Therapeutic Interchange: A Consensus Panel’s View of LMWHs

Pharmacy & Therapeutics Committees evaluate new opportunities for therapeutic interchange (TI) on an ongoing basis. According to a recent survey, more than 80% of general and children’s medical-surgical hospitals in the United States use TI programs.1 These programs promote the interchange of therapeutically equivalent but chemically unique drugs in accordance with established policies and procedures within an organized health care system’s evidence-based formulary. The primary goal is to reduce the total cost of therapy without compromising patient care. As health systems strive to reduce drug budgets, market-share changes can be assessed, and risk can be minimized. Applying these criteria to a LMWH TI program could reduce total costs without compromising patient care.

Essential TI Criteria

A scientifically valid and pharmacoeconomically beneficial LMWH TI program must adhere to six essential criteria: pharmacologic equivalence, clinical evidence supporting interchange, cost or other advantages, a thorough Pharmacy and Therapeutics committee evaluation process, regular monitoring of outcomes, and opportunity for variance. These criteria provide a basic set of standards for evaluating an opportunity for TI so that pharmacologic profiles and clinical efficacy between LMWHs can be compared, financial consequences can be assessed, and risk can be minimized. Applying these criteria to a LMWH TI program will also provide an estimate of the initial and ongoing administrative responsibilities the health-care system must assume. A LMWH TI program would be inappropriate if it does not meet even one of these criteria.

Four-part Review

The six criteria listed above establish standards that a proposed TI program must meet; however, they do not provide a practical mechanism for evaluating the feasibility of the program. Therefore, the second essential element of a potential LMWH TI program is a four-part review, which offers a tangible approach for evaluating a proposed TI program from scientific, tactical, legal, and financial perspectives.

The scientific and tactical evaluation of a TI program is accomplished through a medical assessment and Pharmacy and Therapeutics (P&T) committee review. The medical assessment compares the pharmacologic profile and therapeutic efficacy of each LMWH using pharmacokinetic, pharmacodynamic, and published data from clinical trials. The purpose of the medical review is to determine pharmacologic and therapeutic equivalence within identified indications. The Pharmacy and Therapeutics (P&T) review, sometimes referred to as Medical Policy review, assesses the institution’s ability to implement a TI program safely. Usually completed by the P&T Committee, this review addresses tactical and administrative issues regarding analysis of published data, development of the TI program, education of medical, pharmacy, and nursing staff, and creation of a system of documentation and notification.

It may be impossible to determine if any healthcare systems or providers have been found civilly liable for a patient’s drug-related injury based on a TI program or formulary decision. This is due to the fact that cases settled out of court do not become part of the published legal record. However, if such a case made it to court, it would be brought under allegations of negligence. Although cost reduction is the primary driver of TI today, cost must be a secondary consideration following clinical effectiveness and safety. Legal risk to the institution or health care provider increases significantly if patient outcomes are adversely affected as a result of a TI program.

The financial analysis should employ appropriate scientific models of pharmacoeconomic analysis, such as cost-minimization, cost-benefit, cost-utility, or cost-effectiveness, to determine which agent is best for reducing costs and preserving patient care. The institution must agree on the time frame for assessing benefit and the components in care that affect costs.

Continued on next page
The past seven years have seen the introduction of four LMWHs, enoxaparin, dalteparin, ardeparin, and tinzaparin (the most recently approved agent). Evidence suggests that these LMWHs are generally as effective as standard unfractionated heparin (UFH) with superior safety profiles and more convenient administration. Because of differences in the manufacturing process, each LMWH has a distinct pharmacologic profile. In order to have any chance for success, a TI program for low-molecular-weight heparins (LMWHs) must stand up to the six criteria and undergo the four-part review outlined previously. A TI program that fails to meet these standards may jeopardize patient care, result in financial loss, or possibly create liability issues for the health-care system.

### LMWH TI Criteria

#### Pharmacologic Equivalence:
Pharmacologic equivalence between LMWHs has not been established. Differences exist in molecular weight, structure, and manufacturing process, protein and cell binding, and dosage. LMWHs also differ with regard to half-life, anti-Xa activity, and anti-Xa to anti-IIa activity² (Table 1). In general, the half-lives of LMWHs are two to four times longer than the half-life for heparin, but there are differences within the class. Enoxaparin possesses the longest half-life, and the highest anti-Xa to anti-IIa ratio of 3.8, compared with 2.7 for dalteparin, 1.9 for ardeparin and 2.8 for tinzaparin. This demonstrates its preferential effect on factor Xa. Although the complete clinical relevance of these differences has not been established, experimental models have shown that adjusting the anti-Xa dosage to achieve equal anti-Xa potency does not result in equal antithrombotic activity.³

Thus, evidence is lacking to support pharmacologic and therapeutic homogeneity among LMWHs. Consequently, in addition to WHO and the United States FDA, the American College of Chest Physicians, the American College of Cardiology, and the American Heart Association do not consider LMWHs interchangeable.² ⁴ ⁷

#### Approved Uses:
As a result of the important differences in medical evidence, each LMWH has a different set of FDA-approved indications. Enoxaparin is approved for a number of indications, encompassing the prevention of deep venous thrombosis (DVT) in surgical and acutely ill medical patients, inpatient and outpatient treatment of DVT, and prevention of ischemic complications as a result of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), when given with aspirin. Dalteparin is approved for prophylaxis of DVT and treatment of UA and NSTEMI when administered with aspirin. Ardeparin is approved for a single indication, prevention of DVT, and tinzaparin is approved for inpatient treatment of DVT with or without pulmonary embolism (PE). The specific FDA-approved indications are summarized in Table 2. Once again, the disparity in the number of indications for each LMWH reflects the disparity in the weight of published data from clinical trials available for each agent. Moreover, for a number of indications, there are no clinical data to support the use of one agent in place of another.

#### Clinical Evidence:
Clinical evidence demonstrating equivalent efficacy between LMWHs is lacking due, in part, to a lack 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 controlled trials is not equally distributed among LMWHs. Enoxaparin was the first LMWH approved for use in the United States; it is the most widely studied LMWH and has demonstrated efficacy in a broader range of patient populations than the other LMWHs (Table 3).

#### VTE Prophylaxis
Each of the LMWHs approved for use in the United States has been studied for prophylaxis of DVT; however, equivalent efficacy within specific patient populations has not been established. Enoxaparin has been studied for DVT prophylaxis in various patient populations at risk for thrombotic disease, and is approved for DVT prophylaxis in patients at risk of thromboembolism, including those undergoing hip replacement surgery, knee replacement surgery, abdominal surgery, and acutely ill medical patients with restricted mobility.⁹ Dalteparin is approved for DVT prophylaxis following hip replacement and abdominal surgery.⁹ Ardeparin is approved for DVT prophylaxis following knee replacement surgery¹⁰ and tinzaparin is not approved for DVT prophylaxis.

#### VTE Treatment
For the treatment of DVT, data exist supporting the safety and efficacy of enoxaparin and tinzaparin compared with unfractionated heparin.¹¹ For the treatment of PE, enoxaparin, tinzaparin, and dalteparin have shown efficacy compared with unfractionated heparin.¹¹ However, only enoxaparin and tinzaparin are approved for inpatient treatment of DVT with or without PE, and only enoxaparin is approved for outpatient treatment of DVT.¹¹,¹³ Some of the evidence that supports the safety and efficacy of LMWHs compared with unfractionated heparin has come from meta-analyses. Although meta-analyses are inherently limited and interpretation of results should be done with caution, they provide a tool for integrating and comparing the results of individual studies to arrive at general conclusions about outcomes.

### Acute Coronary Syndromes
LMWHs are increasingly used in acute coronary syndromes; however, results from clinical studies suggest there are clear differences in efficacy between agents. Dalteparin and nadroparin have demonstrated efficacy in the management of patients with UA and NSTEMI equivalent to unfractionated heparin.¹³,¹⁴ Only enoxaparin has demonstrated superiority to unfractionated heparin in this patient population for the combined endpoint of death, myocardial infarction, or recurrent angina at days 14 and 30.¹⁵,¹⁶,¹⁷ Differences in study design, endpoints, and treatment regimens prevent direct comparison of results between studies of LMWHs.
Additional concerns that limit TI between LMWHs are difficulties in determining therapeutically equivalent doses and length of therapy. Therapeutically equivalent doses, even with regard to anti-Xa activity, have not been established; therefore, dose conversion between agents is difficult. Furthermore, for patients who require extended prophylactic therapy, only enoxaparin has been studied for long-term (3 weeks) prophylaxis of DVT following hip replacement therapy.

Patient- and institution-specific concerns make it difficult to make generalizations about the comparative safety profiles of LMWHs. Contraindications, adverse event profile, drug interactions, and patient compliance will influence the safety profile of each particular agent. For example, contraindication to the preservative benzyl alcohol, contained in some multi-dose vials, prohibits use of particular agents, such as dalteparin, in a neonatal unit. Additionally, health-care systems that focus care on specific patient populations may be prohibited from using specific agents. For example, based on the results of studies of LMWHs in UA and NSTEMI, enoxaparin was selected as the agent of choice for a hospital that serves mostly cardiac patients.

**Cost of Outcomes:**

The primary purpose for implementing most TI programs is to lower cost. For LMWHs, drug acquisition costs force an analysis of a preferred agent; however, because clinical studies have demonstrated differences in outcomes between LMWHs, the cost of treating negative outcomes must be considered when assessing the overall cost of therapy. Negative clinical outcomes to be considered may include higher incidences of DVT, PE, ischemic events, and major bleeding. Omitting the cost of treating these potential outcomes may result in a gross understimation of the total cost of therapy.

Without head-to-head clinical trials, comparing therapeutic outcomes is challenging, but comparing impact on total health costs is even more difficult. For example, a recently published management case study on TI with LMWH indicated that dalteparin for DVT prophylaxis following hip and knee replacement was associated with a $90,000 decrease in annual drug acquisition costs. However, a closer analysis of the overall costs associated with the TI, including the projected cost of treating negative outcomes, provides a different perspective on the cost impact for this TI. Because the estimated cost of treating the reported negative outcomes in this report (an additional PE and an additional 1.5 episodes of bleeding per 100 patients treated with dalteparin compared with enoxaparin) and potential mortality (on average, one death for every ten patients who develop PE) were not considered, the total cost of therapy was not assessed and could outweigh any decrease in drug cost. Note that the data from this report are purely observational and that problems with the study prevent extrapolation of the results to any situation. The authors of the report compared data from large, prospective trials with enoxaparin retrospective data collected through chart reviews and telephone interviews for a comparatively small number of dalteparin-treated patients; they compared patients from different populations (67.3% of enoxaparin-treated patients were orthopedic surgery patients compared with 16.7% of dalteparin-treated patients, and 65.6% of dalteparin-treated patients were trauma patients compared with 4.5% of enoxaparin-treated patients), and could not use “comprehensive statistical comparisons.” Consequently, the results are inherently flawed, and their conclusions, even regarding their own patient base, are uncertain at best.

**Four Part Review of LMWHs**

The four-part review of a TI program for LMWHs reveals substantial obstacles to implementation, especially with regard to establishing therapeutic equivalence:

**Medical Review**

A medical analysis of LMWHs reveals that LMWHs are not pharmacologically or therapeutically equivalent. The FDA-approved labeling for enoxaparin contains the following statement regarding LMWHs: “Lovenox injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparin as they differ in manufacturing process, molecular weight, distribution, anti-Xa and anti-lla activities, units, and dosage (PI Lovenox).” Furthermore, each LMWH is labeled for a unique set of indications, underscoring the lack of clinical evidence supporting the use of all LMWHs in every indication.

**P&T Review**

Issues that may arise from the P&T review of a TI program for LMWH, beyond those expected issues that arise with any TI program (e.g., staff education, documentation, establishing criteria for analyses and decision making and a protocol for monitoring outcomes) include establishing the appropriate dose of an agent for an unapproved use, especially when there is little, if any, clinical evidence supporting its efficacy in the particular indication. Basically, it would be a leap of faith to create a LMWH TI management process when such formidable clinical obstacles obviate its need.

**Legal Review**

Although TI programs today are primarily aimed at cost reduction, unequivocal clinical effectiveness and safety must ultimately be the primary consideration in approving and implementing such a program. If therapeutic equivalence has not been demonstrated as part of the medical review, then the potential exists that patient outcomes may be adversely affected. Several published TI programs have clearly been shown to compromise patient outcomes.

Not unexpectedly, health-care systems or providers have not been found civilly liable to date for a patient’s drug-related injury based on a TI program. Most medical negligence and malpractice cases, however, are settled out of court, for significant amounts of money, some sums exceeding $100 million. The degree of legal risk will increase dramatically once negative patient outcomes associated with a TI program are published in the literature. Thus, if a LMWH TI program results in an increase in DVT, PE, major bleeding, or even death, the health care system must be aware and assess the liability.

**Financial Review**

A financial review of a TI program for LMWHs requires consideration of costs, including drug acquisition cost, implementation and monitoring cost of treating negative outcomes (e.g., DVT, PE, and mortality). Some cost analyses consider quality of life as well. However, pharmacoeconomic comparison of LMWHs remains difficult because, to date, no prospective, comparative pharmacoeconomic study of LMWHs has been published.
Based on the results of the previously discussed management case study, a basic pharmacoeconomic analysis using a cost model of outcomes suggests that for every one hundred patients in that cohort who participated in the TI program that used dalteparin in place of enoxaparin, an average $13,500 in costs ($135 per patient to treat negative outcomes) were potentially added to the overall cost of therapy. This calculation assumes a cost of $6,000 for treating an additional PE (range of $1,000 to $10,000) and $7,500 (range of $1,500 to $15,000) for treating 1.5 additional major bleeding episodes when dalteparin was used instead of enoxaparin. Additionally, there is mortality risk associated with pulmonary emboli. Extrapolation of the data from the management case study suggests that for every one thousand patients switched to dalteparin, ten additional PEs are possible, and based on known mortality rates for PE, one of the ten additional PEs might be fatal.

This analysis is limited in that it is based on data from a management case study and not a clinical study; it nevertheless demonstrates the need to incorporate the cost of treating outcomes in the financial review of a TI program. A financial review that includes the cost of treating outcomes provides a better tool for selecting appropriate and cost-effective medical care than a review that includes only drug acquisition costs.

### Conclusion: LMWH TI Inappropriate Now

In an effort to contain costs, health-care systems prudently continue to consider the value of TI programs. If implemented correctly, as an ongoing process for appropriate classes of drugs, a TI program can be a useful tool for minimizing costs. Although reducing the cost of providing health care is very important, the primary concern of any health-care system must be to provide optimal patient care. Consequently, a scientifically valid and pharmacoeconomically beneficial TI program must meet the six essential criteria for TI and withstand a rigorous four-part review before it can be ethically implemented.

Application of the six essential criteria to LMWHs reveals that LMWHs are discrete, non-interchangeable agents with demonstrated pharmacologic and clinical differences. The four-part review, from medical, tactical, legal, and financial perspectives, confirms non-interchangeability. Thus, applying this scientific model to LMWHs indicates that TI with LMWHs is inappropriate at this time. Without this rigorous evaluation and attention to legal issues, a program may be implemented that compromises patient care, increases cost, exposes the health-care system to liability, or places undue administrative burden upon the health-care system.

### Table 1: Pharmacologic Differences Between LMWHs

<table>
<thead>
<tr>
<th></th>
<th>ENOXAPARIN</th>
<th>DALTEPARIN</th>
<th>ARDEPARIN</th>
<th>TINZAPARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>91</td>
<td>87</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td><strong>Elimination T½ SQ (hours)</strong></td>
<td>4.5</td>
<td>3-5</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Mean Molecular Weight</strong></td>
<td>4500</td>
<td>6000</td>
<td>6000</td>
<td>6500</td>
</tr>
<tr>
<td><strong>Anti-Xa/Anti-IIa Ratio</strong></td>
<td>3.8</td>
<td>2.7</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Peak Anti-Xa Activity (hours)</strong></td>
<td>3-5</td>
<td>3-4</td>
<td>2-3</td>
<td>4-6</td>
</tr>
</tbody>
</table>

### Table 2: Approved Labeling for LMWHs

<table>
<thead>
<tr>
<th></th>
<th>ENOXAPARIN</th>
<th>DALTEPARIN</th>
<th>ARDEPARIN</th>
<th>TINZAPARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved Labeling/ SQ Administration:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• <strong>Hip Replacement</strong></td>
<td>30 mg q 12h or 40 mg QD for 7-10 days</td>
<td>5000 U QD for 5-9 days</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>• <strong>Extended Hip Prophylaxis</strong></td>
<td>40 mg QD for 3 weeks</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>• <strong>Knee Replacement</strong></td>
<td>30 mg Q 12h for 7-10 days</td>
<td>n/a</td>
<td>50 U/kg every 12h for 7-10 days</td>
<td>n/a</td>
</tr>
<tr>
<td>• <strong>General Surgery</strong></td>
<td>40 mg QD for 7-10 days</td>
<td>2500 U QD or 5000 U QD (high-risk) for 5-10 days</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>• <strong>DVT with or without PE</strong></td>
<td>1 mg/kg q 12h as a “bridge” to warfarin (O/P Tx permitted) until stable INR</td>
<td>1.5 mg/kg q 24h as a “bridge” to warfarin (IP only) until stable INR</td>
<td>n/a</td>
<td>175 anti-Xa U/kg QD as a “bridge” to warfarin until stable INR</td>
</tr>
<tr>
<td>• <strong>Unstable angina and NSTEMI</strong></td>
<td>1 mg/kg q 12h + aspirin (160-325 mg QD), usual duration 2-8 days</td>
<td>120 U q 12h + aspirin for 5-8 days</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
### Table 3: Efficacy of LMWHs

<table>
<thead>
<tr>
<th></th>
<th>ENOXAPARIN</th>
<th>DALTEPARIN</th>
<th>ARDEPARIN</th>
<th>TINZAPARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name:</strong></td>
<td>Lovenox (Aventis)</td>
<td>Fragmin (Pharmacia &amp; Upjohn)</td>
<td>Normiflo (Schering)</td>
<td>Innohep (Dupont)</td>
</tr>
<tr>
<td><strong>Efficacy: Prevention VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• General Surgical Patients</td>
<td>30% more effective than UFH (5,000 U SQ 2-3 X day), no difference bleeding</td>
<td>30% more effective than UFH (5,000 U SQ 2-3 X day), no difference bleeding</td>
<td>?</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>?</td>
<td>?</td>
</tr>
<tr>
<td>• Knee Replacement</td>
<td>Reduces incidence of thrombosis by ~70% compared to placebo without increasing major bleeding</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>Reduces incidence of DVT by ~60% compared to UFH (5,000 U SQ q 12h) without increasing major bleeding</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>• Neurosurgery</td>
<td>Reduces incidence of DVT by ~60% compared to compression stockings without increasing major bleeding</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>• Acutely III Medical Patients</td>
<td>Reduces incidence of DVT by ~63% compared to placebo without increasing major bleeding</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Efficacy: Treatment VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treatment DVT</td>
<td>At least as effective as UFH</td>
<td>At least as effective as UFH</td>
<td>?</td>
<td>At least as effective as UFH</td>
</tr>
<tr>
<td>• Treatment PE</td>
<td>At least as effective as UFH</td>
<td>At least as effective as UFH</td>
<td>?</td>
<td>At least as effective as UFH</td>
</tr>
<tr>
<td>• Major Bleeding</td>
<td>Equal or less likely to cause major bleeding</td>
<td>Equal or less likely to cause major bleeding</td>
<td>?</td>
<td>Equal or less likely to cause major bleeding</td>
</tr>
</tbody>
</table>

- **Death, MI, Recurr. Angina (14 days)**
  - 16.6% vs. 19.8% (UFH), p=0.019 (ESSENCE)

- **Death, MI, Recurr. Angina (30 days)**
  - 19.8% vs. 23.3% (UFH), p=0.016 (ESSENCE)

- **Death, MI, Recurr. Angina (1 year)**
  - 32.0% vs. 35.7% (UFH), p=0.022 (ESSENCE)

- **Death, MI, Urgent Revascularization (14 days)**
  - 14.2% vs. 16.6% (UFH), p=0.03 (TIMI 11 B)

- **Death, MI, Urgent Revascularization (43 days)**
  - 17.3% vs. 19.6% (UFH), p=0.049 (TIMI 11 B)

- **Death, MI (day 6)**
  - 1.8% vs. 4.8% (placebo), p=0.001 (FRISC)

- **Death, MI, Recurr. Angina (5-8 days)**
  - 9.3% vs. 7.6% (UFH), p=0.33 (FRIC)

- **Death, MI, Recurr. Angina (45 days)**
  - 12.3% vs. 12.3 % (placebo), p=0.96 (FRIC)

- **Death, MI (90 days)**
  - 6.7% vs. 8.0% (placebo), p=0.2 (FRISC II)

**COMPOSITE KEY:**
- D=death; M=MI; U=urgent revasc.; R=any revasc.; I=refractory ischemia

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Acute rheumatic disorder
• Acute respiratory failure
• Acute congestive heart failure, NYHA
  Class III or IV
• Acute lumbar or sciatic pain, vertebral compression (caused by osteoporosis or tumor), acute arthritic episodes of the lower extremities.

MEDENOX Study Design

In 1999, Samama et al. published “A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients.”

A total of 1,102 hospitalized patients participated in this Phase III double-blind study. This multicenter study was conducted at 60 sites in nine European countries. Patients were randomized into one of three parallel groups: Lovenox® (enoxaparin-Aventis Pharmaceuticals), 20mg or 40mg, administered subcutaneously (SC) once daily for 6 to 14 days (10±4 days) versus placebo in patients who were hospitalized for an acute medical disorder. Treatment began within 24 hours of randomization.

The primary endpoint of the study was the development of venous thromboembolism (VTE), defined as DVT or PE or both, in the first 14 days of the study. The secondary endpoint for evaluating efficacy was VTE between days 1 and 110. Venography was performed on patients’ lower extremities between days 6 and 14, or earlier if VTE was suspected because of clinical observations. Suspected cases of PE were confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography, or at autopsy in patients who died.

Three hundred sixty-four (364) patients received enoxaparin 20mg, 367 patients received enoxaparin 40mg, and 371 patients received placebo. Patient characteristics revealed all patient populations to be similar. The average age was 73 years; men and women were included in approximately equal numbers.

Reasons for hospitalization included:
• Acute congestive heart failure, NYHA Class III or IV
• Acute respiratory failure
• Acute rheumatic disorder

References


13. FRAXIS Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction. FRAXIS. Eur Heart J. 1999;20:1555-62.


Risk factors that accompanied those illnesses included:

- Age > 75 years (more than half of the patients)
- Cancer
- History of VTE
- Obesity (a body mass index of at least 30 in men and 28.6 in women)
- Varicose veins
- Hormone therapy
- Chronic heart failure
- Chronic respiratory failure

MEDENOX RESULTS: Enoxaparin Highly Effective

About two-thirds of the patients had two or more risk factors. Of the 866 evaluable patients, 92 developed VTE within the first 14 days (the primary endpoint). Within the first 14 days, VTE developed in 16 patients (5.5%) receiving enoxaparin 40mg, 43 patients (15.0%) of those receiving enoxaparin 20mg, and in 43 patients (14.9%) receiving placebo. Within the first 14 days, the relative risk of patients receiving enoxaparin 40mg who developed disease was 0.37, with a 97.6% confidence interval of 0.22 to 0.63 (p = < 0.001).

Of the 798 patients evaluated at 3 months for the secondary endpoint, 19 (7.0%) of the patients receiving enoxaparin developed VTE, compared to 46 (17.5%) of the patients receiving enoxaparin 20mg and 45 (17.1%) of the patients receiving placebo. The efficacy results are summarized in Table 1.

Table 1: Efficacy of Enoxaparin in MEDENOX Study

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>ENOXAPARIN 20MG N (%)</th>
<th>ENOXAPARIN 40MG N (%)</th>
<th>PLACEBO N (%)</th>
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<tbody>
<tr>
<td>Patients Evaluated</td>
<td>287 (100)</td>
<td>291 (100)</td>
<td>288 (100)</td>
</tr>
<tr>
<td>Total VTE</td>
<td>43 (15)</td>
<td>18 (5.5)</td>
<td>43 (14.9)</td>
</tr>
<tr>
<td>DVT alone</td>
<td>42 (14.8)</td>
<td>18 (5.5)</td>
<td>40 (13.9)</td>
</tr>
<tr>
<td>PE alone</td>
<td>0</td>
<td>0</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>13 (4.5)</td>
<td>5 (1.7)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>30 (10.5)</td>
<td>11 (3.8)</td>
<td>27 (9.4)</td>
</tr>
<tr>
<td>Death from PE</td>
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<td>0</td>
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<table>
<thead>
<tr>
<th>SECONDARY ENDPOINT</th>
<th>ENOXAPARIN 20MG N (%)</th>
<th>ENOXAPARIN 40MG N (%)</th>
<th>PLACEBO N (%)</th>
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<tr>
<td>Patients Evaluated</td>
<td>263</td>
<td>272</td>
<td>263</td>
</tr>
<tr>
<td>Total VTE</td>
<td>44 (17.5)</td>
<td>19 (7.0)</td>
<td>45 (17.1)</td>
</tr>
<tr>
<td>DVT alone</td>
<td>46 (16.7)</td>
<td>17 (6.2)</td>
<td>41 (15.6)</td>
</tr>
<tr>
<td>PE alone</td>
<td>0</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>14 (5.3)</td>
<td>6 (2.2)</td>
<td>17 (6.5)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>31 (11.8)</td>
<td>12 (4.4)</td>
<td>27 (10.3)</td>
</tr>
<tr>
<td>Death from PE</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

Four non-fatal PE were confirmed, three in the placebo group and one in the enoxaparin 20 mg group. The benefit observed with enoxaparin 40mg was maintained at 3 months. Among the 1073 all-treated patients, major hemorrhage occurred in 4 (1.1%), 1 (0.3%) and 6 (1.7%).

The benefits observed with enoxaparin are summarized in Table 1.

Is SQ Heparin a Practical Option in the Medically Ill?

Although low-dose unfractionated heparin (UFH) is used as prophylaxis against thrombosis, it cannot be considered a validated control treatment for medical patients. The few studies supporting its use include small numbers of patients. Conversely, two studies that have evaluated mortality among medical patients given 5000 U of unfractionated heparin SC twice daily are conflicting.4,5 In addition, the recommendations of consensus conferences are not definitive.7-8,13 Comparisons of enoxaparin to UFH SC 5000 U three times daily in the PRIME14 and PRINCE15 trials demonstrated enoxaparin to be comparable in efficacy in preventing VTE in medically ill patients (0.2% vs. 1.2% in the PRIME trial, and 8.4% vs. 10.4% in the PRINCE Trial). While these studies do validate the role of enoxaparin for its benefit in prevention of VTE, they are problematic in that the standard of care in the U.S. is for administration of UFH 5000 U twice daily unlike these studies which compared UFH dosed three times daily. Also, once-daily administered enoxaparin is more convenient than twice daily administered UFH. UFH administered three times daily as in the PRIME and the PRINCE Trials is even more labor intensive and less likely to actually occur in settings outside of a clinical trial which is rigorously controlled.

Conclusion

The results of the MEDENOX study indicate that hospitalized acutely ill medical patients are at significant risk of VTE, and prophylaxis with enoxaparin 40mg SC once daily is safe, effective, and convenient in reducing this risk by 63%.1, 5

As a result of the MEDENOX trial, enoxaparin was recently approved by the FDA for the prophylaxis of VTE in acutely ill medical patients.

Appropriate risk-stratification for the likelihood of development of VTE will identify those patients who will benefit from enoxaparin prophylaxis in this setting.

References

In the Medically Ill
MEDENOX: Preventing VTE
A Consensus Panel's View
Therapeutic Interchange:

Inside:

Value in Thrombosis Management

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Funding for this publication has been provided by an
unrestricted educational grant from Aventis Pharmaceuticals.

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