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

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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 ST-Elevation Myocardial Infarction (STEMI) 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 fondaparinux on in the Adult Hospital Standard Treatment Guideline (AHSTG) and the National Essential Medicines List (EML).

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

The authors were unable to find accurate estimations of the incidence of STEMI in South Africa. In England, the estimated incidence of hospitalised STEMI cases is 0.05% of total population [3], applying this to the South African population who access the public sector would result in approximately 23,000 patients annually. Current procurement volumes of streptokinase indicate approximately 2,000 patients are treated for STEMI within 6 hours of infarction annually, and it is estimated that a further 10,000 patients receive STEMI treatment with either enoxaparin or unfractionated heparin treatments (enoxaparin or unfractionated heparin) in the public health system

Concurrent to this assessment, the use of fondaparinux is also being considered in the treatment and prophylaxis of VTE and Non-ST-Elevation Myocardial Infarction (NSTEMI). 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 STEMI are listed in table 1. Note UFH is not licensed by the MCC for treatment of STEMI.

UFH	Enoxaparin	Fondaparinux
Not indicated	Treatment of STEMI including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).	Treatment of STEMI for the prevention of death, myocardial re-infarction in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.

Table 1 MCC licenced indications for enoxaparin, heparin and fondaparinux in treatment of STEMI (as of February 2018, text extracted from Patient Information Leaflets)

Fondaparinux is being considered in the treatment of STEMI as indicated in the AH-STG in combination with streptokinase if treated with 6 hours of infarction or instead of enoxaparin or UFH if treated after 6 hours of admission. Neither enoxaparin or UFH is listed in the current AHSTG for the treatment of STEMI, although both agents are commonly used in STEMI patients admitted more than 6 hours after infarction[4]. 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	3.2.1 ST Elevation Myocardial Infarction (STEMI)	Recommended thrombolytic: Streptokinase IV 1.5 MU (in addition to aspirin and if hypoxic, clopidogrel)

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

[3] National Institute for Health and Care Excellence (NICE), 2014. Briefing Paper Quality Standards and Indicators, Acute Coronary Syndromes
[4] Clinical Advisory meeting, 23rd March 2018 *(Attendees: Prof P Commerford, Dr R Griesel, T Wilkinson, R Rapithi, T Leong).*

3. METHODS

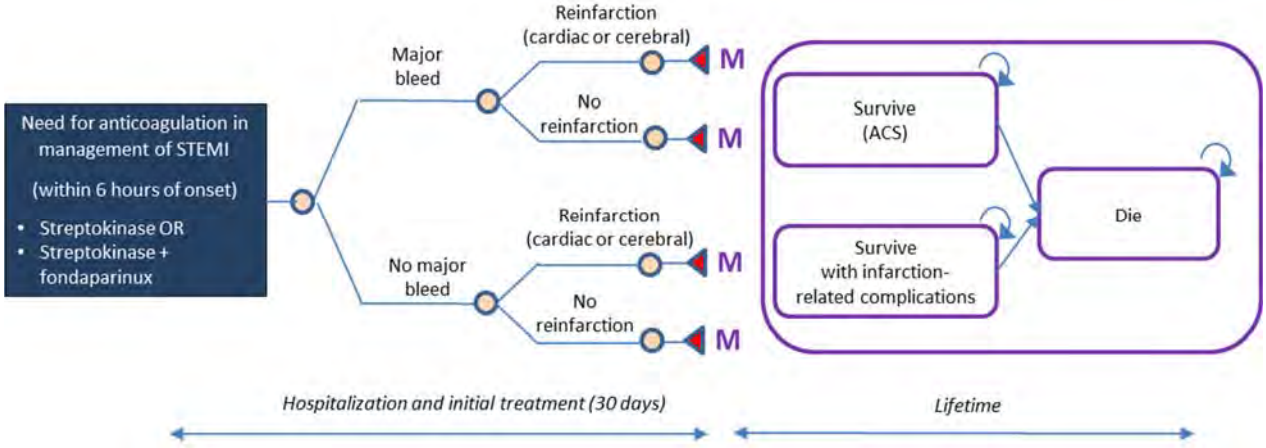
The approach to the assessment is informed by the methodological principles detailed in the International Decision Support Initiative Reference Case[5] and the South African Guidelines for Pharamcoeconomic Analysis[6]. The methodological approach is also informed by previous approaches to costing analysis 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) of fondaparinux in two treatment scenarios in the management of STEMI depending on whether or not the patient is treated within 6 hours post infarction as detailed in table 3.

Indication	Population	Intervention	Comparator	Outcomes	Perspective
Treatment of ACS	Adult patients admitted for management of STEMI within 6 hours of infarction	fondaparinux + streptokinase	Streptokinase	• Major bleed • Myocardial infarction • Death • QALYs • Total cost to health system (annual and 5-year NPV) • Recommended national tender price for fondaparinux	South African national public health system
	Adult patients admitted for management of STEMI 6+ hours after infarction	fondaparinux	*Base case:* enoxaparin *Additional* UFH		

Table 3. Summary table of approach to analyses

Two decision analytic models were developed that estimated the likely clinical outcomes and costs associated with using 1) fondaparinux with streptokinase compared to streptokinase only and 2) fondaparinux compared to either enoxaparin or UFH in the treatment of STEMI (figure 1). Effects and costs were estimated for the immediate treatment period, and extrapolated over a lifetime time horizon. The model consists of a decision tree for the initial inpatient stay where the different comparators are administered. During admission, patients are at risk of a major bleed and/or a cerebral or cardiac reinfarction. To capture progression following discharge, a Markov-model structure was developed where each year, patients will move into either a state of otherwise well following the ACS event (Survive ACS), survive with infarction-related complications, or die. The Markov model is then run for 50 years, at which time all patients will have assumed to have died as a result of natural expected mortality rate across the population, or as a result of complications from infarction or major bleed.



[5] 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..

[6] 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 1. Decision analytic model structure to estimate cost effectiveness of fondaparinux in treatment of STEMI (within 6 hours of infarction)

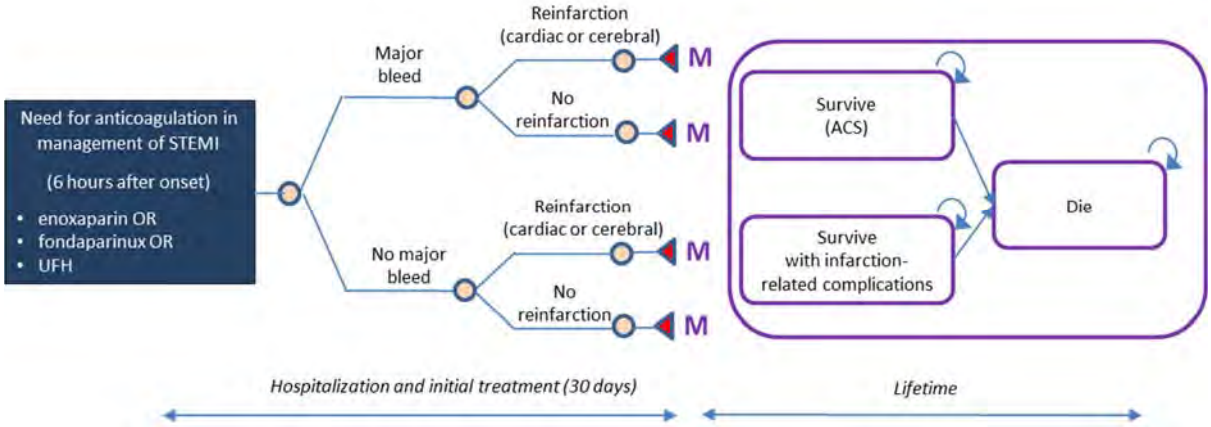


Figure 2. Decision analytic model structure to estimate cost effectiveness of fondaparinux in treatment of STEMI (6 hours after infarction)

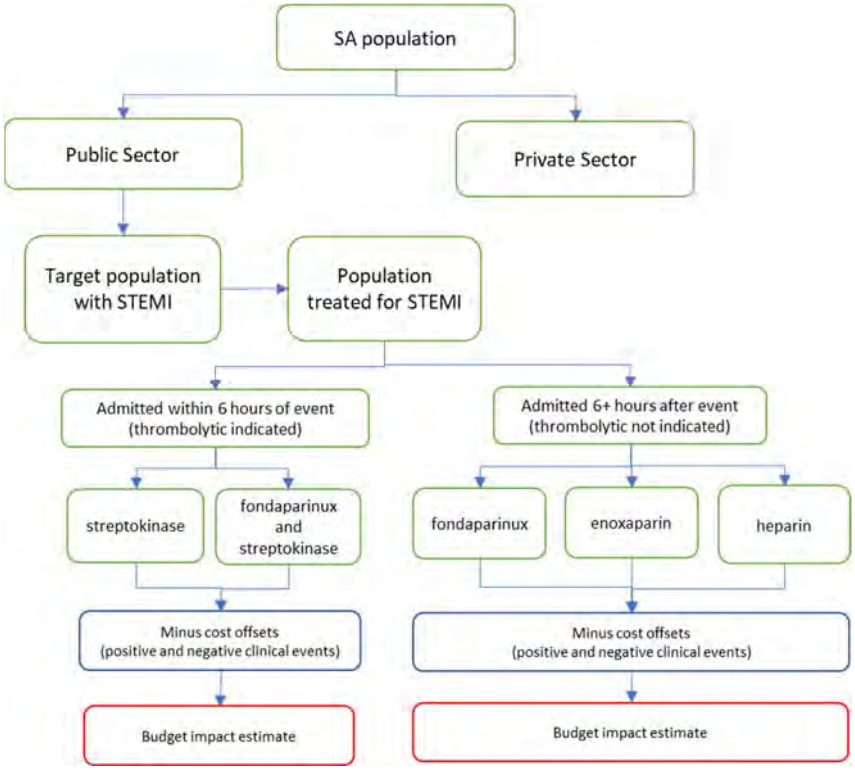


Figure 3. Framework to estimate budget impact of introducing fondaparinux to the South African health system in Treatment of STEMI

A budget impact analysis was developed to explore the likely costs to the South African public health system of introducing fondaparinux as a treatment option for the treatment of STEMI as an adjunct to streptokinase and an alternative to UFH or enoxaparin. The budget impact estimate is based on the annual cost if the entire existing patient population who accesses treatment of STEMI was 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 and/or adding fondaparinux to streptokinase, 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. Cost offsets such as reduced need for management of complications related to major bleed and reinfarction is then added to the budget impact to represent the final result, with key assumptions tested in sensitivity analysis.

4. Clinical Inputs

Clinical effects were derived from the motivation 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 2011	Systematic review	Cochrane Systematic Review including 4 multi-centre RCTs (2 of which compared fondaparinux to enoxaparin for the management of STEMI)
OASIS 6 (Yusuf et al)	Clinical trial	Multi-site RCT investigating efficacy of fondaparinux in ACS (analyses incorporated in Brito 2011)
Peters et al (2008)	Clinical trial	Sub-group analysis of OASIS 6 analysing fondaparinux as adjunct to thrombolytic therapy in acute myocardial infarction

Table 4. Pivotal trials and reviews – treatment of STEMI)

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.

Description	Value	Lower value	Upper value	Source
Within 6 hours				
Probability of reinfarction streptokinase	0.038	0.021	0.035	Peters et al
Probability of reinfarction streptokinase + fondaparinux	0.028	0.029	0.048	Peters et al
Probability of major bleed streptokinase	0.021	0.016	0.026	Peters et al
Probability of major bleed streptokinase + fondaparinux	0.013	0.010	0.016	Peters et al
Post 6 hours				
Probability of reinfarction fondaparinux	0.039	0.029	0.049	Yusuf et al
Probability of reinfarction enoxaparin	0.041	0.031	0.051	Yusuf et al
Probability of reinfarction UFH	0.11	0.083	0.138	Yusuf et al
Probability of Major Bleed fondaparinux	0.033	0.025	0.041	Yusuf et al
Probability of Major Bleed enoxaparin	0.05	0.038	0.063	Yusuf et al
Probability of Major Bleed UFH	0.031	0.023	0.039	Yusuf et al
All				
Probability of death with Major Bleed	0.1	0,08	0,13	Clinical expert advisory
Probability of death with reinfarction	0.29	0.22	0.36	Yusuf et al

Table 5. Key clinical inputs

Utilities

The long-term impact of outcomes associated with treatment for STEMI are calculated by applying an annual estimate of the health-related quality of life that is associated surviving post the ACS event or surviving with complications. The annual costs incurred for a patient with ACS and infarction-related complications are detailed in table 9, with death incurring no annual recurring cost or utility.

Parameter	Value	Lower value	Upper value
Survival (post ACS event)	0.605	0.45	0.76
Survival (infarction-related complications)	0.505	0.38	0.63
Death	0	0	0

Table 6. Markov state utilities

State transition probabilities

The state transition probabilities for STEMI treatment post-6 hours 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 (table 7). For example, the probability that a patient will move from survival (post ACS)) to dead in any one year is 0.055, and includes the underlying average mortality rate in South Africa for that age group.

	Survival (post ACS event)	Survival (with infarction-related complications)	Dead
Survival (post ACS event)	0.945	0	0.055
Survival (with infarction-related complications)	0	0.71	0.29
Dead	0	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 STEMI episode, their quality of life will be the same whether they experienced a myocardial infarction in hospital or not.

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[7].

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

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).

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

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
Streptokinase(pre 6 hours)	IV 1.5 million units diluted in 100 mL sodium chloride 0.9%	1 500 000 iu	R2 920	1	R2 920	R40.03 (1 day)	stat	R 2,960.03
Fondaparinux (pre + post 6 hours)	SC, 2.5mg/0.2ml daily	2.5mg	R41.58	1	R41.58	R9.95	4.5	R231.90
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	5,000IU/mL, 5mL 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 10. Total regimen costs

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 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.

Description	Value	Lower value	Upper value	Source
Once-off Costs (Decision Tree)				
Treatment costs of streptokinase per patient (within 6 hours post infarction)	R 2 960.03	R 2 220	R 3 700	Contract Circular HP06-2017SVP[8]
Treatment costs of fondaparinux per patient (both STEMI scenarios)	R 231.90	R 173	R 290	See Tables 8 -10
Treatment costs of UFH per patient (6+ hours post infarction)	R 449.70	R 337	R 562	Contract Circular HP06-2017SVP
Treatment costs of enoxaparin per patient (6+ hours post infarction)	R 449.87	R 337	R 562	Contract Circular HP06-2017SVP
Cost of treating a major bleed	R 11 268	8451	14085	UPFS
Cost of treating a MI	R 7 079	5309.25	8848.75	UPFS
Costs associated with a patient dying	R 368	276	460	Registry
Annual Costs (Markov Model)				
Costs of patient that survives without complications	R2 000	1500	2500	NOACs costing analysis (Appendix II)
Costs of patient that survives and has infarction-related complications	R17 000	12750	21250	NOACs costing analysis (Appendix II)

Table 11 Model cost inputs

6. Results

a. Cost effectiveness analysis

Listing fondaparinux for treatment of STEMI is as an adjunct to streptokinase is estimated to be more expensive than streptokinase only, but is also expected to yield additional health. The estimated incremental cost effectiveness ratio is 3,093/QALY. The price of fondaparinux used in the analysis is 20% of the current SEP for fondaparinux.

Regimen	Costs	Incr costs	QALYs	Incr QALYs	ICER
Streptokinase only	R18,983		4.12		
Streptokinase with fondaparinux	R21,195	R2,213	4.90	0.78	R2,843 / QALY

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

[8] National Department of Health Master Prcocurement Catalogue: http://www.health.gov.za/index.php/medicine?download=2649:master-procurement-catalogue-05-february-2018

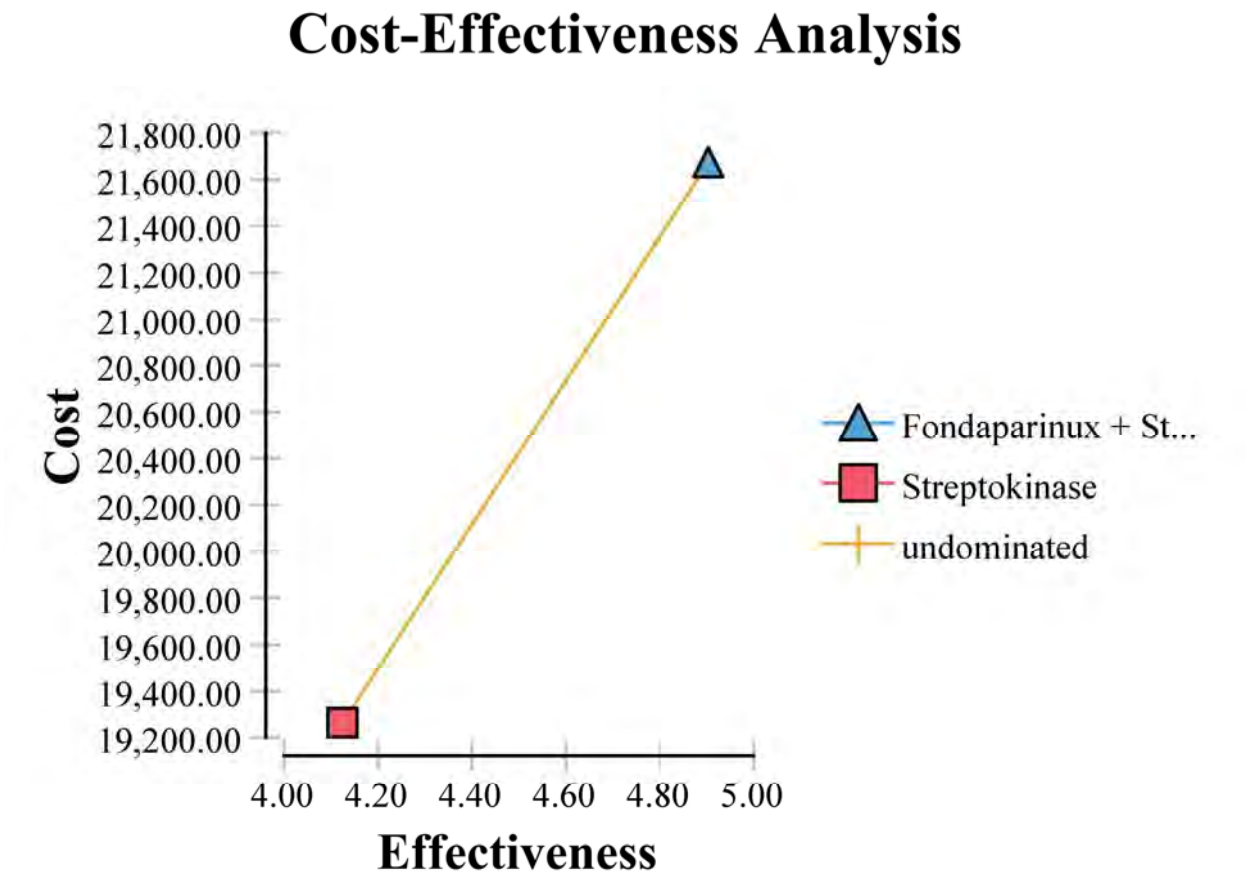


Figure 4. Cost effectiveness plane – management of STEMI within 6 hours of infarction

Listing fondaparinux for treatment of STEMI as an alternative to enoxaparin or UFH in patients admitted post 6 hours after infarction is expected to cost less than either enoxaparin or UFH, but also yield additional QALYs.It is herefore expected to dominate the alternative options.

Regimen	Costs	Incr costs	QALYs	Incr QALYs	ICER
Fondaparinux	R35,046		9.70		
Enoxaparin	R35,449	R401	9.66	-0.03	dominated
UFH	R36,950	R1,902	9.09	-0.61	dominated

Table 13. Summary of cost effectiveness of fondaparinux in the treatment of STEMI post 6 hours of infarction

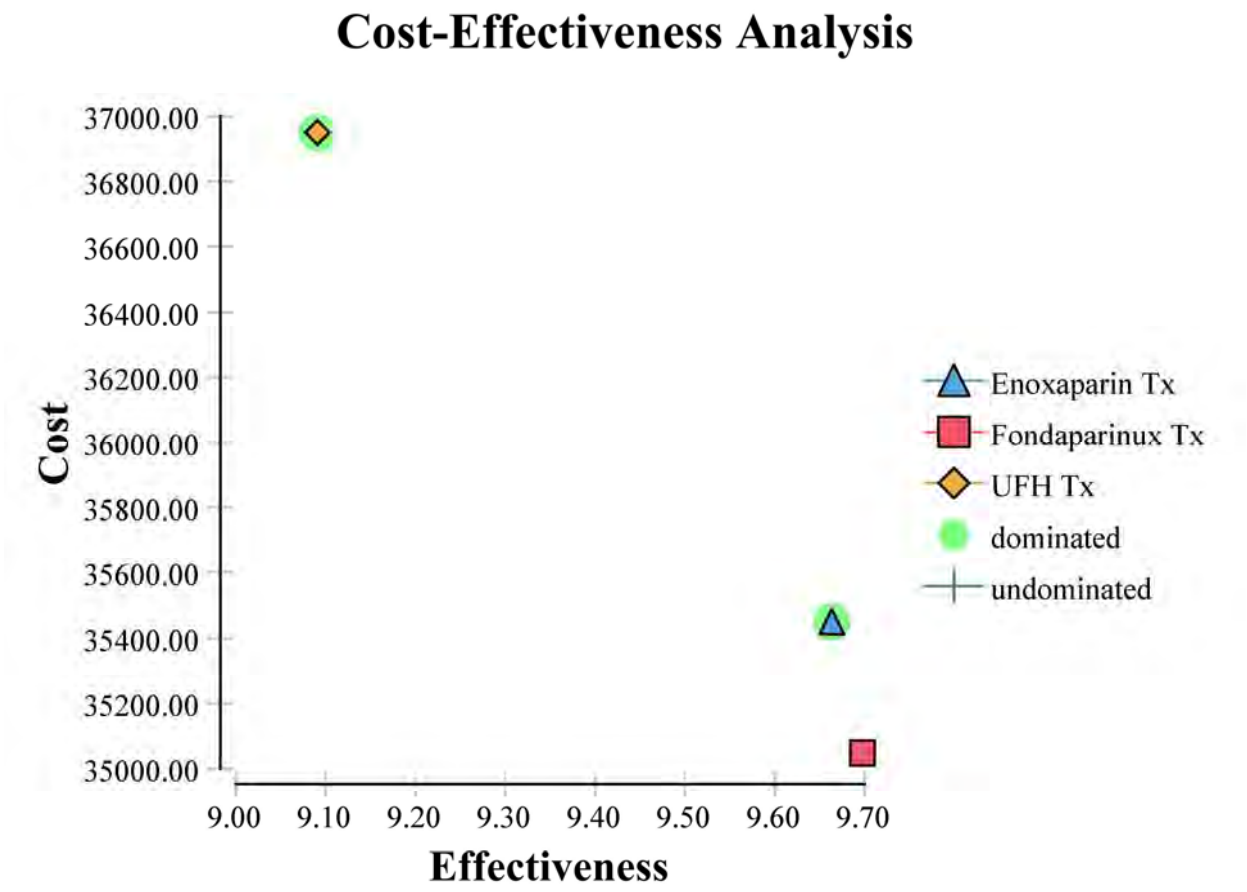


Figure 5. Cost effectiveness plane – management of STEMI post 6 hours of infarction

Sensitivity analysis

One-way sensitivity analysis was conducted on the major clinical and cost parameters to generate the Tornado diagram in figure 6 (streptokinase + fondaparinux vs streptokinase only), and figure 7 (fondaparinux vs enoxaparin). 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. Figure 6 shows that the price of fondaparinux has the greatest impact on the ICER (impacting on variable cFS – cost of the combined regimen of streptokinase with fondaparinux) in the within 6-hour treatment group, and assumptions around the cost of survival and cost of enoxaparin have the most impact on the ICER in the post 6-hour group.

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, and in this analysis, it appears that the findings are relatively robust to changes in most variables.

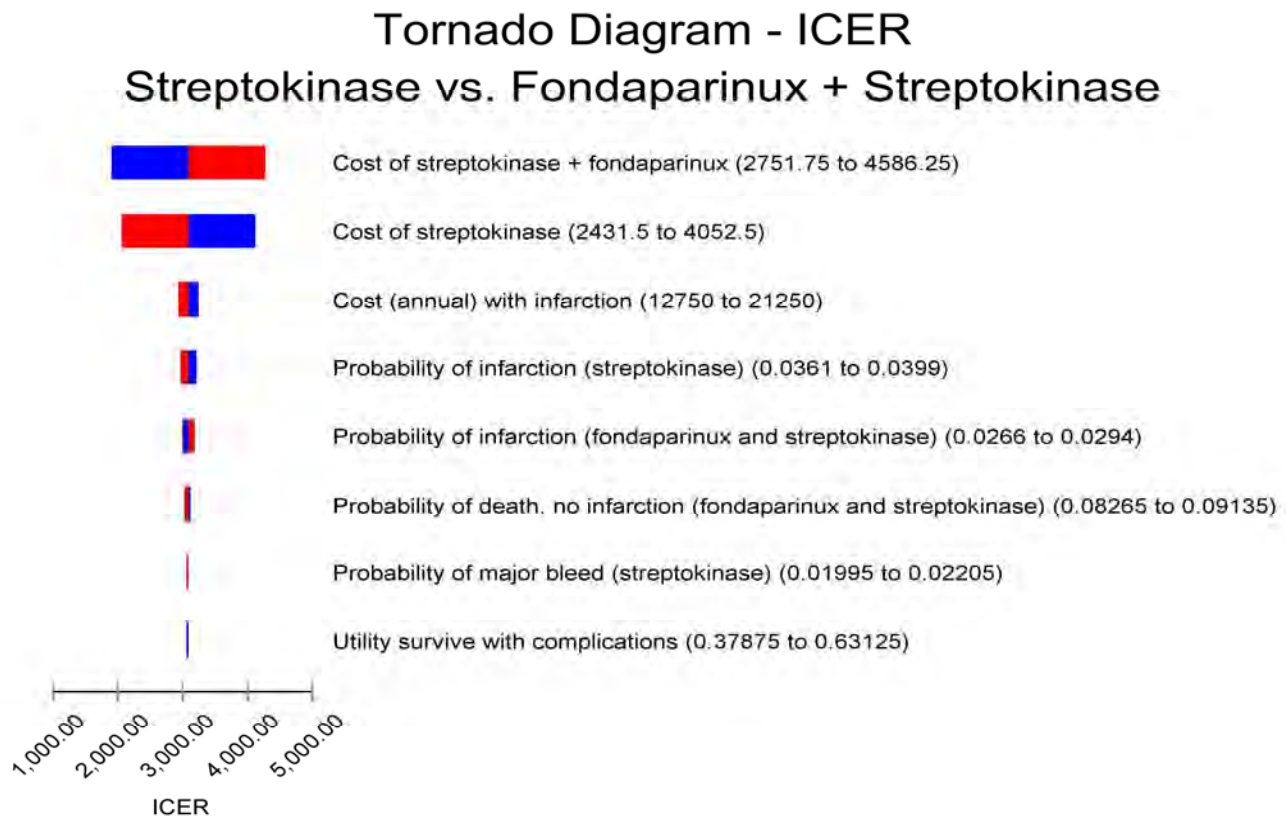


Figure 6. One-way sensitivity analysis - management of STEMI within 6 hours of infarction

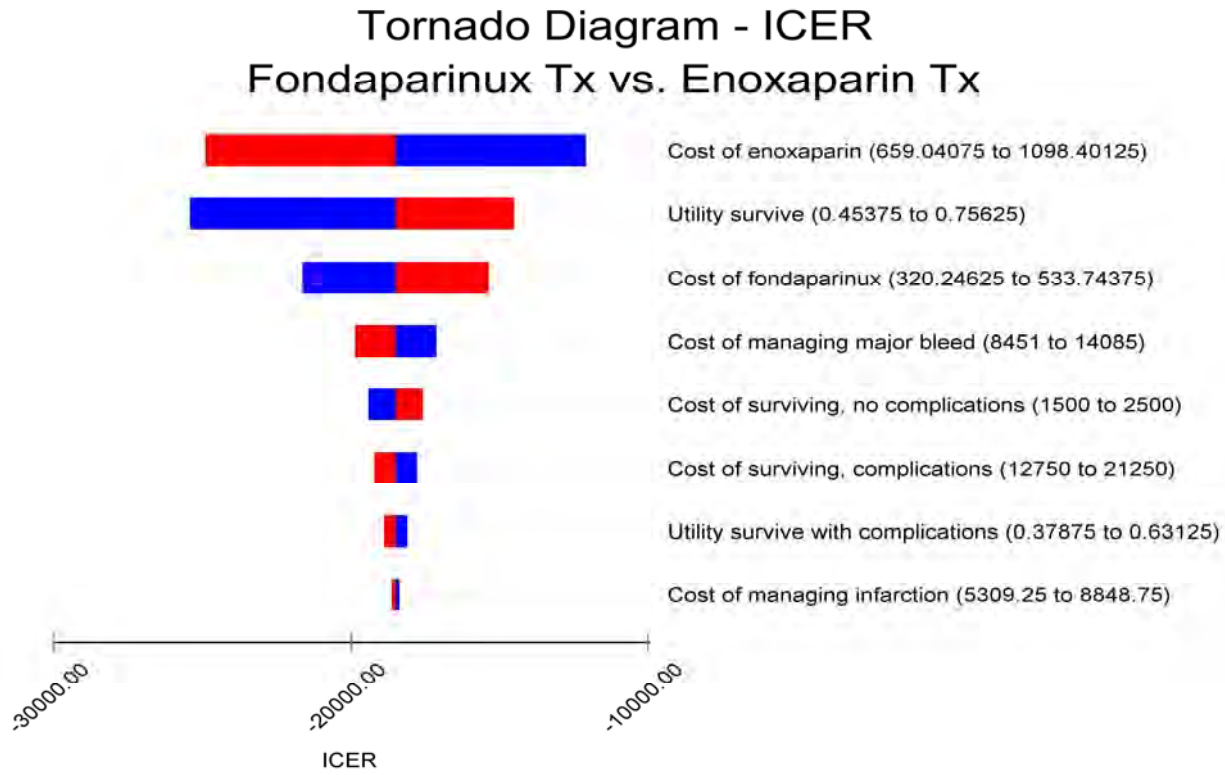


Figure 7. One-way sensitivity analysis - management of STEMI post 6 hours of infarction

b. Budget Impact Analysis

The use of fondaparinux in treatment of STEMI would have an estimated incremental annual cost of R351,597 when used as an adjunct to streptokinase (compared to streptokinase only) in patients treated within 6 hours of infarction (base case at 20% of the SEP for the price of fondaparinux and 50% of patients accessing treamtnet), for drug costs only and R 486 223 when net costs are taken into account (Tables 14 and 15).

		Proportion of patients accessing treatment		
		10% (376 patients)	50% (base case, 1,879 patients)	80% (3,006 patinets)
Price of fondaparinux/2.5 mg	100% of SEP (R207.91)	ZAR 0,35	ZAR 1, 76	ZAR 2,81
	75% of SEP (R155,93)	ZAR 0,26	ZAR 1,32	ZAR 2,11
	50% of SEP (R103,96)	ZAR 0,18	ZAR 0,88	ZAR 1,41
	20% of SEP (R41,58))	ZAR 0,070	ZAR 0,35	ZAR 0,56
	10% of SEP (R20,79)	ZAR 0,035	ZAR 0,18	ZAR 0,28

Table 14. BIA of incremental costs of fondaparinux + streptokinase vs streptokinase only at different assumptions of treatment access and fondaparinux price – within 6 hours of infarction, medicine costs only (in ZAR millions)

		Proportion of patients accessing treatment		
		10% (376 patients)	50% (base case, 1,879 patients)	80% (3,006 patinets)
Price of fondaparinux/2.5mg	100% of SEP (R207.91)	ZAR 2,2	ZAR 3,70	ZAR 17,7
	75% of SEP (R155,93)	ZAR 1,7	ZAR 1,45	ZAR 17,0
	50% of SEP (R103,96)	ZAR 1,1	ZAR 1,01	ZAR 12,7
	20% of SEP (R41,58))	ZAR 0,5	ZAR 0,49	ZAR 7,4
	10% of SEP (R20,79)	ZAR 0,3	ZAR 0,31	ZAR 5,7

Table 15. BIA of incremental costs of fondaparinux + streptokinase vs streptokinase only at different assumptions of treatment access and fondaparinux price – within 6 hours of infarction, health system perspective (in ZAR millions)

The use of fondaparinux in treatment of STEMI post-6 hours would have an estimated incremental annual saving of R2.46 million (base case at 20% of the SEP for the price of fondaparinux and 50% of patients accessing treatment, compared to enoxaparin) taking into account procurement costs only.

	Patients accessing treatment	2,325 patients 10%		11,628 patients 50%		18,604 patients 80%	
		Enox	UFH	Enox	UFH	Enox	UFH
Price fondaparinux/ 2.5 mg unit	100% of SEP (R207.91)	ZAR 1,25	ZAR 1,60	ZAR 6,24	ZAR 7,98	ZAR 9,98	ZAR 12,77
	75% of SEP (R155,93)	ZAR 0,70	ZAR 1,05	ZAR 3,52	ZAR 5,26	ZAR 5,63	ZAR 8,42
	50% of SEP (R103,96)	ZAR 0,16	ZAR 0,51	ZAR 0,80	ZAR 2,54	ZAR 1,28	ZAR 4,06
	20% of SEP (R41,58))	-ZAR 0,49	-ZAR 0,14	-ZAR 2,46	-ZAR 0,72	-ZAR 3,94	-ZAR 1,16
	10% of SEP (R20,79)	-ZAR 0,71	-ZAR 0,36	-ZAR 3,55	-ZAR 1,81	-ZAR 5,68	-ZAR 2,90

Table 16 BIA of fondaparinux incremental to enoxaparin and fondaparinux incremental to UFH at different assumptions of treatment access and fondaparinux price for treatment of STEMI post 6 hours, medicine costs only (in ZAR millions)

Key parameters driving budget impact to the South African public health system are likely to be assumptions relating to the contract price that can be achieved for fondaparinux, and the proportion of patients who access VTE prophylaxis. This variation is shown in Table 14 and 16 where in an extreme scenario of achieving national tender price of 100% SEP and with 80% of patients accessing treatment, listing fondaparinux on the EML for STEMI could represent an annual cost to the pharmaceutical budget of ZAR 15,5 million if the pre-and post 6 hour indication for fondaparinux is combined.

7. 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 STEMI 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 approximately 13,500 patients would gain access and receive treatment for STEMI, with just under 2,000 of those arriving at hospital with 6 hours of infarction. It is likely that up to 23,000 patients nationally may seek treatment in the public sector for STEMI under any policy reform to increase access, and this would subsequently affect the budget impact.

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.

The expected ICER for the pre- 6 hours of infarction for fondaparinux is R 2,843/QALY and fondaparinux dominates both enoxaparin and UFH in treating patients post 6 hours. The authors are unable to advise

on the appropriate threshold that would determine what cost per QALY represented a good value for money investment in the South African public health system for the pre-6 hour scenario. In a recent analysis by Woods et al [9], cost per QALY, "supply side" thresholds were estimated across a range of low and middle-income countries in response to advice from the World Health Organisation that the frequently-used 1xGDP/capita thresholds should not be used for decision making relating to individual technologies. The threshold range for South Africa as estimated by Woods et al was R15,600 -62,700. The ICERs estimated in this analysis are well below even the lower end of this range, indicating that fondaparinux in the treatment of STEMI is likely to represent a good investment whether pre or post 6 hours of infarction.

[9] Woods, B., Revill, P., Sculpher, M. and Claxton, K., 2016. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value in Health*, *19*(8), pp.929-935

Appendix III

Indication Treatment of STEMI

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Cost-effectiveness analysis (ACS):

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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.

Appendix IV

Conficts of interest declared by Adult ERC members providing clinical advise for the costing analyses; assessed by the Chairperson[10].

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

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