.medstar.net/msh/Pharmacy/ layouts/15/WopiFrame.aspx?sourcedoc=/msh/Pharmacy/Guide lines%20and%20Restrictions/PeriOperative%20Management%20of%20Antithrombotic%20Agents%20v3.pdf

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 the course of 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.

Finding	Treatment
Uncomplicated (affected vein segment < 5 cm, < 5 cm from saphenofemoral/saphenopopliteal junction, no medical risk factors)	Supportive: elevation of the extremity, warm or cool compresses, NSAIDS for 2 weeks and possibly compression therapy.
SVT with affected vein segment ≥ 5 cm long, 3- 5 cm from saphenofemoral/saphenopopliteal junction	Supportive therapy plus anticoagulation for 45 days instead of NSAIDS • Fondaparinux 2.5 mg daily (subcut)or • Enoxaparin 40 mg daily (subcut) • Rivaroxaban 10 mg daily
SVT with medical risk factors for DVT, thrombosis within 3 cm of saphenofemoral/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.

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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 telephone
- Geographic (ie too far from hospitals)
 - 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

<u>Treatment</u>

- 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

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*DOAC 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 largely 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

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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.

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