TITLE: Low Molecular Weight Heparins: Review of the Comparative Effectiveness for Various Indications

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CONTEXT AND POLICY ISSUES:

Low molecular weight heparins (LMWH) are a form of pharmacologic anticoagulant intervention used for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE), or for treatment of thromboses that may occur in a broad spectrum of clinical indications including general or orthopaedic surgery, neurosurgery, trauma, unstable angina, non-ST elevated myocardial infarction (NSTEMI), and ST-elevated myocardial infarction (STEMI), amongst others.1-3 While unfractionated heparin (UFH) has often been employed in the past for many of these indications and remains in use, there are concerns regarding a lack of standardization in laboratory monitoring, dosing, and the occurrence of severe adverse events.4 LMWHs are considered to present a lesser risk of side effects and bleeding events,2,5 can be administered on an outpatient basis,6 have a more predictable anticoagulant effect that avoids requirement for therapeutic monitoring as is needed with UFH,4,5,7 and provide high bioavailability after subcutaneous administration.4,7 LMWH inhibits coagulation of blood via interference with activated factor X in the cascade of factors that lead to clotting of blood, and are administered subcutaneously (SC) via injection.7 Past reviews and meta-analyses have found LMWH to be at least as effective as UFH for management of DVT and PE, and with a reduced risk of major bleeds.1,8,9

Debate in past years has speculated as to whether the various LMWHs should be considered as a family of therapies, or whether each should be deemed a distinct therapy.10 Several LMWH products produced by different pharmaceutical companies are available to physicians. These products are prepared via varying methods of chemical or enzymatic depolymerization that lead to differences in physical and biochemical properties,2,7,7,11,12 and have been shown to have distinctive pharmacologic characteristics (table 1) that may be more advantageous compared to one another in the context of managing different diagnoses. The LMWHs available in Canada,13
tinzaparin (Innohep®), enoxaparin (Lovenox®), nadroparin (Fraxiparin®) and dalteparin (Fragmin®), differ in terms of molecular weight (range 4300-6500 Da\textsuperscript{14}), the ratio of anti-Xa activity to anti-IIa activity (range 2.0-4.0\textsuperscript{14}), half-life (range 2.1-4.5\textsuperscript{14}) and bioavailability (range 87-98\%\textsuperscript{14}), and the relevancy of these differences in relation to clinically important outcomes in humans is not clear.\textsuperscript{7,10,14,15} High quality evidence comparing the effectiveness of these therapeutic alternatives would aid hospital pharmacies in the determination of what LMWHs (and associated quantities) should be stocked, thereby improving control of inventory and possibly reducing costs. While clinician preference or historical hospital practice can play a role in the stocking of hospital formularies, an inventory of a larger number of similar products increases the complexity of the administration of hospital pharmacies, and may increase the likelihood of errors of drug administration and dosing.\textsuperscript{16} Given these issues, the uniqueness of each of the LMWHs necessitates their evaluation in pertinent clinical indications to identify important variations in effectiveness.

Table 1: Documented Pharmacokinetic Differences Amongst LMWHs\textsuperscript{14}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Nadroparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight (Da)</td>
<td>4500</td>
<td>6000</td>
<td>6500</td>
<td>4300</td>
</tr>
<tr>
<td>Anti-Xa: Anti-IIa ratio</td>
<td>3.8</td>
<td>2.7</td>
<td>2.0</td>
<td>2.5-4.0</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>92%</td>
<td>87%</td>
<td>87%</td>
<td>89-98%</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>4.5</td>
<td>2.1-2.3</td>
<td>3.4-3.9</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Given the distinguishing pharmacologic properties amongst the LMWH currently available for use in Canada, there is reason to believe that there may exist important differences in clinical effectiveness between alternatives for treatment of patients. The purpose of this review was to identify and summarize published evidence comparing tinzaparin, enoxaparin, nadroparin and dalteparin in terms of clinical effectiveness for a series of selected diagnoses, and to review any drug-specific recommendations noted in the context of clinical guidelines.

RESEARCH QUESTION:

What is the comparative clinical effectiveness of the low molecular weight heparins (dalteparin/Fragmin®, nadroparin/Fraxiparin®, enoxaparin/Lovenox®, tinzaparin/Innohep®) for the following clinical indications:

- Deep vein thrombosis prophylaxis of medical and surgical patients?
- Treatment of thromboembolisms (deep vein thrombosis and pulmonary embolism)?
- Anticoagulation bridging?
- Clotting in hemodialysis and extracorporeal systems?
- Management of acute coronary syndromes (ACS), namely ST-elevation myocardial infarction and non-ST myocardial infarction?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID’s Embase, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2000 and December 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, guidelines, and randomized controlled trials (RCTs).
HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. RCTs and evidence-based guidelines are subsequently presented. Economic evaluations and observational studies were not included in this review.

**SUMMARY OF FINDINGS:**

**Health technology assessments**

No health technology assessments directly comparing clinical measures of effectiveness amongst LMWHs were identified by the literature search.

**Systematic reviews and meta-analyses**

No systematic reviews directly comparing clinical measures of effectiveness amongst LMWHs were identified by the literature search.

**Randomized controlled trials**

Ten published RCTs comparing two or more of the LMWHs of interest in the various indications were identified by the literature search. Pertinent study details are discussed below, and are also summarized in the appendix.

*Prevention of DVT or PE in medical or surgical patients*

Simonneau et al.\textsuperscript{17} (2006) reported findings from a double-blind, multi-center, double-dummy RCT that compared enoxaparin (4000IU for 9±2 days; n=486) and nadroparin (2850IU for 9±2 days; n=464) for prevention of VTE following colorectal surgery for cancer. Treatment began between 2 to 4 hours following surgery. The study’s primary outcome was a composite measure of DVT and PE that occurred prior to twelve days post-surgery, and major bleeds (defined as fatal bleeding, surgical bleeding >1200mL, overt bleeding resulting in early treatment discontinuation, bleeding associated with a need for transfusion, bleeding associated with severe anemia, and bleeding considered to be a serious adverse event) were also assessed. A total of 1271 patients (628 enoxaparin, 643 nadroparin) receiving at least one dose of study drug were available for safety analyses, and 950 patients (486 enoxaparin, 464 nadroparin) having evaluable venography were available for the efficacy analysis. The authors reported similar rates of the primary outcome in the enoxaparin (12.6%) and nadroparin (15.9%) groups, respectively (RR 1.27, 95% CI 0.93-1.74). Proximal DVT frequency was comparable in the enoxaparin and nadroparin groups (2.9% and 3.2%), while a reduced frequency of symptomatic VTE was observed with nadroparin (0.2% versus 1.4%). A significantly reduced rate of major bleeds was noted in the nadroparin group (7.3% versus 11.5%; p=0.012). A total of 3 deaths prior to day twelve of follow-up were seen in the enoxaparin group compared with no deaths in the nadroparin group. The authors concluded that a daily dose of nadroparin may be an appropriate regimen for thromboprophylaxis in patients undergoing colorectal surgery.

Chiu-Tan et al.\textsuperscript{18} (2003) performed an open label, multi-center RCT that compared dalteparin (5000IU once daily; n=45) and enoxaparin (30mg every 12 hours; n=50) for prevention of DVT in patients with acute spinal cord injury (SCI) that occurred within three months prior to enrollment. Patients with complete SCI (54% of the enoxaparin group and 57.8% of the dalteparin group) received treatment for three months, while patients with incomplete SCI (46% of the enoxaparin group and 42.2% of the dalteparin group) received treatment for two months.
Paraplegic injury was present in totals of 50% of enoxaparin patients and 40% of dalteparin patients, and tetraplegic injury was present in corresponding totals of 46% and 55.6%, respectively. DVTs were observed in 6% of patients receiving enoxaparin and 4% of patients receiving dalteparin (p=0.51), respectively, while corresponding bleeding rates of 4% and 2% were observed (p=0.72). The investigators reported that no statistically significant between-group differences were found for health status or satisfaction measures. The authors concluded that dalteparin and enoxaparin showed comparable findings for DVT incidence, bleeding events, health status, and safety. Given the small sample size of the trial and the rarity of events of interest, the power to identify differences was limited.

Ellison et al.\(^ \text{19} \) (2001) reported findings of a single-blinded RCT that provided treatment with tinzaparin (50IU/kg anti-Xa once daily for five days; n=10), enoxaparin (4000IU anti-Xa once daily for five days; n=10), or dalteparin (5000IU anti-Xa once daily for five days; n=10) to pregnant females undergoing caesarian section, and evaluated changes in hemostatic measures (plasma anti-factor Xa activity, tissue factor pathway inhibitor (TFPI), plasma thrombin-antithrombin (TAT)) during the 24 hours following surgery. In addition to undergoing caesarian section, participants were additionally required to possess one or more risk factors from a specified list of criteria: obesity, immobility, age>35 years, parity>4, labour duration of more than twelve hours, presence of varicose veins, current infection, pre-eclampsia, a major current illness, or caesarian section performed as an emergency procedure. Treatment was first provided six hours following surgery. All three LMWHs resulted in increased mean anti-Xa assay, reduction in mean TAT, and increased mean TFPI concentration. Differences in plasma anti-factor Xa activity and the reduction in plasma TAT complex were noted between groups (the enoxaparin and dalteparin groups were significantly higher than tinzaparin for the former, while the enoxaparin group showed a lesser reduction than the tinzaparin and dalteparin groups for the latter), while tissue factor pathway inhibitor (TFPI) concentration was comparable for all three groups. The authors indicated that no thrombotic or hemorrhagic events were observed in any of the intervention groups.

**Treatment of DVT**

Wells et al.\(^ {6} \) (2005) reported findings from a multi-center, physician-blinded RCT comparing tinzaparin (175IU/kg per day for 5 or more days and until the international normalized ratio (INR) was 2.0 or more for two consecutive days; n=254) and dalteparin (200IU/kg per day for 5 or more days and until the INR was 2.0 or more for two consecutive days; n=251) for outpatient treatment of acute DVT and PE in patients presenting to a VTE clinic at one of four participating centers. All patients were provided accompanying warfarin therapy for ninety days. The study’s primary outcome was a composite measure of recurrence of VTE (either DVT or PE) and bleeding events. DVT recurrence was defined as the presence of new sites of non-compressibility or an increase in clot diameter of 4 millimeters or more, and recurrent PE was determined using ventilation-perfusion scans or pulmonary angiography and comparison with previous scans. Intervention groups were comparable at baseline in terms of age, gender, and pertinent risk factors, and median durations of treatment were also similar (6 days in both groups, with interquartile ranges of 3-26 days and 3-31 days for dalteparin and tinzaparin, respectively). Overall, 22.4% of included patients had experienced a prior VTE, 51.5% had idiopathic VTE, 22.4% had active malignancies, and 12.3% had experienced recent surgery or immobilization. Observed incidences of the composite outcome of VTE and bleeding were 4.4% (9 recurrent VTE, 2 major hemorrhages) and 5.9% (10 recurrent VTE, 5 major hemorrhages) in the dalteparin and tinzaparin groups, respectively (risk difference -1.5%, 95% CI -5.3% to +2.4%; p=0.44). The study was stopped early after 470 patients based on findings from an interim analysis, which suggested an inability to identify the originally hypothesized difference.
between groups. The authors concluded that the lack of a difference found between LMWHs suggests that issues like drug price and availability should serve as the decisive element in selection of treatment.

Hemodialysis

Beijering et al.\textsuperscript{20} (2003) reported findings from a multicenter RCT that compared tinzaparin (median dose 4500IU; n=79) and dalteparin (median dose 5000IU; n=80) in patients requiring chronic intermittent hemodialysis. Treatment was administered in a series of two phases; the first phase used titration to determine the optimal dose (as determined by a lack of clotting in the extracorporeal circuit and no bleeding incidents) and lasted for nine dialysis sessions, while the second phase consisted of forty dialysis sessions with the optimal dose of assigned anticoagulant. Patients receiving dalteparin received it as a continuous infusion, while tinzaparin subjects received the intervention as a bolus prior to hemodialysis. Patients and outcome assessors were blinded from treatment assignment. The investigators assessed both the lines and bubble catcher used for the procedure at the end of each session based on the extent of clotting present (no clots, minimal clots, moderate clotting, or severe clotting). Additionally, the dialyser was assessed as being good and clear, medium and pink, poor and partly clotted, or totally clotted and requiring a change of the extracorporeal circuit. More than 50% of patients did not require a dose adjustment during the maintenance phase, while totals of 33 and 36 patients in the dalteparin and tinzaparin groups required at least one adjustment due to one or more clotting events. The authors found no between-group difference in terms of the frequency of satisfactory dialysis (91% for tinzaparin versus 91.8% for dalteparin; p=0.81), the extent of clotting in the dialyser (p=0.68) and bubble catcher (p=0.73), or anti-Xa (p=0.65) and anti-IIa activity (p=0.60). An increased number of patients in the dalteparin group complained of adverse events compared to those in the tinzaparin group (87.3% versus 73.1%; p=0.03). The investigators indicated that 59% of tinzaparin adverse events and 70.9% of dalteparin adverse events were possibly related to the study drug. Each treatment arm incurred one major bleeding episode. The authors concluded that tinzaparin and dalteparin showed comparable efficacy and safety, though dose was 10% lower in the tinzaparin group.

Polkinghorne et al.\textsuperscript{21} (2002) reported findings of an RCT that compared dalteparin (2500IU bolus for 12 sessions over 4 weeks; n=7), enoxaparin (40mg IV bolus for 12 sessions over 4 weeks; n=7) and danaparoid sodium (35IU/kg bolus for 12 sessions over 4 weeks; n=7) in patients with end-stage renal disease undergoing chronic hemodialysis. Prior to randomization, all patients participated in a two-week washout period where UFH was used for anticoagulation. Three patients withdrew from the study during washout (2 dalteparin, 1 enoxaparin), and an additional patient in the dalteparin group withdrew three weeks into the study following hospitalization for an arteriovenous graft infection. The authors reported that no hemorrhagic events, thrombotic events, catheter/dialyzer clotting, or other adverse events attributable to treatment were observed. Based on assessment of anti-factor Xa levels throughout the study, the authors concluded that both dalteparin and enoxaparin provided sufficient anticoagulation, while danaparoid at the recommended dose resulted in a greater extent of anticoagulation and may have an accumulative effect over time.

Patients with ACS, MI, angina

Shafiq et al.\textsuperscript{22} (2006) performed a single center RCT that included enoxaparin (1mg/kg twice daily; n=50), dalteparin (120IU/kg twice daily; n=50), and nadroparin (86 anti-Xa/kg twice daily for three days; n=50) to compare levels of effectiveness and safety for treatment of unstable angina. Information was available only in structured abstract format. Patients with a prior angina
attack, ischaemic heart disease, a VTE or myocardial infarction (MI) in the preceding three months, a history of stroke, reduced hemoglobin level, recent anticoagulant treatment, low systolic blood pressure, or contraindications to anticoagulant therapy were excluded from the study. The study outcomes were cardiac mortality, occurrence of recurrent angina, MI, need for intervention, and a composite outcome of these events. The patients were described as comparable in terms of baseline risk factors collected. At 30-day follow-up, the authors reported similar rates of the composite outcome in the enoxaparin (24%), nadroparin (30%), and dalteparin groups (28%), respectively (p=0.53); the frequency of individual outcomes was not reported, but no differences between groups were reported. No instances of major bleeds or thrombocytopenia were observed in any of the treatment groups. The authors concluded that there was insufficient evidence to suggest a difference in effectiveness of the three LMWHs evaluated. Given the small sample size of the study, the ability to identify between-group differences was not optimal.

Michalis et al.²³ (2003) reported findings from a RCT that compared subcutaneous enoxaparin (100IU/kg twice daily for 7 days; n=220) and tinzaparin (175 anti-Xa IU/kg per day for 7 days; n=218) in patients with non-ST-segment elevation acute coronary syndromes (NSTACS). The primary study outcome was a composite measure of MI, recurrent angina, or death within the first seven days of follow-up. Intervention groups were comparable at baseline. Totals of 11.4% and 11.0% of patients in the enoxaparin and tinzaparin groups were diagnosed with non-Q-wave MI, respectively, while corresponding frequencies of unstable angina were 85% and 85.7%. Most patients (97%) received concomitant aspirin administration, while many patients also received beta blockers (69%) and nitrate derivatives (92%) (no significant differences in co-interventions were noted between groups). At day 7 of follow-up, the rates of the composite outcome (12.3% versus 21.1%) and recurrent angina (19.3% versus 11.8%) were significantly lower in the enoxaparin group (P<0.05 for both), while rates of death (0.5% versus 0.9%) and MI (0.5% versus 1.8%) were comparable. At day 30 of follow-up, the rates of the composite outcome (17.7% versus 28.0%), recurrent angina (17.3% versus 26.1%), and MI (0.5% versus 2.8%) were significantly lower in the enoxaparin group (P<0.05 for all), while the rate of death (0.5% versus 0.9%) remained similar across groups. Requirements for revascularization at both seven days (8.6% versus 17.9%; p=0.01) and thirty days (16.4% versus 26.1%; p=0.019) was significantly smaller in the enoxaparin group. The incidence of serious hemorrhages was comparable (3.6% enoxaparin versus 3.2% tinzaparin) between groups. Based on the observed data, the authors concluded that enoxaparin provided a superior therapeutic benefit compared to tinzaparin during the first 30 days after treatment. A subsequent article reported by Katsouras et al.²⁴ (2005) reported six-month follow-up data for the intervention groups, and indicated that the benefit of enoxaparin remained when considering the primary triple composite outcome (25.5% versus 44.0%; p<0.01), a two-measure composite outcome of death and MI (2.7% versus 6.9%; p=0.046), and need for re-vascularization (23.2% versus 37.2%; p=0.002).

Montalescot et al.²⁵ (2003) reported findings from a multi-center, open label RCT that assigned patients to treatment with enoxaparin (100 anti-factor XA U/kg at 12 hour intervals; n=46), dalteparin (120 anti-factor XA U/kg at 12 hour intervals; n=48), or unfractionated heparin (70U/kg bolus followed by continuous infusion; n=47) for a duration of between 48-120 hours for treatment of unstable angina or NSTEMI. Patients were additionally treated with aspirin, beta blockers, and intravenous nitrates. The authors assessed a one-month composite outcome measure consisting of death, MI, and recurrent ischemia, attempted to identify haemostatic outcomes that showed an association with the occurrence of this outcome measure, and examined major hemorrhage as a safety outcome. At baseline, all three intervention groups were found to be comparable in terms of risk factors evaluated. Frequencies of 13%, 19%, and 28% of the composite outcome measure were seen in the enoxaparin, dalteparin and UFH.
groups, respectively (p-value not reported). Only one major hemorrhage was observed which occurred in the dalteparin group. Amongst all hemostatic measures evaluated, the authors reported that increased plasma levels of von Williebrand factor (vWF) and decreased platelet levels of glycoprotein Ib/IX were identified as being predictive of an adverse outcome at one-month follow-up based on multivariate analysis. Both enoxaparin and dalteparin were found to reduce vWF significantly compared to UFH, while enoxaparin was found to significantly improve glycoprotein levels compared to both dalteparin and UFH.

Ozdemir et al.\textsuperscript{26} (2002) reported findings from a single-center RCT that compared dalteparin (120IU/kg twice daily for 5 days; n=73) and enoxaparin (1mg/kg twice daily for 5 days; n=69) for management of ACS (unstable angina or non-Q-wave MI) in terms of safety and clinical effectiveness. Patients were eligible for enrollment if found to have resting angina for 5 or more minutes during the 24 hour period following presentation to hospital, along with one of three other risk factors (history of prior MI or revascularization, invasive or noninvasive evidence of coronary artery disease, a minimum of 0.1 mV transient or persistent T-wave inversion without accompanying Q waves in 2 or more ECG leads). The primary outcome of interest was a composite measure of death, MI, or angina recurrence within five days of initial treatment. All patients received aspirin (300mg/day), while some additionally received clopidogrel (75mg/day). Patients were comparable at baseline in terms of gender, age, and medical history. The investigators reported that no deaths were experienced by patients in either intervention group, MI was seen in 4% of patients in the dalteparin group, and recurrence of angina occurred in totals of 16% and 15% of the enoxaparin and dalteparin groups, respectively. The composite measure thus occurred in 16% of the enoxaparin group and 19% of the dalteparin group. The time until the occurrence of the first event following treatment initiation was found to be significantly longer with enoxaparin compared to dalteparin (82.3±33.2 hours versus 37.6±23.4 hours; p=0.01). Major bleeds were infrequent (1 enoxaparin, 0 dalteparin), while minor bleeds were more common (25% of enoxaparin group, 29% of dalteparin group). The authors concluded that, while sample size was small, the study showed signs that enoxaparin and dalteparin seemed equally safe and efficacious, and it was suggested that a large, multi-center trial is required to determine the best LMWH for use in ACS management.

**Clinical Guidelines**

A total of six clinical guidelines identified by the literature search provided recommendations pertaining to one or more specific LMWHs.

**DVT Prevention**

The American College of Obstetricians and Gynecologists (ACOG) reported guidelines for prevention of deep vein thrombosis and pulmonary embolism in females undergoing gynecologic surgery.\textsuperscript{27} Electronic searches of Medline, the Cochrane Library, and internal resources of ACOG were performed to identify eligible studies reported in English published from 1985-2006. Original research and past guidelines were of primary interest, while review articles were evaluated and abstracts were excluded from consideration. A systematic review of identified studies was performed, and recommendations were formulated via expert consensus. Recommendations for pre-operative and post-operative surgical prophylaxis, testing for clotting abnormalities, and testing for heparin-induced thrombocytopenia were addressed. For moderate risk patients (defined as either surgery lasting <30 minutes in patients with additional risk factors, surgery lasting <30 minutes in patients aged 40 to 60 years with no additional risk factors, or major surgery in patients younger than 40 years with no additional risk factors) undergoing surgery, LMWH (dalteparin 2500 antifactor-Xa units, or enoxaparin 40 mg;
administered subcutaneously, 12 hours before surgery and once a day postoperatively until discharge) was one of several interventions assigned a grade A recommendation (described as a recommendation based on good and consistent scientific evidence). For high risk patients (defined as surgery lasting <30 minutes in patients older than 60 years or with additional risk factors, or major surgery in patients older than 40 years or with additional risk factors) undergoing surgery (in particular for malignancies), LMWH (dalteparin 5,000 antifactor-Xa units or enoxaparin 40 mg; administered subcutaneously, 12 hours before surgery and once daily postoperatively until discharge) was also assigned a grade A recommendation. In both risk groups, similar recommendations were assigned for compression stockings, pneumatic compression devices, and unfractionated heparin.

**Treatment of DVT or PE**

Buller et al.\(^28\) (2004) reported guidelines for antithrombotic therapy for venous thromboembolic disease pertaining to antithrombotic agents (heparins, fondaparinux, ximelagatran, vitamin K antagonists, and other alternatives), surgical techniques (venous thrombectomy, pulmonary embolecomy, vena caval filters) and other approaches/devices (compression stockings, catheters for thrombolysis or fragmentation, ambulation). Systematic searches of the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Register of Controlled Trials, Medline, Embase, and the ACP Journal Club were searched. Evaluation of past systematic reviews and meta-analyses was performed, and pooling of data was performed using collected data, Expert consensus was used to develop recommendations, which were validated by peer review. In regard to long-term treatment of DVT using LMWH, the authors recommended treatment for a minimum of 3-6 months (grade 1A; described as a strong recommendation with clear risk-benefit ratio based on high quality RCT data), and noted that the regimens established as effective based on data from RCTs are dalteparin (200IU/kg daily for a month followed by 150IU/kg afterwards) and tinzaparin (175IU/kg). Analogously, long-term treatment of PE with LMWH was recommended for 3-6 months (grade 1A; as defined above), with established regimens of dalteparin (200IU/kg daily for a month followed by 150IU/kg afterwards) and tinzaparin (175IU/kg). No other discussion of specific LMWHs was noted.

The Institute for Clinical Systems Improvement (ICSI)\(^29\) compiled guidelines for management of venous thromboembolism, which made recommendations pertaining to diagnosis of DVT/PE, as well as approaches for treatment and prevention. An electronic search of databases was performed to identify relevant clinical trials, meta-analyses and systematic reviews. Evidence tables were constructed, previously published meta-analyses were reviewed, and expert consensus was used to formulate final recommendations that were then validated by peer review. Recommendations stated that LMWH or UFH should be considered for initial treatment of PE, that LMWH is the preferred heparin for initial anticoagulation for a majority of patients with DVT, and that LMWH may be used in both in-patient and out-patient settings. The authors summarized Food and Drug Administration (FDA) positions regarding the various LMWHs available based on data from randomized trials, narrative reviews/consensus reports, cohort studies, and other non-randomized designs, though no specific study references were provided. Discussion of issues of therapeutic equivalence amongst LMWHs was not pursued. Enoxaparin 1mg/kg twice daily was described as the recommended treatment for DVT (FDA approved for both inpatient and outpatient use), tinzaparin 175 anti-Xa IU/kg SC once daily was described as FDA approved for VTE treatment, and dalteparin (100IU/kg and 200IU/kg SC) was described as not FDA approved for VTE treatment.
Patients with ACS, MI, angina

Identified clinical guidelines pertaining to acute STEMI\textsuperscript{30} and antithrombotic therapy for NSTEMI acute coronary syndromes\textsuperscript{31} did not provide discussion regarding head-to-head comparisons of effectiveness of different forms of LMWH. Methods for guideline development were not explicitly reported in either manuscript, as both referenced a separate published article which detailed the approach used.\textsuperscript{32} Enoxaparin of up to eight days was recommended over treatment with UFH for patients with acute STEMI receiving antifibrinolytic therapy with preserved renal function (Grade 2A).\textsuperscript{30} Treatment with LMWH over UFH was recommended for patients with non-segment elevated acute coronary syndromes in whom early conservative or delayed invasive strategies of management are being used (Grade 1B).\textsuperscript{31}

Guidelines for management of patients with unstable angina (UA)/non-ST elevation MI reported by Anderson et al.\textsuperscript{33} sought to provide physicians with appropriate evaluation and management of the aforementioned classes of patients. Electronic database searches and hand searches of published literature were performed. Evidence tables of selected studies were constructed for investigation, and meta-analyses using collected data and evaluation of past systematic reviews were performed. Expert consensus was used to formulate recommendations, which were validated by peer review. In discussion pertaining to anticoagulant therapy, implementation of anticoagulant therapy in UA/NSTEMI patients was recommended immediately following presentation; enoxaparin or UFH was recommended for patients in whom an invasive strategy is selected (grade 1A; described as being based on a clear risk-benefit ratio and multiple population risk-stratified data), and for patients in whom a conservative strategy is selected (grade 1A). A class 2a, level B recommendation (described as having a less clear risk-benefit ratio requiring additional study and limited population risk-stratified data) was assigned for enoxaparin or fondaparinux as being preferred over UFH in patients in whom an initial conservative strategy was chosen, unless coronary artery bypass graft (CABG) surgery is planned in the proceeding 24-hour period. There was no mention of other LMWHs.

Limitations

There are several limitations associated with the published evidence identified in this clinical review:

- **Lack of sufficient data:** A paucity of research pursuing randomized, head-to-head comparisons of LMWHs in the clinical indications of interest was noted. Relevant literature pertaining to VTE prophylaxis and treatment, management of acute coronary syndromes, and hemodialysis was located and summarized. However, no studies pertaining to anticoagulant bridging therapy discussing differences between LMWHs were identified. Heuts et al.\textsuperscript{34} (2004) reviewed available published data for perioperative anticoagulation in recipients of chronic warfarin therapy, and concluded that more data are needed to support LMWH use for bridge therapy in the form of RCTs. Additionally, the extent of influence that observational studies have had on current clinical practice was not assessed, and is unclear.

- **High degree of heterogeneity:** While a large number of trials comparing different forms of LMWH to UFH or other comparators have been published, these studies have been performed in a broad array of clinical indications, amongst varying types of patients (with varying severities of illness), using different study designs, and using different treatment regimens in terms of dosage, timing of treatment, and other factors. Thus, while there is a tendency and desire to debate comparative levels of effectiveness of LMWHs based on studies that involved a common comparator such
as UFH or placebo, a considerable number of factors discourage and invalidate this process.\textsuperscript{7,35}

- **Lack of clarity of association of pharmacologic differences with incidence of clinical outcomes:** While biochemical differences between LMWH are well established, little is understood as to how these differences translate into variations in the incidence of clinically relevant outcome measures. For this reason, past meta-analyses that have synthesized data from trials comparing different LMWH to UFH may be misleading, and may present biased findings by pooling based on the assumption of equivalence of these interventions.

- **Minimal motivation for head-to-head trials:** The ability to provide appropriately informed commentary regarding the comparative effectiveness of LMWHs requires the performance of additional head-to-head trials within all clinically relevant indications.\textsuperscript{7,36} While some may argue enoxaparin to be the best available LMWH based upon available data and its recommendation in several clinical guidelines, this is likely due, at least in part, to the greater abundance of published studies available, primarily of comparisons with UFH.\textsuperscript{10} The lacking quantity of published data for heparins in different clinical fields must be noted.\textsuperscript{1} Given that the different LMWHs available are produced by different manufacturers with little to benefit from comparison with other active alternatives, the paucity of data available to support decision making processes is likely to remain.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

There currently exists relatively little published data for head-to-head comparisons amongst the low molecular weight heparins tinzaparin (Innohep\textsuperscript{®}), enoxaparin (Lovenox\textsuperscript{®}), nadroparin (Fraxiparin\textsuperscript{®}), and dalteparin (Fragmin\textsuperscript{®}). No health technology assessment reports, systematic reviews, or meta-analyses were located in this review. Amongst RCTs that were identified, one trial for prevention of VTE recurrence failed to identify a significant difference between outpatient treatments with tinzaparin or dalteparin.\textsuperscript{6} Studies pertaining to management of acute coronary syndromes\textsuperscript{23,25,26} may suggest differences of effectiveness amongst LMWHs, while two studies involving hemodialysis\textsuperscript{20,21} did not show signs of differences between LMWHs. Two RCTs in patients with unstable angina\textsuperscript{22} and spinal cord injury\textsuperscript{18} failed to identify differences between alternative LMWH preparations, though statistical power may have been particularly limited. In the presence of minimal data for indications of particular interest, there is a tendency to discuss relative levels of effectiveness based on randomized comparisons with other common interventions. However, heterogeneity amongst study populations, treatment regimens, and other factors require careful resolution in health technology assessments addressing this issue. More randomized studies comparing the effectiveness of the therapies in this class of agents in terms of clinically important outcomes are required to further inform choices made by physicians and hospital pharmacies.

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## Appendix: Details of RCT Publications Identified

<table>
<thead>
<tr>
<th>Study and Design</th>
<th>Patient Population</th>
<th>Interventions (sample size)</th>
<th>Outcomes</th>
<th>Study conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT prophylaxis in medical or surgical patients</strong></td>
<td><strong>Exclusions:</strong> emergency surgery; use of locoregional anesthesia; hemorrhagic stroke or stroke of undetermined origin in 2-month period prior to study; neurosurgery in prior 2 months; acute bacterial endocarditis; pregnancy; hemostasis disorder; thrombocytopenia; contraindication to anticoagulant therapy; impaired renal or liver function.</td>
<td>Enoxaparin (4000IU for 9±2 days; n=468) versus nadroparin (2850IU for 9±2 days; n=464)</td>
<td>DVT, PE, major bleeds</td>
<td>Authors concluded that a daily dose of nadroparin may be an appropriate regimen for thromboprophylaxis in patients undergoing colorectal surgery</td>
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<tr>
<td>Simoneau et al(^{17}) (2006)</td>
<td>Patients undergoing elective re-section of colorectal adenocarcinoma</td>
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<tr>
<td>Chiou-Tan et al(^{18}) (2003)</td>
<td>Patients with acute spinal cord injury</td>
<td>Enoxaparin (30mg every 12 hours; n=50) versus dalteparin (5000IU once daily, n=45)</td>
<td>Incidence of DVT, bleeding, short form-health status survey (12 item questionnaire measuring 8 health concepts; based on the SF-36), satisfaction, costs</td>
<td>Dalteparin and enoxaparin displayed similar DVT rates, bleed rates and health status</td>
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<tr>
<td>Ellison et al(^{19}) (2001)</td>
<td>Women undergoing caesarian section</td>
<td>Enoxaparin (4000IU anti-Xa once daily for five days; n=10), tinzaparin (50IU/kg anti-Xa once daily for five days; n=10), dalteparin (5000IU anti-Xa once daily for five days; n=10)</td>
<td>Plasma anti-factor Xa activity, TFPI, TAT, thrombotic events</td>
<td>Findings show LMWHs have different effects on haemostatic parameters, though these differences do not necessarily imply variations in clinical outcomes</td>
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</tbody>
</table>

**Treatment of DVT or PE**

<table>
<thead>
<tr>
<th>Study and Design</th>
<th>Patient Population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Wells et al(^{6}) (2005)</td>
<td>Patients with DVT or PE presenting to a VTE clinic</td>
<td>Outpatient therapy with tinzaparin (175IU/kg per day for 5 or more days; n=254) versus dalteparin (200IU/kg per day for 5 or more days; n=251) 90 days warfarin therapy given to all patients</td>
<td>Incidence of VTE, bleeding events</td>
<td>Rates of VTE and bleeding were not significantly different between groups</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> active bleeding (or high risk thereof); asymptomatic DVT detected by screening; no fixed address; prior case of HIT; renal failure; other requirement for hospitalization; use of UFH or LMWH for &gt;36 hours; PE requiring IV narcotic analgesia</td>
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### Hemodialysis

**Beijering et al** (2003)

Patients requiring chronic intermittent hemodialysis, having stable condition and a stable routine heparin schedule for 2 or more months

**Exclusions:** prior occurrence of heparin induced thrombocytopenia, congenital bleeding disorder or other form of increased bleeding risk, gastrointestinal blood loss due to peptic ulcer, tumors or diverticulosis during the six months before the study; CVA within 6 months of the study; uncontrolled hypertension; pregnancy; oral anticoagulation use.

Tinzaparin (median dose 4500IU; n=79) versus dalteparin (median dose 5000IU; n=80). Administered in phases of titration and maintenance

| Line/bubble catcher/dialyser assessments, anti-Xa activity, anti-IIa activity, major and minor bleeds | Tinzaparin and dalteparin showed comparable efficacy and safety, though dose was 10% lower in the tinzaparin group |

**Polkinghorne et al** (2002)

Patients with end-stage renal disease undergoing chronic hemodialysis

**Exclusions:** current administration of anticoagulants; known hypersensitivity to study drugs; dialysis through a central venous catheter; vascular access thrombosis within 3 months prior to study; history of heparin induced thrombocytopenia

Dalteparin (2500IU bolus for 12 sessions; n=7), enoxaparin (40mg IV bolus for 12 sessions; n=7), danaparoid sodium (35IU/kg bolus for 12 sessions; n=7)

| Bleeding and thrombotic episodes, anti-factor Xa activity, hemoglobin | Both dalteparin and enoxaparin provided sufficient anticoagulation. Danaparoid at the recommended dose resulted in greater anticoagulation and may have an accumulative effect. |

### Patients with ACS, MI, angina

**Shafiq et al** (2006)

Patients requiring treatment for unstable angina

**Exclusions:** ischemic heart disease, a VTE or MI in the preceding three months, a history of stroke, reduced hemoglobin level, recent anticoagulant treatment, low systolic blood pressure, or contraindications to anticoagulant therapy

Enoxaparin (1mg/kg twice daily; n=50), nadroparin (86 anti-Xa/kg twice daily for three days; n=50), dalteparin (120IU/kg twice daily; n=50)

| Cardiac mortality, recurrent angina, MI, need for intervention | Insufficient evidence to suggest a difference in the clinical effectiveness of the interventions compared |

**Michalis et al** (2003)

Patients with non-ST-segment elevation acute coronary syndromes

**Exclusions:** persistent ST-segment elevation ≥0.1mV in 2 adjacent leads; angina with known precipitating cause; body weight outside the range of 40-110kg; contraindication to antithrombotic therapy; pregnancy; renal failure; use of oral anticoagulants

Enoxaparin (100IU/kg twice daily for 7 days; n=220) versus tinzaparin (175 anti-Xa IU/kg per day for 7 days; n=218)

| Mortality, MI, angina, revascularization, major hemorrhage | Enoxaparin provided a significant therapeutic benefit compared to tinzaparin during the first 30 days after treatment |
**Patients with ACS, MI, angina**

| Montalescot et al \(^2\) (2003) | Patients with unstable angina pectoris or non-ST-segment elevation MI | Exclusions: planned revascularization within 48 hours; left bundle branch block; persistent ST-segment elevation or evolving Q-wave MI; secondary UAP with identified precipitating factor; MI or percutaneous transluminal coronary angioplasty in previous month; CABG in previous 2 months; LMWH or UFH treatment of more than 24 hours before enrollment; treatment with glycoprotein IIb/IIIa inhibitors, dipyridamole, ticlopidine or clopidogrel within 2 weeks before study; oral anticoagulant use in the previous five days; acute inflammatory disease; contraindications to anticoagulation. | Enoxaparin (100 anti-factor XA U/kg at 12 hour intervals; n=46), dalteparin (120 anti-factor XA U/kg at 12 hour intervals; n=48), unfractionated heparin (70U/kg bolus followed by continuous infusion; n=47) | Mortality, MI, ischemia, major hemorrhage, hemostatic measures | Some indication of differences in clinical outcomes across groups. vWf and glycoprotein IIb/IX levels were predictive of adverse outcomes, and LMWHs had important effects on these measures |
|---|---|---|---|---|
| Ozdemir et al \(^2\) \(^6\) (2002) | Patients with acute coronary syndromes | Exclusions: Didn’t present until>24 hours after last angina episode; ST segment elevation at presentation; not an adult; developed new Q waves; pericarditis; ongoing heparin/anticoagulant treatment; DBP>120mmHg or SBP <90mmHg; high grade fever; pregnancy; malignancy; surgery within past month. | Dalteparin (120IU/kg twice daily for 5 days; n=73) versus enoxaparin (1mg/kg twice daily for 5 days; n=69) | Death, MI, angina recurrence, major bleeds | Authors concluded that despite a small sample size, there were signs that enoxaparin and dalteparin seemed equally safe and efficacious. Suggested that a large RCT is required to determine the best LMWH for use |

THR=total hip replacement; DVT=deep vein thrombosis; MI=myocardial infarction; PE=pulmonary embolism; VTE=venous thromboembolism, HIT=heparin induced thrombocytopenia; LMWH=low molecular weight heparin; UFH=unfractionated heparin, TAT=thrombin antithrombin, CVA=cerebrovascular accident; vWF=von Willebrand factor; CABG= coronary artery bypass graft; DBP= diastolic blood pressure; SBP=systolic blood pressure; TFPI=tissue factor plasma inhibitor; ACS=acute coronary syndrome