General Principles: There is compelling data in the medical literature to support the safe and effective use of low molecular weight heparin (LMWH) in carefully screened patients for the treatment of deep vein thrombosis (DVT) in an outpatient setting. The safety and efficacy of outpatient treatment 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. In addition, outpatient treatment of DVT with LMWH is supported by ACP (American College of Physicians). Patients should be screened for pain control, adequacy of home circumstances including support from family/friends, telephone service, and ability to return to hospital. The use of these guidelines will enhance the quality of care for patients, as it will allow for outpatient treatment or earlier discharge from the hospital with continued treatment of the patient in their familiar home environment. The protocols encourage outpatient treatment or early discharge of selected low risk patients with deep vein thrombosis. These guidelines are not intended either to replace clinicians’ judgment or to establish a protocol for all patients with a particular condition.

This guideline is based on: CHEST 2012 Supplement: Antithrombotic Therapy for VTE Disease which has been endorsed by the MSH Ambulatory Best Practices Committee.

Key Points:

1. Warfarin should be started the same day as parental anticoagulation. Parenteral anticoagulation should continue for a minimum of 5 days or until the international normalized ratio (INR) is 2.0 or above for at least 24 hours. Target INR is 2.5 with range of 2.0 to 3.0.

2. LMWH or fondaparinux (Arixtra) are appropriate parental therapy for home treatment of DVT.

3. LMWHs are anticoagulants and can cause bleeding. The same precautions that apply to initiating Unfractionated Heparin (UFH) apply to using LMWH.

4. 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.

5. 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.

6. Major hemorrhage can occur in 1-2% of patients treated with LMWH which is at a rate similar to that of
UFH.
7. 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.
8. Patients with a history of antibody induced thrombocytopenia on UFH should not be treated with LMWH.
9. LMWH can be given as a once a day or twice a day regimen. Once a day is preferred if dosing is adequate (i.e., same total dose as BID regimen.)
10. LMWH overlapped with warfarin is recommended above oral factor Xa inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis), edoxaban (Savaysa) and direct thrombin inhibitor dabigatran (Pradaxa), in the treatment of DVT. However, they are an option for outpatient DVT treatment.
11. LMWHs are not fully reversible with protamine because of the differing chain lengths of the LMWH molecule. At present no other reversal agents are available.
12. Oral factor Xa and direct thrombin inhibitors currently do not have any available reversal agents. There is an FDA application in process for approval of a reversal agent for direct thrombin inhibitor, dabigatran.
13. Early ambulation is recommended over initial bed rest.
14. Compressive stockings are recommended for acute therapy and for post thrombotic (phlebitic) syndrome.

TREATMENT OPTIONS:

Traditionally, initial DVT treatment starts with parenteral anticoagulant administration transitioning to a Vitamin K antagonist (e.g. warfarin). Another option is a direct Factor Xa inhibitor. Some of these oral agents remove the need for overlapping parenteral anticoagulant and Vitamin K antagonist.

Low Molecular Weight Heparin Dosing Guidelines

Enoxaparin (Lovenox®) 1 mg/kg subcutaneously every 12 hours. Overlap 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 CCr <30) and monitoring anti-Xa level is recommended.

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 5 days and until INR of 2.0 to 3.0 is achieved.
For most patients with acute DVT, treatment with LMWH (overlapping with a Vitamin K antagonist) is preferred as the first choice, over UFH, factor Xa and direct thrombin inhibitors. Heparin agents and fondaparinux (Arixtra) are typically preferred over factor Xa and direct thrombin inhibitors. This is due to longer clinical experience with these medications as initial anticoagulants as well as their reversibility with available antidotes. The efficacy of these medications is the same. Oral factor Xa and direct thrombin inhibitors may be an acceptable alternative for patients with normal renal function who prefer an oral anticoagulant and do not want daily injections. However, they must be willing to accept the risk of bleeding on an irreversible agent.

**Oral Factor Xa and Direct Thrombin Inhibitors**

<table>
<thead>
<tr>
<th>Apixaban (Eliquis) (direct factor Xa inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Renal Dosing</strong></td>
</tr>
<tr>
<td><strong>Clinical Benefit</strong></td>
</tr>
<tr>
<td><strong>Therapeutic Considerations</strong></td>
</tr>
<tr>
<td><strong>Select Drug Interactions</strong></td>
</tr>
<tr>
<td><strong>Cost of 30 day supply</strong></td>
</tr>
</tbody>
</table>
### Dabigatran (Pradaxa) (direct thrombin inhibitor)

<table>
<thead>
<tr>
<th><strong>Usual Dose</strong></th>
<th>DVT/PE treatment (following 5 to 10 days’ treatment with a parenteral anticoagulant): 150 mg BID. (Start 0 to 2 hours before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Dosing</strong></td>
<td>DVT/PE treatment/prevention: no dosing information for CrCl &lt;30 mL/min or dialysis</td>
</tr>
<tr>
<td><strong>Clinical Benefit</strong></td>
<td>DVT/PE treatment/prevention of recurrence: comparable to warfarin for prevention of recurrent VTE or VTE death (combined endpoint); comparable major bleeding</td>
</tr>
<tr>
<td><strong>Therapeutic Considerations</strong></td>
<td>Requires BID dosing for DVT/PE treatment/prevention indications. Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years or older, poor renal function, or underweight.</td>
</tr>
<tr>
<td><strong>Select Drug Interactions</strong></td>
<td>P-glycoprotein inhibitors may increase dabigatran levels; amiodarone, clarithromycin, dronedarone, quinidine, ketoconazole and other strong P-glycoprotein inhibitors should be avoided if CrCl &lt;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 Pradaxa at least 2 hrs before antacids.</td>
</tr>
<tr>
<td><strong>Cost of 30 day supply</strong></td>
<td>150 mg BID. U.S.: $314.70</td>
</tr>
</tbody>
</table>

### Edoxaban (Savaysa) (direct factor Xa inhibitor)

<table>
<thead>
<tr>
<th><strong>Usual Dose</strong></th>
<th>DVT/PE treatment (following 5 to 10 days’ treatment with a parenteral anticoagulant) (60 mg once daily; 30 mg once daily if body weight &lt;60 kg).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Dosing</strong></td>
<td>DVT/PE treatment: 30 mg once daily for CrCl 15 to 50 mL/min. Not recommended if CrCl &lt;15 mL/min.</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>DVT/PE treatment: About as effective as warfarin, with less bleeding (18 fewer bleeds [composite of major plus clinically relevant nonmajor bleeding] per 1000 patients per year).</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Therapeutic Considerations</td>
<td>Not recommended in moderate or severe hepatic impairment.</td>
</tr>
<tr>
<td>Select Drug Interactions</td>
<td>Caution with antiplatelets. Avoid rifampin (P-glycoprotein inducer) Reduce dose to 30 mg once daily for DVT/PE indication in patients taking azithromycin, clarithromycin, dronedarone, erythromycin, itraconazole (oral), ketoconazole (oral), quinidine, or verapamil (P-glycoprotein inhibitors).</td>
</tr>
<tr>
<td>Cost of 30 day supply*</td>
<td>60 mg or 30 mg once daily. U.S.: $277.20</td>
</tr>
</tbody>
</table>

**Rivaroxaban (Xarelto) (direct factor Xa inhibitor)**

| Usual Dose | DVT/PE treatment/prevention of recurrence (15 mg twice daily x 3 weeks, then 20 mg once daily, with food to improve absorption)  
*Rivaroxaban is used as monotherapy / no parenteral therapy needed.* |
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Renal Dosing</td>
<td>For DVT/PE prevention and treatment, avoid if CrCl &lt;30 mL/min.</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>DVT treatment/prevention of recurrence: comparable to enoxaparin/warfarin for prevention of recurrent VTE; comparable major bleeding or clinically relevant nonmajor bleeding (combined endpoint).</td>
</tr>
<tr>
<td>Therapeutic Considerations</td>
<td>Avoid in patients with moderate or severe liver impairment or liver disease with bleeding risk.</td>
</tr>
<tr>
<td>Select Drug Interactions</td>
<td>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.</td>
</tr>
</tbody>
</table>
### DURATION OF TREATMENT:

<table>
<thead>
<tr>
<th>No treatment</th>
<th>3 months</th>
<th>Extended/Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal LE DVT, asymptomatic and IF doesn't extend when followed with serial imaging. (Treat if extends.)</td>
<td>Distal LE DVT, symptomatic (regardless of cause), or extending asymptomatic</td>
<td>Unprovoked proximal LE DVT (if low or moderate bleed risk)</td>
</tr>
<tr>
<td>Surgery or risk-factor associated Proximal LE DVT (regardless of symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unprovoked proximal LE DVT if high bleed risk</td>
<td></td>
<td>Cancer-associated DVT or PE</td>
</tr>
<tr>
<td>Recurrent, unprovoked LE DVT or PE (high risk)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*Cost per Pharmacist Letter, updated Feb 2015.*
Guidelines for the Outpatient or “Early Discharge” Management of DVT

Does the patient have a DVT and any ONE of the following:

- 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

Treat initially as an inpatient.  
Consider outpatient treatment or early discharge management.

Patient doesn’t want injections and is willing to accept bleeding risk on irreversible agent

Treat with LMWH + warfarin (Coumadin)  
*see next page for guidance on this route.

Treat with rivaroxaban (Xarelto) or apixaban (Eliquis)  
*see next page for guidance on this route
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

*Rivaroxaban (Xarelto) or apixaban (Eliquis) 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


6. Manufacturer’s Dosing Guidelines

7. *Up to Date, Overview of the treatment of lower extremity deep vein thrombosis (DVT), last updated Mar 4, 2015


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.