

Anticoagulants, Injectable Review

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Anticoagulants, Injectable Review

Overview

Drug	Manufacturer
dalteparin (Fragmin [®])	Eisai
enoxaparin (Lovenox [®])	Sanofi-Aventis
fondaparinux (Arixtra [™])	GlaxoSmithKline
tinzaparin (Innohep [®])	Pharmion

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.^{1,2}

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 (40 years or greater).^{3,4}

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 Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines recommends various regimens of parenteral and/or oral anticoagulants with or without mechanical devices such as elastic stockings and intermittent pneumatic compression devices.⁵

Treatment options for VTE consist of at least five days of either intravenous (IV) or subcutaneous (SC) unfractionated heparin (UFH) or SC low molecular weight heparin (LMWH) or selective factor Xa inhibitor. Warfarin is given to overlap the parenteral anticoagulant therapy until the International Normalized Ratio (INR) is therapeutic for two consecutive days. Anticoagulation is continued for a minimum of three months. The American College of Physicians and The American Academy of Family Physicians 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.⁶ For long-term treatment, SC anticoagulants are an alternative therapy for patients in whom oral anticoagulants cannot be used.⁷

FDA-Approved Indications

Drug	DVT prophylaxis				DVT Treatment*
	Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
dalteparin (Fragmin)	X	-	-	X	-
enoxaparin (Lovenox)	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra)	X	X	X	X	X
tinzaparin (Innohep)	-	-	-	-	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 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)

- inpatient treatment of acute DVT with or without PE administered with warfarin
- for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction
- 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.

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. LMWH has a more sustained effect on clotting factor Xa than does UFH, less frequent dosing is required. In addition, the incidence of thrombocytopenia appears to be lower with LMWH than with UFH.⁸

In contrast to the indirect thrombin inhibitors, 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 (Arixtra) does not bind to platelet factor 4, a factor involved in immune-related heparin-induced thrombocytopenia (HIT).⁹

Pharmacokinetics^{10,11,12,13,14,15}

Drug	Bioavailability (%)	Half-life* (hrs)	Average molecular weight (daltons)	Anti-Xa : Anti-IIa activity	Peak Anti-Xa activity (hrs)
dalteparin (Fragmin) ¹⁶	87	2-5	5,000	2-4 : 1	4
enoxaparin (Lovenox) ¹⁷	~ 100	4.5-7	4,500	2.7-3.7 : 1	3-5
fondaparinux (Arixtra) ¹⁸	~ 100	17-21	1,728	Anti-Xa only	3
tinzaparin (Innohep) ¹⁹	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^{20,21,22,23}

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) should not be administered intramuscularly.

Fondaparinux (Arixtra) 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/mm³, therapy with agents in this class should be reevaluated and possibly discontinued.

LMWH 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.

Fondaparinux (Arixtra) is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Fondaparinux (Arixtra) 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 (Arixtra) is contraindicated in patients with bacterial endocarditis due to increased risk of bleeding.

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

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

Drug Interactions^{24,25,26,27}

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[®]), and thrombolytics.

Adverse Effects

Drug	Major bleeding	Thrombocytopenia	Injection site reactions
dalteparin (Fragmin) ²⁸	0 - 4.6	<1	2-12
enoxaparin (Lovenox) ²⁹	< 1-4	0.1-1.3	Reported
fondaparinux (Arixtra) ³⁰	2.2-3.4	0.04-3	Reported
tinzaparin (Innohep) ³¹ Treatment	0.8-2.8	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 PopulationsPediatrics

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

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 warfarin; reduced risk of HIT; and probable reduced risk of osteoporosis with long-term use, which occurs with UFH. LMWH is recommended as first-line therapy for initial thromboembolism by the ACCP guidelines for the treatment of VTE in children. The guidelines also recommend LMWH as second-line therapy, after warfarin, to treat recurrent idiopathic thromboembolisms.³²

A total of 48 children were enrolled in a German case series to investigate the safety and efficacy of dalteparin in prophylaxis and treatment of arterial and venous thrombosis.³³ No VTE occurred in the ten children who received dalteparin for prophylaxis. In the group of eight children receiving LMWH for reocclusion prophylaxis following successful thrombolysis, recanalization was maintained or improved. In the five children receiving LMWH following failed thrombolysis, vascular occlusion persisted under dalteparin. In the 23 children receiving primary antithrombotic therapy, complete recanalization occurred in seven (30 percent), partial recanalization in seven (30 percent), and no recanalization in nine (40 percent) cases. One child being treated for pulmonary veno-occlusive disease had recanalization proven by lung biopsy. Another child being treated for primary pulmonary hypertension also showed clinical improvement. Minor bleeding occurred in two (four percent) of the children.

A study with 27 children evaluated enoxaparin for the treatment of DVT.³⁴ 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 this 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.³⁵ In this 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.^{36,37,38,39}

LMWH is recommended by the ACCP for treatment and/or prophylaxis in pregnant women who have an increased risk for DVT and/or PE.⁴⁰ In contrast to warfarin, LMWH and UFH do not cross the placenta and do not have the potential to cause fetal bleeding and/or malformations.^{41,42} 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, ACCP makes no distinction between enoxaparin (Lovenox) and dalteparin (Fragmin) 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 recent systematic review.⁴³

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.⁴⁴ 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 2011.⁴⁵

Dosages

Drug	DVT prophylaxis				DVT treatment (outpatient)*
	Hip replacement**	Knee replacement	Hip fracture surgery**	Abdominal surgery	
dalteparin (Fragmin) ⁴⁶	5,000 units once daily for 5 to 10 days	--	--	2,500 to 5,000 units once daily for 5 to 10 days	--
enoxaparin (Lovenox) ⁴⁷	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	1 mg/kg every twelve hours
fondaparinux (Arixtra) ⁴⁸	2.5 mg daily for 5 to 9 days	2.5 mg daily for 5 to 9 days	2.5 mg daily for 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) ⁴⁹	--	--	--	--	175 units/kg once daily

All dosages are given subcutaneously.

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

**The ACCP Chest guidelines recommend extended thromboprophylaxis of up to 28 to 35 days in patients undergoing total hip replacement or hip fracture surgery.⁵⁰

Renal impairment: The risk of bleeding with LMWH increases with creatinine clearances of less than 30 mL/min.⁵¹ The 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, although specific dosage adjustment guidelines are not available. Fondaparinux (Arixtra) is contraindicated in patients with severe renal insufficiency (creatinine clearance < 30 mL/min).

Extended treatment in patients with cancer and symptomatic venous thromboembolism:

Dalteparin (Fragmin): For the first 30 days, dalteparin (Fragmin) 200 IU/kg SC administered once daily. Dosage should not exceed 18,000 IU. For months two through six, dalteparin (Fragmin) is given as 150 IU/kg once daily. The daily dose of dalteparin (Fragmin) should be reduced by 2,500 IU for patients who have reduced platelet counts (50,000 to 100,000/mm³) until the platelet count exceeds 100,000/mm³. Patients with platelet counts less than 50,000/mm³ should not receive dalteparin (Fragmin) until platelet count exceeds 50,000/mm³. 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, www.ifpma.org/clinicaltrials, 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.⁵² Fondaparinux was initiated six hours after 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-op day 10 (4.6 versus 6.1 percent for fondaparinux and enoxaparin, respectively). 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.⁵³ 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.⁵⁴ 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 patients with cancer.⁵⁵ 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. Rate of major bleeding for dalteparin plus oral anticoagulant (six percent) and dalteparin alone (four percent) were similar ($p = 0.27$). Mortality rate at six months was 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.⁵⁶ 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.⁵⁷ 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 this 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 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.⁵⁸ 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 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.⁵⁹ 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.⁶⁰ 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 ($p = \text{NS}$). 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 ($p = \text{NS}$). 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 2.0.⁶¹ 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; $p = \text{NS}$). Major bleeding occurred in 1.2 percent of patients receiving enoxaparin and 1.1 percent of patients receiving fondaparinux ($p = \text{NS}$).

tinzaparin (Innohep) versus UFH

A recent trial conducted by the American-Canadian Thrombosis Study Group compared tinzaparin with IV UFH for the treatment of PE.⁶² 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.

Efficacy of Injectable

Anticoagulants^{63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96}

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

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 LMWH, this risk reduction is accompanied by an increase in bleeding.

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

Summary

Two different meta-analyses evaluated the randomized, controlled trials of LMWH versus UFH in the treatment of acute DVT.^{97,98} 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. When used in equipotent dosages, all of the LMWHs will provide a therapeutic anticoagulant effect.

In orthopedic surgery, fondaparinux (Arixtra) appears to be more effective than the LMWHs at reducing the incidence of post-operative VTE. It does so, however, at the risk of increased bleeding.

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.⁹⁹

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