South African National Essential Medicines List
Adult Hospital Medication Review Process
COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSES
Fondaparinux for the treatment of **Non-ST Elevation Myocardial Infarction**
in the South African public health system.

Date: January 2019

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Conflict of Interest: None declared.

1. INTRODUCTION

Medication: Fondaparinux sodium (fondaparinux), 2.5mg/0.5mL; 5mg/0.4mL; 7.5mg/0.6mL; 10mg/0.8mL

Background:
A motivation was submitted by the Western Cape Provincial Pharmaceutics and Therapeutics Committee to consider fondaparinux sodium as an alternative to either unfractionated heparins (UFH) and low molecular weight heparins (LMWH) to the Adult Hospital Expert Review Committee (AH-ERC) of the National Essential Medicines List Committee[1]. The indications included treatment of Acute Coronary Syndromes (ACS), prophylaxis for venous thrombosis treatment of venous thromboembolism in adults. Thus, technical support was requested from Supply Chain Technical Assistance (SCTA), USAID for a costing analysis on fondaparinux sodium (including cost-effectiveness, budget impact analyses and international price comparison analyses) compared to LMWH, enoxaparin and UFH, currently recommended in the Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicine List (EML)[2].

This costing analysis attempts to make reasonable estimations of the budget impact and cost-effectiveness of the use of fondaparinux in the treatment of Non-ST-Elevation Myocardial Infarction (NSTEMI) compared to existing treatments in the South African public health system. The report is developed for consideration by the Adult Hospital Evidence Review Committee (AH-ERC) and the National Essential Medicines List Committee (NEMLC), and is intended to aid consideration of the listing of

[1] Minutes of the Adult Hospital Level meetings, 26 October 2017 and 23 November 2017.
[2] Adult Hospital Level STGs and EML, 2015.

fondaparinux on in the Adult Hospital Standard Treatment Guideline (AHSTG) and the National Essential Medicines List (EML).

Based on current procurement volumes, it is estimated that 70,000 patients annually receive treatment for NSTEMI with the existing treatments (enoxaparin or unfractionated heparin) in the public health system. The authors were unable to find accurate estimations of the incidence of NSTEMI in South Africa. In England, the estimated incidence of hospitalised NSTEMI cases is 0.3% of total population annually[3], applying this to the South African population who access the public sector would result in approximately 140,000 patients annually.

Concurrent to this assessment, the use of fondaparinux is also being considered in the treatment and prophylaxis of (Venous thromboembolism) VTE and ST-Elevation Myocardial Infarction (STEMI). Although these concurrent analyses also consider the use of fondaparinux, they involve different patient populations, underlying clinical evidence, dosing regimens, and have differing cost and cost-effectiveness outcomes. The recommendations following the different analyses should therefore be considered independent to one another.

2. INDICATIONS

Fondaparinux is an anticoagulant medication registered by the Medicine Control Council (MCC) and is currently available for use in South Africa. The MCC-licenced indications for fondaparinux and comparators unfractionated heparin (UFH) and enoxaparin related to treatment of NSTEMI are listed in table 1. UFH is not licensed by the MCC for treatment of NSTEMI, although it is routinely used in South African clinical practice for this indication.

UFH	Enoxaparin	Fondaparinux
Not indicated	To reduce the risk of ischaemic complications of unstable angina or non-Q-wave myocardial infarction, within 24 hours of onset, combined with aspirin for 8 days, or until stabilisation, revascularisation or discharge from hospital.	Treatment of Unstable Angina (UA)/NSEMI ACS for the prevention of death, myocardial infarction and refractory ischaemia.

Table 1 MCC licenced indications for enoxaparin, heparin and fondaparinux in treatment of NSTEMI (as of February 2018, text extracted from product package inserts. [4],[5],[6])

Fondaparinux is being considered in the treatment of NSTEMI as indicated in the AH-STG for enoxaparin or UFH. The Adult Hospital Level Committee considered the evidence submitted for fondaparinux for treatment of STEMI as described in section 4: Clinical inputs.

Chapter of AH STG	Disorder	Indication
3. Cardiovascular	3.2.2 Non-ST Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA)	Anticoagulation treatment: For NSTEMI and UA (also for STEMI not given thrombolytic therapy)

Table 2. Listed indications and dosage for enoxaparin and UFH: South African National Standard Treatment Guidelines (Adult Hospital Level STGs and EML, 2015)

[3] National Institute for Health and Care Excellence (NICE), 2014. Briefing Paper Quality Standards and Indicators, Acute Coronary Syndromes
[4] South African package insert and patient information leaflet for fondaparinux sodium: Pharmacare Limited Arixtra (hard copy)
[5] South African package insert and patient information leaflet for enoxaparin sodium: Sanofi-Aventis Clexane (hard copy)
[6] South African package insert and patient information leaflet for heparin sodium: BODENE PTY (LTD) Heparin sodium-fresenius (http://home.intekom.com/pharm/intramed/heparin.html)

3. METHODS

The approach to the assessment is informed by the methodological principles detailed in the International Decision Support Initiative Reference Case[7] and the South African Guidelines for Pharmacoeconomic Analysis[8]. The methodological approach is also informed by previous approaches to costing analysis to support EDP Medicine Reviews and discussion with EDP team (T Leong) and ERC Lead Reviewers (Prof P Commerford and Dr R Griesel).

The assessment involved a cost effectiveness analysis (CEA) and a budget impact analysis (BIA) compared to existing treatments as detailed in table 3.

Indication	Population	Intervention	Comparator	Outcomes	Perspective
Treatment of ACS	Adult patients admitted for management of NSTEMI/UA	fondaparinux	*Base case:* enoxaparin *Additional* UFH	• Major bleed • Myocardial infarction • Deaths averted • QALYs gained • Total cost to health system (annual and 5-year NPV) • Recommended national tender price for fondaparinux	South African national public health system

Table 3. Summary of approach to analyses

A decision analytic model was developed that estimated the likely clinical outcomes and costs associated with using fondaparinux compared to either enoxaparin or UFH in the treatment of NSTEMI in patients admitted with a confirmed diagnostic of NSEMI (figure 1). Effects and costs were estimated for the immediate treatment period, and extrapolated over a lifetime. The model consists of a decision tree for the initial inpatient stay where either fondaparinux, enoxaparin or UFH is administered. During admission, patients are at risk of a major bleed and/or a MI event. To capture progression following discharge, a Markov-model was developed where each year, patients will move into either a state of otherwise well following the ACS event (survive) or die. The Markov model is then run for 50 years, at which time all patients will have died as a result of expected mortality across the population, or as a result of complications from MI or major bleed.

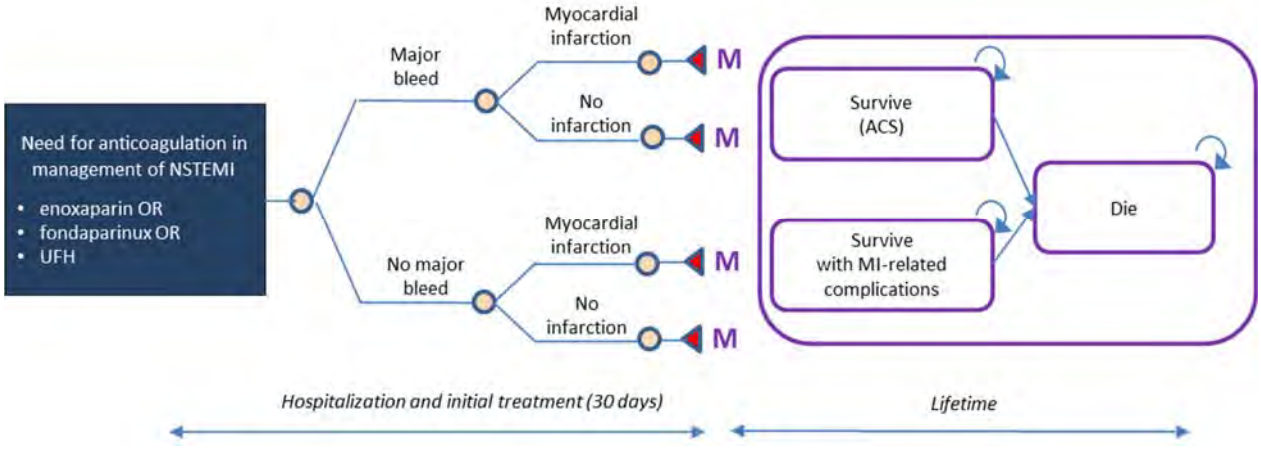

Figure 1. Decision analytic model structure to estimate cost effectiveness of fondaparinux in treatment of NSTEMI

[7] Wilkinson T, Sculpher MJ, Claxton K, Revill P, Briggs A, Cairns JA, Teerawattananon Y, Asfaw E, Lopert R, Culyer AJ, Walker DG. The international decision support initiative reference case for economic evaluation: an aid to thought. Value in Health. 2016 Dec 1;19(8):921-8..
[8] Guidelines for PharamcoEconomic Analysis 2012. National Department of Health, South Africa (the guidelines apply to analysis conducted to inform pharmaceutical pricing regulations in the South African private sector (the Single Exit Price), and so are partially applicable for public sector decision making.

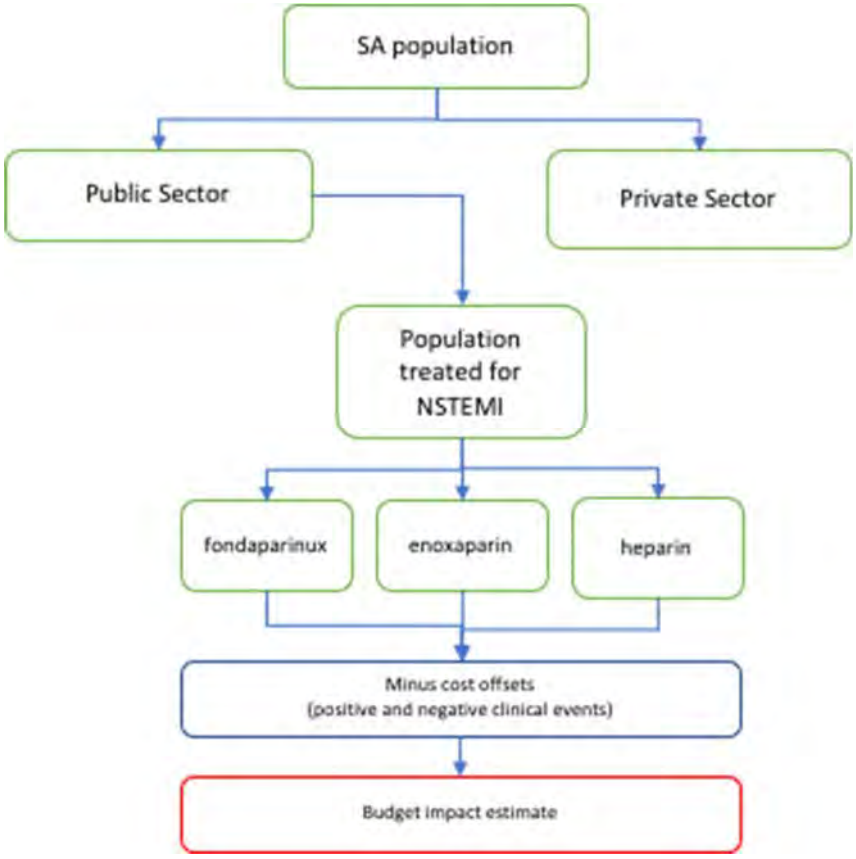

Figure 2. Framework to estimate budget impact of introducing fondaparinux to the South African public health system in Treatment of NSTEMI

A budget impact analysis was developed to explore the likely costs to the South African public health system of introducing fondaparinux as an option for the treatment of NSTEMI as an alternative to UFH or enoxaparin. The budget impact estimate is based on the net annual cost if the entire existing patient population who are currently accessing treatment of NSTEMI were switched to fondaparinux. In reality, local prescribing and market supply would result in a proportion of the market switching from either UFH or enoxaparin to fondaparinux, however the presentation of this extreme scenario is likely to provide some indication of the expected upper limit of the budget impact at a national level. In addition, the budget impact represents only those patients who would access the public health system, and is modified by those who are likely to access treatment, as informed by existing volumes of enoxaparin treatment-doses procured under national tender. Cost offsets such as “reduced need for management of complications related to major bleed” and “cases of MI” is then added to the budget impact to represent the final result, with key assumptions tested in sensitivity analyses.

4. Clinical Inputs

A motivation was submitted by the Western Cape Provincial Pharmacy and Therapeutics Committee (Appendix I). The key trials are detailed in Table 4.

Where clinical inputs were unavailable or not applicable, expert opinion from ERC committee members, Prof P Commerford and Dr R Griesel, was used (Refer to Appendix IV for declared conflicts of interests).

First author, publication year	Study type	Main Study Findings
Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes (Review). Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007038.	Systematic Review	Review of 4 trials involving 27,976 subjects. Fondaparinux reduced all-cause mortality at 30 and 180 days and had reduced incidences of major and minor bleed.
Yusuf, S., S. R. Mehta, S. Chrolavicius, R. Afzal, J. Pogue, and C. B. Granger. "Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes." *N Engl J Med* 354, no. 14 (2006): 1464-1476.	Results from Clinical Trial	Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity.
Permsuwan, Unchalee, Nathorn Chaiyakunapruk, Surakit Nathisuwan, and Apichard Sukonthasarn. "Cost-effectiveness analysis of fondaparinux vs enoxaparin in non-ST elevation acute coronary syndrome in Thailand." *Heart, Lung and Circulation* 24, no. 9 (2015): 860-868.	Cost-Effectiveness Analysis	Fondaparinux is a cost-effective alternative to enoxaparin for NSTE-ACS based on Thailand's context. Importantly, the clinical outcomes associated with ACS used in the evaluation was informed by local Thai registries rather than the OASIS trial.

Table 4. Pivotal trials and reviews – treatment of NSTEMI

The main clinical effects for consideration in the treatment decision analytic model include any differences in the risk associated with receiving treatment with either fondaparinux, enoxaparin or UFH relating to progression to a MI, suffering a major bleed, and death (Table 5).

Description	Value	Lower value	Upper value	Source
Probability of MI fondaparinux	0.038	0.03	0.05	Brito et al
Probability of MI enoxaparin	0.038	0.03	0.05	Brito et al
Probability of MI UFH	0.038	0.03	0.05	Brito et al
Probability of Major Bleed fondaparinux	0.031	0.02	0.04	Brito et al
Probability of Major Bleed enoxaparin	0.05	0.04	0.06	Brito et al
Probability of Major Bleed UFH	0.033	0.02	0.04	Brito et al
Probability of death with MI	0.29	0.22	0.36	Clinical expert advisory
Probability death with Major Bleed	0.1	0.08	0.13	Clinical expert advisory

Table 5. Key clinical inputs

Utilities

The long-term impact of outcomes associated with treatment for NSTEMI are calculated by applying an annual estimate of the health-related quality of life that is associated with surviving post the ACS event, with and without reinfarction occurring. The annual utilities accrued to a patient with ACS are detailed in table 6, with death incurring no utility.

Parameter	Value	Lower value	Upper value
Survival (post ACS event)	0.605	0.575	0.635
Survival with MI complications	0.605	0.575	0.635
Death	0	0	0

Table 6. Markov state utilities

State transition probabilities

The state transition probabilities are calculated from clinical inputs listed in table 5 and determine the chance that a patient will move from one state to another over time. The probabilities are shown in table 7. For example, each year a patient who is in the Survival (post ACS) state will either remain in that state (a 0.907 probability), will progress to an MI (Survival with MI complications, 0.038 probability), or will die (0.055 probability).

	Survival (post ACS)	Survival with MI complications	Dead
Survival (post ACS)	0.907	0.038	0.055
Survival with MI complications	0	0.916	0.084
Dead	0		1

Table 7. Transition probabilities between long-term Markov states

The central assumptions for the model are that

- Patient enters Markov transition model after completion of treatment.
- Each transition state has a one year cycle length.
- A patient does not experience any long-term complications as a result of a major bleed – the negative health effects of the major bleed are experienced immediately during hospital stay and the patient will either recover or die at that point.
- Although suffering a myocardial infarction will have an additional mortality effect, it will not have a morbidity effect over and above the expected quality of life for a generalised ACS patient. Therefore, if a patient survives the NSTEMI episode, their quality of life will be the same whether they experienced a myocardial infarction in hospital or not.
- As there was no evidence to show a significant difference in risk of MI between the agents, the baseline risk of MI across the Brito et al systematic review was applied to fondaparinux,

5. Cost Inputs

The main cost effects included in the treatment decision analytic model were associated with procurement costs of the different anticoagulants and hospital costs associated with management of MI and major bleed. The central costing parameters were drawn from the Pharmaceutical tenders for the State sector, the Uniform patient fee schedule (2017), national staff payment schedules, and previous NEMLC approved costing analyses[9].

Fondaparinux is not currently on the EML thus there is no comparative contract price however utilising the comparison from the table below, an estimate of 20% was applied to determine the potential estimated price (refer to the international pricing analysis report for details).

[9] Rivaroxaban for stroke prevention in atrial fibrillation – Pharmacoeconomics and budget impact analysis 2015 (Appendix II)

Table 8 and 9 below show the Single Exit Price and International Average price by formulation for enoxaparin and fondaparinux respectively. Table 8 also shows the current national contract price for enoxaparin and Table 9 shows the "estimated price" of fondaparinux used in this analysis that may be achieved if fondaparinux was listed on national contract.

Enoxaparin	Formulation	Contract Price (South Africa)	SEP (South Africa)	International Average
Prophylaxis	40mg/0.4mL	R 27.70	R 206.41	R 41.97
Treatment	60mg/0.6mL	R 84.40	R 394.08	R 120.06
	80mg/0.8mL	R 88.66	R 352.98	R 149.31
	100mg/1mL	NA	R 317.74	R 171.21

Table 8. Comparison of contract price, single exit price and international average ex-manufacturer's price for enoxaparin formulations (average daily cost)

Fondaparinux	Formulation	Estimated Price	SEP (South Africa)	International average
Prophylaxis	2.5mg/0.5mL	R 41.59	R 207.91	R 158.06
Treatment	5mg/0.4mL	R 63.34	R 316.70	R 194.05
	7.5mg/0.6mL	R 63.34	R 316.70	R 319.10
	10mg/0.8mL	R 63.34	R 316.70	R 576.29

Table 9. Comparison of contract price, single exit price and international average ex-manufacturer's price for fondaparinux formulations (average daily cost)

Description	Value	Lower value	Upper value	Source
Once-off Costs (Decision Tree)				
Treatment costs of enoxaparin per patient	R 449.87	R 337	R 562	Contract Circular[10] HP06-2017SVP
Treatment costs of fondaparinux per patient	R 231.90	R 173	R 290	See Tables 9 -11
Treatment costs of UFH per patient	R 449.70	R 337	R 562	Contract Circular HP06-2017SVP
Cost of treating a major bleed	R 11 268	R 8451	R 14085	UPFS 2017[11]
Cost of treating a MI	R 7079	R 5309	R 8849	UPFS 2017
Costs associated with a patient dying	R 368	R 276	R 460	UPFS 2017
Annual Costs (Markov Model)				
Costs of patient that survives and is post-ACS	R2000	R 1500	R 2500	NOACs costing analysis (Appendix II)

Table 10. Model cost inputs

The total administration costs for the different treatment regimens were constructed from the unit cost of the medicine, multiplied by the expected number of doses required and any applicable administration costs which were calculated on the assumption that each patient stay where the different agents were administered would require and initial three minutes doctor time to assess and prescribe, and a dispensing fee. Each administration was estimated to require two minutes of nurse time for fondaparinux and enoxaparin, and four minutes nurse time for UFH. Patients receiving UFH would also receive 24 hourly aPTT tests (at R52.48 per test, NHLS fee schedule, test code 2460) requiring an additional five minutes of doctor time to administer and interpret the test. The daily administration cost is then

[10] http://www.health.gov.za/index.php/medicine?download=2649:master-procurement-catalogue-05-february-2018
[11] South African Uniform Patient Fee Schedule. National Department of Health 2017

multiplied by the number of days treatment and added to the medicine cost for the total number of days treatment to determine the "Total Cost for treatment" in Table 11 below. The calculations for the cost workup in table 10 and 11 are available in attached Excel workbook.

Medicine	Dosage	Formulation	Unit cost	Number of units daily	Medicine cost (per day)	Administration cost (per day)	Average treatment duration (days)	Total Cost for treatment
fondaparinux	SC, 2.5mg/0.2ml daily	2.5mg	R41.58	1	R41.58	R9.95	4.5	R231.90
enoxaparin	SC, 1 mg/kg 12 hourly	80mg/0.8ml	R44.33	2	R88.66	R11.31	4.5	R449.87
UFH	IV bolus, 5 000 IU. then 1 000 IU hourly monitored by aPTT q24h	5,000IU/ml, 5 ml vial	R24.85	0.96 *(plus stat dose of 0.2 vial)*	R23.86 *(plus stat dose cost R4.97)*	R77.62	4.5	R449.70

Table 11. Total regimen costs

6. Results

a. Cost effectiveness analysis

It is estimated that listing fondaparinux would be marginally less expensive over the long term than either enoxaparin or UFH, but would generate more QALYs. As shown in table 11, and figure 3, the estimated costs and QALYs for each of the agents are similar, with fondaparinux yielding 6.40 QALYs per person and enoxaparin and UFH yielding 6.39 QALYs per person. Fondaparinux as a treatment option is estimated to be R360 and R378 cheaper than enoxaparin and UFH respectively. The price of fondaparinux used is the "estimated" price that could be achieved on national contract and is 20% of the current SEP.

Regimen	Costs	QALYs	ICER
Fondaparinux	R24,226	6.40	
Enoxaparin	R24,586	6.39	dominated
UFH	R24,604	6.39	dominated

Table 12. Summary of cost effectiveness of fondaparinux in the treatment of NSTEMI

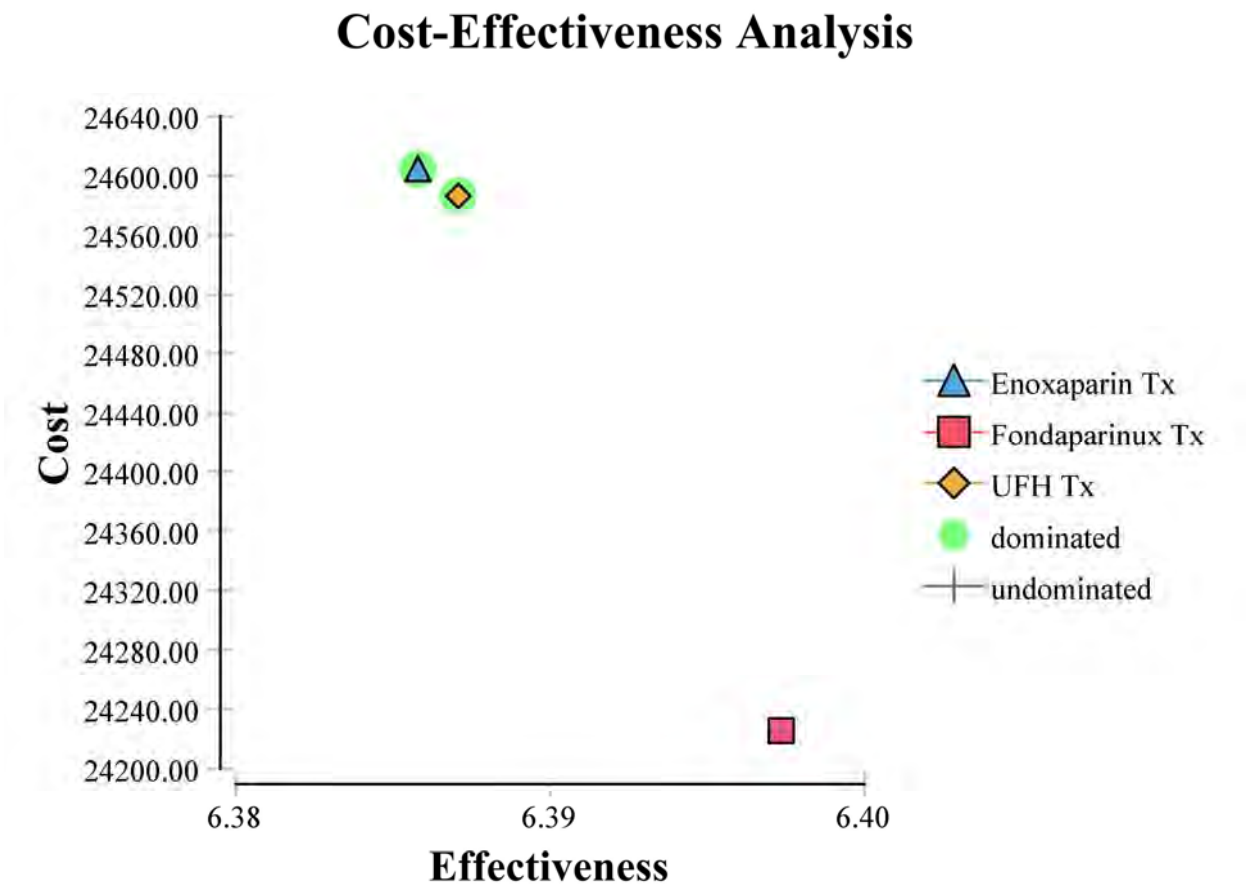

Figure 3. Cost Effectiveness plane including threshold of three treatment strategies for NSTEMI

Sensitivity analysis

One-way sensitivity analysis was conducted on the major clinical and cost parameters to generate the Tornado diagram in figure 4 (fondaparinux vs enoxaparin), and figure 5 (fondaparinux vs UFH). Each bar on the diagram represents the change in the ICER that is associated with changes in the input parameter, with inputs ranked by the magnitude of the change. The diagram below shows that ongoing costs of the costs of fondaparinux, enoxaparin and unfractionated heparin have the biggest impact on the ICER, however altering the cost of the individual medicines does not change the base case finding that fondaparinux dominates enoxaparin and unfractionated heparin.

A limitation of one-way sensitivity analysis is that parameters rarely move independently of one another (eg if the cost of managing a major bleed increases, the cost of managing a VTE is also likely to increase). More complex sensitivity analysis, (e.g. probabilistic sensitivity analysis) is beyond the scope of this assessment. However, this basic sensitivity analysis provides a general overview for key drivers of uncertainty.

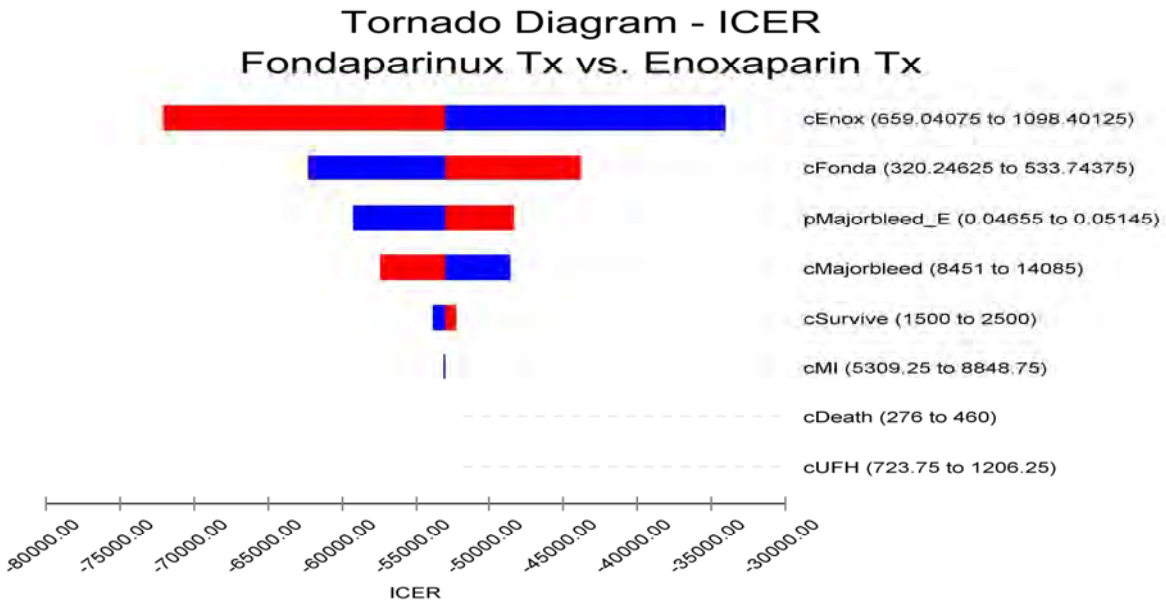

Figure 4. Tornado diagram for Fondaparinux vs. Enoxaparin

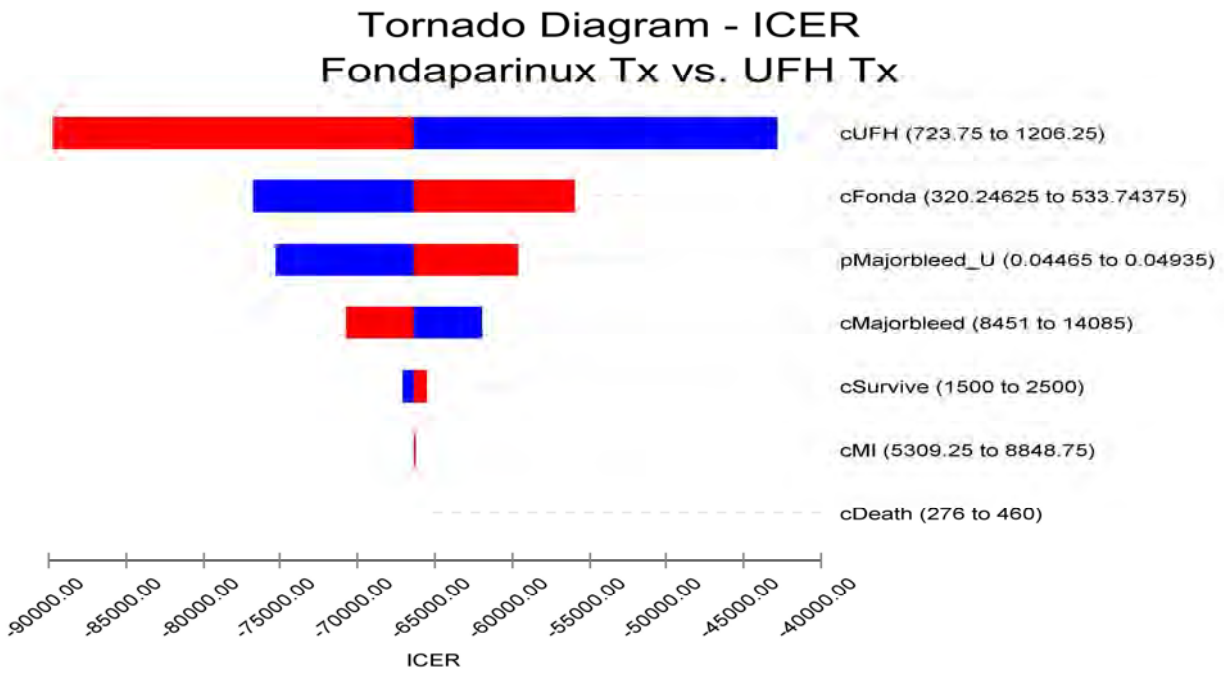

Figure 5. Tornado diagram for Fondaparinux vs. UFH

Key:	
cEnox	cost of enoxaparin
cFonda	cost of fondaparinux
cUFH	cost of unfractionated heparin
cMajor bleed	cost of major bleed
cSurvive	cost of patient surviving post ACS without complications
cDeath	cost of death (health system financial cost)
cMajorbleed	Cost of managing a major bleed
cMI	Cost of managing an MI
pDeath_F	probability of death after MI
pMajor bleed_E	Probability of major bleed with enoxaparin
pMajor bleed_U	Probability of major bleed with heparin

b. Budget Impact Analysis

Table 13 below shows the predicted annual incremental budget impact for medicine procurement only of listing fondaparinux on the EML for the management of NSTEMI at differing expected prices of fondaparinux (as a percentage of current SEP) and at differing assumed numbers of patients.

Table 14 below shows the same scenarios of pricing and patient access for the budget impact of fondaparinux incremental to enoxaparin and incremental to UFH, taking into account of the wider health system costs.

In the base case analysis used in the CEA (50% of patients accessing treatment and 20% of the SEP for the price of fondaparinux), taking into account savings from a reduction in clinical events, the use of fondaparinux in treatment of NSTEMI has an estimated incremental annual cost saving of ZAR 15.7 million compared to enoxaparin and an annual cost saving of ZAR 14.2 million compared to UFH.

	Patients accessing treatment	13,953 patients 10%		69,766 patients 50%		111,625 patients 80%	
		Enox	UFH	Enox	UFH	Enox	UFH
Price of fondaparinux/ 2.5 mg unit	100% of SEP (R207.91)	R 7 487 616	R 9 575 847	R 37 438 082	R 47 879 234	R 59 900 931	R 76 606 775
	75% of SEP (R155,93)	R 4 223 989	R 6 312 219	R 21 119 944	R 31 561 097	R 33 791 911	R 50 497 755
	50% of SEP (R103,96)	R 960 361	R 3 048 592	R 4 801 807	R 15 242 959	R 7 682 891	R 24 388 735
	20% of SEP (R41,58))	-R 2 955 992	-R 867 761	-R 14 779 958	-R 4 338 806	-R 23 647 933	-R 6 942 090
	10% of SEP (R20,79)	-R 4 261 443	-R 2 173 212	-R 21 307 213	-R 10 866 061	-R 34 091 541	-R 17 385 698

Table 13 BIA of fondaparinux incremental to enoxaparin and fondaparinux incremental to UFH at different assumptions of treatment access and fondaparinux price (medicine procurement costs only)

Key parameters driving budget impact to the South African public health system are likely to be assumptions relating to the price that can be achieved for fondaparinux, and the proportion of patients who access NSTEMI treatment.

	Patients accessing treatment	13,953 patients 10%		69,766 patients 50%		111,625 patients 80%	
		Enox	UFH	Enox	UFH	Enox	UFH
Price of fondaparinux/ 2.5 mg unit	100% of SEP (R207.91)	R 572 623	R 4 889 444	R22 860 993	R 24 445 099	R 36 577 800	R 39 112 371
	75% of SEP (R155,93)	R 4 031 165	R 4 347 986	R 20 153 858	R 21 737 965	R 32 246 369	R 34 780 940
	50% of SEP (R103,96)	R 767 342	R 1 084 163	R 3 835 678	R 5 419 785	R 6 137 188	R 8 671 759
	20% of SEP (R41,58))	-R 3 149 246	-R 2 832 424	-R 15 746 138	-R 14 162 032	-R 25 193 831	-R 22 659 260
	10% of SEP (R20,79)	-R 4 454 775	-R 4 137 954	-R 22 273 410	-R 20 689 304	-R 35 637 503	-R 33 102 932

Table 14. Incremental BIA from health system perspective of fondaparinux vs enoxaparin at different assumptions of treatment access and fondaparinux price

7. Summary of international evidence on cost-effectiveness of fondaparinux

The Canadian Agency for Drugs and Technologies in Health (CADTH) undertook a literature review in September 2015, investigating the clinical effectiveness, safety, and cost-effectiveness of enoxaparin compared to fondaparinux as first-line treatment in patients with Acute Coronary Syndrome (ACS) [12] (only studies published after 1 January 2005 were included). The CADTH review identified four relevant publications that addressed the economic and cost issues pertaining to fondaparinux and enoxaparin. Of these, one publication was a systematic review of economic evaluations based on randomised controlled trials of anticoagulants in patients with ACS[13], one was a budget impact analysis[14] and two were formal cost-effectiveness/cost-utility analyses[15,16]. The systematic review (Latour-Perez et al [2012]) included 22 economic evaluations, of which four studies compared fondaparinux to enoxaparin/bivalirudin.

A summary of the publications included in the evidence review on the cost-effectiveness of fondaparinux for ACS are described in table 13 and corresponding results shown in table 14.

[12] https://www.cadth.ca/fondaparinux-vs-enoxaparin-acute-coronary-syndromes
[13] Latour-Perez J, de-Miguel-Balsa E. Cost effectiveness of anticoagulation in acute coronary syndromes. Pharmacoeconomics. 2012 Apr;30(4):303-21.
[14] Kossovsky M, Keller PF, Mach F, Gaspoz JM. Fondaparinux versus enoxaparin in the management of acute coronary syndromes in Switzerland: a cost comparison analysis. Swiss Med Wkly. 2012;142:w13536. Available from: https://smw.ch/article/doi/smw.2012.13536
[15] Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A. Cost-effectiveness analysis of fondaparinux vs enoxaparin in non-ST elevation acute coronary syndrome in Thailand. Heart Lung Circ. 2015 Mar 14.
[16] Pepe C, Machado M, Olimpio A, Ramos R. Cost-effectiveness of fondaparinux in patients with acute coronary syndrome without ST-segment elevation. Arq Bras Cardiol [Internet]. 2012 Jul [cited 2015 Aug 7];99(1):613-22. Available from: http://www.scielo.br/pdf/abc/v99n1/en_aop05712.pdf

Title	Author	Type of Study	Year of publication
Fondaparinux versus enoxaparin in the management of acute coronary syndromes in Switzerland: a cost comparison analysis[5].	Kossovsky M, Keller PF, Mach F, Gaspoz JM.	Cost Comparison / Budget Impact analysis	2012
Cost-effectiveness analysis of fondaparinux vs enoxaparin in non-ST elevation acute coronary syndrome in Thailand[6].	Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A.	Cost-Utility Analysis	2015
Cost-effectiveness of fondaparinux in patients with acute coronary syndrome without ST-segment elevation[7].	Pepe C, Machado M, Olimpio A, Ramos R.	Cost-Effectiveness Analysis	2012
Cost effectiveness of anticoagulation in acute coronary syndromes[4].	Latour-Perez J, de-Miguel-Balsa E.	Systematic review	2012
Four studies compared fondaparinux to enoxaparin.			
1. Cost-effectiveness in France of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome: an analysis using data from OASIS-5[17]	Sculpher M, Lozano-Ortega G, Sambrook J, et al	Cost-Effectiveness Analysis	2007
2. Fondaparinux versus Enoxaparin in non–ST-elevation acute coronary syndromes: Short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial[18]	Sculpher, Mark J., Greta Lozano-Ortega, Jennifer Sambrook, Stephen Palmer, Orges Ormanidhi, Ameet Bakhai, Marcus Flather, P. Gabriel Steg, Shamir R. Mehta, and William Weintraub.	Cost-Effectiveness Analysis	2009
3. Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome[19]	Latour-Perez J, de-Miguel-Balsa E	Cost-Effectiveness Analysis	2009
4. Cost effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes[20]	Maxwell CB, Holdford DA, Crouch MA, Patel DA	Cost-Effectiveness Analysis	2009

Table 15. List of included publications investigating cost-effectiveness of fondaparinux in ACS

First author, publication year and country	Main Cost-Effectiveness Study Findings

[17] Sculpher M, Lozano-Ortega G, Sambrook J, et al. Cost-effectiveness in France of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome: an analysis using data from OASIS-5 [abstract]. Eur Heart J 2007; 28: 4804

[18] Sculpher MJ, Lozano-Ortega G, Sambrook J, et al. Fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. Am Heart J 2009 May; 157 (5): 845–52

[19] Latour-Perez J, de-Miguel-Balsa E. Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome. Pharmacoeconomics 2009; 27 (7): 585–95

[20] Maxwell CB, Holdford DA, Crouch MA, et al. Cost effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes. Ann Pharmacother 2009 Apr; 43 (4): 586–95

Kossovsky, 2012, Switzerland	At the Swiss national level, the use of fondaparinux instead of enoxaparin would generate annual savings ranging from 854,000 CHF (USD $864,000) to 3,400,000 CHF (USD $ 3,440,000) across different scenarios, mainly by reducing bleeding episodes[21]. Cost of anticoagulant therapy (three-day treatment): Fondaparinux 21.95 CHF, Enoxaparin 83.4 CHF (ratio 0.26)
Permsuwan, 2015, Thailand	Fondaparinux dominated enoxaparin from both a healthcare provider and societal perspective by costing 962 THB (USD $29.2) and 1,286 THB (USD $39.0) less than enoxaparin respectively and generating 0.04 more QALYs[22]. Cost of anticoagulant therapy (six-day treatment): Fondaparinux 1320 THB, Enoxaparin 2712 THB (ratio 0.49)
Pepe, 2012, Brazil	The cost analysis showed that treatment with fondaparinux would generate a cost saving of USD $85 per patient. The drug costs accounted for approximately 10% of the total cost, while 77% of the cost difference related to the cost of treating bleeding complications. The economic analysis showed fondaparinux dominated enoxaparin due to lower cost and greater benefit (defined as composite outcome of cardiovascular event and major bleeding)[23]
Latour-Perez, 2012, Spain	In patients with NSTE-ACS, fondaparinux is cost effective compared with enoxaparin[24].
Findings from the three economic evaluations comparing fondaparinux to enoxaparin identified in the systematic review:	
Sculpher, 2007, France	ICER for fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome was €2758/QALY. No sensitivity analysis conducted[25]. (*Could not review original publication)*
Sculpher, 2009, US	Fondaparinux would generate a cost saving of USD $547 per patient at 180 days. Sensitivity analysis suggested that savings could vary between $494 and $733. The CEA showed fondaparinux dominated enoxaparin due to lower cost and greater benefit (defined in terms of quality-adjusted life-years) under most scenarios[26]. Cost of anticoagulant therapy (total treatment): Fondaparinux USD 36.69, Enoxaparin USD 99.06 (ratio 0.37)
Latour-Perez, 2009, Spain	The economic analysis showed fondaparinux dominated enoxaparin (0.023 QALYs, cost savings of $55) and this remained unchanged in the univariate sensitivity analyses. According to Monte Carlo simulation, fondaparinux was cost saving in 99.9% of cases[27].

Table 16. Summary of findings from publications investigating cost-effectiveness of fondaparinux in ACS

8. International recommendations

National Institute for Health and Care Excellence (England and Wales)

[21] Kossovsky M, Keller PF, Mach F, Gaspoz JM. Fondaparinux versus enoxaprin in the management of acute coronary syndromes in Switzerland: a cost comparison analysis. Swiss Med Wkly. 2012;142:w13536. Available from: https://smw.ch/article/doi/smw.2012.13536

[22] Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A. Cost-effectiveness analysis of fondaparinux vs enoxaparin in non-ST elevation acute coronary syndrome in Thailand. Heart Lung Circ. 2015 Mar 14.

[23] Pepe C, Machado M, Olimpio A, Ramos R. Cost-effectiveness of fondaparinux in patients with acute coronary syndrome without ST-segment elevation. Arq Bras Cardiol [Internet]. 2012 Jul [cited 2015 Aug 7];99(1):613-22. Available from: http://www.scielo.br/pdf/abc/v99n1/en_aop05712.pdfFondaparinux

[24] Latour-Perez J, de-Miguel-Balsa E. Cost effectiveness of anticoagulation in acute coronary syndromes. Pharmacoeconomics. 2012 Apr;30(4):303-21.

[25] https://www.cadth.ca/fondaparinux-vs-enoxaparin-acute-coronary-syndromes

[26] Sculpher MJ, Lozano-Ortega G, Sambrook J, et al. Fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. Am Heart J 2009 May; 157 (5): 845–52

[27] Latour-Perez J, de-Miguel-Balsa E. Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome. Pharmacoeconomics 2009; 27 (7): 585–95

No technology appraisal conducted

Clinical Guideline CG94: Unstable angina and NSTEMI: early management

- Offer fondaparinux to patients who do not have a high bleeding risk, unless coronary angiography is planned within 24 hours of admission.
- Offer unfractionated heparin as an alternative to fondaparinux to patients who are likely to undergo coronary angiography within 24 hours of admission.
- Consider unfractionated heparin, with dose adjustment guided by monitoring of clotting function, as an alternative to fondaparinux for patients with significant renal impairment (creatinine above 265 micromoles per litre).
- Offer systemic unfractionated heparin (50–100 units/kg) in the cardiac catheter laboratory to patients receiving fondaparinux who are undergoing PCI[28].

Scottish Medicines Consortium (Scotland)

Fondaparinux is accepted for use within NHS Scotland for the treatment of UA/NSTEMI in patients for whom urgent (<120 minutes) invasive management (Percutaneous Coronary Intervention) is not indicated (it was reported that it is standard practice in South Africa to administer UFH prior to cardiac catheterization laboratory admission for a Percutaneous Coronary Intervention). Fondaparinux was shown to be non-inferior to a low molecular weight heparin in preventing death, myocardial infarction or refractory ischaemia in the nine days following onset of symptoms. Fondaparinux also had a significantly lower major bleeding event rate than a low molecular weight heparin[29].

Pharmaceutical Benefits Scheme (Australia)

- Fondaparinux not approved for ACS
- Enoxaparin is listed for all registered indications without restricted access (with exception of special restricted benefit for use in haemodialysis).

[28] National Institute for Health and Care Excellence. Clinical Guideline CG94: Unstable angina and NSTEMI: early management. 2010. https://www.nice.org.uk/guidance/cg94

[29] Scottish Medicines Consortium. Fondaparinux (Arixtra) | Unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI). 2007. https://www.scottishmedicines.org.uk/medicines-advice/fondaparinux-arixtra-fullsubmission-42007/

9. Discussion

Key limitations in the assessment include the extent to which the underlying clinical inputs are reflective of South African clinical practice and outcomes. This assessment makes a simplifying assumption that the treatment effect of fondaparinux in NSTEMI as observed in clinical trials will be broadly applicable to the South African setting.

Further, the budget impact analysis is sensitive to the proportion of patients who gain access to the health system. The base case budget impact was estimated 70,000 patients would gain access and receive treatment for NSTEMI, but this could be just 50% of patients who may benefit from treatment. Any major policy reforms that increased access to the public health system could be associated with increased usage – assuming 100% of NSTEMI patients gained access, this could represent a R60 million investment annually incremental to existing procurement costs of enoxaparin.

A key driver of costs is the assumption made around the price that is able to be achieved in a national tender for fondaparinux. The existing weighted national contract price for enoxaparin is 20% of the current Single Exist Price (SEP). A critical assumption of the base case assessment is that the National Department of Health will be able to achieve a similar reduction from the existing fondaparinux SEP when securing the national tender price of fondaparinux.

Although fondaparinux is estimated to dominate enoxaparin and UFH, the cost-effectiveness ratios were similar, mainly driven by the underlying evidence base that found difference in major bleed rate between the agents, but non-significant differences in rates of MI. In addition, the lower costs associated with once-daily administration of fondaparinux make it comparable to enoxaparin and substantially less costly than UFH.

When simply taking medicine procurement costs into account, listing fondaparinux on the EML is likely to represent a cost incremental to treating the same patients with either enoxaparin or UFH, however once the broader health system costs are considered, it is estimated to be cost saving (under most scenarios).

Published cost effectiveness analyses in other contexts have generally shown a trend towards improved costs and effects of fondaparinux over enoxaparin in ACS, however caution should be used in applying results to the South African setting, in particular where local procurement costs of fondaparinux are lower than enoxaparin (as modelled in the Thailand cost-effectiveness analysis by Permsuwan et al, 2015)

Appendix III

Main source of clinical inputs[30]:

Indication Treatment of NSTEMI

1. Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes (Review). Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007038.
    a. *Including pivotal trial:* Mehta, Shamir R., et al. "Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial." Journal of the American College of Cardiology 50.18 (2007): 1742-1751.
2. Shah S, Khajuria V, Tandon VR, Gillani ZH, Lal M. Comparative evaluation of efficacy, safety and haemostatic parameters of enoxaparin and fondaparinux in unstable coronary artery disease. J Clin Diagn Res. 2014;8(1): 31-4

References for articles included on cost-effectiveness (ACS):

1. Sculpher MJ, Lozano-Ortega G, Sambrook J, Palmer S, Ormanidhi O, Bakhai A, et al. Fondaparinux versus Enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. Am Heart J. 2009;157:845–52.
2. Latour-Perez J, De-Miguel-Balsa E. Cost Effectiveness of Fondaparinux in Non-ST-Elevation Acute Coronary Syndrome. Pharmacoeconomics. 2009;27(7):585–95.
3. Kossovsky M, Keller PF, Mach F, Gaspoz JM. Fondaparinux versus enoxaparin in the management of acute coronary syndromes in Switzerland: a cost comparison analysis. Swiss Med Wkly. 2012;142:w13536.
4. Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A. Cost-effectiveness analysis of fondaparinux vs. enoxaparin in non-ST elevation acute coronary syndrome in Thailand. Heart Lung Circ. 2015; 24:860–68.

[30] Informed by Griesel R, Ntsekhe Motivation for Application to Provincial Pharmacy and Therapeutics Committee – fondaparinux (Appendix I)

Appendix IV

Conflicts of interest declared by Adult ERC members providing clinical advice for the costing analyses; assessed by the Chairperson[31].

Committee member	Name of Organisation	Nature of what was received	Classification of COI*
Prof P Commerford	• GSK	• Served on steering committee of the trials evaluating fondaparinux (OASIS) in CV disease and was a co-author on some of the papers. My institution received payment for conducting the studies.	Clearly significant
Dr R Griesel	• UCT	• Involved in drafting the initial motivation for fondaparinux, submitted to the Western Cape PTC.	Potentially significant

[31] Minutes of the Adult Hospital Level Committee meeting, 19 April 2018