Low-Molecular-Weight Heparins:
Formulary Drug Class Review

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The past eight years have seen the introduction of four LMWHs, namely ardeparin, dalteparin, enoxaparin, and tinzaparin (the most recently approved agent). All are still marketed in the U.S., except for ardeparin, which was voluntarily withdrawn from the market in 2000. Unfractionated heparin (UFH) produces its anticoagulant effects by complexing with antithrombin III (AT III) to inactivate both thrombin (IIa) and activated factor Xa. The shorter saccharide chains in LMWHs allow for the inhibition of activated factor X but are not long enough to complex with thrombin and inactivate it as fully as UFH. The preferential effect of LMWHs on factor Xa over thrombin contributes to less bleeding potential, a diminished effect on platelets and platelet aggregation, and a prolonged anticoagulant effect. It also eliminates the need for aPTT monitoring in most patient populations. Inhibition of one molecule of factor Xa can indirectly prevent the formation of hundreds of thrombin molecules because of its higher position in the coagulation cascade.

Each LMWH is a heterogeneous mix of polysaccharide chains of differing length and weight, uniquely prepared from standard UFH by chemical or enzymatic depolymerization. Pharmacologic equivalence between LMWHs has not been established. Differences exist in molecular weight, structure, and manufacturing process, protein and cell binding, and dosage.11 LMWHs also differ with regard to half-life, anti-Xa activity, anti-Xa to anti-IIa activity, effect on platelet aggregation, and bioavailability (Table 1).11 It is well recognized that UFH is a potent stimulant of platelet aggregation. A recent report by Montalescot et al. evaluated levels of von Willebrand factor (vWF) in unstable angina patients.2 A rise in vWF is generally associated with increased platelet aggregation and negative ischemic outcomes. The study assessed the effect of UFH, enoxaparin, dalteparin, and peg-hirudin on short-term vWF release. The four different anticoagulants did not provide the same level of protection from vWF release. The release of vWF was significantly lower with enoxaparin compared to UFH and dalteparin. These findings could have important prognostic implications and might begin to explain different results observed in LMWH trials in acute coronary syndrome patients. Again, this differentiation of effects on platelet aggregation is particularly important in the treatment of arterial thrombosis (acute coronary syndromes), where platelets and platelet aggregation play a central role in the pathogenesis of the disease.

The half-lives of LMWHs are two to four times longer than the half-life of heparin, but there are differences within the class. Enoxaparin possesses the longest half-life, and its anti-Xa to anti-IIa ratio is 3.8, compared to 2.8 for tinzaparin and 2.7 for dalteparin. Experimental models have shown that adjusting the anti-Xa activity to achieve an equivalent dosage based on anti-Xa potency does not result in equal antithrombotic activity.3 Without evidence to support the pharmacologic and therapeutic equivalence of LMWHs, it is reasonable to assume that differences in pharmacologic profile will affect clinical outcomes. There is agreement in the literature regarding pharmacologic and therapeutic inequivalence within the class. In addition, statements by the Food and Drug Administration (FDA), the World Health Organization (WHO), the American College of Chest Physicians (ACCP), the American College of Cardiology, and the American Heart Association (AHA) indicate that LMWHs should not be considered interchangeable.4-6

Clinical Efficacy and Indications

Clinical evidence demonstrating equivalent efficacy between LMWHs is lacking, in part, because of an absence of head-to-head comparisons and a lack of uniformity in study design, subjects, and outcomes measured in heparin- or placebo-controlled studies. Moreover, the number of randomized con-
trolled trials is not equally distributed among LMWHs. Each drug has been studied in a variety of patient populations, but enoxaparin has been tested for efficacy in the broadest range of patient populations.

Each LMWH is FDA-approved for a unique set of indications (Table 2). Enoxaparin is approved for seven indications, including the prevention of deep venous thrombosis (DVT) in surgical and non-surgical patients (for general surgery, hip and knee replacement, and in the medically ill), for extended prophylaxis following hip replacement surgery, in patient treatment of VTE (DVT and PE), outpatient treatment of DVT, and prevention of ischemic complications in unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) when given with aspirin. Dalteparin is approved for three indications, including prophylaxis of DVT in general surgery and hip replacement and treatment of UA/NSTEMI when administered with aspirin. Tinzaparin is approved for the treatment of DVT with or without pulmonary embolism (PE). The specific FDA-approved indications and dosing are summarized in Table 3. For a number of indications, there are no clinical data to support the use of one agent in place of another.

Pivotal clinical trials for each LMWH, as well as recent meta-analyses, must be reviewed to fully consider the therapeutic equivalence of LMWHs. Also, the recently published Sixth ACCP Consensus Conference on Antithrombotic Therapy, which provides a comprehensive review of data from clinical trials of LMWHs as well as therapeutic recommendations, must be considered (Table 4).

DVT Prophylaxis
All of the LMWHs available in the U.S. has been studied for prophylaxis of DVT; however, equivalent efficacy within specific patient populations has not been firmly established. As shown in Table 4, enoxaparin and dalteparin have been shown to be 30% more effective than UFH in the prophylaxis of VTE in general surgical patients. Enoxaparin, dalteparin, and tinzaparin have been demonstrated to reduce the incidence of thrombosis by 70% compared to placebo in hip replacement surgery. A head-to-head study comparing enoxaparin and tinzaparin for thromboprophylaxis following hip replacement surgery showed that both were equally safe and effective; however, tinzaparin is not approved for this indication. Again, as shown in Table 4, enoxaparin has been studied for DVT prophylaxis in various patient populations, and is approved for DVT prophylaxis in patients at risk of thromboembolism, including those undergoing hip replacement surgery, knee replacement surgery, and abdominal surgery.

Samama et al. recently published a comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients (MEDENOX study). This study showed that hospitalized acutely ill medical patients are at significant risk of developing VTE and prophylaxis with enoxaparin 40 mg SC once daily was safe, effective, and convenient in reducing this risk by 63%. As a result of the MEDENOX trial, enoxaparin was recently approved by the FDA for the prophylaxis of VTE in acutely ill medical patients.

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VTE Treatment
The success of LMWHs for DVT prophylaxis led to the study of their efficacy and safety in the treatment of VTE. Enoxaparin and tinzaparin have demonstrated safety and efficacy for treatment of DVT compared to UFH, and dalteparin, enoxaparin, and tinzaparin have demonstrated efficacy for the treatment of PE compared with unfractionated heparin. However, a recent meta-analysis of LMWH versus UFH indicated that although there were no major differences in overall efficacy and safety between LMWHs, they differed within certain categories (treatment of VTE, treatment of PE, major bleeding, and total mortality). Although meta-analyses are inherently limited and results should be interpreted with caution, they provide a tool for integrating and comparing the results of individual studies to arrive at general conclusions about outcomes.

Dalteparin has been shown to be effective in the treatment
Table 1 Pharmacologic and Pharmacokinetic Differences Between LMWHs

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin</th>
<th>Enoxaparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name:</td>
<td>Fragmin</td>
<td>Lovenox</td>
<td>Innohep</td>
</tr>
<tr>
<td>(Pharmacia &amp; Upjohn)</td>
<td></td>
<td>(Aventis Pharmaceuticals)</td>
<td>(Dupont Pharma)</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>87</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>Elimination T1/2 SC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration (hours)</td>
<td>3-5</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Mean Molecular Weight</td>
<td>6000</td>
<td>4500</td>
<td>6500</td>
</tr>
<tr>
<td>Anti-Xa/Anti-IIa Ratio</td>
<td>2.7</td>
<td>3.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Peak Anti-Xa Activity (hours)</td>
<td>3-4</td>
<td>3-5</td>
<td>4-6</td>
</tr>
</tbody>
</table>

T 1/2 = half-life; SC = subcutaneous

Table 2 Comparison of Enoxaparin, Dalteparin, and Tinzaparin

**Enoxaparin**
- Seven indications (abdominal surgery, both hip and knee replacement surgery, extended hip prophylaxis, prophylaxis in medically ill, treatment of VTE inpatient, treatment of DVT outpatient, treatment of UA/NSTEMI)
- Most extensive clinical evidence for all indications
- Clinically superior to UFH in UA/NSTEMI
- Only LMWH with strong clinical evidence and FDA labeling in the prophylaxis of the medically ill with QD dosing
- Cost-effectiveness demonstrated in VTE treatment (inpatient and outpatient) and in UA/NSTEMI
- Unique pharmacologic effects (i.e. decreased release of vWF in UA)
- Evolving evidence in neurosurgery and trauma prophylaxis
- Evolving evidence in “bridge” therapy
- Evolving evidence in ACS and STEMI patients
- Lack of a multiple-dose vial (coming fall 2001)

**Dalteparin**
- Three indications (abdominal surgery and hip replacement prophylaxis, treatment UA/NSTEMI)
- Little evidence and no FDA labeling for knee replacement surgery
- Some evidence but no indication for VTE treatment
- Efficacy equal to UFH in UA/NSTEMI, not superior
- Little published cost-effectiveness or pharmacoeconomic data

**Tinzaparin**
- One indication for the treatment of VTE (evidence derived from inpatient populations)
- Once-daily therapy (with limitations in high-risk patients)
- Little evidence and no indications in VTE prophylaxis
- No evidence and no indication in UA/NSTEMI treatment
- No pre-filled syringes

of DVT; however, questions remain regarding dosing and the frequent need for dosage adjustment.19 Currently, only enoxaparin and tinzaparin are approved for the treatment of DVT with or without PE, and only enoxaparin is specifically labeled for outpatient treatment of DVT. All three LMWHs have been shown to be effective when administered once daily. However, in high-risk populations (obesity and cancer patients), the efficacy of once-daily dosing appears to be reduced.20 Tinzaparin is only labeled to be administered once-daily in the treatment of VTE. The efficacy of once-daily administration of the drug in these high-risk populations is unknown.

**Acute Coronary Syndromes**
LMWHs are increasingly used in acute coronary syndromes (ACS). Dalteparin has been studied and is FDA-approved in the treatment of UA and NSTEMI. In the FRIC trial, which compared dalteparin to UFH in UA/NSTEMI, the efficacy and safety of the drug was found to be equal to UFH.21

The TIMI 11B and ESSENCE trials provide the best efficacy data for the use of LMWHs in the treatment of ACS (UA/NSTEMI).22-23 Both of these trials compared enoxaparin with UFH. The composite endpoints for these trials were death, MI, and urgent revascularization in the TIMI 11B trial, and death, MI, and recurrent angina in the ESSENCE trial.

The ESSENCE trial demonstrated a significant reduction in the composite endpoint at 14 days, 30 days, and at one year, compared to UFH. In the short-term phase of the TIMI 11B trial, there was a significant reduction in the composite endpoint at 14 days compared to UFH. In the long-term treatment phase (enoxaparin treatment for 43 days), the composite endpoint was again reduced significantly compared to UFH as shown above. The ESSENCE and TIMI 11B trials demonstrated that there was a greater benefit from enoxaparin in the meta-analysis than in the two individual studies. Thus, both of these studies showed that enoxaparin was superior to UFH for the treatment of UA/NSTEMI. Further, enoxaparin has shown continued benefit over UFH at one-year follow-up.24 Differences in study design, endpoints, and treatment regimens prevent direct comparison of results between studies of LMWHs. The role of LMWHs in combination with GP IIb/IIIa blockers in acute coronary syndrome patients is rapidly evolving as a result of trials such as NICE 3 and NICE 4, which have assessed the use of enoxaparin in this setting. In ST segment elevation myocardial infarction (STEMI), enoxaparin has been shown to be effective and safe when combined with fibrinolytics in the AMI-SK and HART-2 trials.

**Adverse Effects**

The concurrent use of epidural or spinal anesthesia or spinal puncture and an LMWH increases the risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. Indwelling epidural catheters or the simultaneous use of drugs affecting hemostasis increases the risk of these events. Patients receiving both an LMWH and neuraxial anesthesia should be monitored frequently for possible neurological impairment.
Other adverse effects include bleeding, thrombocytopenia, anemia, and hematomas. Some patients might experience pain, discomfort, or hematoma at the injection site. Thrombocytopenia (platelet count ≤100,000 mm$^3$) is reported to occur in about 1% of patients treated with LMWHs, which is considerably lower than UFH. In addition, the incidence of actual heparin-induced thrombocytopenia (HIT) is lower with the LMWHs. However, LMWHs should not be used in patients with HIT. Lepirudin, danaparoid, or argatroban are the agents of choice in this situation. Injection site hematomas occur in 5% to 10% of patients receiving LMWHs; however, they generally do not limit therapy. The incidence of serious bleeding ranges between 4% and 6%.

Hyperkalemia and lipid abnormalities have also been documented. Asymptomatic and reversible elevations of the transaminases can occur with the use of LMWHs. Osteoporosis and hypersensitivity reactions have also been reported. No important differences in adverse effects have been reported between LMWHs.

The LMWHs are eliminated renally and therefore should be used with caution in patients with renal impairment. Patients with a creatinine clearance of less than 30 ml/min might require alternate therapy with UFH or close monitoring of anti-Xa levels.

### Drug Interactions

No clinically significant drug interactions have been reported with the LMWHs. Other antithrombotic agents such as anticoagulants, antiplatelets (including NSAIDS), and fibrinolytics might potentiate their anticoagulant effects.

### Cost-Effectiveness of LMWHs

The number of pharmacoeconomic studies with LMWHs is somewhat limited. Most of the pharmacoeconomic data has been reported with enoxaparin. Gould et al. reported the results of a cost-effectiveness analysis of enoxaparin compared with UFH for the treatment of acute DVT. Total costs for inpatient treatment were essentially equal for both treatment groups. The cost of initial care was higher with LMWH, but this was offset by reduced costs for early complications. LMWH increased quality-adjusted life years (QALYs) by about 0.02 years. The incremental cost-effectiveness (cost-utility) of inpatient LMWH was $8,000 per QALY gained. This indicates that enoxaparin therapy is highly cost-effective.

O’Brien et al. performed an economic evaluation of outpatient treatment with enoxaparin for proximal DVT. He concluded that treatment at home with LMWH was less costly than hospital-based treatment with UFH. From a cost-minimization standpoint, the costs associated with LMWH were about $2,000 less per patient at 90 days. There was no compromise in clinical outcomes or patients’ quality of life.

In a managed care setting, Spyropoulos et al. recently analyzed the implementation and feasibility of an outpatient-based treatment protocol for uncomplicated DVT using enoxaparin by measuring utilization and outcomes data and pharmacoeconomic indicators. A pharmacist-managed anticoagulation service and home health service support were part of the protocol. He reported that 61% of all patients with DVT in the system were treated as outpatients, with 42% treated completely at home. There were no significant differences in the incidence of recurrent VTE or other primary or secondary adverse outcomes. An average institution-wide savings of $2,473 per patient was reported when prefilled enoxaparin syringes were used. Pharmacoeconomic data for dalteparin and tinzaparin are pending.

### Table 3 FDA-Approved Labeling and Dosing for LMWHs

<table>
<thead>
<tr>
<th>Approved Labeling and Dosing/SQ Administration</th>
<th>Dalteparin</th>
<th>Enoxaparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement Surgery Prophylaxis</td>
<td>5000 IU QD for 5-10 days</td>
<td>30 mg Q12h for 7-10 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Extended Hip Prophylaxis</td>
<td>n/a</td>
<td>40 mg QD for 3 weeks</td>
<td>n/a</td>
</tr>
<tr>
<td>Knee Replacement Surgery Prophylaxis</td>
<td>n/a</td>
<td>30 mg Q12h for 7-10 days</td>
<td>n/a</td>
</tr>
<tr>
<td>General Surgery Prophylaxis</td>
<td>2500 IU QD or 5000 IU QD (high-risk) for 5-10 days</td>
<td>40 mg QD for 7-10 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Prophylaxis in acute medically ill</td>
<td>n/a</td>
<td>40 mg QD for 6-14 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Treatment of DVT with or without PE</td>
<td>n/a</td>
<td>1 mg/kg Q12h as a “bridge” to warfarin (O/P Tx permitted) until stable INR</td>
<td>175 anti-Xa IU/kg QD as a “bridge” to warfarin until stable INR</td>
</tr>
<tr>
<td>Unstable angina and Non-ST-segment elevation MI</td>
<td>120 IU/kg Q12h for 5-8 days + aspirin indefinitely</td>
<td>1 mg/kg Q12h for 2-8 days + aspirin indefinitely</td>
<td>n/a</td>
</tr>
</tbody>
</table>

QD = daily; Q 12h = every 12 hours; O/P = outpatient; Tx = treatment; INR = International Normalized Ratio; IU = International Units
As for the pharmacoeconomics of enoxaparin in UA and NSTEMI, the ESSENCE trial demonstrated a cumulative cost savings of nearly $1,200 per patient at the end of 30 days (using a cost-minimization analysis). Most of this savings was achieved with a decrease in the use of major resources such as repeat cardiac catheterization and PCI procedures. Additional non-U.S. economic data is currently being assembled on some of the other LMWHs.

### Economic Considerations

Reimbursement of LMWHs must be considered in the overall cost-containment picture. In some patients, depending on the payer, when LMWHs that do not have FDA-approved indications are used, they might not be reimbursable. The actual acquisition costs for LMWHs vary depending on the whole-

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#### Table 4 Efficacy of LMWHs

<table>
<thead>
<tr>
<th>Generic name:</th>
<th>Dalteparin</th>
<th>Enoxaparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy: Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Surgical Patients</td>
<td>30% more effective than UFH (5,000 U SC 2-3 X day), no difference bleeding</td>
<td>30% more effective than UFH (5,000 U SC 2-3 X day), no difference bleeding</td>
<td>?</td>
</tr>
<tr>
<td>Hip Replacement</td>
<td>Reduces incidence of thrombosis by 70% compared to placebo without increasing major bleeding</td>
<td>Reduces incidence of thrombosis by ~70% compared to placebo without increasing major bleeding</td>
<td>Reduces incidence of thrombosis by ~70% compared to placebo without increasing major bleeding</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>?</td>
<td>Reduces incidence of thrombosis by 70% compared to placebo without increasing major bleeding</td>
<td>?</td>
</tr>
<tr>
<td>Trauma</td>
<td>?</td>
<td>Reduces incidence of DVT by ~60% compared to UFH (5,000 U SC 12h) without increasing major bleeding</td>
<td>?</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>?</td>
<td>Reduces incidence of DVT by ~60% compared to compression stockings without increasing major bleeding</td>
<td>?</td>
</tr>
<tr>
<td>Acutely Ill Medical Patients</td>
<td>?</td>
<td>Reduces incidence of DVT by ~63% compared to placebo without increasing major bleeding</td>
<td>?</td>
</tr>
<tr>
<td><strong>Efficacy: Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>As effective as UFH</td>
<td>As effective as UFH</td>
<td>As effective as UFH</td>
</tr>
<tr>
<td>PE</td>
<td>As effective as UFH</td>
<td>As effective as UFH</td>
<td>As effective as UFH</td>
</tr>
<tr>
<td><strong>Efficacy: Treatment</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>UA/NSTEMI</td>
<td>Death, MI (day 6) 1.8% vs. 4.8% (placebo), P=0.001 (FRISC)</td>
<td>Death, MI, Recurrent Angina (14 days) 16.6% vs. 19.8% (UFH), P=0.019 (ESSENCE)</td>
<td>n/a</td>
</tr>
<tr>
<td>Death, MI, Recurrent Angina (5-8 days) 9.3% vs. 7.6% (UFH), P=0.33 (FRISC)</td>
<td>Death, MI, Recurrent Angina (30 days) 19.8% vs. 23.3% (UFH), P=0.016 (ESSENCE)</td>
<td></td>
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</tr>
<tr>
<td>Death, MI, Recurrent Angina (45 days) 12.3% vs. 12.3% (placebo), P=0.96 (FRISC)</td>
<td>Death, MI, Recurrent Angina (1 year) 32.0% vs. 35.7% (UFH), P=0.022 (ESSENCE)</td>
<td></td>
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</tr>
<tr>
<td>Death, MI (90 days) 6.7% vs. 8.0% (placebo), P=0.2 (FRISC II)</td>
<td>Death, MI, Urgent Revascularization (14 days) 4.2% vs. 11.6% (UFH), P=0.03 (TIMI 11 B)</td>
<td></td>
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</tr>
<tr>
<td>FRISC = Fragmin during instability in coronary artery disease; SC = subcutaneous</td>
<td>Death, MI, Urgent Revascularization (43 days) 17.3% vs. 19.6% (UFH), P=0.049 (TIMI 11 B)</td>
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</tbody>
</table>
saler, individual group purchasing agreement, and the actual market share that is attained for the particular LMWH. Nearly all market share agreements indirectly require blanket therapeutic interchange programs to reach a significant shift in utilization to achieve any real savings.

The cost of treating negative outcomes must also be considered when assessing the overall cost of therapy. Negative clinical outcomes can include higher incidences of DVT, PE, ischemic events, and major bleeding. Omitting the cost of treating these potential outcomes can result in a gross underestimation of the total cost of therapy to a health system. A management case study on therapeutic interchange with LMWH is the only pharmacoeconomic report to date to evaluate a therapeutic interchange program for LMWHs. The results of the study suggested that dalteparin for DVT prophylaxis following hip and knee replacement surgery was associated with a decrease in annual drug acquisition costs compared to the cost of therapy with enoxaparin. However, an analysis of the published data in the study reveals that the cost analysis was limited to acquisition costs and did not include switching costs or the cost of treating negative clinical outcomes. When the costs of these negative clinical outcomes are included in a rough outcome cost analysis, it is very likely that no overall cost savings were realized in implementing this program.

Conclusion

The pharmacologic and pharmacokinetic advantages of LMWHs over UFH are well-recognized, as is their clinical superiority in VTE prophylaxis and treatment and in UA/NSTEMI treatment (in the case of enoxaparin). As a result, their use in clinical practice is greatly increasing. It is considered optimal to have only one LMWH product available on the formulary, because maintaining multiple products increases the risk of medication errors and places an administrative burden on the system. However, there is insufficient evidence to support pharmacologic and therapeutic equivalence of LMWHs; each LMWH is approved for a unique set of indications.

To consider therapeutic interchange of LMWHs, pharmacologic equivalence, clinical evidence supporting therapeutic equivalence, and cost benefit (considering both acquisition costs and costs of negative clinical outcomes) must be demonstrated. Careful attention must be paid to the quantity and quality of data analyzed in making recommendations. Decisions based on data from case reports or studies of clinical practice populations are not always reliable, because most of these studies are not powerful enough to detect small but significant differences in patient outcomes. LMWHs are discrete, non-interchangeable agents with demonstrated pharmacologic and clinical differences. A blanket therapeutic interchange program could compromise patient care and potentially increase overall outcome cost.

References


11. Hull RD, Raskob GE, Brant RF, Pineo GF, Elliott G, Stein PD et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary


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