



REPORT NUMBER 5

Should the MUHC use low-molecular-weight heparin in inpatient treatment of deep vein thrombosis with or without pulmonary embolism?

By

**The Technology Assessment Unit (TAU)
of the McGill University Health Centre (MUHC)**

**This analysis was prepared for the Technology Assessment Unit (TAU) of the
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Invitation. *This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.*

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Abbreviations:

| | |
|-------|---|
| ACCP: | American College of Chest Physicians |
| ACS: | Acute coronary syndromes |
| AD: | Absolute difference |
| APTT: | Activated partial thromboplastin time |
| AT: | Antithrombin |
| CI: | Confidence interval |
| CPS: | Compendium of pharmaceuticals and specialties |
| DVT: | Deep vein thrombosis |
| FEM: | Fixed-effects model |
| HIT: | Heparin-induced thrombocytopenia |
| INR: | International normalized ratio |
| i.v.: | Intra-venous |
| PT : | Prothrombin time |
| LMWH: | Low-molecular-weight heparin |
| MI: | Myocardial infarction |
| MGH: | Montreal General Hospital |
| MUHC: | McGill University Health Centre (in this report, the MGH and RVH are the sites on which clinical data are obtained) |
| OR: | Odds ratio |
| PCS: | Patient care system |
| PE: | Pulmonary embolism |
| PF4: | Platelet factor 4 |
| REM: | Random-effects model |
| RR: | Relative risk |
| RVH | Royal Victoria Hospital |
| s.c.: | Sub-cutaneous |
| UA: | Unstable angina |
| UFH: | Unfractionated heparin |
| VTE: | Venous thromboembolism |

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EXECUTIVE SUMMARY

Objectives

This report compares the effectiveness and safety of low-molecular-weight heparin (LMWH) with unfractionated heparin (UFH) in the in-patient treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE), compares their direct costs to the MUHC, and formulates recommendations concerning the use of LMWH for inpatient treatment of these indications.

Efficacy

Based on two well-designed meta-analyses and two more recently published randomized controlled trials, LMWH appears to be at least as effective, and possibly even slightly superior to UFH in preventing recurrent deep vein thrombosis and pulmonary embolism.

Safety

LMWH is associated with either the same or possibly slightly fewer serious hemorrhagic events than UFH. In addition, its use reduces the frequency of heparin-induced thrombocytopenia compared to UFH.

Costs

Substitution of LMWH for UFH would be a cost saving approach for the treatment of DVT and PE. For example, it is estimated that direct costs from the point of view of the MUHC, would be \$127 lower per case treated with enoxaparin, the LMWH preparation currently used at the MUHC (this report does not consider which of the LMWHs is preferable).

However, such savings are largely attributable to the lower nursing workload associated with LMWH use, and are unlikely to be recovered in the short term. If they are excluded from calculations, the estimated savings per patient resulting from use of enoxaparin instead of UFH would be only \$3. The reduced nursing workload would of course have other benefits such as reduction of stress and increased attention to other tasks.

Budget Impact

In 2001, 515 patients were treated for DVT and PE with UFH at the MUHC. Some patients cannot be given LMWH because of the slow reversibility of its effect. If 450 patients were treated with enoxaparin instead of UFH the MUHC would theoretically save \$57,150 per year. However, as pointed out above, it is unlikely that the cost savings associated with reduced nursing workload would be recovered. With these costs excluded, the saving to the MUHC budget would be \$1,350.

Although we have assumed therapeutic equivalence, several studies suggest that LMWH may be associated with lower rates both of recurrence of DVT and PE and of major bleeding events. If correct, the net savings resulting from the introduction of LMWH (enoxaparin) would be greater, possibly by as much as an additional \$20,250 per year.

It is also possible that the routine use of LMWH for inpatient treatment of thromboembolic disease might result in earlier discharge of patients to outpatient management. This number has not been estimated, but this factor might result in considerable additional cost savings. Again, the beds so freed would not be reflected as dollar savings, but would permit the treatment of additional patients, thus increasing productivity rather than reducing budget.

Apart from any effect on the MUHC overall budget, the treatment of 450 patients per year would have significant effects on the budgets of different cost centres. Thus there would be a net increase in Pharmacy budget of \$58,801, a factor that should be taken into account if this recommendation is approved.

Recommendation

The TAU Committee recommends that the MUHC approve the replacement, when clinically indicated, of unfractionated heparin by low-molecular-weight heparin for the inpatient treatment of deep vein thrombosis, with or without pulmonary embolism.

Foreword

On May 23, 2002, Mr. André Bonnici, the coordinator of the Pharmacy and Therapeutics Committee, requested the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) to evaluate the clinical and economic impact of replacing Unfractionated Heparin (UFH) by Low-molecular-weight heparins (LMWHs), for:

- In-patient treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE);
- In-patient management of acute coronary syndromes (ACS);
- Prophylaxis of thrombo-embolism in general surgery.

Although there is some evidence suggesting that LMWHs may offer clinical advantages over UFH as well as simplifying administration, the drug acquisition costs of LMWHs remain far higher than UFH. To formulate a recommendation for the MUHC on this issue, the TAU agreed to proceed to a formal evaluation of the health benefits and costs of these two heparin preparations. The present report addresses the first issue, namely the treatment of DVT with or without PE.

Introduction

Unfractionated heparin (UFH) has been the mainstay of anticoagulation therapy for decades. Over the past 20 years, several different heparin fractions -- collectively known as low-molecular-weight heparins (LMWHs) -- have emerged and have been shown to have some distinct advantages over UFH and to be at least as effective as UFH for anticoagulant treatment. The benefits of using LMWHs include providing more predictable levels of anticoagulation, diminishing the necessity for repeated testing, easier administration, and improved safety with less frequent drug induced thrombocytopenia. However, they also have important disadvantages. These include: a longer time to reverse the anticoagulant effect (12-24 h for LMWHs vs. 2-3 h for UFH), which can be problematic when invasive procedures must be performed urgently; the need for dose adjustment and anti-factor Xa activity monitoring in the presence of renal failure; and higher drug acquisition costs compared to UFH.

Currently at the MUHC two types of LMWHs, enoxaparin and tinzaparin, have been incorporated into clinical practice. However, UFH has remained the drug of choice for the in-patient treatment of DVT and PE. The pharmacy at the MUHC has received requests to change from UFH to LMWHs in this clinical setting. The present document reports the comparison of LMWH with UFH for the in-patient treatment of DVT with or without PE. Recommendations are based on estimates of efficacy and safety of these two preparations based on the literature, and their estimated costs in the MUHC setting.

1. Clinical efficacy and safety

Methods

A literature search was performed using the PubMed databases for the topic of in-patient treatment of DVT with or without PE. The review of clinical effectiveness considered all citations that satisfied the following criteria: 1) randomized controlled trial; 2) inclusion of at least one of the LMWHs available in Canada in one study arm (dalteparin, enoxaparin, nadroparin, and tinzaparin); 3) use of objectively confirmed clinical endpoints; and 4) publication in English. No unpublished studies were considered and there were no time restrictions. The preparation of this report was based on two well-designed meta-analyses of the published reports and on two randomized controlled trials appearing since their publication.

Results

Siragusa et al. (1996)¹ conducted a meta-analysis of randomized trials for the period from 1980 to 1994, comparing the efficacy and safety of LMWH and UFH in the treatment of patients with a first episode of deep venous thrombosis (DVT) confirmed by contrast venography, and/or acute pulmonary embolism (PE) confirmed by high-probability ventilation perfusion lung scan. UHF or LMWH heparin were given for from 5 to 14 days, and oral anticoagulant therapy was usually commenced on day 3. Among all 33 identified published articles (unpublished data were also sought, but no data found), only 13 studies met their inclusion criteria (Appendix IV). Eligible studies were further classified as level 1 if they were double blind or if there was a blinded assessment of outcome, and the remainder were classified as level 2. Three studies were classified as level 1, and three as level 2 when evaluating recurrent thromboembolism. Three studies

were classified as level 1, and seven as level 2 when evaluating bleeding events. Only three studies were used in the estimation of mortality.

Results from level 1 studies showed less recurrent symptomatic thromboembolism for LMWH, both during the first 15 days (3/365 vs. 12/371, relative risk (RR)=0.24, 95% CI: 0.06, 0.800, P=0.02), and over the full 3 months of anticoagulant therapy (10/365 vs. 24/371, RR=0.39, 95% CI: 0.3, 0.8, P=0.006). In addition, quantitative venographic assessment in level 1 studies showed a significantly greater reduction in thrombus size in patients receiving LMWH (65.3%) than patients using UHF (52%) while an increase in thrombus size was seen in 5.6% of patients with LMWH vs. 10.3% of patients with UHF (P=0.0001). No significant differences in the rates of recurrent symptomatic thromboembolism were observed in level 2 studies.

Major bleeding was less frequent for LMWH in 3 level 1 studies (12/394 vs. 27/402, RR=0.42, 95% CI: 0.2, 0.9, P=0.01), but was not significantly different in 7 level 2 studies (RR=0.85, 95% CI: 0.04, 5.7, P=0.5).

The overall mortality rate for the entire period was lower in the LMWH arm (21/648 vs. 38/640, RR=0.51, 95% CI: 0.2, 0.09, P=0.01). Surprisingly however, while this difference was chiefly due to deaths of cancer patients, no significant reduction in mortality was found in sub-group analysis for cancer patients treated with LMWH during the initial 15 days, the time when the maximum therapeutic effect of LMWH would be expected to occur.

This appears to be a meticulously executed meta-analysis. Unfortunately, insufficient details are included to completely explain why the authors selected different studies for different endpoints, and for this reason selection bias cannot be excluded.

Gould et al. (1999)² reported another meta-analysis employing data from randomized clinical trials conducted between 1991 and 1997. This updated meta-analysis included six studies that had been incorporated in the previous one¹ and added five trials published thereafter, making a total of 11 of 37 studies that met the author's inclusion criteria (Appendix IV), involving over 3500 patients. Follow-up varied from three to six months from the initiation of therapy. Studies included participants with lower extremity DVT, with or without coexisting PE, and all were characterized by random assignment,

double blinding, and objective methods to confirm the presence of DVT (used only for patient selection) and recurrent thromboembolic events.

The overall frequency of recurrent thromboembolic events within three to six months from the initiation of therapy was slightly lower in patients receiving LMWH, but the difference was not statistically significant (odds ratio (OR)=0.85, 95% CI: 0.63, 1.14, $P>0.2$; absolute number: 97 recurrent thromboembolism occurred among 1792 patients treated with UFH vs. 82/1774 patients treated with LMWH). LMWH was also associated with a lower mortality rate (OR=0.71, 95% CI: 0.53, 0.94, $P=0.02$; absolute number: 122 deaths occurred among 1792 patients treated with UFH vs. 88/1774 patients treated with LMWH). There were also fewer major bleeding complications with the LMWH treatment (OR=0.57, 95% CI: 0.33, 0.99 $P=0.047$; absolute number: 35 major bleedings recorded among 1853 patients treated with UFH vs. 20/1821 patients treated with LMWH).

ORs for major bleeding and recurrent thromboembolism and mortality rates from each study included in the meta-analysis by Gould (1999) are depicted in Appendix V & VI.

Simonneau et al. (1997)³ randomized 612 hospitalized patients with acute symptomatic but submassive PE to receive once-daily, fixed-dose, subcutaneous (s.c.) tinzaparin or standard continuous-infusion UFH. The primary end-point was a combined outcome defined as death, symptomatic recurrent thromboembolism or bleeding occurring in the first three months. There were no significant differences in the rate of recurrent thromboembolic events between the two groups (absolute difference (AD)=0.3%, 95% CI: -1.8, 2.4), death (AD=0.6%, 95% CI: -2.6, 3.8), or major bleeding (AD=0.6%, 95% CI: -1.8, 3.0). Analysis by the log-rank test, which takes into account the length of time to the first clinical event, did not show any significant difference between groups ($P=0.55$) in the frequency of the combined endpoint.

Hull et al. (2000)⁴ compared fixed-dose, once-daily sc Tinzaparin with iv UFH for the treatment of 200 hospitalized patients with acute PE in a random, double blind, controlled trial. By 3 months follow-up, a significantly lower incidence of recurrent VTE was observed for LMWH (none of 97) compared to that for UFH [7 of 103 (6.8%)] (AD=6.8%, 95% CI: 1.94, 11.70). The overall incidence of death was higher in the UFH group (9/103 vs. 6/97). However, most deaths occurred during late follow-up during warfarin treatment, and two deaths in the UHF group were documented with inadequate

control of therapeutic prothrombin times at the time of the recurrent thromboembolic event. Deaths occurring under 75 days were almost identical, 4/103 in UFH and 3/97 in LMWH. There were 1 and 2 major haemorrhages in LMWH and UFH arm, respectively.

Comments:

It is possible that management of UFH therapy has improved over time. In the most recent meta analysis², a small reduction in the rates of recurrent thromboembolic events associated with LMWH did not reach statistical significance, and in the more recent and very substantial randomized controlled study of PE³, there was no evidence of superiority of either medication in terms of recurrent thromboembolic events. Similarly, while there were fewer major bleeding events with LMWH in Gould's (1999)² analysis, in the more recent study of Hull (2000)⁵ the incidence of such events was not statistically different with either therapy.

In summary, it can be concluded from the above evidence, that in terms of both efficacy and risk of causing haemorrhage, LMWH is at least equivalent to UFH, and is possibly slightly superior. However, there are two other complications of heparin treatment, Heparin Induced Thrombocytopenia (HIT) and Osteoporosis.

Heparin-Induced Thrombocytopenia (HIT).

HIT is an antibody-mediated process occurring with heparin treatment. Its frequency varies with the clinical circumstances and the definition of HIT that is used⁶. Estimates of its frequency vary from 3 - 5% with UFH⁷⁻¹⁰, and from 0% to less than 1% with LMWH^{7,10}.

Failure to recognize HIT can result in complications caused by intravascular thrombotic events. When these are intra-arterial (approximately 10%), the consequence may be serious and the costs generated considerable. These are considered in Appendix VIII.

Heparin Associated Osteoporosis

Heparin induced osteoporosis is another feared side effect of heparin treatment. However, the risk of this complication becomes significant only with long-term heparin treatment or treatment during pregnancy¹¹ Thus, in our report, treatment of this complication was not considered.

2. Costs

Comparison of the cost of treatment with UFH and LMWH has been the subject of three previous reports^{5,12,13}. Unfortunately, none of these are directly applicable to MUHC at this time. Each used estimates of the frequency of recurrent thromboembolic and of major hemorrhagic events that favoured LMWH, and largely for this reason they found the use of LMWH to be cost saving. However, current evidence does not clearly indicate that LMWH is superior in this respect (see above). Furthermore, none of the three studies considered the cost of treatment of HIT. Accordingly, it is necessary to estimate the costs of these two forms of treatment in the context of the MUHC, at the present time.

In the year 2002, the average length of in-patient treatment for DVT/PE at the MUHC was 7.3 days, a figure consistent with the literature^{5,12,13}. Table 1 lists direct costs to the MUHC for initial in-patient treatment of DVT and PE. A detailed cost calculation is presented in Appendix VII.

Table 1. Direct costs per patient to the MUHC for the treatment of DVT and PE with LMWH and UFH (average duration of treatment and hospitalization, 7.3 days).

| Item (\$) | UFH | Enoxaparin (Lovenox) | Tinzaparin (Innohep) | Dalteparin (Fragmin) |
|---|-------------|----------------------|----------------------|----------------------|
| <u>Average cost per patient per day</u> | | | | |
| Drug acquisition ¹ | 3.5 | 21.4 | 20.1 | 17.5 |
| Pharmacy preparation ² | 0.57 | 2.5 | 2.5 | 2.5 |
| Nursing work associated with drug administration ³ | 18.0 | 1.1 | 1.1 | 1.1 |
| APTT test † | 8 | --- | --- | --- |
| INR + PT test | 4 | 4 | 4 | 4 |
| Hospitalization stay | 273 | 273 | 273 | 273 |
| HIT treatment# | 98 | 8 | 8 | 8 |
| Total cost to the MUHC (including nursing) ‡ | 2340 | 2213 | 2203 | 2184 |
| Cost difference (LMWH-UFH) | --- | -127 | -137 | -156 |
| Total cost to the MUHC (not-including nursing) * | 2208 | 2205 | 2195 | 2176 |
| Cost difference (LMWH-UFH) | --- | -3 | -13 | -32 |

^{1,2,3}: See appendix VII for detailed calculations.

#: See appendix VIII for detailed calculations.

†: APTT test: unit price for APTT test is \$4, and each patient with UFH should receive such test twice a day.

‡: Total cost to the MUHC (including nursing) = (drug acquisition + pharmacy preparation + nursing + monitoring test (APTT and INR + PT) + hospitalization stay) x 7.3 days + HIT treatment.

*: Total cost to the MUHC (excluding nursing) = (drug acquisition + pharmacy preparation + monitoring test (APTT and INR + PT) + hospitalization stay) x 7.3 days + HIT treatment.

From the above table, it can be seen that, even ignoring any potential cost savings that might result from a lower incidence of recurrent embolism and of major haemorrhage, the use of each of **the LMWHs costs less than UFH** per in-patient treatment. The saving per inpatient treated would be: \$127 with enoxaparin, \$137 with tinzaparin, and \$156 with dalteparin. Such cost saving are largely attributable to the reduced nursing workload and are unlikely to be recovered. If they are excluded from the estimates, the saving compared to UFH will be smaller: enoxaparin \$3, tinzaparin \$13, and dalteparin \$32.

Budget impact at the MUHC of the use of LMWHs for in-patient treatment of DVT and PE with LMWH instead of UFH

Although, from the preceding analysis it can be seen that LMWH treatment costs less than treatment with UFH, when considering the budgetary impact on the MUHC, several factors must be considered.

In fiscal year 2001, 515 patients were treated for DVT and PE at the MUHC (data extracted from patient care system PCS). However, LMWH would not be the appropriate treatment in all of these patients. UFH is preferred when surgical intervention is a possibility, because of the slow reversibility of the LMWH effect. The proportion of such cases is unknown, but in the context of treatment of already existing DVT/PE, it is probably small. For the purpose of estimating budget impact we will assume that LMWH would be used for treating of 450 cases of thromboembolic disease per year at the MUHC.

Firstly, the savings associated with LMWH are partly the result of the lower nursing workload associated with its administration. However, as noted above, the liberated nursing time would almost certainly be taken up by other nursing tasks, and although this would have real benefits, such as reduced stress, and an ability to undertake other nursing duties, it is unlikely that these costs would be directly recovered, at least in the short term. If these costs were included in the estimates, the treatment of 450 patients with LMWH, enoxaparin, would cause a theoretical saving to the budget of the MUHC of \$57,150 per year (450x\$127). However, when these costs are excluded, the saving to the MUHC budget are reduced to \$1,350 (450 x \$3).

Furthermore, a policy of switching to LMWH (enoxaparin) for the treatment of DVT and PE would have different effects on different cost centres. It would lead to a cost increase (drug acquisition) of \$58,801 $\{450 \times \$ (21.4-3.5) \times 7.3\}$ yearly in the pharmacy budget. There would be theoretical savings in the nursing budget of \$55,517 $(450 \times \$ (18.0-1.1) \times 7.3 \text{ days})$ yearly, which as noted above would not be recovered in dollars. There would also be savings in the haematology lab of \$13,140 $(450 \times \$4 \times 7.3 \text{ days})$ yearly. Although only the supplies component of this sum would be recoverable, the reduced laboratory workload would also result in real benefits.

Secondly, although far from certain, it is possible that use of LMWH would result in fewer major haemorrhages and a lower rate of recurrent post treatment DVT and PE. If this were so, the cost advantage of LMWH use would be even greater. For example, if we accepted the results of the meta-analysis reported by Roger¹³, with a probability of recurrent thromboembolism with UFH of 2.3%, and enoxaparin of 1.2%, and rates of major hemorrhagic events with UFH of 7%, and enoxaparin of 4.4%, the estimated cost of the two forms of treatment would be modified, as shown in Appendix IX. The treatment of 450 patients with enoxaparin would then lead to an additional cost saving of \$20,250, or \$19,350 with nursing costs excluded.

Thirdly, use of sc. LMWH facilitates the management of treatment of these patients in the outpatient department, and a program for treating DVT patients with LMWH as outpatients has already been implemented at the MUHC. However, if patients were already receiving treatment with LMWH in the hospital, it is probable that some might be considered outpatient eligible at an earlier date. The proportion of such patients is unknown. However, if only 10% of patients were well enough to be discharged as outpatients five days earlier, there could be an additional cost saving of \$61,425 $(273^* \times 5 \times 450 \times 10\%)$. (Note: *hospital stay includes direct nursing cost only. Pharmacy costs, drugs, overheads are excluded. Based on MUHC annual report, AS 471.2001-2.)

Comments:

There would almost certainly be a cost saving to the MUHC of using LMWH instead of UFH for the treatment of deep vein thrombosis and pulmonary embolism whenever clinically indicated. The extent of this saving might be very considerable. There would also be beneficial effects resulting from the reduced nursing workload, and possibly from

a reduction in bed use. These latter effects would be reflected as increased productivity rather than as budget savings.

3. Recommendations

The TAU committee considered the following evidence:

- In terms of both the therapeutic efficacy and the frequency of significant hemorrhagic complications, LMWH is at least equivalent to UFH and possibly slightly superior. Furthermore, it significantly reduces the frequency of heparin-induced thrombocytopenia, and the complication of intravascular thrombosis that may result from it.
- In addition to improved clinical efficacy, a change of policy from use of UFH to LMWH whenever clinically indicated would be a cost saving intervention. However, the costs potentially saved as a result of reduced nursing workload would not be immediately reflected in the budget. Even excluding this potential saving, the treatment of 450 patients per year with LMWH (enoxaparin) instead of UFH would result in a net saving of approximately \$1,350 per year. If this policy change, as is quite likely, also resulted in lower costs for treatment of hemorrhagic and recurrent thromboembolic events, there would be an additional cost saving of \$19,350. Substantial further cost reduction might be associated with shorter hospital stay resulting from the use of LMWH in hospital.

Accordingly, the TAU recommends that the MUHC approves the replacement of unfractionated heparin by low-molecular-weight heparin for the treatment of deep vein thrombosis and pulmonary embolism whenever this may be clinically indicated.

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Appendix I:

Mechanism of the action of unfractionated heparin and low - molecular - weight heparin

Both unfractionated Heparin (UFH), discovered by McLean in 1916 and its derivative, low-molecular-weight heparin (LMWHs), are effective antithrombotic agents that have been used in various clinical settings. It is now known that UFH inhibits platelet thrombus formation by way of interacting with plasma antithrombin (AT), causing a conformational change in AT that accelerates its interaction with thrombin (factor IIa) and activated factor X (factor Xa) by about 1000 times. Similar to UFH, LMWHs exert their anticoagulant activity by activating AT. But unlike UFH, which has equivalent activity against factor Xa and thrombin, LMWHs have greater activity against factor Xa and have minimal effects on factor IIa. Figure I illustrates the catalysis of antithrombin-mediated inactivation of thrombin or factor Xa by UFH or LMWHs.

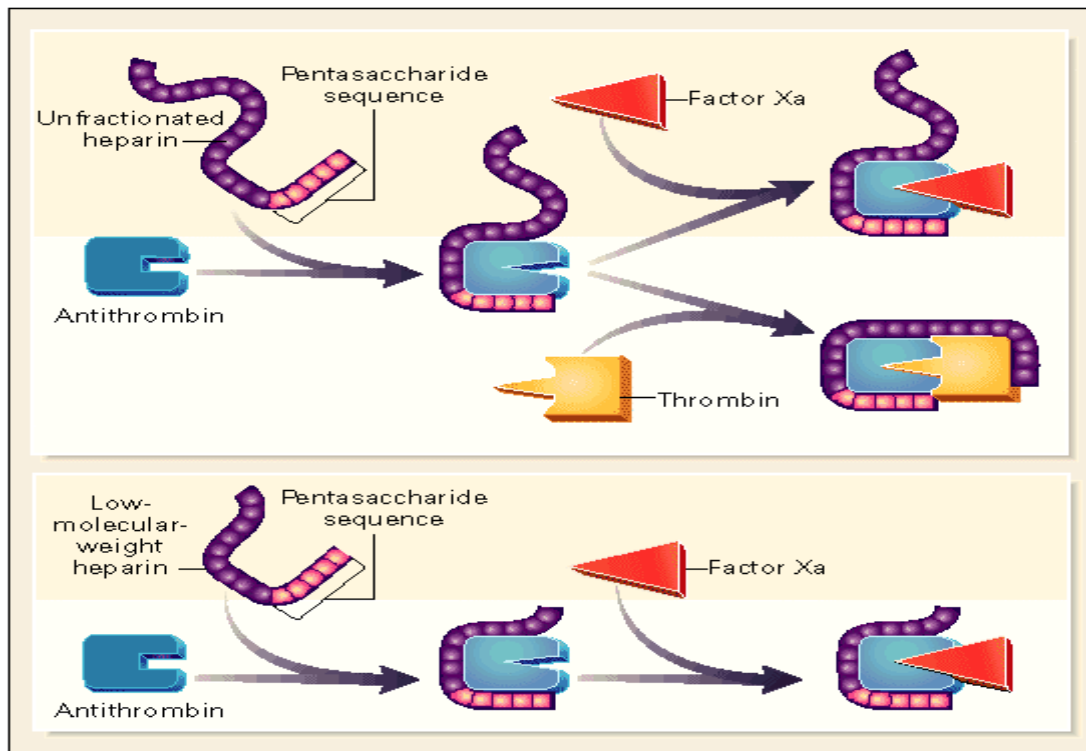


Figure 1. Catalysis of Antithrombin-Mediated Inactivation of Thrombin (Factor IIa) or Factor Xa by Unfractionated Heparin or Low-Molecular-Weight Heparins (source: Weitz J.I. *N Engl J Med* 1997;337: 689)¹⁴.

Appendix II:

Pharmacological and pharmacokinetic comparison of unfractionated heparin and low-molecular-weight heparins

Heparins are composed of a heterogeneous mixture of polyanionic glycoaminoglycans. UFH varies in molecular weight from 3,000 to 30,000 (mean 15,000). Low - molecular - weight heparin is a derivative of UFH by either chemical or enzymatic depolymerization producing smaller molecular weights ranging from 3000 to 7000 (mean 5000). These size differences of molecular weight between heparins influence their pharmacology and pharmacokinetic properties and result in the varying anticoagulant profiles among heparins.

When administered by continuous intravenous infusion (IV), UFH has an unpredictable dose-response relationship, due to non-specific binding to plasma proteins and endothelial cells. UFH is also susceptible to inactivation by platelet factor 4 (PF4), produced by activated platelets. Thus, to optimize its effectiveness, when administered by IV, UFH dosing must be monitored by serial APTT tests. Also, it has been shown that using UFH can be associated with significant side effects, including significant rates of thrombocytopenia and heparin-induced thrombocytopenia with or without concomitant thrombosis.

LMWHs offer a number of pharmacological advantages over the UFH (Table 4). LMWHs have a longer half-life (2 to 4 times that of UFH) and a superior bioavailability on subcutaneous administration (>90% compared with 30%), making once or twice daily administration feasible. LMWHs also present a more predictable dose response so that laboratory monitoring is rarely needed. In addition, LMWHs have a reduced theoretical potential to cause bleeding compared with UFH, because they are less likely to increase micro vascular permeability or interfere with platelet-vessel wall interaction. Other features of LMWHs that are of clinical relevance are a decreased sensitivity to PF4 and lower rates of unintended effects including platelet activation, heparin-induced thrombocytopenia and osteoporosis^{15,16}.

There are several different types of low-molecular weight heparins, which emerge from differences in the manufacturing processes (either depolymerization or fractionation), resulting in different compositions, molecular weight distributions and molecular end-structures¹⁵. These variations confer important differences among LMWHs with respect to the ratio of anti-Xa to anti-IIa activity, bioavailability after subcutaneous administration, elimination half-life and interaction with plasma proteins, endothelial cells, and platelets. However, whether these pharmacological differences translate into differences in clinical outcomes remains largely unresolved.

Table 4: Pharmacological Comparison in Low-Molecular-Weight Heparin vs Unfractionated Heparin.

| Variable | UFH | LMWHs |
|--|-----------------------------|------------------------------|
| Mean molecular weight | 15,000 | 5,000 |
| Anti Xa:IIa | 1:1 | 2-4:1 |
| Tissue factor pathway inhibitor release | + | ++ |
| Binding to plasma proteins and cells | Avid | Weak |
| Plasma half-life | Dose-dependent (0.5-4hours) | Dose-independent (2-4 hours) |
| Bioavailability after subcutaneous injection | 30% | "90% |
| Direct platelet effects | ++ | + |

| | | |
|-------------------------------------|----------------------|--|
| Heparin-induced thrombocytopenia | ++ | + |
| Neutralization by platelet factor 4 | ++ | + |
| Neutralization by protamine sulfate | ++ | + |
| Neutralization by heparinase | ++ | ++ |
| Elimination | Renal (nonsaturable) | Low-dose cellular uptake (saturable), High-dose renal (nonsaturable) |
| Increase in vascular permeability | ++ | + |
| Osteoporosis | ++ | + |
| Cost | Inexpensive | Expensive |

Appendix III:

Available LMWHs and approved indications for each use in Canada

Currently, there are four LMWHs available for use in Canada (Table 5). Table 6 lists labeled indications for the LMWHs in Canada.

Table 5. Characteristics of LMWHs available for use in Canada.

| Characteristic (trade name) | Median molecular weight | Anti-Xa IU/mg | Anti- IIa IU/mg | Anti-Xa:anti-IIa ratio |
|-----------------------------|-------------------------|---------------|-----------------|------------------------|
| Dalteparin (Fragmin) | 5000 | 122 | 60 | 2.0 |
| Enoxaparin (Lovenox) | 4800 | 104 | 32 | 3.3 |
| Nadroparin (Fraxiparine) | 4500 | 94 | 31 | 3.0 |
| Tinzaparin (Innohep) | 4500 | 90 | 50 | 1.8 |

Table 6. Current labelled indications for the LMWHs in Canada (Compendium of Pharmaceuticals and Specialties (CPS) 2002, page 723).

| Indication | Dalteparin | Enoxaparin | Nadroparin | Tinzaparin |
|--|------------------|------------|------------|------------------|
| <i>Prophylaxis of deep vein thrombosis in:</i> | | | | |
| General surgery | Yes | — | Yes | Yes ¹ |
| Orthopaedic surgery | — | — | Yes | Yes |
| Orthopaedic surgery, specifically of Knee or hip | Yes ² | Yes | — | — |
| High-risk abdominal, gynaecological or urological surgery | — | Yes | — | — |
| Colorectal surgery | — | Yes | — | — |
| Treatment of deep vein thrombosis | Yes | Yes | Yes | Yes |
| Prevention of clotting in the extra corporeal system during hemodialysis and hemperfusion in patients with chronic renal failure | Yes | — | Yes | Yes |
| Treatment of UA or non-Q-wave MI concurrently with ASA | Yes | Yes | — | — |

¹ In patients at high risk for developing postoperative venous thromboembolism.

² Elective hip surgery.

Appendix IV:**Inclusion criteria for the meta-analysis by Siragusa et al (1996)¹:**

- 1) a target population of patients with a first episode of acute DVT, objectively confirmed by contrast venography, and/or acute PE, confirmed by a high-probability ventilation perfusion lung scan or by pulmonary angiography;
- 2) a randomized comparison between LMWH and UFH in the treatment of patients with acute VTE;
- 3) eligible studies were further classified as level 1 if they were double-blind or if there was blinded assessment of the outcome measures (both efficacy and safety), otherwise, studies were classified as level 2.

Each study was reviewed independently and rated by two investigators using explicit criteria listed above.

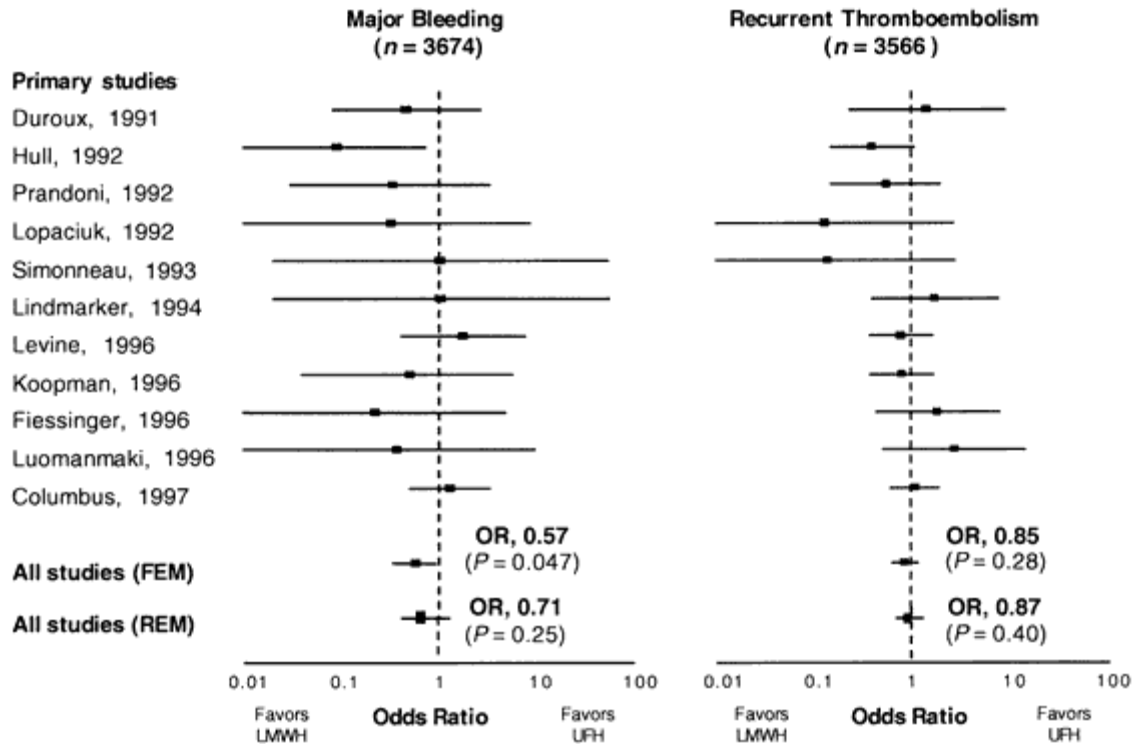
Inclusion criteria for the meta-analysis by Gould et al²:

- 1) enrolled participants with acute lower-extremity deep venous thrombosis, with or without coexisting pulmonary embolism;
- 2) randomly assigned participants to treatment groups;
- 3) compared subcutaneously administered, fixed-dose low-molecular-weight heparin with adjusted-dose unfractionated heparin for the initial treatment of deep venous thrombosis;
- 4) used objective methods to confirm the initial episode of deep venous thrombosis;
- 5) used objective methods to assess one or more clinical outcomes, including major bleeding complications, recurrent thromboembolic events, and mortality rates.
- 6) for studies to be included in analyses of recurrent thromboembolism and mortality rates, at least 3 month followup was required for participants.

Those dose-ranging studies and studies that permitted a change in the dose of low-molecular-weight heparin during the trial were excluded. Abstracts were included only when investigators supplied full reports of their methods and results. Two investigators independently evaluated studies for possible inclusion and subsequently resolved any disagreements by discussion. Investigators were not blinded to journal, author, or institution.

Appendix V:

Summary of odds ratios (ORs) for major bleeding and recurrent thromboembolism in each study included in the meta-analysis by Gould et al. (1999)².

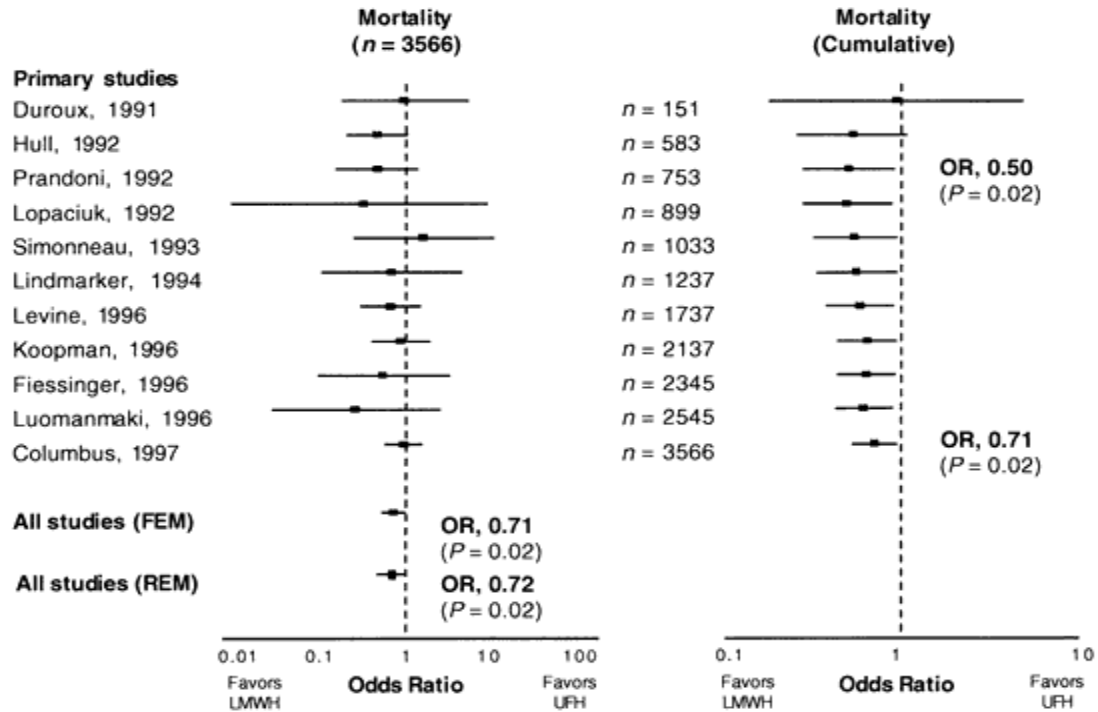


Notes: Odds ratios are indicated by boxes. Horizontal lines represent 95% CIs. Odds ratios less than 1.0 favour low-molecular-weight heparins (LMWH); odds ratios greater than 1.0 favour unfractionated heparin (UFH). The summary odds ratio for major bleeding favours low-molecular-weight heparins, but this finding is not statistically significant under the assumptions of the random-effects model (REM). The CI for the summary odds ratio for recurrent thromboembolism also crosses 1, indicating no statistically significant difference between the treatments. FEM = fixed-effects model.

(Reference: Gould et al². Ann Intern Med. 1999; 130:805).

Appendix VI:

Summary of mortality rates obtained from each study included in the meta-analysis by Gould et al. (1999)².



Notes: The left portion illustrates conventional meta-analysis results showing a statistically significant benefit for low-molecular-weight heparin (LMWH) treatment. The right portion illustrates the results of cumulative meta-analysis, in which the summary odds ratio (OR) is recalculated after individual studies are added one at a time by year of publication. A statistically significant benefit for low-molecular-weight heparin is apparent after the addition of the third study. The direction and statistical significance of the treatment effect remain constant with the addition of each new study, although the magnitude of the effect lessens slightly over time. FEM = fixed-effects model; REM = random-effects model; UFH = unfractionated heparin.

(Reference: Gould et al². Ann Intern Med. 1999; 130:806)

Appendix VII:

Relevant information on cost calculation at the MUHC:

Current treatment for patients with DVT with or without PE at the MUHC:

At the MUHC, UFH is administered in an IV, which comes pre-mixed. On the ward, when there is no I-V line installed, the nurse must start an IV and programme the pump settings. APTT-monitoring is required. Based on the APTT results, the settings of the pump may need to be changed. At the MUHC, approximately 2 APTT tests are carried out per patient a day (Pharmacy, MUHC).

Total patients treated for DVT and PE and related length of hospital stay at the MUHC:

For the fiscal period 2001, there were **515 patients** in-patient treated for DVT and PE (data was extracted from patient care system). Data extracted from the pharmacy system (BDM) showed that the mean duration of heparin i.v. treatment was **7.3 days** at the MUHC. This is quite close to the data (at least 5 days of combined heparin and warfarin therapy plus at least 2 consecutive days) from the literature (James et al.)

Drug acquisition cost at the MUHC

Three types of LMWHs, including enoxaparin, tinzaparin and dalteparin, could be candidates for DVT and PE treatment, replacing UFH. However, another type of LMWH, nadroparin is not considered for DVT treatment, as it comes only in pre-mixed syringes which creates a problem in terms of dosing flexibility on the ward.

UFH:

25000u/bag, i.v. dose 25000 u/day, cost = **3.50\$/day**

Enoxaparin (Lovenox):

100 mg/ml - 3 ml vials (21.38), sc. dose 1.5 mg/kg/day, 105 mg (70Kg) cost = **21.4\$/day**

Tinzaparin (Innohep):

40 000u/ml - 2 ml vial (65.60), dose 175 u/Kg/day, 12250 u (70kg) cost = **20.1\$/day**

Dalteparin (Fragmin):

25 000u/ml - 3.8ml vial (118.85), dose: 200u/kg/day, 14000u (70kg) cost = **17.5\$/day**

Pharmacy preparation cost

Time related to pre-prepare heparin IV bag (25000u):

RVH: 1.65 minutes per bag (assemble, label, record IV, admixture of already prepared drug and dispense)

MGH: 0.81 minutes per bag (including tasks of fill and account for ward stock med).

Average time for i.v. heparin at the MUHC: 1.23 minutes.

LMWH syringe:

Time to prepare, dispense and verify 1 dose: 5.35 minutes per syringe.

Average pharmacy technician's hourly salary 28\$/hour.

Drug preparation cost per day per patient for:

UFH: $1.23/60 \times 28 =$ **\$0.57**

LMWH: $5.35/60 \times 28 =$ **\$2.5**

Nursing workload measurement at the MUHC:

The allocated times for each task related to nursing work for administering heparin were obtained from the PRN workload measurement system for the RVH and GASAP system for the MGH:

At the RVH: S/c injections (1-3) =5 min

IV med (1-3) = 10 min

Starting an IV (1puncture) = 20 min

IV solution (1solution) =20 min

At the MGH: S/c injections (1-4 times) =3 min

IV med (1-4 times) = 13 min

Starting an IV (1puncture) = 5min

IV therapy = 16 min

IV administered with pump =11 min

An average time for each task was assigned to calculate the nursing cost for medical treatment of DVT or PE at the MUHC.

SC injection = 2.5 min

IV med = 6.6 min

Starting an IV = 12.5 min

IV solution = 24 min

Nursing salary at the MUHC:

Approximately, 70% of nurses at the MUHC have college diplomas and 30% of nurses have bachelor degrees. Among college diploma nurses, there are 12 different salary scales, and among bachelor degree nurses, there are 18 different salary scales at the MUHC. To calculate the nursing cost, the value of the middle category of each of salary scales was used. A weighted average nursing salary at the MUHC is **\$25.26 per hour**. Table 7 provides nursing salary and benefits at the MUHC.

Table 7. Information on nursing salary at the MUHC.

| The type of nurse | The median category of salary + benefit without social charges | Salary +benefit +social charges (x 1.12) |
|-----------------------|--|---|
| College diploma nurse | 21.02 (\$/hour) | 23.54 (\$/hour) |
| Bachelor degree nurse | 26.13 (\$/hour) | 29.27 (\$/hour) |

* Nurse in the MUHC in general works 7.25 hours per day.

Weighted nursing cost calculation:

$$23.54 \times 0.7 + 29.27 \times 0.3 = 25.26 \text{ (\$/hour)}$$

Nursing cost for administrating LMWH or UFH

$$\text{UFH: } (6.6 + 12.5 + 24) \times 25.26 / 60 = \$18.0$$

$$\text{LMWH: } 2.5 \times 25.26 / 60 = \$1.1$$

Appendix VIII

Costs of treating heparin induced thrombocytopenia (HIT)

HIT is an antibody-mediated process occurring in the first 4-12 days of heparin treatment. For this reason the platelet counts of such patients are monitored every second day. HIT is suspected when counts fall below 150,000 per cubic mm, in the absence of any other likely cause.

There is little evidence on which to base estimates of the frequency of HIT. With UFH use it is reported in from 3 to 5%⁷⁻¹⁰. Incidence varies with the clinical background and the definition of HIT that is used by the authors. Using the strict definition of a reduction in platelet count (below 150,000 per cubic mm on two successive tests), that began five or more days after the start of heparin therapy, together with a positive test for heparin-dependent IgG antibodies, Warkentin⁷ and colleagues found an incidence of HIT of 9/332(2.7%) with UHF, in the context of elective hip surgery.

There is even less evidence concerning the frequency of HIT in association with LMWH. The practical treatment Guidelines of the thrombosis Interest Group of Canada reported a frequency of "under 1%"¹⁰. Warkentin et al.⁷ found an incidence of 0% in 333 patients receiving LMWH in the context of elective hip surgery. Pautas¹⁷ and colleagues administered tinzaparin to a population of 200 elderly patients (average age 85 years) for an average of 19 days, mostly in the context of thromboembolic disease, and all with impaired renal function. Even such prolonged treatment in this susceptible population resulted in HIT in only 2%.

Failure to recognize HIT can result in serious complications caused by intravascular thrombotic events, in 39%¹⁸ to 50% of cases^{19,20}. These are usually venous. In one report involving 78 patients with various diagnoses, studied over a 14 year period in Hamilton, Ontario: the ratio of venous to arterial thrombotic events was 4:1⁶. Intra-arterial thrombotic events have serious outcomes. Peripheral tissue necrosis, adrenal haemorrhagic necrosis, necrosis of patches of skin, stroke, and myocardial infarction have all been reported⁶. In the 14 year follow-up study reported by Warkentin²⁰, intravascular thrombotic events occurred in 52% of uncomplicated HIT patients(intra-arterial in 19%).

The following estimates of the costs of treating HIT are based on conservative estimates of the frequency of HIT and conservative estimates of the frequency of the intra-arterial thrombotic events which may result from it (less conservative estimates would favour use of LMWH). It is also assumed that in the context of treatment of DVT the occurrence of venous thrombosis due to HIT will not significantly prolong treatment or increase costs.

Assumptions:

- 1) Incidence of HIT with UFH = 2.7%⁷
- 2) Incidence of HIT with LMWH =0.2% (Arbitrary estimate, based on^{7,10}.
- 3) Incidence of veno-thrombotic events =40% of cases of HIT.
Assumed, that in the context of DVT such cases will not involve significantly increased treatment or treatment costs.
- 4) Incidence of arterio- thrombotic events=10% of cases of HIT²⁰.

Assumed, that such cases will on average prolong hospital stay by 30 days (arbitrary estimate) at \$273/day.

5) Current treatment of HIT at the MUHC is by i.v. danaproid sodium using 5,000u/day, for on average 7 days (M Warner, personal communication).

6) Cost of danaproid = \$123/day (Pharmacy, MUHC)

7) Cost of PF4/heparin ELISA test = \$46 (Haematology lab, MUHC)

With these assumptions the cost per case of treatment of uncomplicated HIT would be as follows:

Drug costs = $\$123 \times 7 = \861

Hospital costs = $\$273 \times 7 = \$1,911$

PF4/heparin ELISA test x 1 = \$46

Total cost per HIT patient treated = $\$861 + \$1,911 + \$46 = \$2,818$

Average cost of HIT treatment per patient treated with UFH: $\$2,818 \times 2.7\% = \76

Average cost of HIT treatment per patient treated with LMWH: $\$2,818 \times 0.2\% = \6

Average cost per patient treated with UFH, attributable to arterio-thrombotic events:

$30\text{days} \times \$273 = \$8,190 \times 2.7\% \times 10\% = \22

Average cost per patient treated with LMWH, attributable to arterio-thrombotic events:

$\$8,190 \times 0.2\% \times 10\% = \2

All costs (HIT + thrombotic complications) per UFH treatment = $\$76 + \$22 = \$98$

All costs (HIT + thrombotic complications) per LMWH treatment = $\$6 + \$2 = \$8$

Appendix IX:

Costs to the MUHC for in-patient treatment of recurrent DVT and PE with LMWH (enoxaparin) and UFH and treatment of hemorrhagic events

This report does not consider the relative merits of LMWH preparations. Enoxaparin, the most expensive of these is the preparation predominately used at the MUHC. For this reason, it is used in the following cost comparison.

Expected cost per patient treated with recurrent DVT/PE:

The probability of DVT/PE recurrence (Roger et al. 1998):

UFH: 2.3%
Enoxaparin: 1.2%

Considering nursing cost :

UFH: 2.3% x 2340 (see table 1) = \$54
Enoxaparin: 1.2% x 2213 (see table 1) = \$27

Expected cost difference of the treatment of recurrent DVT/PE (enoxaparin-UFH): \$-27

Without considering nursing cost:

UFH: 2.3% x 2208 (see table 1) = \$51
Enoxaparin: 1.2% x 2205 (see table 1) = \$26

Expected cost difference of the treatment of recurrent DVT/PE (enoxaparin-UFH): \$-25

Expected cost for per patient treated with major bleeding:

The probability of major bleeding (Roger et al 1998):

UFH: 7.0%
Enoxaparin: 4.4%

Assuming a major haemorrhage adds 2.5 additional hospital days as estimated by Gould et al.¹², at the average cost per day at the MUHC, the cost per patient treated for major bleeding is \$683 (Considering direct nursing costs only, \$273 per day. MUHC. Annual Report AS471.2001-2).

UFH: 7.0% x 683 = \$48
Enoxaparin: 4.4% x 683 = \$30

Expected cost difference of treatment of major bleeding (enoxaparin-UFH): \$-18

Therefore, if the probability of recurrent thromboembolic events and bleeding complications were realised, the treatment of 450 patients with DVT and PE at the MUHC, using enoxaparin compared to UFH, would lead to a cost saving of:

For initial DVT/PE treatment:

Considering nursing cost: **-57,150**
450 x \$-127 (see table 1) = \$-57,150

Without considering nursing cost: **\$-1,350**

450 x \$-3 (see table 1) = \$-1,350

For recurrent VTE treatment:

Considering nursing cost: **\$-12,150**

450 x (-27) (expected cost difference of the treatment of recurrent DVT/PE) = \$-12,150

Without considering nursing cost: **\$-11,250**

450 x \$-25 (expected cost difference of the treatment of recurrent DVT/PE) = \$-11,250

Major bleeding treatment: **\$-8,100**

450 x \$-18 (expected cost difference of treatment of major bleeding) = \$-8,100

In total, 450 patient with DVT/ PE treated with enoxaparin will lead to a **cost saving of \$77,400:**

$(-57,150) + (-12,150) + (-8,100) = \$-77,400$

However, without including nursing costs, use of enoxaparin would **increase costs by \$20,700:**

$(-1,350) + (-11,250) + (-8,100) = \$-20,700$

Appendix X:

ACCP (American College of Chest Physicians) recommendations

Recommendations from the 6th ACCP Consensus Conference on Antithrombotic Therapy addressing effective regimens for the treatment of DVT acknowledge that LMWH, in comparison with unfractionated heparin, offers the major benefits of convenient dosing and facilitation of outpatient treatment. Furthermore, LMWH may result in slightly less recurrent DVT and may offer a survival benefit in patients with cancer. On evidence from grade 2B* clinical trials, the ACCP recommends that clinicians use LMWHs over UFH for the treatment of DVT.

*Grade 2B:Clarity of risk/benefit: risk/benefit unclear;

Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodological flaws*);

Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances.