Low Molecular Weight Heparins (LMWHs)
A Brief Overview, Bridging Noted, Outpatient Focus

1. Are there any Emmi® programs in this subject area?
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3. A brief look at the coagulation cascade.
4. What is the difference between LMWHs and Unfractionated Heparin (UFH)?
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6. Strategies for bridge therapy using LMWHs:
7. Major adverse effects associated with LMWHs:
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9. The risk of osteoporosis and LMWH therapy:
10. Do LMWHs need routine monitoring and what type of monitoring assay should be used?
11. When is OUTpatient TREATMENT of DVT with LMWHs appropriate?
12. What OTC or herbal products should be avoided during LMWH therapy?
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Agents in this Review:
- Lovenox® (enoxaparin)
  - [FDA label]
  - Download “Lovenox At Home Brochure”
- Fragmin® (dalteparin)
  - [FDA label]
- Innohep® (tinzaparin)
  - [FDA label]

“CME Style” Questions: Select the correct answer to go to the linked info (answer key on last pg):

1. Compared to Unfractionated heparins (UFH’s), Low Molecular Weight heparins (LMWH’s):
   a. Are smaller in size;  
   b. Have a more predictable anti-coagulant effect 
   c. Do not require routine laboratory monitoring;  
   d. All of the above are correct
2. Which of the following is NOT a pharmacokinetic advantage of LMWH’s compared to UFH’s?
   a. Better bioavailability;  
   b. Prolonged plasma half life 
   c. Higher affinity for plasma proteins;  
   d. Dose-independent clearance
3. If protamine sulfate is administered to neutralize the effects of LMWH, what percentage of antithrombotic activity is protamine expected to neutralize?
   a. 25% - 40%;  
   b. 40% - 65% 
   c. 60% - 75%;  
   d. 80% - 95%
4. In patients on LMWH requiring measurement of anticoagulant effect, the most appropriate laboratory test is:
   a. PT/INR;  
   b. aPTT 
   c. anti-Xa activity;  
   d. antithrombin (anti-IIa activity)
5. LMWHs may increase the risk of osteoporosis through which of the following? (note: similar risk w/warfarin as well)
   a. Decreasing the rate of bone formation;  
   b. Increasing the rate of bone resorption 
   c. Both answers are correct
6. In terms of cost-containment, at this point in time, the American College of Chest Physicians recommends the use of LMWHs over UFH for those patients who require temporary interruption of vitamin K antagonist therapy (i.e. warfarin)?
   a. True;  
   b. False
Are there any Emmi programs in this subject area?
Unfortunately, there are NOT any programs that deal specifically with LMWHs at the present time. However, there are a few programs on related topics. Click on the number link to the right of each program to view the Emmi demo program.

---Note: You must use the DOB of “1/1/1970” in order to view these demos---

- Taking Warfarin (Coumadin) – 15150038741
- Shoulder Replacement - 16113520577
- Total Knee Replacement - 19816577399
- Medication History (Patient) – 14335172061

Virchow’s Triad: The regulation of clot formation:
- Virchow’s triad addresses the role played by blood vessels, circulating elements in the blood, and the speed of blood flow in the regulation of clot formation. The description of the 3 broad categories are as follows:
  - Hypercoagulability:
    - This describes alteration in the constitution of blood. Possible risk factors include hyperviscosity, deficiency of antithrombin III, nephritic syndrome, changes after severe trauma or burn, cancer, late pregnancy, obesity, and whether the patient is a smoker.
  - Hemodynamic Changes:
    - This describes alterations in normal blood flow and includes such situations as turbulence, stasis, mitral stenosis, and varicose veins.
  - Endothelial Injury/Dysfunction:
    - This describes injury and/or trauma to the endothelium. This includes damage to the veins arising from such conditions as shear stress or hypertension.

![Virchow’s Triad](image)

A brief look at the coagulation cascade:
- The coagulation cascade is a step-wise series of enzymatic reactions that result in formation of a fibrin mesh. Clotting factors circulate in the blood as inactive forms. Specific stimuli convert an inactive clotting factor into its active form that, in turn, converts the next clotting factor in the sequence. Factors V and VIII have no enzymatic activity themselves; however, they serve as cofactors that accelerate the enzymatic activity of others. The final steps in the cascade are the conversion of prothrombin to thrombin and fibrinogen to fibrin. Not only is thrombin responsible for the production of fibrin, but also for converting factors V and VIII into their active forms, which creates a positive feedback loop to increase further production of thrombin.
Traditionally, the coagulation cascade has been divided into 3 distinct parts: the intrinsic, extrinsic, and common pathways. The extrinsic pathway (also called the tissue factor pathway) is initiated by exposure of tissue during trauma. Tissue factor and factor VIIa form a complex, which goes on to activate factor X in the common pathway. The intrinsic pathway is initiated when circulating factor XII comes in contact with the subendothelial membrane. In the common pathway, the activation and inhibition of factor X plays a key step in the regulation of clot formation. Along with its cofactor, factor Va, factor Xa converts prothrombin (II) to thrombin (IIa), which then cleaves fibrinogen to form fibrin monomers. As the fibrin monomers reach a critical concentration, they begin to precipitate and polymerize to form fibrin strands. Finally, factor XIIIa covalently bonds each strand to one another.  

**What is the difference between LMWHs and Unfractionated heparin (UFH)?**

- LMWH’s are fragments of UFH produced by either chemical or enzymatic depolymerization with approximately one third the molecular weight of UFH. They prevent the growth and propagation of formed thrombi. Similar to UFH, LMWH’s enhance and accelerate the activity of anti-thrombin through binding to a specific pentasaccharide sequence. Less than one-third of LMWH molecules contain the specific sequence necessary to interact with anti-thrombin. The major difference between the pharmacological activity of LMWH and UFH is the degree to which they inhibit factor Xa and thrombin. Because LMWH’s have smaller chain lengths, they have limited activity against thrombin. Less than 50% of the LMWH molecules have the requisite chain length to simultaneously bind anti-thrombin and thrombin. For this reason, LMWH have proportionally greater anti-
factor Xa activity. The ratio of anti-factor Xa-to-IIa activity varies between 2:1 and 5:1 depending on the specific LMWH, whereas the activity ratio for UFH is 1:1. Although UFH and LMWH share similarities in their mechanisms of action, their molecular weight distributions vary, which results in differences in their activity against factor Xa and thrombin, their affinity for plasma proteins, their ability to release tissue factor pathway inhibitor, and their duration of action.

**Pharmacokinetics (PK):**

- As compared with UFH, LMWH’s have a more predictable anti-coagulant response. The improved PK profile of LMWH’s is the result of reduced binding to plasma proteins and cells.
- The bioavailability of LMWH’s approaches 100% when administered sub-Q, whereas the absorption of UFH is rather poor and erratic. Peak anticoagulant effect is seen in approximately 3-5 hours after LMWH therapy.
- Predominantly, LMWH’s are eliminated renally; therefore, medication half-lives may be increased in patients with renal dysfunction.
- Longer heparin chains bind to macrophages and are rapidly degraded. Therefore, anti-factor Xa activity, which is mediated by smaller heparin molecules, persists longer than antithrombin activity.
- The plasma half life of LMWH’s is two to four times longer than UFH and the clearance is independent of dose.
- Overall, LMWHs have several advantages over UFH including predictable anticoagulation dose response, improved sub-Q bioavailability, dose-independent clearance, longer biological half lives, lower incidence of heparin induced thrombocytopenia (HIT), and a reduced need for routine laboratory monitoring.

**Pharmacokinetic kinetic properties of LMWHs:**
Although there is NO proven method for reversing LMWHs, if major bleeding does occur in a patient receiving therapy it is recommended that IV protamine sulfate be administered. However, because of its limited binding to the shorter LMWH chains, protamine sulfate can NOT completely neutralize the anticoagulant effects.

- When given in equimolar concentrations, **protamine neutralizes an estimated 60% to 75%** of the antithrombotic activity of LMWHs.

- The recommended dose is **1 mg/1 mg of enoxaparin or 1 mg/100 anti-factor Xa units of dalteparin or tinzaparin administered in the previous 8 hours**.

- If the LMWH dose was given in the previous 8 to 12 hours, a 0.5 mg dose of protamine should be given for every 100 anti-factor Xa units.

- The use of protamine is not recommended if the LMWH was administered more than 12 hours earlier.

**Protamine Dose for reversal of LMWH:**

<table>
<thead>
<tr>
<th>LMWH</th>
<th>&lt;8 hr</th>
<th>8–12 hr</th>
<th>&gt;12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>1 mg/100 anti-Xa units</td>
<td>0.5 mg/100 anti-Xa units</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/1 mg</td>
<td>0.5 mg/1 mg</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>1 mg/100 anti-Xa units</td>
<td>0.5 mg/100 anti-Xa units</td>
<td>Not necessary</td>
</tr>
</tbody>
</table>

**General Indications for LMWHs:**

**Indications and doses for LMWHs:**

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**Figure 4**

**Figure 5**
Literature Review:

- **LMWHs for the treatment of DVT:**
  - In a meta-analysis including 17 studies in which UFH was administered IV (in 3 of the older studies UFH was administered sub-Q). LMWHs were associated with fewer thrombotic complications (3.6% vs. 5.4%; OR 0.68; 95% CI 0.55-0.84), less major bleeding (1.2% vs. 2.0%; OR 0.57; 95% CI 0.39-0.83), and fewer deaths (4.5% vs. 6.0%; OR 0.76; 95% CI 0.62-0.92).
  - Wells et al. conducted a study comparing once daily administration of dalteparin and tinzaparin in the outpatient treatment of VTE using 497 patients. There was no difference in recurrent VTE at 3 months (4.5% vs. 5.9%; RR 0.91; 95% CI 0.38-2.2), major bleeding at 7 days (0.4% vs. 1.2%; RR 0.34; 95% CI 0.04-3.26), or death at 3 months (4.8% vs. 5.5%; RR 0.87; 95% CI 0.41-1.84).
  - The American College of Chest Physicians suggests that for the treatment of VTE there is similar efficacy and safety between once and twice daily administration, outpatient and inpatient administration, and the use of different preparations of LMWHs.

- **Treatment of PE on an outpatient basis:**
  - Kearan et al. conducted a study which compared fixed dose weight-adjusted UFH and LMWH for acute treatment of VTE. This was a randomized, open-label, adjudicator-blinded, non-inferiority trial of 708 patients aged 18 and older. Recurrent VTE occurred in 13 patients in the UFH group (3.8%) compared with 12 in the LMWH group (3.4%; AR 0.4%; 95% CI -2.6% -3.3%). Major bleeding during the first 10 days of treatment occurred in 4 patients in the UFH group (1.1%) compared with 5 in the LMWH group (1.4%; AR -0.3%; 95% CI -2.3%-1.7%). Overall, the authors conclude that LMWH is as safe and effective as fixed dose sub-Q UFH for acute VTE.
LMWH therapy in PCI:

- In a study conducted by Montalescot et al. the authors looked at enoxaparin vs. UFH in elective PCI. This prospective, open-label, multicenter, randomized trial included 3528 patients with PCI to receive enoxaparin (0.5 or 0.75 mg/kg body weight) or UFH adjusted for activated clotting time stratified according to the use or non-use of GP IIb/IIIa inhibitors. The primary endpoint was the incidence of major or minor bleeding not related to CABG and the secondary endpoint was the percentage of patients in whom the target anticoagulation levels were reached. The results showed that patients treated with enoxaparin showed a significant reduction in the rate of non-CABG related bleeding in the first 48 hours as compared with UFH (5.9% vs. 8.5%; AR -2.6; 95% CI -4.7—0.6; p=0.01). Target anticoagulation levels were reached in significantly more patients who received enoxaparin (79% in 0.5 mg/kg group; 92% in the 0.75 mg/kg group) than who received UFH (20%, p<0.001). The authors conclude that in elective PCI, a single IV bolus of enoxaparin 0.5 mg/kg is associated with reduced rates of bleeding, and enoxaparin 0.75 mg/kg yields rates similar to those of UFH, with more predictable anticoagulation levels.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval</th>
<th>Route of Administration</th>
<th>Frequency of Administration</th>
<th>Contraindications to use for all LMWHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>03/1993</td>
<td>Sub-Q</td>
<td>Every 12 hours Or Every 24 hours</td>
<td>Hypersensitivity to LMWHs, UFH, pork products, methylparaben, or propylparaben. History of HIT or suspected HIT</td>
</tr>
<tr>
<td>(Lovenox®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>12/1994</td>
<td>Sub-Q</td>
<td>Every 24 hours</td>
<td></td>
</tr>
<tr>
<td>(Fragmin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>07/2000</td>
<td>Sub-Q</td>
<td>Every 24 hours</td>
<td></td>
</tr>
<tr>
<td>(Innohep®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Strategies for bridge therapy using LMWHs:

- Why overlap LMWH therapy while starting warfarin therapy?
  - Overlap ~5 days or until INR therapeutic (typically after 2 consecutive readings). We must overlap (bridge) anticoagulant therapy when starting warfarin because of the initial hypercoagulable state created due to protein C, protein S (both are endogenous anticoagulants) being inhibited immediately, followed by slower inhibition of coagulation factors 2, 7, 9, 10 (each have various length in half lives).

- **High Risk**
  - In patients with a mechanical heart valve, atrial fibrillation, or venous thromboembolism (VTE) at high risk for thromboembolism, the American College of Chest Physicians (ACCP) recommends bridging anticoagulation with therapeutic-dose LMWH or IV UFH over no bridging during temporary interruption of vitamin K antagonist (i.e. warfarin) therapy.
  - Further, they suggest therapeutic-dose LMWH over other management options.

- **Moderate Risk**
  - In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, they suggest bridging anticoagulation with therapeutic-dose LMWH, therapeutic-dose IV UFH, or low-dose LMWH over no bridging during temporary interruption of vitamin k antagonist therapy.
  - Further, they suggest therapeutic-dose LMWH over other management options.

- **Low Risk**
  - In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, they suggest low-dose LMWH or no bridging over bridging with therapeutic-dose LMWH or IV UFH.
In patients who require temporary interruption of vitamin K antagonist therapy and are to receive bridging anticoagulation, from a cost-containment perspective, the ACCP recommends the use of LMWH administered in an outpatient setting where feasible instead of inpatient administration of IV UFH.

Patients receiving bridging anticoagulation w/therapeutic-dose LMWH, ACCP recommends administering last dose of LMWH 24h before surgery or a procedure over administering LMWH closer to surgery;
- For the last preoperative dose of LMWH, they recommend administering approximately half the total daily dose instead of 100% of the total daily dose.

In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic-dose LMWH, the ACCP recommends resuming this regimen approximately 24 h after the procedure when there is adequate hemostasis over a shorter (eg, < 12h) time interval. In patients undergoing major surgery or a high bleeding risk surgery/procedure and for whom post-operative therapeutic-dose LMWH/UFH is planned, they recommend either delaying the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured, administering low-dose LMWH/UFH after surgery when hemostasis is secured, or completely avoiding LMWH or UFH after surgery over the administration of therapeutic-dose LMWH/UFH in close proximity to surgery.
- They recommend considering the anticipated bleeding risk and adequacy of post-operative hemostasis in individual patients to determine the timing of LMWH or UFH resumption after surgery instead of resuming LMWH or UFH at a fixed time after surgery in all patients.

**Major adverse effects associated with LMWHs:**
- Bleeding is the most common adverse event.
- Injection site reactions and allergic reactions
- Cases of spinal hematoma have been reported with epidural anesthesia or spinal puncture leading to long-term injury or permanent paralysis. Use with extreme caution and hold dose for 12-24 hours prior to procedure, based on half-life of the specific agent.
- Thrombocytopenia
- Elevated hepatic enzymes
- Osteoporosis (the true incidence of osteoporosis is uncertain, however, it is less than UFH)
- Rare cases of hyperlipidemia

**Incidence of some of the adverse events of LMWHs:** (Figure 8)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Dalteparin (Fragmin®) %</th>
<th>Enoxaparin (Lovenox®) %</th>
<th>Tinzaparin (Innohep®) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0–3</td>
<td>&lt;2–16</td>
<td>NR</td>
</tr>
<tr>
<td>Fever</td>
<td>Rare</td>
<td>0–16.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0–7</td>
<td>0</td>
<td>≥1</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0–8.9</td>
<td>0–6.5</td>
<td>0.5–2.8</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1.5–28</td>
<td>1.8–28</td>
<td>1.3–5.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>NR</td>
<td>2.5–9.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Serum aminotransferase</td>
<td>2.5</td>
<td>0.4–6.1</td>
<td>8.8–13</td>
</tr>
<tr>
<td>elevation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0–1</td>
<td>0.4–1.2</td>
<td>NR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0–2</td>
<td>0.2–3.2</td>
<td>1–3.1</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>NR</td>
<td>0.1–0.3</td>
<td>NR</td>
</tr>
</tbody>
</table>

LMWH=low-molecular-weight heparin; NR=not reported.

**What is the difference between heparin-induced thrombocytopenia (HIT) type 1 and type 2?**
- **HIT type 1** → This is a benign, mild reduction in platelet counts typically seen in as many as 25% of patients receiving heparin therapy. Also known as non-immune mediated heparin-associated thrombocytopenia (HAT),
this condition produces a transient fall in platelet count that occurs early, typically between days 2 and 4 of therapy. The degree of thrombocytopenia is usually mild, with platelet counts rarely going below 100,000. **Patients that acquire this type of HAT do NOT require discontinuation of heparin therapy as platelet counts will generally rebound back to baseline values with continued use.**

- **HIT Type II** – Also known as immune-mediated HIT, this is a severe pathologic adverse effect of heparin with a significant potential to cause thrombotic complications. Platelet counts typically begin to fall days 5 to 10 following initiation of heparin and reach their lowest by days 7 to 14. The development of thrombocytopenia can be delayed (delayed onset HIT) up to 20 days, or occur immediately (rapid-onset HIT) in patients with a recent previous exposure to heparin. Generally, a drop in platelet count greater than 50% from baseline is considered indicative of HIT. This type of HIT is dangerous as it is an IgG mediated response to the heparin molecule leading to platelet activation and thrombin generation. Activated platelets release PF-4, which heparin binds to, forming a negatively charged molecule that is highly antigenic and stimulates the production of IgG antibodies. In patients who develop HIT, the heparin-PF4-IgG complexes bind to the Fc receptor on platelets, which leads to further platelet activation and further release of PF-4. Overall, this cascade of events leads to an increased risk of thrombotic events despite moderate to severe thrombocytopenia.

- LMWH’s cause HIT less often than UFHs, but still on the order of 0.5%. This turns out to be a significant number of patients when you consider the number of patients receiving anti-coagulation therapy with LMWH’s. The majority of HIT antibodies cross react with PF-4 mediated by LMWH’s, therefore, LMWH’s are typically considered contraindicated once HIT ensues from any heparin therapy.
  - i.e., **if HIT with UFH then cross-sensitivity for HIT using LMWHs is near 100%, and vice versa.**

- The American College of Chest Physicians recommends that for patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, an alternative, non-heparin anti-coagulant be used, rather than the further use of UFH or LMWH, or initiation/continuation of a vitamin K antagonist. Medications to consider include; danaparoid (heparinoid), lepirudin, argatroban, bivalirudin (direct thrombin inhibitors), or fondaparinux (factor Xa inhibitor).

**The risk of osteoporosis and LMWH therapy:**

- LMWHs may carry a lower risk of osteoporosis than UFH. Dalteparin, 5,000 anti-Xa U sub-Q, was compared with UFH, 10,000 U sub-Q bid, for 3 to 6 months in 80 patients with DVT. Of the patients who received UFH, 6 of the 40 patients developed spinal fractures, compared to 1 patient receiving dalteparin. There was a dose-dependent decrease in cancellous bone volume in rats treated with UFH or the LMWH tinzaparin (0.5 to 1.0 μg) for 32 days, but UFH caused significantly greater cancellous bone loss than LMWH. Furthermore, although UFH and LMWH decreased osteoblast and osteoid surface similarly, only UFH increased osteoclast surface. Both UFH and LMWH reduced serum alkaline phosphatase (a biochemical marker of bone formation), consistent with reduced bone formation. Whereas UFH decreases cancellous bone volume both by decreasing the rate of bone formation and increasing the rate of bone resorption, LMWH causes less osteopenia, decreasing only the rate of bone formation.
When is OUTpatient TREATMENT of DVT with LMWHs appropriate?²¹

LMWHs for outpatient treatment of DVT and PE?


- A randomized, controlled trial of 505 patients with DVT or PE; patients were randomized to receive either subcutaneous tinzaparin (n=254), 175 IU/kg every 24 hours or subcutaneous dalteparin (n=251), 200 IU/kg every 24 hours.
- All patients received oral anticoagulation therapy with warfarin on the day of randomization or within 24 hours of the first dose of LMWH and continued for 3 months.
- LMWHs were given for a minimum of 5 days and until INR was ≥2 on two consecutive days.
- In the tinzaparin group, 2 major hemorrhages and 9 recurrent venous thromboembolic events (5 DVT and 4 PE).
- In the dalteparin group, 5 major hemorrhages and 10 recurrent venous thromboembolic events (8 DVT and 2 PE).
- The differences in composite end-point between tinzaparin and dalteparin were not statistically significant (P= 0.44).
- Thus, the authors concluded that both tinzaparin and dalteparin are safe and effective for the treatment of DVT or PE in outpatient setting.

Savage KJ, et al.²³ “Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity.”

- A prospective cohort study of 46 patients with upper extremity DVT received subcutaneous dalteparin 200 U/kg daily for 5-7 days. First dose was given in the outpatient clinic and subsequent doses to be administered at home.
- Warfarin therapy started on the first day with target INR of 2 - 3.
- LMWH was discontinued once target INR (>2) was achieved for two consecutive days.
- Results: 1 patient had recurrent DVT, 1 patient with major upper GI bleed, and 7 patients died of underlying disease. No pulmonary emboli or bleeding complications were observed.
- The study concluded that LMWHs are safe and effective in the treatment of upper extremity DVT.

Unfractionated heparin vs. LMWH for outpatient treatment of DVT


- A randomized, open-label, adjudicator-blinded study of 708 patients with DVT of the legs or PE; patients were randomized to receive either subcutaneous unfractionated heparin (n=345), initial dose of 333 U/kg, followed by a fixed dose of 250 U/kg every 12 hours or subq LMWHs (dalteparin or enoxaparin), 100 IU/kg every 12 hours (n=352).
- UFH and LMWHs were given for at least 5 days and until INR was ≥2 for two consecutive days.
- Treatment was administered entirely in the outpatient setting in 72% of the UFH group and 68% of the LMWHs group.
- Warfarin started on the same day and continued for at least 3 months with target INR of 2.0-3.0.
- 13 patients had recurrent venous thromboembolism in the UFH vs. 12 patients in the LMWHs group.
- Major bleeding during the first 10 days occurred in 4 patients in the UFH group vs. 5 patients in the LMWHs group.
- The study concluded that fixed-dose of UFH is as safe and effective as LMWH for outpatient treatment of acute DVT.
Do LMWHs need routine monitoring and what type of monitoring assay should be used?

- The activated partial thromboplastin time (aPTT) is a parameter used to guide the efficacy of both the intrinsic and common coagulation pathways. It is used in conjunction with the prothrombin time (PT), which measures the extrinsic pathway to monitor heparin and warfarin therapy. Typically, because LMWH’s achieve a predictable anticoagulant response when given via the sub-Q route, **routine lab monitoring is not required.** However, the dose of LMWH may be difficult to determine in specific patient populations, such as those at the age extremes, obese patients, and those with renal failure (CrCl < 30 ml/min), so lab monitoring has been suggested. Also, periodic monitoring may be useful in patients requiring prolonged therapy (longer than 14 days), patients at a high risk of bleeding or thrombotic recurrence, or in women treated during pregnancy. LMWH’s don’t prolong the aPTT significantly enough to use it as a marker of efficacy, instead, measurement of anti-factor Xa activity along with complete blood cell and platelet counts has become the most widely used method for monitoring.

- When anti-factor Xa activity is monitored, the sample should be drawn after steady state has been achieved (typically after the second or third dose) and approximately 4 hours after a sub-Q dose, which correlates to the peak period of anti-factor Xa activity. It should be noted that a therapeutic range for anti-factor Xa activity has not been well defined and is not clearly correlated with the risk of bleeding\(^7\).

What OTC or herbal products should be avoided during LMWH therapy?

- Over the counter non-steroidal anti-inflammatory medications (NSAIDS) may increase your risk of bleeding and should be avoided while on anti-coagulant therapy.
- Alcohol intake can affect the risk of bleeding and should be avoided.
- Many herbal medications have anti-coagulant properties themselves. Further, many herbal products do not list all of their ingredients and make assessing the risk of bleeding very difficult\(^19\).

***For any OTC or herbal medication it is important to make sure a healthcare provider is contacted and consulted with prior to starting if a patient is taking anti-coagulation therapy***

More in table below...
Dietary Supplements that can affect platelet function and anticoagulation status:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladderwrack</td>
<td>Has anticoagulant effect</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Boldo</td>
<td>Constituents may have antiplatelet effects</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Decreased platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Burdock</td>
<td>Decreased platelet aggregation by inhibiting platelet activation factor</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Caffeine</td>
<td>May have antiplatelet activity, not reported in humans</td>
<td>Increased risk of bleeding or bruising, found in black tea, green tea, guarana, mate, oolong tea</td>
</tr>
<tr>
<td>Clove</td>
<td>Eugenol has antiplatelet activity</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>May inhibit platelet aggregation</td>
<td>Increased risk of bleeding or bruising; avoid concomitant use</td>
</tr>
<tr>
<td>Coltsfoot</td>
<td>May inhibit platelet aggregation</td>
<td>Increased risk of bleeding or bruising; avoid concomitant use</td>
</tr>
<tr>
<td>Danshen</td>
<td>Decreased platelet aggregation; may also have antithrombotic effects</td>
<td>Increased risk of bleeding or bruising; avoid concomitant use</td>
</tr>
<tr>
<td>Dong quai</td>
<td>May inhibit platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Constituents may have antiplatelet effects, concentration may not be clinically significant</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>Has antiplatelet effects</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Flax seed</td>
<td>Decreased platelet aggregation and increased bleeding time</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Gamma linolenic acid (GLA)</td>
<td>Has anticoagulant effects</td>
<td>Increased risk of bleeding or bruising; found in borage and evening primrose oil</td>
</tr>
<tr>
<td>Garlic</td>
<td>Has anticoagulant effects and may inhibit platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Ginger</td>
<td>Inhibit thromboxane synthetase and decreased platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Decreased platelet aggregation; ginkgolide B, a component of ginkgo, is a potent inhibitor of PAF</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Ginseng, panax</td>
<td>Components may decreased platelet aggregation through PAF antagonism; not shown in humans</td>
<td>Increased risk of bleeding or bruising; use with caution until more is known</td>
</tr>
<tr>
<td>Ginseng, Siberian</td>
<td>A component, dihydroxybenzoic acid, may inhibit platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Unknown, might increased the anticoagulant or antiplatelet effect, decreased prothrombin activity observed</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Nattokinase</td>
<td>Has thrombolytic activity</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Onion</td>
<td>Decreased platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Pantethine</td>
<td>Decreased platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Policosanol</td>
<td>Inhibits platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Poplar</td>
<td>Contains salicylates and may cause decreased platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Reservatrol</td>
<td>Has antiplatelet effects</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Sea buckthom</td>
<td>Inhibits platelet aggregation</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Decreased platelet aggregation; has antiplatelet effects</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Vinpocetine</td>
<td>Has antiplatelet effects</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Inhibits platelet aggregation and antagonizes the effects of vitamin-k dependent clotting factors</td>
<td>Dose dependent and significant with doses greater than 800 units per day, advise patients to avoid high doses of vitamin E, increased risk of bleeding or bruising</td>
</tr>
<tr>
<td>Willow bark</td>
<td>Decreased platelet aggregation, has antiplatelet effects but less than aspirin</td>
<td>Increased risk of bleeding or bruising</td>
</tr>
</tbody>
</table>
Future anticoagulants in the pipeline:

Inhibitors of the factor VIIa-tissue factor complex:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>MOA</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tifacogin</td>
<td>IV</td>
<td>Inhibits factor VIIa in a factor Xa-dependent fashion</td>
<td>Phase III</td>
</tr>
<tr>
<td>NAPc2</td>
<td>Sub-Q</td>
<td>Inhibits factor VIIa in a factor X or Xa-dependent fashion</td>
<td>Phase II</td>
</tr>
<tr>
<td>Factor VIIai</td>
<td>IV</td>
<td>Competes with factor VIIa for tissue factor</td>
<td>Halted</td>
</tr>
</tbody>
</table>

Factor IXa Inhibitors:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>MOA</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB006</td>
<td>IV</td>
<td>Factor IXa-directed inhibitory RNA aptamer</td>
<td>Phase I</td>
</tr>
<tr>
<td>TTP889</td>
<td>Oral</td>
<td>Inhibits factor IXa incorporation into intrinsic tenase</td>
<td>Stopped at Phase II</td>
</tr>
</tbody>
</table>

Direct Factor Xa Inhibitors:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otamixaban</td>
<td>IV</td>
<td>Phase II</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>YM-150</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Inhibitors of Factor Va:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>MOA</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drotrecogin</td>
<td>IV</td>
<td>Proteolytically degrades and inactivates factor Va</td>
<td>Licensed for severe sepsis</td>
</tr>
<tr>
<td>ART-123</td>
<td>Sub-Q</td>
<td>Binds thrombin and promotes its activation of protein C</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Thrombin Inhibitors:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>MOA</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odiparcil</td>
<td>Oral</td>
<td>Primes the synthesis of dermatan sulfate-like glycosaminoglycans</td>
<td>Stopped at Phase II</td>
</tr>
<tr>
<td>Ximelagatran</td>
<td>Oral</td>
<td>Prodrug of melagatran, a reversible inhibitor of the active site of thrombin</td>
<td>Briefly licensed in Europe and now withdrawn worldwide</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Oral</td>
<td>Prodrug of dabigatran, a reversible inhibitor of the active site of thrombin</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Figures 10-14^2
References:

10.) Keanon C, Kahn S, Agnelli G, Goldhaber S, Raskob G, Comerota A. Antithrombotic Therapy for Venous Thromboembolic Disease. CHEST. 2008; 133; 454S-545S.

Quiz Answers:
1.) D
2.) C
3.) C
4.) C
5.) A
6.) A