

# Anticoagulants, Injectable Review

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## Anticoagulants, Injectable Review

### FDA-Approved Indications

Drug	Manufacturer	DVT prophylaxis				DVT Treatment*
		Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
dalteparin (Fragmin <sup>®</sup> ) <sup>1</sup>	Eisai	X	-	-	X	-
enoxaparin (Lovenox <sup>®</sup> ) <sup>2</sup>	Sanofi-Aventis	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra <sup>™</sup> ) <sup>3</sup>	GlaxoSmithKline	X	X	X	X	X
tinzaparin (Innohep <sup>®</sup> ) <sup>4</sup>	Pharmion	-	-	-	-	X (inpatient setting only; with or without PE)

\*administered in conjunction with warfarin.

Other indications:

#### dalteparin (Fragmin)

- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI) when concurrently administered with aspirin
- DVT prophylaxis for immobile medical patients who are at risk for thromboembolic complications
- extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer

#### enoxaparin (Lovenox)

- for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction in conjunction with aspirin
- DVT prophylaxis to prevent thromboembolic complications in medical patients with severely restricted mobility during acute illness
- treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI)

#### fondaparinux (Arixtra)

- treatment of acute PE when initial therapy is administered in the hospital and with warfarin.

The focus of this review will be on the outpatient use of the injectable anticoagulants, which include the LMWHs and fondaparinux.

## Overview

Venous thromboembolism (VTE) is a significant public health problem in the US. The disease manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major consequence of various surgical procedures and medical conditions. DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the extremities, most commonly the legs. Embolization of a thrombus results in PE if it lodges in the pulmonary artery or one of its branches and blocks pulmonary blood flow.<sup>5,6</sup>

There are over 100,000 cases of PE annually in the United States. The National Institutes of Health (NIH) ranks PE as the third most common cause of death in hospitalized patients; if left untreated, approximately 30 percent of patients who develop PE will die within the first few hours of the event.<sup>7</sup>

Clinical risk factors for VTE include immobility or paralysis; trauma or surgery involving the lower extremities, pelvis, hips, or abdomen; malignancy; a history of VTE; obesity; any state leading to increased estrogen levels, including pregnancy and hormone replacement therapy; indwelling central venous catheters; cardiac dysfunction; inflammatory bowel disease; nephrotic syndrome; and acquired (e.g. cancer) or inherited hypercoagulability disorders. Generally, the risk of VTE increases with the number of risk factors present, major traumas, and age.<sup>8,9</sup>

Due to the risk of morbidity and fatal PE associated with DVT, prophylaxis has become the standard of care for patients at high risk for thrombosis. Based on presence of the risk factors outlined above, the Eighth American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published in 2008, recommend various regimens of parenteral and/or oral anticoagulants with or without mechanical devices such as graduated compression stockings and/or intermittent pneumatic compression devices.<sup>10</sup> For DVT prophylaxis, these guidelines add fondaparinux (Arixtra) as an alternative agent to subcutaneous (SC) low molecular weight heparin (LMWH) and low-dose unfractionated heparin (UFH) for general medical patients, and certain patients undergoing general, vascular, thoracic, gynecologic, bariatric, or urologic surgery. In patients undergoing total hip replacement, knee replacement, or hip fracture surgery, DVT prophylaxis with LMWH, fondaparinux, or vitamin K antagonist [(VKA) e.g. warfarin] is recommended postoperatively for at least ten days and up to 35 days.

Treatment options for VTE consist of at least five days of either intravenous (IV) or SC UFH, SC LMWH or, fondaparinux, and until the international normalized ratio (INR) is therapeutic for at least 24 hours. Vitamin K antagonist (VKA) is given to overlap the parenteral anticoagulant therapy; it is initiated on the first treatment day rather than delayed initiation of VKA. For patients with VTE secondary to a transient (reversible) risk factor, treatment with VKA is recommended for three months. For patients with first episode of unprovoked DVT or PE, treatment with VKA is recommended for at least three months. The guidelines recommend VKA therapy be discontinued after three months with distal DVT and continued long-term for proximal DVT or PE in patients at low bleeding risk and good anticoagulant monitoring. For patients with unprovoked VTE who have a strong desire for less frequent INR monitoring, the guidelines recommend after the first three months of therapy with INR goal of 2 to 3 (conventional-intensity therapy) the INR goal be lowered to 1.5 to 1.9 (low-intensity therapy) with less frequent monitoring in lieu of discontinuing VKA therapy. The American College of Physicians (ACP) and The American Academy of Family Physicians (AAFP) in 2007 jointly recommend anticoagulation for three to six months for VTE secondary to transient risk factors and for more than 12 months for recurrent VTE. Although the appropriate duration of anticoagulation for

idiopathic or recurrent VTE is not known, the ACP/AAFP guidelines state that there is evidence of substantial benefit for extended-duration therapy.<sup>11</sup> For long-term treatment, SC anticoagulants are an alternative therapy for patients in whom oral anticoagulants cannot be used.<sup>12</sup>

The agents in this review have different instructions for use and are not considered interchangeable, unit for unit. They differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, as well as units and dosage.<sup>13</sup>

### Pharmacology

Unfractionated heparin and LMWH (dalteparin [Fragmin], enoxaparin [Lovenox], tinzaparin [Innohep]) are classified as indirect thrombin inhibitors because the agents exert anticoagulant action, in part, by binding to and potentiating the activity of antithrombin III (ATIII), a naturally occurring thrombin inhibitor. UFH exerts its anticoagulant effect by enhancing the capacity of ATIII to inactivate thrombin. LMWH also produces anticoagulant action through ATIII, however LMWH primarily inhibits clotting factor Xa rather than thrombin. Therefore, LMWH has less effects on partial thromboplastin time (PTT), virtually eliminating the need for (and expense of) laboratory monitoring. LMWH exhibits more consistent bioavailability, resulting in less interpatient dose-response variation, and permitting standardized dosing. Another advantage of LMWH is the SC route of administration does not require an IV infusion pump. In addition, the incidence of thrombocytopenia appears to be lower with LMWH than with UFH.<sup>14</sup>

Fondaparinux (Arixtra) is a selective factor Xa inhibitor which binds to ATIII. By inhibiting factor Xa, thrombin generation and thrombus formation are inhibited without direct effects on thrombin. Also, fondaparinux does not bind significantly to platelet factor 4, a factor involved in immune-related heparin-induced thrombocytopenia (HIT).<sup>15</sup>

### Pharmacokinetics<sup>16,17,18,19,20,21</sup>

Drug	Bioavailability (%)	Half-life* (hrs)	Average molecular weight (daltons)	Anti-Xa : Anti-IIa activity	Peak Anti-Xa activity (hrs)
dalteparin (Fragmin) <sup>22</sup>	87	2-5	5,000	2-4 : 1	4
enoxaparin (Lovenox) <sup>23</sup>	~ 100	4.5-7	4,500	2.7-3.7 : 1	3-5
fondaparinux (Arixtra) <sup>24</sup>	~ 100	17-21	1,728	Anti-Xa only	3
tinzaparin (Innohep) <sup>25</sup>	86.7	3-4	5,500-7,500	1.5-2.8 : 1	4-5

Data presented for pharmacokinetics are for SC administration of all products.

\*Delayed elimination of all the products may occur with severe liver or kidney insufficiency.

### **Contraindications/Warnings**<sup>26,27,28,29</sup>

All agents in the class carry a black box warning regarding the risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is performed in patients who are anticoagulated or scheduled to be anticoagulated with LMWHs, heparinoids, or fondaparinux (Arixtra) for prevention of thromboembolic complications. Epidural or spinal hematomas can result in long-term or permanent paralysis. Patients at highest risk are those with indwelling epidural catheters for administration of analgesia and patients concurrently on NSAIDs, platelet inhibitors, and other anticoagulants. Increased risk is also seen in traumatic or repeated epidural or spinal puncture. Frequent monitoring for signs and symptoms of neurologic impairment should be performed.

LMWHs are contraindicated in patients with hypersensitivity to any LMWH, unfractionated heparin, or pork products.

Tinzaparin (Innohep) is not intended for intramuscular or intravenous use. Fondaparinux (Arixtra), enoxaparin (Lovenox), and dalteparin (Fragmin) should not be administered intramuscularly.

Fondaparinux and LMWH are contraindicated in patients with active major bleeding as well as patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of the respective agent. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup>, therapy with agents in this class should be reevaluated and possibly discontinued.

LMWH should be used with extreme caution in patients with heparin-induced thrombocytopenia (HIT); this is considered a contraindication for tinzaparin.

Dalteparin is contraindicated in unstable angina, non-Q-wave MI, or acute venous thromboembolism in patients undergoing regional anesthesia.

Known hypersensitivity to benzyl alcohol is considered a contraindication only for tinzaparin and the multi-dose formulation of enoxaparin. Dalteparin multi-dose vials contain benzyl alcohol as a preservative.

For enoxaparin use associated with PCI, hemostasis at the puncture site should be obtained before sheath removal following percutaneous coronary revascularization.

Enoxaparin has not been adequately studied in pregnant women with mechanical prosthetic heart valves.

LMWHs and fondaparinux should be used cautiously in patients with renal insufficiency as the kidneys are the primary elimination route for the agents and such patients are at increased risk of major bleeding.

Tinzaparin should not be used in elderly patients with renal insufficiency due to increased risk of death.

Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Fondaparinux is also contraindicated in patients with body weight less than 50 kg when used for prophylaxis for abdominal surgery, hip fracture surgery, or hip or knee replacement surgery. In clinical trials, occurrence of major bleeding was doubled in patients

with body weight less than 50 kg (5.4 percent) compared to heavier patients (2.1 percent). Fondaparinux is contraindicated in patients with bacterial endocarditis due to increased risk of bleeding.

LMWHs cannot be used interchangeably (unit for unit) with heparin or other LMWHs as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

**Drug Interactions**<sup>30,31,32,33</sup>

Due to the increased risk of bleeding, injectable anticoagulants should be used with caution with oral anticoagulants or platelet inhibitors, including aspirin, salicylates, NSAIDs, dipyridamole, dextran, ticlopidine, clopidogrel (Plavix<sup>®</sup>), and thrombolytics.

**Adverse Effects**

Drug	Major bleeding	Thrombocytopenia	Injection site reactions
dalteparin (Fragmin) <sup>34</sup>	0 - 4.6	<1	2-12
enoxaparin (Lovenox) <sup>35</sup>	< 1-4	0.1-1.3	Reported
fondaparinux (Arixtra) <sup>36</sup>	2.2-3.4	0.04-3	Reported
tinzaparin (Innohep) <sup>37</sup> Treatment	0.8	0.13-1	16

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not comparative. All adverse effects are reported for prophylaxis except tinzaparin (Innohep) which is only approved for treatment of VTE.

Direct comparison of bleeding risks among the injectable anticoagulants is difficult due to different definitions of bleeding in various clinical studies.

**Special Populations**<sup>38,39,40,41</sup>

Pediatrics

Safety and effectiveness of LMWH and fondaparinux in pediatric patients have not been established.

The 2008 ACCP guidelines state that despite their unproven efficacy, LMWHs have rapidly become the anticoagulant of choice in many pediatric patients, both for primary prophylaxis and treatment of thromboembolism.<sup>42</sup>

Potential advantages of LMWH in children include predictable pharmacokinetics requiring minimal monitoring, which is critically important in pediatric patients with poor or nonexistent venous access; SC administration; lack of drug or food interactions, such as those that exist for vitamin K antagonist (VKA); reduced risk of HIT; and probable reduced risk of osteoporosis with long-term use, which occurs with UFH. The guidelines point out that although they use the term LMWH and present dosing schedules for a number of different LMWHs, the majority of all clinical data with respect to LMWH use in children is from studies that used enoxaparin.<sup>43</sup>

The 2008 ACCP guidelines recommend anticoagulant therapy with either UFH or LMWH in children with DVT. Initial treatment with UFH or LMWH should be for at least five to ten days. If VKA will be subsequently prescribed, oral VKA should be initiated as early as day one and discontinue LMWH or UFH on day six or later than day six if the INR has not exceeded 2.0. After the initial five to ten day treatment period, the guidelines suggest LMWH rather than VKA therapy if therapeutic levels are difficult to maintain on VKA therapy or if VKA therapy is challenging for the child and family (Grade 2C). Vitamin K antagonist (VKA) or alternatively LMWH are recommended for children with idiopathic thromboembolism as in children with secondary thrombosis (in whom the risk factor has resolved) for at least six months and at least three months, respectively (Grade 2C).

A study with 27 children evaluated enoxaparin for the treatment of DVT.<sup>44</sup> Neonates through adolescents were included. Doses of enoxaparin administered were 1.5 mg/kg twice daily for neonates and infants, and 1 mg/kg twice daily for children. Mean duration of treatment was 16.5 days followed by a mean prophylaxis period of 9.8 months. Anti-Xa activity treatment goals were achieved in 85 percent of patients. Re-thrombosis and HIT were not observed in any patient in the study.

Children over three months old with DVT were treated with enoxaparin to a target four-hour anti-factor Xa activity between 0.5-0.8 IU/mL.<sup>45</sup> In the open-label trial of 80 children, the patients were stratified to receive once daily or twice daily doses of enoxaparin for a median duration of five months. Endpoints were post-thrombotic syndrome, re-thrombosis, bleeding, and therapy-related death. No significant differences were observed between treatment groups. No bleeding or therapy-related deaths occurred. The median follow-up was 24 months.

### Pregnancy

All four agents in this class are Pregnancy Category B.

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Hemorrhage can occur at any site and may lead to death of mother and/or fetus.

Pregnant women have a five-fold increased risk of an event compared with non-pregnant women. According to the 2007 ACP/AAFP guidelines, there is insufficient evidence to make specific recommendations for types of anticoagulation management of VTE in pregnancy.<sup>46</sup>

LMWH or UFH are recommended by the 2008 ACCP for treatment and/or prophylaxis in pregnant women who have an increased risk for DVT and/or PE.<sup>47</sup> In contrast to VKA, LMWH and UFH do not cross the placenta and do not have the potential to cause fetal bleeding and/or malformations.<sup>48,49</sup> Although the efficacy of LMWH and UFH for this indication has not been verified by randomized, controlled trials, extrapolation of data from non-pregnant patients, along with the relative safety in this patient population, support the recommendation. Because of the

lack of data, the ACCP guidelines make no distinction among enoxaparin (Lovenox), dalteparin (Fragmin), or tinzaparin (Innohep) for this use. More randomized, well-controlled trials are needed to evaluate use of LMWH as prophylaxis in pregnancy and the early post-natal period, according to a systematic review.<sup>50</sup> There are only limited data available regarding the safety of fondaparinux (Arixtra) during pregnancy. Therefore, the 2008 ACCP guidelines recommend against its general use in pregnancy.<sup>51</sup>

A substudy of the ongoing Thrombophilia in Pregnancy Prophylaxis study (TIPPS) determined long term prophylactic dalteparin (Fragmin) in pregnancy did not result in a significant decrease in maternal bone mineral density.<sup>52</sup> Based on data from 62 patients, there was no difference in mean BMD between the patients receiving dalteparin or the control group. TIPPS is expected to conclude in 2011.<sup>53</sup>

The Efficacy of Thromboprophylaxis as an Intervention during Gravidity (ETHIG) was a prospective trial of 810 pregnant women assigned to one of three management strategies according to predefined VTE risk factors.<sup>54</sup> The low risk (group I) received dalteparin 50-100 IU/kg body weight for 14 days postpartum. The high (group II) or very high risk (group III) received dalteparin 50-100 IU/kg/day and 100-200 IU/kg/day, respectively) from enrollment until six weeks postpartum. Symptomatic VTE occurred in 5/810 women (0.6 percent, 95% CI, 0.2-1.5) (group I, 0 of 225; II, 3/469; III, 2/116). Serious bleeding occurred in three percent (95% CI, 1.9-4.4); 1.1 percent (95% CI, 0.5-2.2) was possibly dalteparin-related. There was no evidence of heparin-induced thrombocytopenia (HIT) and one case of osteoporosis. Risk-stratified heparin prophylaxis was associated with a low incidence of symptomatic VTE and few clinically important adverse events.

#### Renal Impairment

The risk of bleeding with LMWH increases with creatinine clearance of less than 30 mL/min.<sup>55</sup> The dose and/or frequency of administration of enoxaparin (Lovenox) should be reduced to daily in patients with severe renal insufficiency. Dalteparin (Fragmin) and tinzaparin (Innohep) should be used with caution in patients with renal insufficiency. Fondaparinux (Arixtra) is contraindicated in patients with severe renal insufficiency (creatinine clearance < 30 mL/min).

#### Hepatic Impairment

Patients with hepatic impairment may be particularly vulnerable to bleeding during fondaparinux (Arixtra) therapy. Although not evaluated, enoxaparin (Lovenox) should be used with caution in patients with hepatic impairment.

**Dosages**

Drug	DVT prophylaxis					DVT treatment (outpatient)*
	Hip replacement**	Knee replacement**	Hip fracture surgery**	Abdominal surgery	Medical	
dalteparin (Fragmin) <sup>56</sup>	5,000 units once daily for 5 to 10 days	--	--	2,500 to 5,000 units once daily for 5 to 10 days	5,000 units once daily for 12 to 14 days	--
enoxaparin (Lovenox) <sup>57</sup>	30 mg every 12 hours OR 40 mg once daily for 7 to 10 days	30 mg every 12 hours for 7 to 10 days	--	40 mg once daily for 7 to 10 days	40 mg once daily for 6 to 11 days	1 mg/kg every 12 hours
fondaparinux (Arixtra) <sup>58</sup>	2.5 mg daily for 5 to 9 days	2.5 mg daily for 5 to 9 days	2.5 mg daily for 5 to 9 days and up to 24 days	2.5 mg daily for 5 to 9 days	--	Based on patient's weight: <50 kg: 5 mg daily 50-100 kg: 7.5 mg daily >100 kg: 10 mg daily
tinzaparin (Innohep) <sup>59</sup>	--	--	--	--	--	175 units/kg once daily

All dosages are given subcutaneously.

\*Given for at least five days (at least six days for tinzaparin) and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0).

\*\*The ACCP Chest guidelines recommend at least ten days and an extended thromboprophylaxis of up to 35 days after surgery in patients undergoing total hip replacement, hip fracture, or knee replacement surgery.<sup>60</sup>

**Renal impairment:** Dalteparin (Fragmin) and tinzaparin (Innohep) should be used with caution in patients with renal insufficiency, although specific dosage adjustment guidelines are not available.

Recently the Innohep in Renal Insufficiency Study (IRIS) compared tinzaparin (Innohep) and UFH in the initial treatment of DVT and/or PE in elderly patients with renal insufficiency (patients ≥ 70 years with estimated CrCl ≤ 30 mL/min or patients ≥ 75 years with estimated CrCl ≤ 60 mL/min). Study treatment was continued for at least five days and until INR was therapeutic. Oral anticoagulant was overlapped and continued for 90 days after start of treatment. Mortality rate in the tinzaparin and UFH groups were 11.2 and 6.3 percent, respectively. Due to this increased risk of death with tinzaparin, alternatives to tinzaparin should be considered when treating all elderly patients with renal insufficiency for DVT with or without PE.<sup>61</sup>

The 2008 ACCP guidelines suggest that if LMWHs are used in patients with severe renal insufficiency, 50 percent of the recommended LMWH dose be used (Grade 2C).<sup>62</sup>

Extended treatment in patients with cancer and symptomatic venous thromboembolism:

Dalteparin (Fragmin): For the first 30 days, dalteparin 200 IU/kg SC is administered once daily. Dosage should not exceed 18,000 IU. For months two through six, dalteparin is given as 150 IU/kg once daily. The daily dose of dalteparin should be reduced by 2,500 IU for patients who have reduced platelet counts (50,000 to 100,000/mm<sup>3</sup>) until the platelet count exceeds 100,000/mm<sup>3</sup>. Patients with platelet counts less than 50,000/mm<sup>3</sup> should not receive dalteparin until platelet count exceeds 50,000/mm<sup>3</sup>. Dose reductions are also necessary for patients with impaired renal function.

Availability

Drug	Prefilled syringes	Vials
dalteparin (Fragmin)	2,500, 5,000, 7,500, 10,000, 12,500, 15,000 or 18,000 units	10,000 units/mL in 9.5 mL MDV 25,000 units/mL in 3.8 mL MDV
enoxaparin (Lovenox)	30, 40, 60, 80, 100, 120, 150 mg	100 mg/mL in 3 mL MDV
fondaparinux (Arixtra)	2.5, 5, 7.5, 10 mg	-
tinzaparin (Innohep)	-	20,000 units/mL in 2 mL MDV

MDV = multiple-dose vial

**Clinical Trials**

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for the FDA-approved indications used in the outpatient setting. Randomized, controlled trials comparing agents for either the treatment or prophylaxis of DVT in the outpatient setting are considered the most relevant in this category. Comparative trials are the most important, but when comparative trials were unavailable, placebo-controlled trials were considered relevant. In comparisons with UFH, studies utilizing weight-based dosing of UFH with adjustments according to laboratory parameters were considered most useful. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

### ***Prophylaxis***

#### dalteparin (Fragmin) versus fondaparinux (Arixtra)

In the Pentasaccharide General Surgery (PEGASUS) study, 2,297 surgical patients were randomized in double-blind fashion to receive either fondaparinux 2.5 mg or dalteparin 5,000 units SC daily.<sup>63</sup> Fondaparinux was initiated six hours after high risk abdominal surgery. Dalteparin was initiated as 2,500 units given two hours preoperatively and repeated 12 hours later. There was no difference between the two treatment arms in occurrence of venous thromboembolism up to post-operative day 10 (4.6 versus 6.1 percent for fondaparinux and dalteparin, respectively), a relative risk reduction of 24.6 percent [95% Confidence Interval (CI), -9.0 to 47.9, p=0.144]; this met the pre-determined criterion for non-inferiority of fondaparinux. No difference was detected in the primary safety outcome, major bleeding, during the initial treatment period. The rate of major bleeding was 3.4 percent in the fondaparinux group and 2.4 percent in the dalteparin group.

#### dalteparin (Fragmin) versus warfarin

In the double-blind, North American Fragmin trial, 1,472 patients were randomized to dalteparin given once daily immediately or early after surgery or post-operative warfarin for DVT prophylaxis in patients undergoing hip arthroplasty.<sup>64</sup> Venograms were performed five days after surgery. The dalteparin group had 10.7 percent positive for any DVT whereas the warfarin group had 24 percent positive for any DVT (p<0.001). Proximal DVTs were identified in 0.8 percent of dalteparin patients and three percent of the warfarin patients (p=0.03 and p=0.04). Serious bleeding was similar in both groups. Pre-operative dalteparin patients experienced more major surgical site bleeding than did the warfarin patients (p=0.01). When evaluating extended out-of-hospital use for up to 35 days with dalteparin or placebo, new proximal DVT rates were 0.7 to 1.3 percent of dalteparin patients and 4.8 percent for the inpatient warfarin group.<sup>65</sup> Overall, the cumulative incidence of all DVT was 17.2 to 22.2 percent with dalteparin and 36.7 percent with in-hospital warfarin/out-of-hospital placebo group. Cumulative proximal DVT rates were 2 to 3.1 percent for dalteparin and 9.2 percent for the warfarin/placebo groups. No major bleeding occurred during the extended prophylaxis time period.

A multicenter, randomized, open-label trial compared the efficacy of dalteparin with a coumarin derivative to prevent recurrent thrombosis in 672 patients with cancer.<sup>66</sup> Patients with cancer who had acute, symptomatic proximal DVT, PE or both were randomized to dalteparin 200 IU/kg daily SC for five to seven days and an oral anticoagulant, warfarin or acenocoumarol, for six months (INR target 2.5) or dalteparin alone given as 200 IU/kg daily for one month followed by 150 IU/kg for five months. Recurrent venous thromboembolism was reported in 8 percent and 15.8 percent of patients receiving dalteparin and oral anticoagulant, respectively over the six-month study period (hazard ratio=0.47, p=0.002). The probability of recurrent thromboembolism at six months was 17 percent in the dalteparin plus oral anticoagulant group and 9 percent in the dalteparin only group. Rates of major bleeding for dalteparin plus oral anticoagulant (six percent) and dalteparin alone (four percent) were similar (p=0.27). Mortality rates at six months were 39 percent in the dalteparin only group and 41 percent in the dalteparin plus oral anticoagulant group (p=0.53).

enoxaparin (Lovenox) versus fondaparinux (Arixtra)

A multicenter, randomized, double-blind trial compared enoxaparin and fondaparinux in patients undergoing elective knee surgery.<sup>67</sup> Patients (n=1,049) were randomized to receive enoxaparin 30 mg SC twice daily or fondaparinux 2.5 mg SC once daily. Both drugs were started postoperatively. The primary efficacy endpoint, incidence rate of VTE, was determined by day 11. Diagnosis of VTE was completed by bilateral leg venography assessing for DVT, and for PE, diagnosis was made by lung scan indicating a high probability of pulmonary embolism, by pulmonary angiography, by helical computed tomography, or at autopsy. The primary safety outcome was major bleeding. Incidence of VTE by day 11 was significantly lower in the fondaparinux group (12.5 percent) than the enoxaparin group (27.8 percent;  $p < 0.001$ ). The rate of symptomatic venous thrombosis was similar between the groups. More major bleeding was observed in the fondaparinux group ( $p = 0.006$ ).

In a multicenter, randomized, double-blind trial, enoxaparin 40 mg and fondaparinux 2.5 mg, each given SC once daily, were compared in 1,711 patients undergoing hip fracture surgery.<sup>68</sup> Enoxaparin therapy was initiated pre-operatively whereas fondaparinux was initiated post-operatively; treatment continued for at least five days in both groups. The primary efficacy endpoint was the rate of VTE up to day 11; the primary safety outcomes were major bleeding and all-cause mortality through six weeks. In the study, the incidence of VTE was significantly lower in the fondaparinux group (8.3 percent) than the enoxaparin group (19.1 percent;  $p < 0.001$ ). Symptomatic venous thrombosis was similar between the groups. There were no significant differences between the two groups in the incidence of death or rate of clinically relevant bleeding.

In the double-blind European Pentasaccharide Hip Elective Surgery Study (EPHESUS), 2,309 consecutive adult patients undergoing elective hip replacement surgery were randomly assigned in a double-blind manner to fondaparinux 2.5 mg SC daily, starting postoperatively, or enoxaparin 40 mg SC daily, starting preoperatively.<sup>69</sup> The primary efficacy outcome was VTE up to day 11; primary safety outcomes were bleeding and death through six weeks. Primary efficacy analysis was performed in 908 fondaparinux patients and 919 enoxaparin patients. By day 11, four percent of fondaparinux patients experienced VTE whereas nine percent of enoxaparin patients had positive findings for VTE (55.9 percent relative risk reduction,  $p < 0.0001$ ). The two groups did not differ significantly in incidence of death or rate of clinically relevant bleeding.

In the similarly designed PENTATHLON 2000 study, 2,275 consecutive adult patients who were undergoing elective hip replacement surgery were randomized in a double-blind manner to receive either fondaparinux 2.5 mg SC once daily or enoxaparin 30 mg SC twice daily.<sup>70</sup> The primary efficacy of the presence of VTE was assessed to day 11 in 1,584 patients. Venous thromboembolism was reported in six percent of patients on fondaparinux and eight percent of patients receiving enoxaparin ( $p = \text{NS}$ ). The two groups did not differ in the number of patients who died or in the number who had clinically relevant bleeding.

enoxaparin (Lovenox) versus tinzaparin (Innohep)

A multicenter trial randomly assigned 499 consecutive patients undergoing total hip replacement to either tinzaparin 4,500 units or enoxaparin 40 mg SC daily for the prevention of DVT.<sup>71</sup> In the blinded study, LMWH was given 12 hours before and 12 hours after surgery, then daily. A total of 440 patients underwent a venogram. At 12 to 14 days after surgery, the overall

rate of DVT was 21.7 percent in the tinzaparin group and 20.1 percent in the enoxaparin group (p=NS). The rate of proximal DVT was similar in both groups, occurring in 10.5 percent of the enoxaparin group and 9.5 percent of the tinzaparin group (p=NS). No major bleeding was observed.

### ***Treatment (Outpatient)***

#### enoxaparin (Lovenox) versus fondaparinux (Arixtra)

MATISSE DVT trial was a multicenter, double-blind study including 2,205 patients with acute symptomatic DVT. The patients were randomized to receive enoxaparin 1 mg/kg SC twice daily or fondaparinux 7.5 mg SC once daily for at least five days and until the INR was above 2.0.<sup>72</sup> Vitamin K antagonist therapy was initiated within 72 hours of either randomized therapy. Doses for fondaparinux were adjusted for patients weighing less than 50 kg (fondaparinux 5 mg SC daily) and more than 100 kg (fondaparinux 10 mg SC daily). The rates of recurrent thromboembolic events (primary outcome) were similar in the enoxaparin and fondaparinux groups (4.1 and 3.9 percent, respectively; p=NS). Major bleeding occurred in 1.2 percent of patients receiving enoxaparin and 1.1 percent of patients receiving fondaparinux (p=NS).

#### tinzaparin (Innohep) versus UFH

A trial conducted by the American-Canadian Thrombosis Study Group compared tinzaparin with IV UFH for the treatment of PE.<sup>73</sup> In the double-blind trial, 200 patients with high-probability lung scans were randomized to once daily SC tinzaparin or to adjusted-dose IV UFH. New VTE was documented in none of the patients who received tinzaparin compared with 6.8 percent of patients who received UFH (p=0.01). Major bleeding occurred in one patient (one percent) on tinzaparin and two patients (1.9 percent) on UFH. The results of the study support that tinzaparin is at least as effective as UFH for preventing recurrent VTE in patients with PE.

#### Meta-analysis

Two different meta-analyses evaluated the randomized, controlled trials of LMWH versus UFH in the treatment of acute DVT.<sup>74,75</sup> The LMWHs were shown to reduce mortality rates after acute DVT and appeared as safe as UFH and provide similar efficacy. Initial therapy of PE with LMWH also appears as effective as UFH.

A Cochrane database systemic review evaluated the safety and efficacy of three types of anticoagulants: LMWH, UFH, and fondaparinux (Arixtra) for the initial treatment of VTE in cancer patients.<sup>76</sup> A meta-analysis of 11 studies showed a statistically significant mortality reduction in patients treated with LMWH compared with those treated with UFH [relative risk (RR)=0.71, 95% CI, 0.52 to 0.98]. A meta-analysis of three studies comparing LMWH with UFH in reducing recurrent VTE was inconclusive (RR=0.78, 95% CI, 0.29 to 2.08). No data were available for bleeding outcomes, thrombocytopenia or postphlebotic syndrome. Fondaparinux showed a non-statistically significant benefit compared to UFH for death (RR = 0.52, 95% CI, 0.26 to 1.05). One study compared dalteparin to tinzaparin and showed a non-statistically significant mortality reduction with dalteparin (RR=0.86, 95% CI, 0.43 to 1.73). The study results support LMWH over UFH in the initial treatment of VTE cancer patients.

A meta-analysis of four randomized, double-blind, multicenter trials for prevention of VTE in 7,344 patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture compared SC fondaparinux 2.5 mg daily starting six hours after surgery to SC

enoxaparin regimens.<sup>77</sup> Fondaparinux significantly reduced the primary efficacy outcome of VTE by day 11 compared with enoxaparin, 6.8 versus 13.7 percent, respectively (common odds reduction of 55.2 percent (95% CI, 45.8 to 63.1 percent; p<0.001). Fondaparinux as compared to enoxaparin resulted in increased risk of major bleeding, 2.7 versus 1.7 percent, respectively (p=0.008). However, the incidence of clinically relevant bleeding (leading to death or re-operation or occurring in a critical organ) did not differ between groups. In a post-hoc efficacy and safety analysis, the incidence of major bleeding was significantly less in patients receiving fondaparinux ≥ six hours versus < six hours following surgery (e.g. skin closure), 2.1 versus 3.2 percent, respectively.<sup>78</sup> There was no significant difference in the incidence of VTE at these different time points.

***Efficacy of Injectable***

***Anticoagulants***<sup>79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112</sup>

Drug	Prophylaxis: Development of post-operative DVT (%)				Treatment: Recurrent VTE (%)
	Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
dalteparin (Fragmin)	4-30	--	*30	3.9-4.4	*0-9
enoxaparin (Lovenox)	6-38	19-37	*19.1	9.7	3.3-4.1
fondaparinux (Arixtra)	1.7-5.6	12.5	8.3	4.2	3.9
tinzaparin (Innohep)	*21-31	*45	--	--	0-4.2

\*off-label

Review of overall occurrence of DVT in patients undergoing orthopedic surgery does not reveal any significant advantage of one LMWH over another for prophylaxis. While fondaparinux (Arixtra) has been shown to reduce the development of post-operative DVT to a greater extent than enoxaparin, this risk reduction can be accompanied by an increase in risk of bleeding. Administration of fondaparinux before six hours after surgery has been associated with an increased risk of major bleeding.<sup>113</sup> After hemostasis has been established, the recommended timing of the first fondaparinux injection is six to eight hours after surgery.<sup>114</sup>

Examination of data from VTE treatment trials reveals similar overlap in frequency of events as well as between-study variability.

***Summary***

The injectable anticoagulants, LMWHs and fondaparinux (Arixtra), are important treatment options in DVT and PE management. They offer advantages over UFH including lack of need for laboratory coagulation monitoring, ease of dosing, and reduced risk of heparin-induced thrombocytopenia (HIT). LMWHs have been shown to reduce mortality rates after acute DVT

and provide similar efficacy. Initial therapy of PE with LMWH also appears as effective as UFH. When used in equipotent dosages, all of the LMWHs will provide a therapeutic anticoagulant effect.

Fondaparinux (Arixtra) has shown a reduction in preventing post-operative VTE compared to enoxaparin (Lovenox) following major orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). Fondaparinux (Arixtra) has been associated with an increased risk of bleeding; however the timing of administration can affect the risk of bleeding. Fondaparinux (Arixtra) has been shown to be non-inferior to dalteparin (Fragmin) in preventing post-operative VTE in patients undergoing major abdominal surgery.

The Eighth American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend extended-duration LMWH, fondaparinux (Arixtra), or vitamin K antagonist (VKA) for DVT prophylaxis in patients undergoing total hip replacement, knee replacement, or hip fracture surgery. For treatment of DVT or PE, the ACCP guidelines recommend anticoagulation with LMWH, fondaparinux (Arixtra), or VKA for a minimum of three months.

Although each product has different FDA-approved indications, the ACCP makes no distinction among the agents for orthopedic surgery prophylaxis or treatment of VTE. While SC anticoagulants have subtle differences in methods of preparation, pharmacokinetics parameters, and anti-Xa activity, the clinical characteristics are similar.

## References

- <sup>1</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>2</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>3</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>4</sup> Innohep [package insert], Summit, NJ; Celgene; December 2008.
- <sup>5</sup> Erdman SM, Chuck SK, Rodvold KA. Thromboembolic disorders. In: DiPiro JT, Talbert RL, Yee GC et al., eds. *Pharmacotherapy: a pathophysiologic approach*. 4th ed. Stamford, CT: Appleton & Lange; 1999:295-326.
- <sup>6</sup> Yusef RD, Eby C, Walgreen R. Disorders of hemostasis. In: Green GB, Harris IS, Lin GA, et al., eds. *The Washington Manual of Medical Therapeutics*. 32nd ed. Lippincott Williams and Wilkins. 2007:510-547.
- <sup>7</sup> American College of Physicians. on-line.  
[http://www.acponline.org/clinical\\_information/journals\\_publications/acp\\_hospitalist/mar08/focus.htm](http://www.acponline.org/clinical_information/journals_publications/acp_hospitalist/mar08/focus.htm). Accessed December 3, 2009.
- <sup>8</sup> Erdman SM, Chuck SK, Rodvold KA. Thromboembolic disorders. In: DiPiro JT, Talbert RL, Yee GC et al., eds. *Pharmacotherapy: a pathophysiologic approach*. 4th ed. Stamford, CT: Appleton & Lange; 1999:295-326.
- <sup>9</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest*. 2008; 133(6S):71S-109S.
- <sup>10</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest*. 2008; 133(6S):71S-109S.
- <sup>11</sup> Snow V, Qaseem A, Barry P, et al. The Joint American College of Physician/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Fam Med*. 2007; 5(1):74-80. Available at <http://www.annfammed.org/content/vol5/issue1/>. Accessed December 3, 2009.
- <sup>12</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest*. 2008; 133(6S):71S-109S.
- <sup>13</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest*. 2008; 133(6S):71S-109S.
- <sup>14</sup> Laposata M, Green D, Van Cott EM, et al. The clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med*. 1998; 122:799-807.
- <sup>15</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>16</sup> Friedel H, Balfour JA. Tinzaparin: a review of its pharmacology and clinical potential in the prevention and treatment of thromboembolic disorders. *Drugs*. 1994; 48:638-660.
- <sup>17</sup> Cornelli U, Fareed J. Human pharmacokinetics of low-molecular weight heparins. *Semin Thromb Hemost*. 1999; 25 (suppl 3):57-61.
- <sup>18</sup> Fegan CD. Tinzaparin as an anti-thrombotic: an overview. *Hosp Med*. 1998; 59: 145-148.
- <sup>19</sup> Heit JA. The Potential Role of Fondaparinux as Venous Thromboembolism Prophylaxis After Total Hip or Knee Replacement or Hip Fracture Surgery. *Arch Int Med*. 2002; 162(16).

- <sup>20</sup> Haines ST, Bussey HI. Thrombosis and the pharmacology of antithrombotic agents. *Ann Pharmacother.* 1995; 29: 892-905.
- <sup>21</sup> Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost.* 2000; 26 Suppl 1:31-8.
- <sup>22</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>23</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>24</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>25</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>26</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>27</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>28</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>29</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>30</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>31</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>32</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>33</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>34</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>35</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>36</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>37</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>38</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>39</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>40</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>41</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>42</sup> Mongale P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest.* 2008; 133(6S):887S-968S.
- <sup>43</sup> Mongale P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest.* 2008; 133(6S):887S-968S.
- <sup>44</sup> Merkel N, Gunther G, Schobess R. Long-term treatment of thrombosis with enoxaparin in pediatric and adolescent patients. *Acta Haematol.* 2006; 115(3-4):230-6.
- <sup>45</sup> Schobess R, Doring C, Bidlingmaier C, et al. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. *Haematologica.* 2006; 91(12):1701-1704.
- <sup>46</sup> Snow V, Qaseem A, Barry P, et al. The Joint American College of Physician/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Fam Med.* 2007; 5(1):74-80. Available at <http://www.annfam.org/content/vol5/issue1/>. Accessed December 3, 2009.
- <sup>47</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest.* 2008; 133(6S):71S-109S.
- <sup>48</sup> Hall JAG, Paul RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med.* 1980; 68:122-140.
- <sup>49</sup> Becker MH, Genieser NB, Finegold M, et al. Chondrodysplasia punctata: is maternal warfarin a factor? *Am J Dis Child.* 1975; 129:356-359.
- <sup>50</sup> Gates S. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Rev Abstract.* 2006.
- <sup>51</sup> Bates SM, Greer IA, Pabinger I, et al. Venous Thromboembolism, Thrombophilia Antithrombotic Therapy, and Pregnancy American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133(6S):844S-886S.
- <sup>52</sup> Rodger MA, Kahn SR, Cranney A, et al for the TIPPS investigators. Long-term dalteparin in pregnancy not associated with a decrease in bone mineral density: substudy of a randomized controlled trial. *J Thromb Haemost.* 2007; 5(8):1600-6.
- <sup>53</sup> Available at: <http://www.controlled-trials.com/ISRCTN87441504/ISRCTN87441504>. Accessed on December 3, 2009.
- <sup>54</sup> Bauersachs RM, Dudenhausen J, Faridi A, et al. The EthIG Investigators. Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women. *Thromb Haemost.* 2007; 98(6):1237-1245.
- <sup>55</sup> Lim W, Dentali F, Eikelboom JW, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Int Med.* 2006; 144(9):673-684.
- <sup>56</sup> Fragmin [package insert]. Teaneck, NJ; Eisai; April 2007.
- <sup>57</sup> Lovenox [package insert]. Bridgewater, NJ; Aventis; July 2009.
- <sup>58</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>59</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>60</sup> Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* 2004; 126:338S-400S.
- <sup>61</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>62</sup> Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition). *Chest.* 2008; 133(6S):71S-109S.
- <sup>63</sup> Agnelli G, Bergqvist D, Cohen AT, et al and the PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Brit J Surg.* 2005; 92(10):1212-1220.
- <sup>64</sup> Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs. warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. *Arch Intern Med.* 2000; 160(14):2199-2207.

- <sup>65</sup> Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs. in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. *North American Fragmin Trial Investigators. Arch Intern Med.* 2000; 160:2208-2215.
- <sup>66</sup> Lee AY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003; 349(2):146-153.
- <sup>67</sup> Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective knee surgery. *N Engl J Med.* 2001; 345:1305-1310.
- <sup>68</sup> Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med.* 2001; 345:1298-1304.
- <sup>69</sup> Lassen MR, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomized double blind comparison. *Lancet.* 2002; 359:1715-1720.
- <sup>70</sup> Turpie AGG, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomized double-blind trial. *Lancet.* 2002; 359:1721-1726.
- <sup>71</sup> Planes A, Samama MM, Lensing AWA, et al. Prevention of deep vein thrombosis after hip replacement. Comparison between two low-molecular-weight-heparins, tinzaparin and enoxaparin. *Thromb Haemost.* 1999; 81:22-25.
- <sup>72</sup> Buller HB, Davidson BL, Decousus H, et al. Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Vein Thrombosis. A Randomized Trial. *Ann Intern Med.* 2004; 140:867-873.
- <sup>73</sup> Hull RD, Raskob GE, Brant RF, et al. Low-Molecular-Weight Heparin vs. Heparin in the Treatment of Patients with Pulmonary Embolism. *Arch Intern Med.* 2000; 160:229-236.
- <sup>74</sup> Gould MK, Dembitzer AD, Doyle RL, et al. Low-Molecular Weight Heparins Compared with Unfractionated Heparin for Treatment of Acute Deep Venous Thrombosis. *Ann Intern Med.* 1999; 130:800-809.
- <sup>75</sup> Segal JB, Bolger DT, Jenckes MW, et al. Outpatient therapy with low molecular weight heparin for the treatment of venous thromboembolism: a review of efficacy, safety, and costs. *Am J Med.* 2003; 115(4):298-308.
- <sup>76</sup> Akl EA, Rohilla S, Barba M, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev.* 2008; 23(1):CD006649.
- <sup>77</sup> Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med.* 2002; 162(16):1833-1840.
- <sup>78</sup> Turpie AG, Bauer KA, Eriksson BI, et al. Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Efficacy and safety of fondaparinux in major orthopedic surgery according to the timing of its first administration. *Thromb Haemost.* 2003; 90(2):364-366.
- <sup>79</sup> Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery -- results of a double-blind, prospective, randomized, placebo-controlled study with dalteparin (Fragmin®). *Thromb Haemost.* 1997; 77:26-31.
- <sup>80</sup> Torholm C, Broeng L, Jorgensen PS, et al. Thrombo-prophylaxis by low molecular weight heparin in elective hip surgery. *J Bone Joint Surg.* 1991; 73B(suppl):434-438.
- <sup>81</sup> Jorgensen PS, Knudsen JB, Broeng L, et al. The thrombo-prophylactic effect of a low molecular weight heparin (Fragmin) in hip fracture surgery. *Clin Orthop.* 1992; 278:95-100.
- <sup>82</sup> Eriksson BI, Zachrisson BE, Teger-Nilsson AC, et al. Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. *Br J Surg.* 1988; 75:1053-1057.
- <sup>83</sup> Eriksson BI, Kalebo P, Anthmyr BA, et al. Prevention of deep venous thrombosis and pulmonary embolism after total hip replacement. *J Bone Joint Surg.* 1991; 73A(suppl):484-493.
- <sup>84</sup> Warwick D, Harrison J, Glew D, et al. Comparison of the use of a foot pump with the use of low molecular weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *J Bone Joint Surg Am.* 1998; 80:1158-1166.
- <sup>85</sup> Bergqvist D, Benoni G, Bjorgell O, et al. Low molecular weight heparin (enoxaparin) as prophylaxis against thromboembolism after total hip replacement. *N Engl J Med.* 1996; 335:696-700.
- <sup>86</sup> Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of deep vein thrombosis after major knee surgery -- a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost.* 1992; 67:417-423.
- <sup>87</sup> Fauno P, Suomalainen O, Rehnberg V, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. *J Bone Joint Surg Am.* 1994; 76A:1814-1818.
- <sup>88</sup> Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: A randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost.* 1988; 60:407-410.
- <sup>89</sup> Eriksson BI, Wille-Jorgensen P, Kalebo P, et al. A comparison of recombinant hirudin with a low molecular weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med.* 1997; 337:1329-1335.
- <sup>90</sup> Colwell CW Jr, Spiro TE, Trowbridge AA, et al. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. The enoxaparin clinical trial group. *Clin Orthop.* 1995; 321:19-27.
- <sup>91</sup> Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med.* 1996; 124:619-626.
- <sup>92</sup> Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. *Acta Orthop Scand.* 1999; 62:33-38.
- <sup>93</sup> Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low molecular weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med.* 1993; 329:1370-1306.
- <sup>94</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>95</sup> Holmstrom M, Berglund C, Granqvist S, et al. Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. *Thromb Res.* 1992; 67:49-55.

- <sup>96</sup> Alhenc-Gelas M, Guernic CJL, Vitoux JF, for the Fragmin Study Group. Adjusted versus fixed doses of the low molecular weight heparin Fragmin in the treatment of deep vein thrombosis. *Thromb Haemost.* 1994; 71:698-702.
- <sup>97</sup> Bratt GA, Tornebohm E, Johanson M, et al. Clinical experiences in the administration of a low-molecular weight heparin (Fragmin, Kabi-Vitrum) to healthy volunteers and in the treatment of established deep venous thrombosis. *Acta Chir Scand.* 1988; 543(suppl):96-100.
- <sup>98</sup> Holm HA, Ly B, Handeland GF, et al. Subcutaneous heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Haemostasis.* 1986; 16(suppl 2):30-37.
- <sup>99</sup> Handeland GF, Abildgaard U, Holm HA, et al. Dose-adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Eur J Clin Pharmacol.* 1990; 39:107-12.
- <sup>100</sup> Albada J, Nieuwenhuis HK, Sixma JJ. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin). *Circulation.* 1989; 80:935-940.
- <sup>101</sup> Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low molecular weight heparin Fragmin versus intravenous unfractionated heparin in the treatment of acute non-massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost.* 1995; 74:1432-435.
- <sup>102</sup> Partsch H, Kechavarz B, Mostbeck A, et al. Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with one-or-twice-daily low molecular weight heparin. *J Vasc Surg.* 1996; 24:774-782.
- <sup>103</sup> Fiessinger J, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost.* 1996; 76:195-199.
- <sup>104</sup> Luomanmaki K, Granqvist S, Hallert C, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. *J Intern Med.* 1996; 240:85-92.
- <sup>105</sup> Lindmarker P, Holmstrom M, Granqvist S, et al. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost.* 1994; 72:186-190.
- <sup>106</sup> Bratt G, Aberg W, Johansson M. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep vein thrombosis (DVT). *Thromb Haemost.* 1990; 64:506-510.
- <sup>107</sup> Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med.* 1993; 153:1541-1546.
- <sup>108</sup> Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med.* 1992; 326:975-982.
- <sup>109</sup> Simonneau G, Sors H, Charbonnier B, et al. A comparison of low molecular weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med.* 1997; 337:663-669.
- <sup>110</sup> Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs. heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med.* 2000; 160:229-336.
- <sup>111</sup> Buller HB, Davidson BL, Decousus H, et al. Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Vein Thrombosis. A Randomized Trial. *Arch Intern Med.* 2004; 140:867-873.
- <sup>112</sup> Innohep [package insert], Summit, NJ: Celgene; December 2008.
- <sup>113</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.
- <sup>114</sup> Arixtra [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2009.