ENOXAPARIN or FONDAPARINUX
CHOOSE YOUR ANTITHROMBOTIC AGENT

For many years unfractionated heparin (UFH) was the only antithrombotic agent available in the United States. However, during the past decade new antithrombotic agents have become available. The first of these agents were the low-molecular weight heparins (LMWHs) followed more recently by the direct anti-Xa inhibitors, of which only fondaparinux is available in the United States. Low-molecular weight heparins have replaced the use of unfractionated heparin in Europe and in many cases in the United States, primarily on the basis of convenience of use and a lower incidence of heparin-induced thrombocytopenia.

HEPARINS

Unfractionated heparin is a heterogeneous mixture of sulfated polysaccharide chains containing D-glucosamine and either glucuronic or iduronic acid that range in molecular weight from 3000 to 30,000. The low-molecular weight heparins are produced by the enzymatic or chemical digestion of UFH to produce fragments with a mean molecular weight of about 5000. Both UFH and LMWH exert their antithrombotic activity by activating antithrombin. This interaction with antithrombin is mediated by a unique pentasaccharide sequence in the polysaccharide chain. The binding of this pentasaccharide active site to antithrombin causes a conformational change in the antithrombin molecule that accelerates its interaction with thrombin and activated factor Xa. Either penta saccharide-containing heparin chain can inhibit factor Xa by binding to antithrombin and causing a conformational change. However, in order to inactivate thrombin, heparin must bind to both antithrombin and thrombin and form a tertiary complex. This complex can only form if the heparin molecule contains at least 16 saccharide units. Since fewer of the LMWH molecules are 16 saccharide units long they are unable to form this complex. Therefore, unfractionated heparin has equivalent activity against both thrombin and factor Xa, while LMWHs have greater activity against factor Xa.

The pharmacokinetic differences seen between LMWH and UFH are primarily a more predictable anticoagulant response with LMWH due to its lower binding to plasma proteins, such as histidine-rich glycoprotein and better bioavailability due to a lower binding to endothelium. The LMWHs also have a longer half-life of two to six hours compared to 90 minutes for UFH.

There are three LMWHs available in the United States: enoxaparin (Lovenox™), dalteparin (Fragmin™) and tinzaparin (Innohep™). There are other LMWHs available in Europe. Each LMWH is produced by depolymerization of UFH using different methods resulting in slight differences in pharmacology. This results in differences in the number of saccharide units with more or less than 16 units between the different products. This in turn affects the ratio of inhibition of thrombin and factor Xa. Although it is not clear if this has any clinical significance, the Food and Drug Administration and the World Health Organization have classified each LMWH as a distinct drug. In spite of this classification, most journal articles and books refer to these products generically as low-molecular weight heparins. Because there are often considerable price differences between the available LMWHs the question often occurs as whether the LMWHs can be considered therapeutically interchangeable.

Chemically, since each LMWH is produced by a different chemical method of depolymerization, the size range of the heparin molecules varies between products resulting in a different ratio of antithrombin to anti-factor Xa activity. Whether this ratio has clinical meaning in antithrombotic therapy is unproved. It is possible that LMWHs have other mechanisms of action such as affecting the release of tissue factor pathway inhibitor. The true test of therapeutic interchange involves head-to-head randomized clinical trials. Unfortunately, there have been very few studies that directly compared two LMWH products and those have been underpowered to determine if there are clinically meaningful differences in either efficacy or safety.

One study compared deep vein thrombosis prophylaxis of enoxaparin (n = 219) to tinzaparin (n = 221) in high-risk orthopedic surgery patients. The study showed that these two LMWHs were essentially equivalent. The incidence of venographically defined thrombosis was 20% in patients receiving enoxaparin and 22% in those receiving tinzaparin. This study also measured antithrombin and anti-factor Xa activity in the patients. On average the levels of antithrombin activity were higher among the patients receiving tinzaparin, whereas the anti-factor Xa activity was higher in those patients receiving enoxaparin. This study suggests that the ratio of antithrombin activity and anti-factor Xa activity has little clinical relevance. A smaller study comparing enoxaparin to dalteparin in patients with fractured hips showed no differences in efficacy or safety but lacked statistical power.

A meta-analysis of studies comparing LMWHs with placebo or UFH for prophylaxis of thromboembolism in patients undergoing general surgery has been published. Comparison of outcomes (asymptomatic deep venous thrombosis or pulmonary embolus) showed a trend in favor of LMWH with a significant reduction in clinical venous thromboembolism (P = 0.049). However, LMWHs at doses below 3400 anti factor Xa units seemed to be as effective as and safer than UFH, while at higher doses showed slightly superior efficacy, but with an increased risk of hemorrhage. Overall, LMWHs appear to be as effective and safe as UFH, but the optimal dose regimen for LMWHs requires further investigation.

Another meta-analysis examined nine clinical trials (n = 4669 patients) comparing UFH with LMWH for prophylaxis in hospitalized medical
patients with exclusions for patients with acute myocardial infarction or ischemic stroke. There were no significant differences between the two types of treatment in rates of venous thromboembolism, clinical pulmonary embolism or mortality, but patients receiving LMWH had a lower rate of major bleeding ($P = 0.049$).

There have been no published clinical trials that have directly compared different LMWHs in the treatment of acute venous thromboembolism. One large clinical trial was reported in abstract form comparing dalteparin to tinzaparin in the treatment of symptomatic venous thrombosis or pulmonary embolus. After 370 patients were enrolled, the trial was terminated because no significant differences between the two LMWHs were noted in either recurrent thromboembolism or bleeding.

Most clinical trials of LMWHs in treatment of thromboembolic disease have compared the LMWH with intravenous unfractionated heparin. Meta-analyses of the various studies are difficult to evaluate since there are relatively few studies with each LMWH. This precludes making any definite conclusions regarding the presence or absence of any clinical differences between the different LMWH products. Nonetheless, there appears to be no significant difference between the LMWHs when clinical outcomes such as death or recurrent thromboembolism are measured. When a comparison by meta-analysis is made between LMWHs and intravenous UFH, there are no statistically significant differences between the two therapies for recurrent thromboembolism, pulmonary embolism or bleeding (major and minor). The various LMWHs are at least as effective as intravenous UFH in the treatment of venous thromboembolism.

Acute coronary syndrome (ACS) is usually composed of patients with unstable angina or non-ST elevated myocardial infarction (NSTEMI). Treatment usually involves aspirin and a parenteral antithrombotic agent, often UFH. However, the role of an antithrombotic agent is unclear, and there is conflicting evidence regarding any difference in efficacy or safety between LMWH and UFH. A meta-analysis of randomized clinical trials comparing LMWH or UFH with placebo or untreated control patients has been done. The end points of interest were death, myocardial infarction and major bleeding. A total of 12 clinical trials involving 17,157 patients were found. The odds ratio (OR) for myocardial infarction or death during the first seven days in patients receiving LMWH or UFH compared to placebo or no antithrombotic was 0.53; 95% CI 0.38–0.73, $P = 0.0001$. When LMWH and UFH were compared in five trials using the same outcomes the OR was 0.88; 95% CI 0.69 – 1.12, $P = NS$. In terms of safety, there was no difference in the risk of major bleeding during treatment with UFH or LMWH. In aspirin-treated patients with ACS, short-term (< 7 days) treatment with UFH or LMWH halves the risk of myocardial infarction or death. There is no convincing difference in efficacy or safety between LMWH and UFH.

**ENOXAPARIN**

A planned meta-analysis of two of the studies in the above larger meta-analysis is often cited as showing superiority for the LMWH, enoxaparin over UFH. There have been concerns that the baseline characteristics of enrolled patients were not completely comparable and favored enoxaparin. There are also concerns that anticoagulation control in the patients receiving UFH was not adequate. Finally, most of the statistical significance is driven by soft end points such as recurrent angina or urgent revascularization. In summary, in patients with ACS, LMWH is more effective than placebo and at least as effective as UFH in reducing the hard end points of death and myocardial infarction. Any claims of superiority rely on the softer end points of recurrent angina. The risk of major bleeding is approximately equal to UFH, but the risk of minor bleeding is increased. The main benefit of enoxaparin over UFH is the ease of administration and the lack of laboratory monitoring.

The results of the two study meta-analysis has led the American Heart Association to recommend that enoxaparin be used in place of UFH in patients with ACS. However, since that time the results of the Superior Yield of New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) have become available. SYNERGY was a prospective, randomized, open-label trial designed to evaluate the efficacy and safety of enoxaparin versus UFH when administered according to a guidelines-based therapy that included glycoprotein IIb/IIIa inhibitors, aspirin and clopidogrel in high-risk patients with ACS who were to be managed with early PCI. The outcomes measured were the composite of all-cause death or nonfatal myocardial infarction during the first 30 days after randomization and major bleeding or stroke.

The primary efficacy end point occurred in 14.0% of patients receiving enoxaparin and 14.5% of patients receiving UFH, OR = 0.96; 95% CI, 0.86 – 1.06. There were also no statistically significant differences in the individual rates of death or myocardial infarction. However, there was significantly more major bleeding by TIMI criteria in patients who received enoxaparin (9.1% vs. 7.6%, $P = 0.008$). This clinical trial showed that enoxaparin was not superior to UFH but was noninferior in the treatment of high-risk patients with ACS and has a modest increase in the rate of major bleeding.

The A to Z trial was a prospective, open-label, randomized, noninferiority trial of patients with non-ST-segment elevation ACS. All patients received intravenous tirofiban and aspirin and were randomized to receive enoxaparin 1 mg/kg every 12 hours ($n = 2026$) or laboratory-adjusted intravenous UFH ($n = 1961$). The main outcomes were death, recurrent myocardial infarction or refractory ischemia at seven days with boundaries set for superiority and noninferiority. The TIMI classification system was used to assess bleeding complications.

A total of 8.4% of patients randomized to enoxaparin experienced death, myocardial infarction or refractory ischemia compared with 9.4% of patients randomized to UFH, HR = 0.88, 95% CI, 0.71 – 1.08. This met the prespecified criterion for noninferiority of enoxaparin. All components of the composite end point trended toward enoxaparin except death. Rates for any TIMI grade bleeding were low (3.0% for enoxaparin and 2.2% for UFH, $P = 0.13$). In patients receiving tirofiban and aspirin, enoxaparin is a suitable alternative to UFH for patients treated for non-ST-elevated ACS.

Taken together, these new studies and meta-analyses can provide evidence supporting better efficacy for either anticoagulant. However, each of these trials suffers from their own complexities that make clear interpretation of results difficult. For example, nearly two-thirds of patients enrolled in...
SYNERGY and the A to Z trials were already receiving a LMWH or UFH resulting in prerandomization crossover. There were outcome differences between patients who received and those who did not receive prerandomization anticoagulation. There were also a significant number of patients who switched anticoagulant therapy before undergoing PCI (postrandomization crossover). It should also be remembered that patients who undergo early PCI (early invasive therapy) generally have better outcomes for death or acute MI than patients receiving conservative or delayed intervention. The Antman meta-analysis of ESSENCE and TIMI outcomes for death or acute MI than patients receiving conservative or (postrandomization crossover). If PCI is done at that time or sooner, there will be little or no further difference in outcomes seen between enoxaparin and UFH.

Probably the best that can be said is that enoxaparin is a reasonable alternative to UFH in the treatment of patients with ACS. There are some local beliefs or habits that may influence anticoagulant choice at a given institution. For instance, there are some interventional cardiologists who prefer UFH during procedures since the degree of anticoagulation can be monitored with the ACT, and protamine is a more effective antagonist for UFH than for enoxaparin. The longer half-life of enoxaparin may also be seen as a potential disadvantage.

The American College of Cardiology, the American Heart Association and the European Society of Cardiology recommend the use of intravenous UFH with the dose adjusted by the activated clotting time (ACT) during percutaneous coronary intervention (PCI). They also recommend that LMWH is a reasonable alternative to UFH in patients with unstable angina/non-ST-elevation myocardial infarction. Further recommendations allow consideration of LMWH as an alternative to UFH in patients with ST-elevation myocardial infarction. These recommendations have been made on the basis of uncontrolled clinical trials, so definite conclusions about efficacy between LMWH and UFH cannot be done. The Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) trial, was a prospective, open-label trial comparing intravenous enoxaparin at a dose of 0.5 mg (n = 1070) or 0.75 mg per kilogram (n = 1228) with intravenous UFH (n = 1230) in patients undergoing elective PCI. The primary end point in this study was the incidence of major or minor bleeding, since the trial was not large enough to provide a definitive comparison of ischemic events.

Patients who were scheduled to undergo elective PCI were randomized to receive a single intravenous bolus of enoxaparin after sheath insertion and immediately before PCI regardless of whether the patient was also receiving a glycoprotein IIb/IIIa inhibitor. Patients receiving UFH had doses adjusted by ACT and whether they received a glycoprotein IIb/IIIa inhibitor. Enoxaparin at a dose of 0.5 mg/kg was associated with a significant reduction in bleeding in the first 48 hours, as compared with unfractionated heparin [5.9% vs. 8.5%; 95% CI, -4.7 to -0.6, P = 0.01], but the higher dose of enoxaparin was not [6.5% vs. 8.5%; 95% CI, -4.0 to 0.0, P = 0.051]. Major bleeding was also significantly less frequent in both the enoxaparin groups compared to UFH. The incidence of death from any cause or nonfatal myocardial infarction during the first 30 days after PCI did not differ significantly among the three groups. During an interim analysis of the study, the 0.5 mg/kg enoxaparin enrollment was terminated due to excess mortality. This study demonstrated that, depending on dose, intravenous enoxaparin is associated with bleeding rates that are similar to or lower than those with UFH in patients undergoing elective PCI. Whether the rates of cardiac events are similar for enoxaparin and UFH has not been firmly established, since the group with the lowest incidence of bleeding was terminated prematurely due to excess mortality. Also of note is that the study used a unique definition of major and minor bleeding. When the standard TIMI index of major and minor bleeding was used, there were no differences in rates of bleeding between either of the enoxaparin groups and UFH. The TIMI definition of major bleeding is intracranial hemorrhage or a 5 g/dl decrease in hemoglobin level. The TIMI criteria for a minor bleeding event include a decrease of 4 g/dl in hemoglobin level, a decrease of 3 g/dl in hemoglobin level with overt bleeding, retroperitoneal hemorrhage, and/or hematuria or hematemesis. Therefore, it seems that the rates of bleeding may vary depending on the bleeding index used. Before the 0.5 mg/kg dose of enoxaparin can be considered safe and effective for use in patients undergoing PCI a much larger clinical trial must be done.

Fibrinolysis is the most common method of reperfusion used for patients with ST-elevation myocardial infarction. In addition to the use of a fibrinolytic agent combined with aspirin, guidelines recommend the routine administration of UFH, usually for not more than 48 hours. On May 24, 2007, the FDA approved enoxaparin for treatment of acute ST-segment elevation myocardial infarction based on the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-Thrombolysis in Myocardial Infarction (TIMI) 25 trial.

EXTRACT-TIMI 25 was designed to compare enoxaparin with UFH as adjunctive therapy for fibrinolysis in more than 20,000 patients with ST-elevation myocardial infarction. Patients with ischemic symptoms for at least 20 minutes and ST-segment elevation on EKG who were scheduled to undergo fibrinolysis with streptokinase, tenecteplase, alteplase or reteplase were randomized to receive adjuvant enoxaparin or UFH. All patients received 150 to 325 mg of aspirin. UFH was administered as a bolus followed by an infusion, with dose adjusted to maintain an activated thromboplastin time of 1.5 to 2.0 times control values. The infusion was to be given for at least 48 hours. Enoxaparin doses were adjusted based on patient age and renal function. For patients younger than 75 years, enoxaparin was given as a 30 mg intravenous bolus, followed 15 minutes later by a subcutaneous injection of 1 mg/kg every 12 hours. The enoxaparin was to be administered for a maximum of eight days or until hospital discharge. The primary efficacy end point was the composite of death or nonfatal myocardial infarction in the first 30 days after randomization. Bleeding was classified according to the TIMI criteria. The patient groups were well matched with respect to concomitant therapy and a fibrinolytic agent was administered to 99.7% of the patients, with most receiving a fibrin-specific agent. Treatment with enoxaparin lasted a median of 7.0 days and treatment with UFH lasted a median of 2.0 days. The primary end point occurred in 12.0% of patients receiving UFH and 9.9% of patients receiving enoxaparin [P < 0.001]. The rate of nonfatal myocardial infarction was 4.5% in the UFH group and 3.0 in the enoxaparin group [P < 0.001]. The mortality rate was not significantly higher in the UFH group, 7.5% vs. 6.9%, [P = 0.11]. Major
bleeding (including intracranial hemorrhages) at 30 days was significantly more frequent in patients receiving enoxaparin, 2.1% vs. 1.4% [P < 0.001]. Major bleeding was also significantly more frequent at eight days in patients receiving enoxaparin, 1.8% vs. 1.2% [P < 0.001].

In patients receiving fibrinolysis for ST-elevation myocardial infarction, treatment with enoxaparin throughout hospitalization is superior to 48 hours of UFH in reducing the rates of recurrent myocardial infarction and urgent revascularization, but not death and is associated with significantly more major bleeding. These results may be accounted for by the longer period of administration of enoxaparin compared to UFH.

Taking all of the above cited studies into consideration the fairest conclusion that can be reached is that enoxaparin is a reasonable alternative to UFH. They are likely therapeutically equivalent and it is questionable whether there is more or less major bleeding with the use of enoxaparin. Differences in rates of bleeding have depended on the definition or bleeding scale used.

Neither drug has shown consistently clear superiority or safety over the other, and the results are often driven by the study design. In choosing between the two agents cost can be a consideration, but there are some potential advantages for enoxaparin. For one, it does not require laboratory monitoring, and can more reliably attain therapeutic levels with a fixed dose. It also seems to have a lower incidence of heparin-induced thrombocytopenia, better bioavailability on subcutaneous administration and a longer half-life.

As mentioned previously, there are three LMWHs available in the United States. The above discussion involves mainly enoxaparin since it is the most widely used LMWH and has more FDA-approved indications and study data behind it. In specific situations, successful therapeutic interchange has been accomplished between LMWHs for specific indications.(17)

FONDAPARINUX

Fondaparinux (Arixtra™) is the first of a new class of antithrombotic agents called pentasaccharides. It is a synthetic pentasaccharide that acts as a selective, indirect inhibitor of activated factor X (factor Xa). Fondaparinux is derived entirely from chemical synthesis, rather than extracted from animal tissues. The molecule consists of five sulfated saccharide units that bind exclusively to antithrombin III. By selectively binding to antithrombin III, fondaparinux induces a conformational change that results in inhibition of factor Xa, but not thrombin.

Fondaparinux is almost 100% bioavailable after subcutaneous injection with maximum plasma levels attained within 1 to 3 hours after subcutaneous injection. Fondaparinux has a half-life of between 13 and 15 hours, is not metabolized by the liver and is primarily excreted through the kidneys. Fondaparinux was approved by the FDA in December 2001 for the prevention of deep vein thrombosis in orthopedic surgery. Since then, other studies have been done that have expanded the usefulness of fondaparinux as an antithrombotic agent.

The fondaparinux clinical development program was designed to compare the efficacy and safety of fondaparinux with enoxaparin for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery of the lower limbs. More than 8000 patients have been enrolled in these phase 2 and phase 3 clinical trials. In all these trials, the primary measure of efficacy was based on bilateral venography. There were two clinical trials conducted in elective hip arthroplasty (EPHESUS and PENTATHLON), one in major knee surgery (PENTAMAKS) and one in hip fracture surgery (PENTHIFRA). Patients in these clinical trials were randomized to receive fondaparinux 2.5 mg subcutaneously daily beginning 6 hours postoperatively or enoxaparin 40 mg once daily starting 12 hours preoperatively or 30 mg twice daily starting 12 to 24 hours after surgery. The primary outcomes for efficacy were the occurrence of deep vein thrombosis (DVT) or pulmonary embolus (PE) up to day 11.

Secondary outcomes were the incidence of total, proximal and distal-only DVT and symptomatic venous thromboembolism to day 11 or PE up to day 49. The primary safety outcome was major bleeding. The study designs were planned to be similar for the purpose of performing a meta-analysis of their data. (18)

Overall, fondaparinux significantly reduced the incidence of venous thromboembolism at day 11 (6.8% in 2682 patients) compared with enoxaparin (13.7% in 2703 patients) P < 0.001. This effect was consistent across all types of surgery and subgroups. The incidence of proximal DVT was also significantly different, 1.3% in fondaparinux-treated patients vs. 2.9% in enoxaparin treated patients. Major bleeding was significantly more common in the fondaparinux-treated group (2.7%) versus the enoxaparin-treated group (1.7%) P = 0.008, but this was accounted for by a higher incidence of bleeding index ≥ 2 (2.3% vs. 1.5%, respectively). The bleeding index is calculated as the number of units of packed red blood cells or whole blood transfused plus prebleeding minus post-bleeding hemoglobin values in grams per deciliter. The incidence of fatal bleeding, critical organ bleeding and bleeding events leading to reoperation did not differ between the two groups. [See table 1.]

In patients undergoing orthopedic surgery, 2.5 mg of fondaparinux once daily, beginning six hours postoperatively, showed a major clinical benefit over enoxaparin without increasing the risk of clinically important bleeding.

Fondaparinux has also received FDA approval for deep vein thrombosis (DVT) prophylaxis in general surgery patients. Patients scheduled for major abdominal surgery under general anesthesia (> 45 minutes) were randomized to receive fondaparinux 2.5 mg started 6 hours after surgery, then once daily (n= 1027) or dalteparin 2500 units given 2 hours before and 12 hours after the first dose, then 5000 units daily (n = 1021). (19)
The treatments were continued for a mean of 7 days. The primary outcome measure was a composite of DVT detected by bilateral venography, symptomatic DVT or pulmonary embolus up to day 10.

The rate of venous thromboembolism was 4.6% in patients receiving fondaparinux vs. 6.1% in patients receiving dalteparin [P = 0.144]. There were also no significant differences in the rates of proximal DVT or symptomatic thromboembolic events. Major bleeding was observed in 3.4% of patients given fondaparinux and 2.4% of patients given dalteparin [P = 0.122]. This study showed that fondaparinux is at least as effective as perioperative dalteparin in patients undergoing high-risk abdominal surgery.
Medical patients at bed rest are now known to be at risk for developing venous thromboembolism. The ARTEMIS study randomized medical patients who were at least 60 years old and expected to remain in bed for at least four days to prophylactic treatment with 2.5 mg of fondaparinux or placebo injection administered once daily for 6 to 14 days. Patients were considered for inclusion if they had class III/IV heart failure, acute respiratory illness in the presence of chronic lung disease or acute infections or inflammatory disorders. All patients were to be given bilateral venography between days 6 and 15. The primary efficacy outcome was the composite of DVT or symptomatic venous thromboembolism. The primary safety outcome was major bleeding.

Venous thromboembolism was detected in 5.6% of patients treated with fondaparinux and 10.5% of those receiving placebo [P = 0.029]. Consistent reductions were seen in the incidence of total, proximal and distal DVT. There were five cases of fatal pulmonary embolism, all in the placebo group. Major bleeding occurred in one patient in each treatment group during the study. Fondaparinux is effective in the prevention of asymptomatic and symptomatic venous thromboembolic events in older acute medical patients. These clinical outcomes are similar to those seen in medical patients receiving 40 mg of enoxaparin daily.

Pulmonary embolism is a frequent and potentially life-threatening event that is often seen in hospitalized patients. In hemodynamically stable patients, the reference treatment is UFH, followed by oral anticoagulation with a vitamin K antagonist. Since UFH requires continuous intravenous infusion along with regular laboratory monitoring and dose adjustment, patients are required to be hospitalized during this part of their treatment. Since these patients are often healthy enough to be discharged, a less complex parenteral treatment is desirable to facilitate early discharge. The MATISSE study was designed to determine whether a fixed-dose, once daily regimen of subcutaneous fondaparinux is at least as effective as intravenous UFH for the initial treatment of symptomatic pulmonary embolus.

Patients with acute symptoms of pulmonary embolus and either a defect on spiral computed tomography of the chest or pulmonary angiogram or a high-probability ventilation-perfusion scan were eligible for inclusion. Patients were randomized to receive 5.0 mg, 7.5 mg or 10.0 mg of fondaparinux based on body weight or a bolus of UFH, followed by a continuous infusion adjusted to maintain an activated partial thromboplastin time of 1.5 to 2.0 times a control value. In both groups, treatment with a vitamin K antagonist was begun as soon as possible. Administration of fondaparinux or UFH was continued for at least five days and until the INR was greater than 2.0 for two consecutive days. The primary study outcome was symptomatic, recurrent venous thromboembolism during the three-month study period. The main safety outcomes were major bleeding during the initial treatment period and death during the three-month study period.

Forty-two of the 1103 patients (3.8%) randomly assigned to receiving fondaparinux had recurrent thromboembolic events, as compared with 56 of the 1110 patients (5.0%) receiving UFH. These results demonstrated the noninferiority of fondaparinux compared to UFH. Major bleeding during initial treatment occurred in 1.3% of fondaparinux-treated and in 1.1% of UFH-treated patients. Bleeding contributed to death in one patient in each group. Any major or clinically relevant bleeding occurred in 4.5% of fondaparinux-treated and 6.3% of UFH-treated patients (P = NS). The three-month mortality rates were similar in the two groups.

This study showed that once-daily, subcutaneous fondaparinux without laboratory monitoring is at least as effective and safe as adjusted-dose intravenous UFH in the initial treatment of pulmonary embolus. Subcutaneous administration of fondaparinux allowed for early discharge in 14.5% of the patients in that group who continued to receive the drug on an outpatient basis.

Treatment of patients with deep vein thrombosis can be initiated with either intravenous UFH or once- or twice-daily subcutaneous LMWH. The use of a LMWH allows patients to self-administer injections at home. Fondaparinux may also be a suitable therapeutic agent for the initial treatment of DVT since its half-life allows for once daily administration and it has a very low incidence of thrombocytopenia associated with use. A study was designed to evaluate the efficacy and safety of fondaparinux or enoxaparin in patients with DVT.

### Table 1

<table>
<thead>
<tr>
<th>Outcomes in Orthopedic Surgery. Enoxaparin vs. Fondaparinux</th>
<th>Arixtra</th>
<th>Lovenox</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All venous thromboembolic events</td>
<td>6.8%</td>
<td>13.7%</td>
<td>0.45 (0.37 – 0.54) P &lt; 0.001</td>
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<td>Symptomatic VTE</td>
<td>0.6%</td>
<td>0.4%</td>
<td>P = NS</td>
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<tr>
<td>Proximal DVT</td>
<td>1.3%</td>
<td>2.9%</td>
<td>0.43 (0.27 – 0.64)</td>
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<tr>
<td>Major Bleeding</td>
<td>2.7%</td>
<td>1.7%</td>
<td>1.54 (1.11 – 2.16) P = 0.008</td>
</tr>
<tr>
<td>Bleeding index ≥ 2</td>
<td>2.3%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Any transfusion</td>
<td>53.9%</td>
<td>51.5%</td>
<td>P = 0.04</td>
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</tbody>
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Adapted from reference # 18
Patients who presented with acute symptomatic DVT of the lower extremities were randomized to receive 5.0 mg, 7.5 mg or 10.0 mg of fondaparinux once daily based on body weight or enoxaparin 1.0 mg/kg twice daily. In both groups, a vitamin K antagonist was started as soon as possible but within 72 hours. Patients received parenteral therapy for at least five days and until the INR was greater than 2.0 for two consecutive days. The primary efficacy outcome was the incidence of symptomatic recurrent venous thromboembolism during the three month study period. The main safety outcomes were major bleeding during the initial treatment period and three-month mortality.

In the patients receiving fondaparinux, 3.9% of 1098 patients developed recurrent thromboembolic events compared to 4.1% of 1107 patients receiving enoxaparin, demonstrating noninferiority between the two therapies. Major bleeding developed in 1.1% of patients receiving fondaparinux and 1.2% of patients receiving enoxaparin. Major or clinically relevant nonmajor bleeding during parenteral treatment occurred in 3.7% of patient receiving fondaparinux and 4.2% of patients receiving enoxaparin. During the three month study, 3.8% of patients who received fondaparinux and 3.0% of patients who received enoxaparin died. The majority of deaths in each group were due to underlying disease or unexplained causes.

Once-daily subcutaneous fondaparinux is at least as effective and safe as twice daily, body weight-adjusted enoxaparin in the initial treatment of patients with symptomatic deep vein thrombosis.

The SYNERGY(12) and A to Z trials(13) showed that enoxaparin was not inferior to UFH in the treatment of acute coronary syndrome, while a planned meta-analysis of two previous studies(8) showed superiority of fondaparinux. Recently, a study compared fondaparinux and enoxaparin in the treatment of acute coronary syndrome.(24) The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial was designed to compare the efficacy and safety of fondaparinux and enoxaparin in high-risk patients with unstable angina or non-ST-segment myocardial infarction.

OASIS-5 was a randomized, double-blind, double-dummy noninferiority trial that assigned patients within 24 hours after the onset of symptoms to treatment with either fondaparinux or enoxaparin, if they were at least 60 years of age, had an elevated level of troponin or creatine kinase MB isoenzyme or ECG changes indicative of ischemia. The primary efficacy outcome was death, myocardial infarction or refractory ischemia. The primary safety outcome was to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding. Patients received either 2.5 mg of fondaparinux once daily plus placebo enoxaparin twice daily or enoxaparin 1 mg/kg twice daily plus placebo fondaparinux. All injections were given subcutaneously. Fondaparinux could be given until hospital discharge or for up to eight days, and enoxaparin was to be given for two to eight days or until the patient was clinically stable. Patients received other standard treatments at the investigators’ discretion.

The number of patients with primary outcome events was similar in the two groups, 5.8% with fondaparinux (n = 10,057) and 5.7% with enoxaparin (n = 10,021) [hazard ratio = 1.01, 95% CI, 0.90 – 1.13]. This satisfied the noninferiority criteria of the trial. The rates of death or myocardial infarction (hard end points) were similar, 4.1% in each group. At 30 days, the mortality rate in fondaparinux-treated patients was 2.9% vs. 3.5% in patients treated with enoxaparin [P = 0.02]. Major bleeding was also significantly less with fondaparinux (4.3%) compared to enoxaparin 5.8% [P < 0.001], as was the rate of fatal bleeding [P = 0.005]. The patient group who received fondaparinux had a significantly reduced number of deaths at 30 days (295 vs. 352, P = 0.02) and at 180 days (574 vs. 638, P = 0.05) compared with enoxaparin. These results were also seen in the subgroup of patients (n = 7932) who underwent PCI.

In patients with acute coronary syndrome, fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but substantially reduces the risk of major bleeding and improves long-term mortality.

The ExTRACT-TIMI 25 trial compared enoxaparin with UFH in patients with ST-elevation myocardial infarction (STEMI). (16) OASIS-6 was a similarly designed trial comparing fondaparinux with UFH in patients with STEMI. (25) Trials designed to improve mortality rates in patients with STEMI have frequently failed this objective and are often associated with an increased risk of bleeding. The results seen in OASIS-5 gave impetus to the design of the OASIS-6 trial. OASIS-6 was a randomized, double-blind, double-dummy trial of fondaparinux versus the usual standard of care in more than 12,000 patients with STEMI. (25) Randomization was stratified based on whether patients were candidates for UFH use (concurrent of fibrinolytic therapy or primary PCI). Patients were randomized to receive fondaparinux 2.5 mg daily or placebo for up to 8 days or until hospital discharge. The control patients received intravenous UFH with a target activated partial thromboplastin time of 1.5 to 2.0. The primary efficacy outcome was death or reinfarction at 30 days, with the same outcomes assessed at nine days and at three or six months. Bleeding was classified by TIMI criteria and in addition by the criteria used in the OASIS-5 trial. The TIMI definition of major bleeding is intracranial hemorrhage or a 5 g/dl decrease in hemoglobin level. The TIMI criteria for a minor bleeding event includes a decrease in hemoglobin of 4 g/dl, a decrease of 3 g/dl with overt bleeding, retroperitoneal hemorrhage and/or hematuria or hematemesis.

Death or reinfarction at 30 days was significantly reduced from 11.2% of 6056 patients in the control group to 9.7% of 6036 patients in the fondaparinux group [hazard ratio = 0.86, 95% CI, 0.77 – 0.96; P = 0.008]. These results were also seen at nine days (8.9%) vs. (7.4%), P = 0.003 and at study end (three to six months). The mortality rate at 30 days was reduced from 8.9% in the control group to 7.8% in the fondaparinux group [P=0.03]. Mortality was also significantly reduced in the fondaparinux group at nine days and at study end. There was a nonsignificant trend toward fewer severe hemorrhages with fondaparinux compared with the control group, 1.3% vs. 1.0% (TIMI classification) or the OASIS-5 classification.

In patients with STEMI, particularly those not undergoing PCI, fondaparinux significantly reduces mortality, primarily from cardiac causes, and reinfarction without an increase in bleeding or hemorrhagic stroke. The results of OASIS-6 and OASIS-5 strongly suggest that UFH can be safely used with fondaparinux in patients during PCI, with a reduction in the risk of catheter thrombosis regardless of the study design used. Regardless of how the data are evaluated in either of these two studies, there is no
inhibitor, was associated with a noninferior rate of the composite ischemia end point (7.7% vs. 7.3%, respectively).

Bivalirudin plus a GP IIb/IIIa inhibitor, as compared with UFH/enoxaparin plus a GP IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia end point (7.8% vs. 7.3%, respectively). However, there was considerably less major bleeding in the bivalirudin alone group compared with the UFH/enoxaparin plus GP IIb/IIIa inhibitor group (3.0% vs. 5.7%, P < 0.001).

In patients with moderate or high-risk ACS undergoing PCI with a GP IIb/IIIa inhibitor, bivalirudin was associated with rates of ischemia and bleeding that were similar to those receiving heparin/enoxaparin. Bivalirudin alone was associated with similar rates of ischemia and a significantly lower rate of bleeding. There are other studies that show bivalirudin compared to other antithrombotic agents reduces the risk of major bleeding during and after procedures. This may be a function of its half-life of 25 minutes and the fact that only 20% of it is excreted by the kidneys. In addition, there is a potential for cost savings if bivalirudin can be administered alone rather than UFH/enoxaparin plus a GP IIb/IIIa inhibitor.

The therapeutic niche for bivalirudin is the cardiac catheterization lab. It is particularly useful as an antithrombotic agent in patients with renal insufficiency or those who have a history of heparin-induced thrombocytopenia. Based on REPLACE-2 and ACUITY bivalirudin has similar efficacy end points in patients with ACS undergoing PCI compared to UFH or enoxaparin. Its advantage is a lower rate of major bleeding and a lower usage of GP IIb/IIIa inhibitors. A recent observational study confirmed the efficacy of and safety of bivalirudin compared to UFH in patients undergoing PCI. (28)

The medical records of 539 patients who received bivalirudin and 536 patient who received UFH undergoing PCI were reviewed. Bivalirudin use was associated with a significant reduction in TIMI major bleeding [5.0% vs. 9.7%, P = 0.003], REPLACE -2 major bleeding [5.4% vs. 12.9%, P < 0.001], and TIMI minor bleeding [1.7% vs. 6%, P < 0.001]. Significantly fewer patients in the bivalirudin group received GP IIb/IIIa inhibitors [27.3% vs. 62.7%, P < 0.001] and had significantly fewer myocardial infarctions after catheterization [10.7% vs. 18.0%, P = 0.007].

**ANTITHROMBOTIC SELECTION**

One question is whether enoxaparin and fondaparinux can be therapeutically interchanged within an institution. It may be possible to use one product exclusively since the FDA-approved indications along with large clinical studies provide efficacy data for each drug. See table 2 for the major therapeutic uses of each agent. Table 3 contains the appropriate doses for each of these indications. Since the major adverse effect of each agent is bleeding, this is likely to be a secondary consideration. Finally, since both agents have contract pricing depending on market share or usage tiers, moving to a single agent can improve overall price and probably lower institutional costs.

The gold standard for choosing between two therapeutic agents is a randomized, double-blind, controlled clinical trial between the two agents. In several cases this has been done with enoxaparin and fondaparinux. In head-to-head clinical trials in orthopedic surgery fondaparinux is statistically and clinically better than enoxaparin in preventing all venous thromboembolic events and proximal DVTs. There is no significant difference between the drugs in the incidence of asymptomatic DVTs. (118) Enoxaparin and fondaparinux have also been compared in a randomized...
In OASIS-5, the rate of major bleeding was significantly less in patients receiving fondaparinux than in patients receiving enoxaparin. In this trial, fondaparinux was at least as effective as enoxaparin, and there were no differences in the rate of major bleeding or mortality. In OASIS-5, enoxaparin and fondaparinux were compared in patients with acute coronary syndrome. In this study fondaparinux was shown to be noninferior to enoxaparin for the primary outcome of death, myocardial infarction or refractory ischemia at nine days. However, there was significantly less major bleeding seen in patients receiving fondaparinux.

In most other studies, enoxaparin (or another LMWH) and fondaparinux have been compared to UFH administered either by subcutaneous injection or intravenous infusion. As expected, there were no significant differences in clinical outcomes in either surgical or medical DVT prophylaxis or treatment of symptomatic DVT or pulmonary embolus. Overall, it would appear that based on the available evidence the two agents should be considered to give equivalent therapeutic outcomes with the exception of orthopedic surgery, where the thromboembolic outcomes seem to favor fondaparinux. At a minimum, it would be safe to say that fondaparinux is not inferior to enoxaparin for any clinical outcomes for the uses in which they have been investigated. An additional point to remember is that each of these studies can be criticized for choice of end points, combination of end points, time point of outcome measures, patient enrollment or exclusion criteria, drug regimen used, etc. This point can also be magnified when meta-analyses are done.

As expected the major adverse effect of these two agents is bleeding and major bleeding is the end point most frequently measured. One of the issues is that there are several ways to categorize clinical bleeding, so the bleeding outcomes often vary between studies and even within the same study. Major bleeding may include a fall in hemoglobin level of anywhere from 2.0 to 5.0 g/dl. This can make assessment of bleeding rates between different trials difficult. In the head-to-head clinical trials between fondaparinux and enoxaparin, bleeding rates often varied between the treatment groups. In the orthopedic surgery studies the rates of major bleeding were significantly higher with fondaparinux when the bleeding index is included. The bleeding index is calculated by summing the number of units of packed red blood cells transfused plus prebleeding hemoglobin concentration (g/dl) minus postbleeding hemoglobin concentration (g/dl). The bleeding index was designed by the study investigators and has not been used in other clinical trials. When the bleeding index is excluded there is no difference in rates of major bleeding or the mean number of units of blood transfused between the two treatment arms.

In OASIS-5, the rate of major bleeding was significantly less in patients receiving fondaparinux than in patients receiving enoxaparin. In the head-to-head study of fondaparinux vs. enoxaparin in the treatment of patients with symptomatic DVT there was no difference in the rates of major bleeding. Again, there is little evidence that there is any difference in the rates of major bleeding between these two agents, when the bleeding index is excluded from the analysis.

There should be little debate when looking at either efficacy or adverse effects that fondaparinux and enoxaparin appear to be at least equivalent when considering all potential uses. Certainly fondaparinux is superior in the area of DVT prophylaxis in orthopedic surgery. As was also shown in some of the meta-analyses and individual studies, either of these agents could be replaced by UFH for some indications. However, UFH is most often administered by continuous intravenous infusion and requires intensive laboratory monitoring. The administration of fondaparinux and enoxaparin is most often by subcutaneous injection, which offers convenience to both the patient and nursing staff. In addition, neither drug requires routine laboratory monitoring. This presents an opportunity to discharge the patient early to continue therapy at home.

There have been some pharmaco-economic studies published comparing the costs of fondaparinux and enoxaparin. These studies have all dealt with orthopedic procedures and were often done using non-Unites States databases and costs. Since in the orthopedic surgery area, fondaparinux is clinically superior to enoxaparin in the prevention of DVTs it is not surprising that fondaparinux was also associated with lower overall treatment costs. Whether an individual hospital will decrease medication or total hospital costs will depend on the case mix in which fondaparinux or enoxaparin is being used. In orthopedic surgery, fondaparinux and a low-molecular weight heparin give superior clinical outcomes for DVT prophylaxis compared to UFH. Maybe more important is the fact that fondaparinux is also clinically superior to enoxaparin in orthopedic surgery. However, when it comes to treatment of symptomatic DVT or pulmonary embolus UFH is also a viable treatment option, along with the other two agents. This is also the case in cardiology where fondaparinux, enoxaparin or unfractionated heparin can be used in the treatment of ACS. Many cardiologists prefer UFH in these cases, if there is a chance the patient will be a candidate for PCI.

The choices for an individual hospital are to use fondaparinux for all patients requiring DVT prophylaxis, treatment and ACS. The other alternative can be the use of fondaparinux for orthopedic surgery and reserving enoxaparin or UFH for use in cardiology and general medicine. If an institution has care plans in place, the preferred agent(s) could be part of the care plans for orthopedic surgery, DVT prophylaxis or treatment of ACS. The direction an institution takes will depend on the ability to sell these ideas to the prescribing physicians. This review of the key studies should give you the background information for discussions at pharmacy and therapeutics or other meetings with physicians. The key to cost savings will likely be in the ability to move market share to a single product. Outside of orthopedics, any of these antithrombotic agents should have similar clinical outcomes.
### Table 2
**Therapeutic Uses of Enoxaparin and Fondaparinux**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT Prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hip arthroplasty</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>--</td>
<td>X</td>
</tr>
<tr>
<td>Medical patients</td>
<td>X</td>
<td>ref. 20</td>
</tr>
<tr>
<td><strong>DVT Rx in-patient</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>DVT Rx out-patient</strong></td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td><strong>PE in-patient</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Acute Coronary Syndrome</strong></td>
<td>X</td>
<td>ref. 24</td>
</tr>
<tr>
<td><strong>ST-elevated MI</strong></td>
<td>X</td>
<td>ref. 25</td>
</tr>
</tbody>
</table>

X = FDA approved indication, DVT = deep vein thrombosis, Rx = treatment, MI = myocardial infarction

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### Table 3
**Doses of Enoxaparin and Fondaparinux for Clinical Use**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT Prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>40 mg SQ daily</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td>Hip arthroplasty</td>
<td>40 mg SQ daily (started 12 hr prior to surgery) OR 30 mg SQ Q12 hr (started 12 to 24 hr after surgery)</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>same as hip arthroplasty</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>no recommendation</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td>Medical patients</td>
<td>40 mg SQ daily</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td><strong>DVT Rx in-patient</strong></td>
<td>1 mg/kg SQ Q12 hr OR 1.5 mg/kg SQ Q 24 hr</td>
<td>5.0 mg SQ daily (≤ 50 kg) OR 7.5 mg SQ daily (50 – 100 kg) OR 10.0 mg SQ daily (&gt; 100 kg)</td>
</tr>
<tr>
<td><strong>DVT Rx out-patient</strong></td>
<td>1 mg/kg SQ Q 12 hr</td>
<td>no recommendation</td>
</tr>
<tr>
<td><strong>PE in-patient</strong></td>
<td>1 mg/kg SQ Q12 hr OR 1.5 mg/kg SC Q 24 hr</td>
<td>5.0 mg SQ daily (≤ 50 kg) OR 7.5 mg SQ daily (50 – 100 kg) OR 10.0 mg SQ daily (&gt; 100 kg)</td>
</tr>
<tr>
<td><strong>Acute Coronary Syndrome</strong></td>
<td>1 mg/kg SQ Q 12 hr</td>
<td>2.5 mg SQ daily</td>
</tr>
<tr>
<td><strong>ST-elevated MI</strong></td>
<td>30 mg IV bolus, followed By 1 mg/kg SQ Q 12 hr</td>
<td>2.5 mg SQ daily</td>
</tr>
</tbody>
</table>
References:


