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# CLIN-IQ PROJECT

## Clin-IQ Project 2006

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**Question:** Is initial treatment of patients with DVT with LMWH ~~is~~ more effective, safer and/or less expensive than treatment with UFH?

**Answer:** More effective: yes; Cost-effective: yes; Safer: yes

**Date the answer was determined:** 10/22/2005

**Level of Evidence:** RTC, Meta-analysis. Level 1

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### Summary of the Issues:

Deep venous thrombosis (DVT) is a major national health concern in USA. DVT involves more than 600,000 hospitalizations, and at least 200,000 deaths due to pulmonary embolism (PE).<sup>1</sup> In 1997 the National expenditures involved in DVT management was estimated to be \$1.5 billion.<sup>2</sup> Patients with an acute DVT have traditionally been hospitalized and treated with unfractionated heparin (UFH) followed by oral anticoagulation therapy in the past. The use of low-molecular-weight heparin (LMWH) in an outpatient program for the management of DVT provides a treatment alternative to hospitalization in selected patients.

Traditional treatment for DVT is to administer UFH for 5-7 days, followed by oral anticoagulant (warfarin) therapy. UFH requires hospitalization for continuous intravenous infusion and requires close laboratory monitoring by an activated partial thromboplastin time (aPTT) test every 6 hours. Once the patient is adequately anti-coagulated on warfarin, the patient is maintained on oral warfarin for 3-6 months. Enoxaparin is a LMWH that was recently labeled by the U.S. Food and Drug Administration to manage DVT with or without PE, both in an in-patient or outpatient setting. Dosing of LMWH is weight-based and is generally administered once or twice daily. Warfarin is generally begun concomitantly with enoxaparin on day 1. The international normalized ratio (INR) is checked daily for approximately 5 days, until the INR is > 2, at which time LMWH is discontinued and the patient is maintained on warfarin. If the patient or a family member is unable to administer LMWH, the physician can arrange for home health care if the patient is eligible. Neither laboratory

monitoring of the anticoagulant response to LMWH (anti-Xa levels) or platelet levels nor dose adjustment is necessary with patients treated with LMWH.<sup>3</sup>

LMWHs have better bioavailability and dose independent clearance because they have a more predictable anticoagulant response than UFH. The pharmacokinetic difference between LMWH and UFH is that the former has decreased binding to plasma proteins, endothelial cells and macrophages and a longer T<sub>1/2</sub> (by 2-4 times) than the former, which binds more efficiently to plasma proteins.<sup>3</sup> Thrombocytopenia and heparin resistance may occur in patients treated with UFH but not with LMWHs.

Enoxaparin for 5 days costs \$4500, in a patient weighting 70kg. Medicaid covers this medication, as does Medicare Part D, where it is usually Tier 2. Both Medicare and Medicaid also cover UFH. Even though UFH costs only \$15.00 for one thousand Units, the cost incurred with this therapy includes cost of hospitalization, administration, nursing care and laboratory evaluation. This cost outweighs the cost of enoxaparin.

### Summary of the Evidence:

#### Efficacy and Safety

Several meta-analyses have shown that LMWHs are superior to UFH in the treatment of patients with established DVT.<sup>4</sup> In summation, the results of these studies reveal statistically significant reductions in thrombus size, recurrent venous thromboembolism, major bleeding events as well as a pooled long-term mortality rate. These studies show that there is a greater efficacy of LMWH, in terms of long-term mortality rate, even in a high risk population like cancer patients.

In a Cochrane collaborated meta-analysis, covering 22 studies and a patient population of 8867 patients, it was determined that LMWH is more effective than UFH for the initial treatment of venous thromboembolism.<sup>5</sup> Thrombotic complications occurred in 151/4181 (3.6%) participants treated with LMWH, compared with 211/3941 (5.4%) participants treated with UFH (odds ratio (OR) 0.68; 95% confidence intervals (CI) 0.55 to 0.84, 18 trials).

Thrombus size was reduced in 53% of participants treated with LMWH and 45% treated with UFH (OR 0.69; 95% CI 0.59 to 0.81, 12 trials). Major hemorrhages occurred in 41/3500 (1.2%)

participants treated with LMWH, compared with 73/3624 (2.0%) participants treated with UFH (OR 0.57; 95% CI 0.39 to 0.83, 19 trials). In eighteen of the twenty-two trials, 187/4193 (4.5%) participants treated with LMWH died, compared with 233/3861 (6.0%) participants treated with UFH (OR 0.76; 95% CI 0.62 to 0.92). Nine of the twenty-two studies (n = 4451) examined proximal thrombosis; 2192 participants treated with LMWH and 2259 with UFH. Subgroup analysis showed statistically significant reductions favoring LMWH in thrombotic complications and major hemorrhage.<sup>5</sup>

### Cost-Effectiveness

Spyropoulos MD et al determined by a randomized controlled trial, that the treatment of acute proximal DVT with enoxaparin in a primarily outpatient setting can be accomplished safely and yield savings by avoidance or minimization of inpatient stays. Mean  $\pm$  SD cost per patient was \$9,347  $\pm$  8,469 in the enoxaparin group compared with \$11,930  $\pm$  10,892 in the UFH group, a difference of -\$2,583 (95% asymmetrical confidence interval, -\$6,147, +\$650). This study covered 354 patients.<sup>6</sup> As both Medicaid and Medicare cover Enoxaparin, it can be given to patients for the treatment of DVT in the outpatient setting.

Woessner et al found that in patients with acute DVT, enoxaparin use reduced the average length of hospitalization from 5.4 days to 0.97 days indicating that LMWH is a less expensive treatment than UFH, even though the medication cost is higher.<sup>7</sup>

Yeager & Matheny have shown that DVT therapy with LMWHs is more cost-effective. Results showed a 20 percent reduction in disease management costs attributable to decreased length of hospital stay (by 60 to 70 percent), without an increase in the cost of home-health, and an average cost savings of over \$900 per patient.<sup>4</sup>

### Impact on Quality of life:

Patients receiving LMWH for the treatment of DVT report a higher quality of life, probably because they are not hospitalized for IV access, daily blood draws and dose adjustment of medications. They also report a greater sense of physical and social well being.

### Comments:

The success of an outpatient program for the management of DVT depends on familiarity with currently available LMWH and a multidisciplinary approach consisting of physicians, nurses, pharmacists and other health care professionals, where each contributes to planning and implementing a protocol to manage patients with LMWH on an outpatient basis.<sup>4</sup>

The studies referred to in this report are from the perspective of treatment centers and not from the patient's perspective.

### Search terms

Thromboembolism, medical cost, LMWH, UFH, administration

### Inclusion and exclusion criteria

humans, English, RCT, meta-analysis, OVID, Cochrane, pubmed, AAFP, google

### References

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