South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW:

1. Executive Summary

Date: April 2018
Medicine (INN): Low Molecular Weight Heparin (LMWH)
Medicine (ATC): B01AB
Indication (ICD10 code): Venous thromboembolism (treatment & prevention); Acute coronary syndromes (I80.0-3/I80.8-9/I81/I82.0-3/I8.8-9/I26.0/I26.9/ I21.0-I21.4/I21.9/I22.0-1/I22.8-9/ I21.4/I21.9/I20.0)
Patient population: Adult patients, prophylaxis and therapy of venous thromboembolism, Acute Coronary Syndromes and Medically ill patients with prolonged immobilization
Prevalence of condition: The risk of deep-vein thrombosis (DVT) in medically ill patients is comparable to that in moderate risk surgical patients (10 - 20%). After major surgery, the prevalence of DVT ranges from 15% to 60%. Pulmonary embolism (PE) contributes to 10% of all hospital deaths. Approximately 75% of these deaths occur in medically ill patients. In patients with hip fractures and those undergoing hip and knee replacement surgery, prevalence ranges from 40% to 60%.(1) Data from the registry of South African patients in the ACCESS trial shows a one-year mortality among non-ST segment elevation myocardial infarction patients of 5%.(2)
Level of Care: Hospital level
Prescriber Level: Primary level of care (nurse prescriber, doctor)
Current standard of Care: Unfractionated Heparin (UFH)
Efficacy estimates: LMWH vs. UFH
Venous Thromboembolism(3):

- Lower rate of recurrent VTE (Peto OR 0.72, 95%CI 0.59-0.88; P = 0.001).
- Major haemorrhages occurred less frequently (Peto OR 0.69, 95% CI 0.50 to 0.95; P = 0.02). NNT=470
- No difference in overall mortality between participants treated with LMWH and those treated with UFH.

Acute Coronary Syndromes(4):

- RR 0.83; 95%CI 0.70-0.99 for MI occurrence and the need for revascularization procedures (RR = 0.88; 95% CI: 0.82-0.95). A decrease in the incidence of thrombocytopenia (RR 0.64; 95% CI 0.44-0.94). No difference in recurrent angina, major and minor bleeds.
- NNT for MI = 125 and NNT for revascularization procedure = 50.

Medical patients who are immobilised and after major surgery(5):

- i.e. DVT incidence for LMWH vs Placebo: OR 0.45, 95% CI 0.33 to 0.61
- NNTB =59

Motivator/reviewer name(s): Dr S Takuva, Dr T Kredo
PTC affiliation: N/A

2. Name of author(s)/motivator(s):

Primary reviewer: Dr S Takuva
Secondary reviewer: Dr T Kredo

3. Authors affiliation and conflict of interest details:

Dr S Takuva: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand; Adult Hospital Level Expert Review Committee (2017-2020). *Conflicts of interest declared:* Author is a medical monitor and safety physician for the NIH-funded HIV Vaccine Trials Network that conducts candidate HIV vaccine candidate trials of products developed by Novartis Vaccines, GSK Biologicals, Janssen Pharmaceuticals and Vaccines and Sanofi Pasteur.
Dr T Kredo: Cochrane South Africa, South African Medical Research Council; NEMLC Committee member; no conflicts of interest declared.

4. Introduction

The management of venous thromboembolic disease (VTE) is rapidly evolving. Low-molecular-weight heparins (LMWHs) are a new class of anticoagulants derived from unfractionated heparin (UFH). LMWH is at least as effective and as safe as classic intravenous heparin therapy and more convenient to administer.(6) The simplified therapy provided by low-molecular-weight heparin may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting. They have a number of advantages over UFH that have led to their increasing use for a number of thromboembolic indications.(7) These advantages are translated clinically into (i) greater convenience afforded by the ability to administer LMWH by subcutaneous injection without laboratory monitoring and the associated cost reduction resulting from reduced hospital stay and (ii) a lower incidence of heparin induced thrombocytopenia (HIT) and (iii) possibly a lower risk of bone complications i.e. osteopenia. LMWHs appear to be as safe and effective as UFH for the treatment of venous thrombosis and pulmonary embolism and at least as safe and effective as UFH for the treatment of patients with unstable angina.(8–10)

5. **Purpose /Objective of Review:** To compare the efficacy and safety of LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes.

Population	Adult patients who are OR with: • Medical patients with restricted mobility during acute illness and patients after major surgery. • Venous thromboembolism (VTE) (from proximal to pulmonary embolism) • Acute coronary syndromes (ACS) (unstable angina or non-ST segment elevation MI)
Intervention	Low molecular weight heparin (LMWH)
Comparison	Unfractionated heparin (UFH)
Outcomes	Efficacy and Safety*: All-cause mortality, major bleeding, minor bleeding, revascularization, bleeding complications, inter-operative blood loss, post-operative blood loss, thrombocytopenia, Heparin induced thrombocytopenia, Composite outcomes (*clinical outcomes, laboratory outcomes excluded)

6. Methods

a. **Data sources:** The following databases were searched, PubMed (via the PubMed/MEDLINE interface using the "PICO" option) and Cochrane (via The Cochrane Library using MeSH terms and qualifiers). See search strategy below.

b. Search strategy: Restricted to RCTs published after 2000 and of adults at least 18 years of age.

Search terms: ((((Low molecular weight heparin) OR LMWH OR Enoxaparin OR fondaparinux OR tinzaparin OR dalteparin OR nadroparin))) AND (angina OR angina pectoris OR non-STEMI OR (myocardial infarction)). Also included ((((Low molecular weight heparin) OR LMWH OR Enoxaparin OR fondaparinux OR tinzaparin OR dalteparin OR nadroparin))) AND (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*). Also included ((((Low molecular weight heparin) OR LMWH OR Enoxaparin OR fondaparinux OR tinzaparin OR dalteparin OR nadroparin))) AND (surgery or operation or immobilization or post-operative or fracture).

Also searched reference lists from papers and systematic reviews.

c. Selection of studies: Included were randomised trials directly comparing LMWH with UFH for prevention and treatment of VTE and acute coronary syndromes, use in medically ill patients and safety. Systematic Reviews were also scanned. In total for all indications, just above 350 studies, guidelines and review reports were identified and a total of 31 studies, guidelines and review reports were fully reviewed. Studies were excluded for the following reasons: not providing head

to head comparison between a LMWH and UFH including within class comparisons, LMWH vs placebo comparison, LMWH vs other agents, non-standardised heparin used, LMWH used in combination with another agent, were dose ranging studies and also duplicate studies. (See references for the full list of studies reviewed)

d. Evidence synthesis:

I. <u>Indication</u>: Venous thromboembolism treatment.

LMWH at a standard dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and heparin-induced thrombocytopenia were reported in one study. There was clinical benefit of LMWH in terms of all cause mortality, possible clinical benefit of LMWH in terms of PE and heparin-induced thrombocytopenia, although all these findings could also be consistent with no difference. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and major bleeding, however there was some uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision. Below is a synopsis of studies examining LMWH vs UFH in the treatment of venous thromboembolism.

Guidelines:

The NICE Guideline - *Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism* was appraised by two reviewers independently using the AGREE Instrument. Overall the guidelines recommend use of LMWH as first line agents for treatment and prevention of VTE. (11) The overall quality of this guideline was 7/7 (excellent quality). Guideline is recommended for use with modifications, i.e. the clinical recommendations are rigorous and evidence based, however local resources need to be considered. This guideline was developed for a developed country. See Appraisal – Appendix C.

Systematic Reviews:

van Den Belt AG et al, Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Systematic Review, 2000. The objective of this review was to determine the effect of fixed-dose, subcutaneous low molecular weight heparins compared with adjusted-dose, intravenous or subcutaneous, unfractionated heparin for initial treatment of acute deep venous thrombosis or pulmonary embolism. Fourteen studies with a total of 4754 patients were included. By the end of follow up in ten trials, thrombotic complications occurred in 86 (4.3%) of the 1998 patients treated with low molecular weight heparin, compared with 113 (5.6%) of the 2021 patients treated with unfractionated heparin (OR 0.76, 95% CI 0.57 to 1.01). At the end of the initial treatment period, in all 14 of the trials, major haemorrhages occurred in 30 (1.3%) of the 2353 patients treated with low molecular weight heparin, compared with 51 (2.1%) of the 2401 patients treated with unfractionated heparin (OR 0.60, 95% CI 0.39 to 0.93). By the end of follow up in 11 trials, 135 (6.4%) of the 2108 patients treated with low molecular weight heparin had died, compared with 172 (8.0%) of the 2137 patients treated with unfractionated heparin (OR 0.78, 95% CI 0.62 to 0.99). Low molecular weight heparin was at least as effective as unfractionated heparin in preventing recurrent venous thromboembolism, and significantly reduced the occurrence of major haemorrhage during initial treatment and overall mortality at the end of follow-up.(12) In this good systematic review and other similar reviews conducted 1999-2000 for the indications of acute coronary syndromes and prophylaxis in medical patients, in addition to synthesizing the evidence, the authors included appraisals of the trials and did GRADE. In the synopsis of individual trials we therefore focused on trials conducted post-2000.

Robertson et al, Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Updated Cochrane Review, 2017: A total of 29 included studies (n = 10,390). At the end of follow-up, LMWH probably results in **a lower rate of recurrent VTE** than UFH (Peto OR 0.72, 95%CI 0.59 to 0.88; P = 0.001; moderate-quality evidence). LMWH may result in a **reduction in thrombus size** compared to UFH (Peto OR 0.71, 95% CI 0.61 to 0.82; P < 0.00001; low-quality evidence), but there was moderate heterogeneity. **Major haemorrhages probably occurred less frequently** in participants treated with LMWH than in those treated with UFH (Peto OR 0.69, 95% CI 0.50 to 0.95; P = 0.02; moderate-quality evidence). There was probably **no difference in overall mortality** between participants treated with LMWH and those treated with UFH (Peto OR 0.84, 95% CI 0.70 to 1.01; P = 0.07; moderate-quality evidence).

Conclusion was that the review presented moderate-quality evidence that fixed dose LMWH probably reduced the incidence of recurrent thrombotic complications and occurrence of major haemorrhage during initial treatment; and low-quality evidence that fixed dose LMWH may reduce thrombus size when compared to UFH for the initial treatment of VTE. There was probably no difference in overall mortality between participants treated with LMWH and those treated with UFH (moderate-quality evidence).

Randomized Control Trials (Venous Thromboembolism)

Author	Population	N	LMWH	Follow-up	Key results
Breddin, N Engl J Med, 2001(13)	Ppts with acute DVT	649	Reviparin	21 and 90 days	Reviparin (bd) was significantly more effective than UFH (RH of thrombus regression, 1.28; 97.5% CI, 1.08 to 1.52), as was reviparin (od) (RH, 1.29; 97.5% CI, 1.08 to 1.53). Mortality and the frequency of episodes of major bleeding were **similar** in the three groups. Reviparin is more effective than UFH for the prevention of recurrent thromboembolism and equally safe.
Findik, Respiration, 2002 (14)	Ppts with acute pulmonary thromboembolism	59	Enoxaparin	8 and 90 days	UFH (10%) vs. enoxaparin (3.4%) symptomatic recurrent VTE (p = 0.508) Initial subcutaneous treatment with enoxaparin appeared to be as effective and safe as UFH in acute PTE
Pérez de Llano LA, Arch Bronconeumol, 2003 (13)	Ppts submassive pulmonary thromboembolism (PTE)	56	Enoxaparin	6 months	There were no significant differences (p>0.05). Enoxaparin seems to be as effective and safe as unfractionated heparin in the initial treatment of PTE.
Kakkar, Thromb Haemost. 2003 (15)	Ppts with DVT	378	Bemiparin	12 weeks	Mortality, recurrent thromboembolic events and bleeding were similar Both bemiparin regimens were more effective than UFH in reducing thrombus size during the acute phase of treatment. The efficacy in terms of recurrence of venous thromboembolism and safety of Bemiparin is similar to UFH.
Prandoni, Arch Intern Med. 2004 (16)	spectrum of ppts with venous thromboembolism (VTE),	720	Nadroparin	3 months	4.2% UFH had recurrent thromboembolic events vs. 3.9% Nadroparin (absolute difference

	including recurrent VTE and pulmonary embolism				between rates, 0.3%; 95% CI, -2.5% to 3.1%). UFH (1.1%) vs. nadroparin (0.8%) had episodes of major bleeding (absolute difference between rates, 0.3%; 95% CI, -1.2% to 1.7%). Overall mortality was 3.3% in each group
Merli, Ann Intern Med. 2001(17)	ppts with symptomatic lower-extremity deep venous thrombosis, including 287 (32%) with confirmed pulmonary embolism in 74 hospitals across 16 countries	900	Enoxaparin	3 months	Equivalent efficacy was seen in the heparin group and both enoxaparin groups (treatment difference was 0.2% (95% CI, -3.04% to 3.49%) for once-daily enoxaparin) Recurrence of symptomatic VTE was 4.4% in UFH vs. 4.1% in enoxaparin group Incidence of major haemorrhage did not differ among the three treatment groups (2.1% UFH vs. 1.7% in the enoxaparin OD dose)

II. <u>Indication</u>: Acute coronary syndromes (prevention and treatment).

In ACS, patients with ST-segment elevation myocardial infarction treated with fibrinolysis and LMWH seem to have a lower incidence of death or non-fatal recurrent myocardial infarction but a higher rate of major bleeding than those treated with fibrinolysis and UFH. (18) Similarly, in unstable angina/non-ST-segment elevation myocardial infarction, LMWH therapy reduced the incidence of death, myocardial infarction, or urgent revascularization when compared to UFH.(19) Below is a synopsis of RCTs and Reviews that have compared efficacy and safety of LMWH and UFH in ACS.

Systematic Reviews:

The following thorough Cochrane Review by Magee et al was identified.

Magee K, et al Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. Cochrane Review, 2003: Seven included studies, with a total of 11,092 patients being included in this systematic review. **In this review, LMWH and UFH had similar risk of mortality, recurrent angina, and major or minor bleeding but LMWH had decreased risk of MI, revascularization and thrombocytopenia**. The authors recommended that newer trials with longer follow up are required. The effect estimates for LMWH vs. UFH as follows, Mortality (RR=1.0; 95% CI: 0.69-1.44), occurrence of MI (RR=0.83; 95% CI: 0.70-0.99), need for revascularization procedures (RR=0.88; 95% CI: 0.82- 0.95). No significant differences in occurrence of recurrent angina (RR= 0.83; 95% CI: 0.68-1.02), major bleeds (RR=1.00; 95% CI: 0.80-1.24) or minor bleeds (RR=1.40; 95% CI: 0.66-2.90). "A decrease in the incidence of thrombocytopenia (RR=0.64; 95% CI: 0.44-0.94) was observed for patients given LMWH. From these results, 125 patients need to be treated with LMWH to prevent 1 additional MI and 50 patients need to be treated to prevent 1 revascularization procedure." (20).

Randomized Control Trials (Acute Coronary Syndromes)

Author	Population	N	LMWH	Follow-up	Key results
Lavi, Am Heart J. 2012 TRANSFER-AMI trial (21)	Ppts with high-risk STEMI receiving fibrinolysis	946	Enoxaparin	30 days	Composite end point of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days occurred in 11.9% vs. 11.6% of the patients who received enoxaparin and UFH, respectively (adjusted odds ratio 0.95 [95% CI 0.60-1.51], P = .84). Enoxaparin use was associated with more access site bleeding (5.0% vs 2.9%, P = .04) and mild bleeding (12.1% vs 7.8%, P = .03). **Similar efficacy** compared with UFH, but there was **more minor bleeding** with enoxaparin
Montalescot, Lancet, 2011 (ATOLL trial)(22)	Ppts presenting with STEMI for PCI	910	Enoxaparin	30 days	Incidence of death (enoxaparin, [4% vs heparin, 6% p=0·08), complication of myocardial infarction (20 [4%] vs 29 [6%]; p=0·21), procedure failure (100 [26%] vs 109 [28%]; p=0·61), and major bleeding (20 [5%] vs 22 [5%]; p=0·79) **did not differ between groups**. Enoxaparin resulted in a significantly reduced rate of the main secondary endpoint (30 [7%] vs 52 [11%] patients; RR 0·59, 95% CI 0·38-0·91, p=0·015). Death, complication of myocardial infarction, or major bleeding (46 [10%] vs 69 [15%] patients; p=0·03), death or complication of myocardial infarction (35 [8%] vs 57 [12%]; p=0·02), and death, recurrent myocardial infarction, or urgent revascularisation (23 [5%] vs 39 [8%]; p=0·04) **were all reduced with enoxaparin** LMWH vs. UFH significantly reduced clinical ischaemic outcomes without differences in bleeding and procedural success. Therefore, enoxaparin provided an improvement in **net clinical benefit** in patients undergoing primary PCI.
Antman, N Eng J Med, 2006 (18)	Ppts with STEMI who were scheduled to undergo fibrinolysis	20,506	Enoxaparin	30 days	The composite of death, nonfatal reinfarction, or nonfatal intracranial haemorrhage (a measure of net clinical benefit) occurred in 12.2 percent of patients given unfractionated heparin and 10.1 percent of those given enoxaparin (P<0.001). However LMWH was associated with more bleeding episodes
Yeh, Am J Cardiol, 2007 (23)	Ppts presenting with non-ST-elevation ACS	3,910	Enoxaparin	14 days	Incidence of **thrombocytopenia** similar across LMWH vs. UFH
STEEPLE Investigators (22)	Ppts undergoing elective PCI	3,528	Enoxaparin	365 days	The **1-year mortality rates were low and comparable** between patients receiving enoxaparin and UFH during elective PCI. Periprocedural ischemic or bleeding events were the strongest independent predictors of 1-year mortality.
Baid, Eur Heart J, 2002 (24)	Ppts receiving fibrinolytic therapy post- acute MI	300	Enoxaparin	90 days	**Death, non-fatal reinfarction, or readmission** with unstable angina occurred more frequently in patients receiving UFH rather than enoxaparin (36% vs. 26%; P=0.04). Recurrent cardiac event < with LMWH. No difference in major haemorrhage between those receiving enoxaparin (3%) and unfractionated heparin (4%)

ESSENCE study, 2000 (25)	Ppts with unstable angina pectoris or non-STEMI	3,171	Enoxaparin	365 days	Composite end point of death, MI or recurrent angina incidence was lower LMWH vs. UFH (32.0% vs. 35.7%, p = 0.022). At one year, the need for diagnostic catheterization and coronary revascularization was lower in the enoxaparin group (55.8% vs. 59.4%, p = 0.036 and 35.9% vs. 41.2%, p = 0.002, respectively). **Sustained benefit at 1 year**
Malholtra, Int J Clin Pharmacol Ther. 2001 (26)	Ppts with unstable angina	93	Enoxaparin	-	Enoxaparin appeared to be **superior in efficacy** to UFH and **similar to UFH in safety**.
Jolly, Am J Cardiol. 2007 (27)	ESSENCE & INTERACT trial ppts		Enoxaparin	365 days	Enoxaparin significantly decreased the composite of **silent AMI or clinical AMI and death** at 1 year (9.3% vs 21%, p = 0.0001).
CLARITY-TIMI 28 Trial, 2005 (28)	STEMI ppts undergoing fibrinolysis	2860	enoxaparin or dalteparin or nadroparin	30 days	LMWH associated with a significantly **lower rate of a closed infarct-related artery or death or MI** before angiography (13.5% versus 22.5%, adjusted OR 0.76, P=0.027) Treatment with LMWH was associated with a **significantly lower rate of cardiovascular death or recurrent MI** (6.9% vs 11.5%, adjusted OR 0.68, P=0.03)
SYNERGY trial, 2006 (25)	High-risk ppts undergoing early percutaneous coronary intervention for acute coronary syndrome	4687	Enoxaparin	30 days	Enoxaparin avoids the need for monitoring and achieves **similar effectiveness** (non-inferior to UFH for the 30-day primary end point of death/MI) to UFH but is associated with **more bleeding**.

III. <u>Indication</u>: Medical patients with restricted mobility during acute illness and patients after major surgery

For Medical patients with restricted mobility during acute illness and patients after major surgery requiring parenteral VTE prophylaxis, LMWHs are generally preferred to UFH.(29,30) LMWHs require fewer injections and produce fewer adverse events. In a meta-analysis examining hospitalized medical patients receiving thromboprophylaxis, compared to control, LMWH was associated with a much lower risk of deep vein thrombosis (DVT), fewer injection site hematomas, and no differences in bleeding when compared with UFH.(31) In this analysis of 36 studies, compared with the control, UFH was also associated with a reduced risk of deep venous thrombosis (DVT) (RR=0.33; 95% CI, 0.26-0.42) and pulmonary embolism (RR, 0.64; 95% CI, 0.50-0.82), as was LMWH (RR, 0.56; 95% CI, 0.45-0.70; and RR, 0.37; 95% CI, 0.21-0.64, respectively). Neither UFH nor LMWH reduced mortality.

When directly compared with UFH, LMWH was associated with a lower risk of DVT (RR, 0.68; 95% CI, 0.52-0.88) and injection site hematoma (RR, 0.47; 95% CI, 0.36-0.62), but no difference was seen between the 2 agents in the risk of bleeding or thrombocytopenia. The authors concluded that while both UFH and LMWH do reduce venous thromboembolic risk in hospitalized medical patients, neither agent altered mortality. When directly compared, LMWH was more effective in preventing DVT.

An updated Cochrane review published in April 2017 was identified which examined LMWH vs. UFH in patients after surgery. (32) In this update, 3 trials involving 1398 postoperative participants were included. Participants had been through major and minor general surgical procedures. LMWH may result in lower risk of HIT compared with UFH (RR=0.23, 95% CI 0.07 to 0.73); low-quality evidence. The NNT for an additional beneficial outcome (NNTB) was 59. Risk of HIT may be reduced comparing participants undergoing major surgical procedures and treated with LMWH or UFH (RR 0.22, 95% CI 0.06 to 0.75); low-quality evidence. The occurrence of HIT complicated by venous thromboembolism may be lower in participants receiving LMWH compared with UFH (RR 0.22, 95% CI 0.06 to 0.84); low-quality evidence. The NNTB was 75. There were no amputations or deaths documented. Although limited evidence is available, it appears that HIT induced by both types of heparins is common in people undergoing major surgical procedures (incidence greater than 1% and less than 10%).

Another Cochrane review published in 2017 examined the effectiveness of LMWH for the prevention of venous thromboembolism in patients with lower-limb immobilization in an ambulatory setting.(5) This review did not however compare head to head a LMWH vs. UFH. Eight studies were included with a total of 3680 participants. Incidence of DVT was 4.3% to 40% in patients who had a leg injury that had been immobilized in a plaster cast or a brace for at least one week, and who received no prophylaxis, or placebo. “This number was significantly lower in patients who received daily subcutaneous injections of LMWH during immobilization, with event rates ranging from 0% to 37% (OR 0.45, 95% confidence interval (CI) 0.33 to 0.61, moderate-quality evidence). Comparable results were seen in the following groups of participants: patients with below-knee casts, conservatively treated patients (non-operated patients), operated patients, patients with fractures, patients with soft-tissue injuries, and patients with distal or proximal thrombosis. No clear differences were found between the LMWH and control groups for pulmonary embolism (OR 0.50, 95% CI 0.17 to 1.47, low-quality evidence). The studies also showed less symptomatic VTE in the LMWH groups compared with the control groups (OR 0.40, 95% CI 0.21 to 0.76; with minimal evidence of heterogeneity: I^2 = 16%, P = 0.31; six studies; 2924 participants; low-quality evidence). One death was reported in the included studies, but no deaths due to pulmonary embolism were reported. Complications of major adverse events were rare, with minor bleeding the main adverse events reported”.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	Indication – Prophylaxis in medical patients and treatment of venous thromboembolism: Evidence from the 2017 Cochrane Review which included 29 studies illustrates that fixed dose LMWH reduced the incidence of recurrent thrombotic complications and occurrence of major haemorrhage during initial treatment; and fixed dose LMWH reduced thrombus size when compared to UFH for the initial treatment of VTE. There was no difference in overall mortality between participants treated with LMWH and those treated with UFH (moderate quality evidence).(3) Indication – Acute Coronary Syndromes: Patients with ST-segment elevation myocardial infarction treated with fibrinolysis and LMWH seem to have a lower incidence of death or non-fatal recurrent myocardial infarction than those treated with fibrinolysis and UFH. (17) Similarly, in unstable angina/non-ST-segment elevation myocardial infarction, LMWH therapy reduced the incidence of death, myocardial infarction, or urgent revascularization when compared to UFH.(18) **NICE Guideline:** Overall the guidelines recommend use of LMWH as first line agents for treatment and prevention of VTE.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	In an updated Cochrane review that included 3 trials involving 1398 postoperative participants, pooled analysis showed lower incidence of HIT, and HIT complicated by venous thromboembolism, in postoperative patients undergoing thromboprophylaxis with LMWH compared with UFH. The risk of HIT in people undergoing major surgical procedures was also lower when treated with LMWH compared to UFH (low quality evidence).(32)
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [x] No [ ] List the members of the group. Other LMWH: Enoxaparin OR fondaparinux OR dalteparin OR nadroparin List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: Enoxaparin and fondaparinux are the current therapeutic alternatives licensed and available in South Africa. References: South Africa Medicines Formulary (SAMF), 2016 edition
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	

RESOURCE USE	**How large are the resource requirements?** More intensive: x Less intensive: Uncertain:	Cost of medicines/dose: **Medicine** / **Cost (ZAR)** Enoxaparin 40mg/0.4ml, prefill: 31.30* Enoxaparin 60mg/0.6ml, prefill: 47.68* Enoxaparin 80mg/0.8ml, prefill: 53.66* Enoxaparin 100mg/ml, 1ml: 192.55* Heparin 1000IU/ml 5 ml: 19.21* Heparin 5000IU/ml 5 ml: 35.57* Fondaparinux 2.5mg/0.5ml: 133.22** Fondaparinux 5mg/0.4ml: 157.77** Fondaparinux 7.5mg/0.6ml: 226.20** Fondaparinux 10mg/0.8ml: 294.62** Dalteparin 2500IU/0.2ml: 75.22** Dalteparin 5000IU/0.2ml: 105.41** Dalteparin 12500IU/0.5ml: 259.05** Dalteparin 15000IU/0.6ml: 302.48** Dalteparin 18000IU/0.72ml: 354.61** Nadroparin 1900IU/0.2ml: 40.36** Nadroparin 2850IU/0.3ml: 56.48** Nadroparin 3800IU/0.4ml: 72.27** Nadroparin 5700IU/0.6ml: 103.87** Nadroparin 7600IU/0.8ml: 134.91** Nadroparin 9500IU/1ml: 163.41** *Contract circular RT289-2019 **SEP database 21 December 2018 **Additional resources:** CEAs for fondaparinux vs UFH and enoxaparin for VTE (treatment and prophylaxis) and ACS. Accessible at: www.health.gov.za
EQUITY	**Would there be an impact on health inequity?** Yes: No: x Uncertain:	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: No: Uncertain: x	The current response is uncertain though it could be more feasible and easier – as administration and monitoring is simpler. Also availability of UFH needs to considered.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	**X**	☐

Recommendations: Based on this evidence review, the Adult Hospital Level Committee reccommends that:

- LMWH preparations be reccomended as the preferred therapeutic agent of choice versus UFH for the following indications:
  - VTE prophylaxis after major surgery.
  - VTE prophylaxis for hospitalised medically ill patients with prolonged immobilization; but that criteria for management with LMWH be clearly defined using an appropiate risk scoring tool.
  - Tretament of VTE (from proximal DVT to pulmonary embolism).
  - Acute coronary syndromes (unstable angina or non-ST segment elevation MI).
- In renal impairment the dose of LMWH should be reduced based on locally agreed protocols (see Appendix A which describes dosing issues).
- LMWH dosing for VTE treatment recommended as either once daily or twice daily - see Appendix A.
- LMWH recommended as a therapeutic group for specific indications (medicines in the group includes enoxaparin, dalteparin, fondaparinux and nadoparin) – see Appendix B.

Rationale:

- Compared with UFH, LMWH preparations are at least as effective and as safe as classic intravenous heparin therapy and have the advantage of being more convenient to administer.
- The simplified therapy provided by LMWH may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting.
- The LMWH have greater convenience in the ability to administer by subcutaneous injection without laboratory monitoring and the possible associated cost reduction resulting from reduced hospital stay and also a lower incidence of HIT.
- LMWHs appear to be as safe and effective as UFH for the treatment of venous thrombosis and pulmonary embolism and at least as safe and effective as UFH for the treatment of patients with unstable angina.
- Availability of UFH: Heparin 25000 IU/ml has recently been discontinued from the South African market.
- While the Fixed-Dose Heparin (FIDO) RCT suggested that fixed-dose, weight-adjusted S.C. UFH, without PTT monitoring, was comparable to fixed-dosed, unmonitored S.C; this may not be generalisable to the South African population (public sector patients with VTEmay have multiple co-morbidities, are thinner and younger than the study participants). (33)

Level of Evidence: I non-inferiority RCTs and Systematic Reviews

Other factors and considerations:

- Cost
- Within class therapeutic alternatives – refer to Appendix B

NEMLC MEETING OF 27 SEPTEMBER 2018, 21 FEBRUARY 2019 AND 28 SEPTEMBER 2019:
NEMLC accepted the recommendations proposed above, noting that enoxaparin could be dosed daily for treatment of VTE and that a risk scoring tool will be included in the Standard Guidelines to guide management of VTE prophylaxis in hospitalised medically ill patients.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status:

Vital	Essential	Necessary
	x	

Monitoring and evaluation considerations

Research priorities
Dosing issues in Pregnancy, Obesity and Renal failure.

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APPENDIX A

Overview of the dosing of fixed dose of subcutaneous LMWH (LMWH) for the treatment of venous thromboembolism (VTE)

Enoxaparin (a low molecular weight heparin) is indicated for the prevention and treatment of venous thromboembolism. In venous thromboembolism (VTE), it is uncertain if enoxaparin should be given twice or once daily. A number of current guidelines recommend once or twice daily administration of Enoxaparin for the treatment of VTE. (1)(2)(3)(4) The American College of Chest Physicians (ACCP) guidelines suggest once daily over twice daily administration (Grade 2C), but this recommendation only applies when the approved once daily regimen uses the same daily dose as the twice daily regimen (i.e. the once daily injection contains twice the dose of each twice daily injection). (3) However for enoxaparin, the once daily dose is a dose only 50% (1.5 mg/kg) higher than each twice daily injection (1.0 mg/kg).

Purpose /Objective of Rapid Review: To compare the efficacy and safety of once vs. twice daily administration of LMWH for the prophylaxis and treatment of venous thromboembolism.

Population	Adult patients who are eligible for prophylaxis and treatment of venous thromboembolism using LMWH
Intervention	Once daily - LMWH
Comparison	Twice daily - LMWH
Outcomes	Efficacy (recurrent venous thromboembolism, Mortality) and Safety (major haemorrhagic events)

Methods

a. **Data sources:** The following databases were searched, PubMed (via the PubMed/MEDLINE interface using the "PICO" option) and Cochrane (via The Cochrane Library using MeSH terms and qualifiers). See search strategy adapted from a Cochrane meta-analysis below.

Search Criteria

The search strategy was adapted from the updated 2013 Cochrane Review on once vs. twice daily enoxaparin for initial treatment of venous thromboembolism.(5). We restricted the search to only RCTs and Systematic Reviews/Meta-analysis comparing once vs. twice daily LMWH in treatment of VTE.

Summary of Evidence

No additional meta-analysis was retrieved. Five studies were included in 2013 Cochrane review with a total of 1508 participants. (6–10) One of the five included studies included people with PE and DVT. (10) The other four studies included only people with DVT. The five included studies used four brands of LMWH, namely, enoxaparin, tinzaparin, dalteparin and nadroparin. The pooled findings are shown below;

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent thromboembolic events	3	1281	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.39]
2 Haemorraghic events	5	1508	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.40, 1.45]
3 Improvement of thrombus size	2	107	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.66, 3.01]
4 Mortality	4	1421	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.62, 2.08]

The authors found no statistically significant difference in efficacy and safety. This systematic review concluded that once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH at least in the short term. Of note, no data was available on the effect of dosing frequency on long-term recurrent thromboembolic events.

An additional study was retrieved to those included in the 2013 Cochrane Review.(11) The summary ls is shown below.

Author, Year	No. of participants, Follow-up	Population	LMWH	Key Results
Pannucci, 2018	94 vs. 118 (212 ppts), 90 days	Data from 2 trials of different enoxaparin doses compared	Enoxaparin	-twice daily dosing was superior VTE risk reduction to once daily dosing (0% vs. 5.3%, p=0.012) -twice daily dosing increased clinically relevant bleeding but differences were not significant (6.8% vs. 3.2%, p=0.25)

However, this was not study designed to compare the two different dosing strategies, but a comparison of two RCTs that use two different doses. Larger well-designed RCTs are required to test the equivalence of once daily vs. twice daily LMWH in the treatment of VTE.

The current data does not demonstrate compelling evidence to support one strategy over the other. Clinicians may consider patient convenience and cost in making a decision.

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APPENDIX B

Comparison of therapeutic alternatives of LMWHs

INDICATION	*THERAPEUTIC ALTERNATIVE OF LOW MOLECULAR WEIGHT HEPARINS*
VENOUS THROMBOEMBOLISM PROPHYLAXIS	
a) DVT prophylaxis in medically ill patients	Enoxaparin 40 mg SC daily **OR** Dalteparin 0.2 ml SC daily **OR** Nadroparin 0.3ml SC daily
b) DVT prophylaxis in surgical patients: Higher-risk procedures (major surgery) with no patient-related risk factors OR low-risk procedures with additional patient-related risk factors	Enoxaparin 40 mg SC daily **OR** Dalteparin 0.2 ml SC daily **OR** Nadroparin » Abdominal surgery: 0.3 ml SC 2 hours pre-operatively and 8 hours after surgery, followed by 0.3ml daily for 7 days » Knee and hip replacement surgery: 38 anti-Xa units/kg SC 12 hours pre-operatively and repeat 12 hours after surgery and daily on days 1-3, with 57 anti-Xa units/kg sc from day 4 for a minimum of 10days
c) DVT prophylaxis in surgical patients: Higher-risk procedures (major surgery) with additional patient-related risk factors OR very high-risk procedures (orthopaedic or trauma surgery)	Enoxaparin 40 mg SC daily **OR** Dalteparin 0.4 ml SC daily **OR** Nadroparin: » Abdominal surgery: 0.3 ml SC 2 hours pre-operatively and 8 hours after surgery, followed by 0.3 ml daily for 7 days » Knee and hip replacement surgery: 38 anti-Xa units/kg SC 12 hours pre-operatively and repeated 12 hours after end of surgery and daily on days 1 - 3, with 57 anti-Xa units/kg sc daily from day 4 for a minimum of 10 days **OR** Fondaparinux 2.5mg SC daily
TREATMENT OF VENOUS THROMBOEMBOLISM	
a) Treatment of VTE	The following medicines should be given for at least 5 days: Enoxaparin 1 mg/kg SC twice daily or 1.5mg/kg SC daily **OR** Nadroparin 0.1 ml/10 kg SC twice daily **OR** Dalteparin 100 anti-Xa U/kg SC twice daily **OR** Fondaparinux: » Weight to 50 kg: 5 mg SC every 24 hours » Weight 50–100 kg: 7.5 mg SC every 24 hours » Weight 101 kg and above: 10 mg every 24 hours
b) Acute coronary syndrome (ACS)*	
• Unstable angina and non-ST segment elevation MI	• Enoxaparin 1 mg/kg SC every 12 hours usually for 2–8 days
• Acute STEMI in patients	• <75 years of age: Initially 30 mg IV, followed by 1 mg/kg for 1 dose, then 1 mg/kg SC every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only

	• ≥75 years of age: 0.75 mg/kg SC every 12 hours (no bolus) (max. per dose 75 mg), maximum dose applies for the first two doses only
OTHER CONSIDERATIONS	
a) General	» The duration of treatment needs to be individualised according to the patient's thromboembolic risk level » Warfarin should be started at a dose of 5 mg orally daily from day 2 of anticoagulation. NOTE: The practice of giving a loading dose' has been discontinued. » The INR should be measured 2 - 3 days after starting warfarin and then daily, with dose adjustments to achieve a therapeutic range of 2 - 3 (for most indications). » LMWH must be given for at least 5 days even if the INR has reached the therapeutic level. » LMWH can be discontinued once the INR has been in the therapeutic range for 2 consecutive days. » For massive thrombosis or PE, LMWH should be given for 7 - 10 days. » For massive PE, thrombolytic therapy is indicated in the presence of haemodynamic compromise *(Adapted SASTH guideline, 2013)*
b) Renal impairment	» Risk of bleeding increased; reduce dose if eGFR < 30 mL/minute/1.73 m2. » Use of UFH may be preferable.

* For anticoagulation in Acute Coronary Syndromes, European Guidelines mentions that enoxaparin is the most studied LMWH and for which there is the most clinical experience and enoxaprin is recommended as the LMWH option for ACS.

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