National Institute for Health and Care Excellence

Consultation

Acute Coronary Syndromes

[C] Antithrombins for unstable angina and non-ST-segment elevation myocardial infarction

NICE guideline

Intervention evidence review

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Antithrombin therapy in unstable angina and non- ST-segment elevation myocardial infarction

1.1 Review question: What is the clinical and cost effectiveness of fondaparinux, with or without intra-procedural i.v. heparin compared to low molecular weight or unfractionated heparin (LMWH/UFH) in the management of patients with unstable angina and non- ST-segment elevation myocardial infarction undergoing coronary angiography?

1.2 Introduction

People admitted with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) will generally be given an antithrombin, the available options being unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or bivalirudin. CG94 recommended fondaparinux for most people as the most effective and cost-effective treatment. The exception was when angiography was planned within 24 hours, in which case UFH was recommended. This was because a subgroup analysis in the pivotal OASIS-5 trial found that fondaparinux alone was associated with a small increase in catheter-related thrombosis for those undergoing PCI. A separate recommendation was made to consider bivalirudin under some limited circumstances as an alternative to UFH.

It has been suggested that the recommendation to avoid using fondaparinux if coronary angiography is planned in the following 24 hours is inappropriate, since there is no increase in the incidence of catheter thrombosis as long as additional intravenous heparin is given during the procedure. This review therefore aims to reconsider the evidence for fondaparinux compared to heparin in this population.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over with unstable angina or non ST-segment elevation myocardial infarction being considered for percutaneous coronary intervention
Intervention	Fondaparinux in combination with dual antiplatelet therapy with or without additional intra-procedural heparin and with or without Glycoprotein IIb/IIIa Inhibitors
Comparison	Unfractionated or low molecular weight heparin in combination with dual antiplatelet therapy with or without additional intra-procedural heparin and with or without Glycoprotein IIb/IIIa Inhibitors
Outcomes	**CRITICAL** • All cause mortality – up to 30 days (or nearest time point but less than 1

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	year)_(specify if in hospital) • Cardiac mortality – up to 30 days • New myocardial infarction – up to 30 days • Catheter related thrombosis – 30 days • Complications related to bleeding including haemorrhagic stroke – up to 30 days (access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: ○ BARC ○ Author's definition ○ TIMI ○ GUSTO • Where possible, bleeding outcomes will be categorised into: ○ Major bleeding (including BARC 3-5 and as reported by author) ○ Minor bleeding (including BARC 2, TIMI and as reported by author). • Health-related quality of life including EQ5D and SF-36. All data for the stated quality of life measures will be collected. Only overall scores will be reported for meta-analysis and GRADE. **IMPORTANT** • Repeat revascularisation- up to 30 days • Stent thrombosis (acute, early or late) 30 days • Stroke - up to 30 days • Length of hospital stay
Study design	• Randomised Controlled Trials (RCT) • Systematic Reviews (SR) of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[12] Methods specific to this review question are described in the review protocol in Appendix A:

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

Three studies were included in the review[41, 65, 66]. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:and GRADE tables in Appendix F:.

1.5.2 Excluded studies

See the excluded studies list in Appendix I

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1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Mehta 2007[41] (OASIS 5)	Fondaparinux (n=3134): 2.5 mg once daily subcutaneously for a maximum 8 days LMWH (n=3104): Enoxaparin 1 mg/kg twice daily or once daily in those with Ccr <30 ml/min for a maximum 8 days	People with unstable angina or NSTEMI	30 days • Death • Myocardial infarction • Stroke • Major bleeding • TIMIl major bleeding • Minor bleeding 6 months • Death Unspecified time point (presumably during procedure) • Catheter thrombosis	Sub-study of OASIS-5 with only those who had PCI Following reports of catheter thromboses in a small number of patients, it was permissible to give open-label UFH before PCI in addition to the protocol-mandated study drug. The results of the 1758 patients in this subgroup were also reported separately.
Yan 2011[65]	Fondaparinux (n=150): 2.5mg once daily subcutaneously LMWH (n=150): Nadroparin 0.1 ml/10kg twice daily subcutaneously if Ccr was 30-60 ml/min, or 0.1 ml/10kg once daily if Ccr <30 ml/min	People with unstable angina or NSTEMI who presented with angina up to 48 hours before randomisation. 88% had PCI during initial hospitalisation	30 days • Death • Myocardial infarction • Stroke • Bleeding 180 days • Death Unspecified time point • Catheter thrombosis	All participants in both the fondaparinux and LMWH received UFH during PCI. The dose of UFH was 7000–10 000 U without the glycoprotein IIb/IIIa inhibitor tirofiban and 5000–7000 U if tirofiban was used during PCI
Zhao 2015[66]	Fondaparinux (n=229): 2.5mg once daily subcutaneously for	People with non-ST elevation ACS	30 days	All participants in both the fondaparinux and LMWH received

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Study	Intervention and comparison	Population	Outcomes	Comments
	2-8 days maximum or until hospital discharge LMWH (n=232): Enoxaparin 0.1 ml/kg subcutaneously twice daily or 0,075 ml/10 kg twice daily if Ccr was between 30-60 ml/min, or 0.1 ml/10 kg once daily if Ccr was below 30 ml/min	All patients underwent PCI	• Death • Myocardial infarction • Stroke • Major bleeding • Minor bleeding 6 months • Death Unspecified time point • Catheter thrombosis	UFH during PCI. The dose of UFH was 7000–10 000 U if tirofiban was not used during PCI or 5000–7000 U if tirofiban was used.

See Appendix D:for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Fondaparinux versus heparin for UA/NSTEMI

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Heparin	Risk difference with Fondaparinux (95% CI)
All-cause mortality - 30 days	6938 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	N/A[4]	17 per 1000	1 fewer per 1000 (from 9 fewer to 0 more)
All-cause mortality - 6 months	6938 (3 studies)	⨁⨁⊖⊖ LOW[1,3] due to risk of bias, imprecision	N/A[4]	22 per 1000	2 fewer per 1000 (from 7 fewer to 7 more)
Myocardial infarction - 30 days	6938 (3 studies)	⨁⨁⨁⊖ MODERATE[1,]	RR 1.02 (0.83 to 1.24)	40 per 1000	1 more per 1000 (from 7 fewer to 10 more)

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Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Heparin	Risk difference with Fondaparinux (95% CI)
		due to risk of bias			
Myocardial infarction- 6 months	6938 (3 studies)	⨁⨁⊖⊖ LOW[11,2] due to risk of bias, imprecision	RR 1.07 (0.89 to 1.27)	40 per 1000	3 more per 1000 (from 4 fewer to 11 more)
Stroke - 30 days	6938 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	N/A[4]	0 per 1000	2 less per 1000 (from 5 fewer to 2 more)3
Stroke - 6 months	6938 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	N/A[4]	4 per 1000	1 fewer per 1000 (from 4 fewer to 0 more)
Major bleeding - 30 days	6938 (3 studies)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.42 to 0.68)	26 per 1000	12 fewer per 1000 (from 8 fewer to 15 fewer)
Major bleeding - 6 months	6938 (3 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.55 (0.44 to 0.69)	39 per 1000	18 fewer per 1000 (from 12 fewer to 22 fewer)
Minor bleeding – 30 days	6938 (3 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.41 (0.31 to 0.54)	53 per 1000	31 fewer per 1000 (from 24 fewer to 37 fewer)
Minor bleeding- 6 months	6938 (3 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.43 (0.34 to 0.56)	53 per 1000	30 fewer per 1000 (from 23 fewer to 35 fewer)
TIMI Major bleeding - 30 days	6177 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.54 (0.33 to 0.87)	15 per 1000	7 fewer per 1000 (from 2 fewer to 10 fewer)
TIMI Major bleeding - 6 months	6177	⨁⨁⊖⊖	RR 0.52	17 per 1000	8 fewer per 1000

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Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Heparin	Risk difference with Fondaparinux (95% CI)
	(1 study)	LOW[1,2] due to risk of bias, imprecision	(0.33 to 0.82)		(from 3 fewer to 11 fewer)
Catheter thrombosis (UFH before PCI) - 6 months	916 (3 studies)	⊕⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	N/A[4]	0 per 1000	2 more per 1000 (from 4 fewer to 8 more)3
Catheter thrombosis (no UFH before PCI) - 6 months	1603 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2.3 (0.71 to 7.43)	5 per 1000	6 more per 1000 (from 1 fewer to 32 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%– no imprecision
4 No relative effect due to 0 events. Risk difference calculated in Review Manager

See Appendix F: for full GRADE tables.

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1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:

1.6.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.6.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. Table 4 summarises unit costs and estimated costs per day for fondaparinux, enoxaparin (LMWH) and unfractionated heparin. Other LMWHs are available but are not generally used for ACS in the UK and so costs are not presented here. People that are administered fondaparinux will be given a bolus of IV unfractionated heparin during the angiography or PCI procedure and this cost is listed below. People receiving ongoing unfractionated heparin will have monitoring costs associated with it that are not included here.

Table 4: UK costs of antithrombins

Drug	Cost per vial/syringe		Daily dose[c]	Estimated cost per day[d]
	List price	Average NHS cost		
Fondaparinux				
Arixtra 2.5mg/0.5ml solution for injection pre-filled syringes (Aspen Pharma Trading Ltd)	£6.28	n/a	2.5mg per day	£6.28
Fondaparinux sodium 2.5mg/0.5ml solution for injection pre-filled syringes (Dr Reddy's Laboratories (UK) Ltd)	£5.97			£5.97
Unfractionated heparin[a]				
Heparin sodium 1,000units/1ml solution for injection ampoules (Wockhardt UK Ltd)	£1.49	£0.86	5,000 units IV bolus injection	£1.65 (list price); £1.29 (average NHS cost)
			18 units/kg/hr maintenance dose	£11.40 (list price); £8.88 (average NHS cost)
			5,000 – 15,000 units IV bolus injection (for use alongside fondaparinux)	Ranging from £1.65 - £4.95 (list price); £1.29 - £3.86 (average NHS cost)
Low molecular weight heparin: enoxaparin[b]				
Clexane 80mg/0.8ml solution for injection pre-filled syringes	£5.51	n/a	1mg/kg every	£11.03

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Drug	Cost per vial/syringe		Daily dose[(c)]	Estimated cost per day[(d)]
	List price	Average NHS cost		
(Sanofi)			12 hours	
Enoxaparin Becat 80mg/0.8ml solution for injection pre-filled syringes (ROVI Biotech Ltd)	£5.51			£11.03
Inhixa 80mg/0.8ml solution for injection pre-filled syringes (Techdow Pharma England Ltd)	£4.41			£8.82
Clexane 300mg/3ml solution for injection multidose vials (Sanofi)	£21.33			£11.38

Source: List prices are the NHS indicative prices from the BNF accessed July 2018[26]; NHS average costs are from eMIT (based on average of costs March to June 2017)[14]

(a) Many different preparations and manufacturers are available; these are example unit costs.

(b) Other preparations of enoxaparin pre-filled syringes are also available: 20mg, 40mg, 50mg, 60mg, 80mg, 120mg and 150mg. These are lower and higher cost depending on the dose.

(c) Daily dose of fondaparinux and enoxaparin based on ACS dose from summary of product characteristics; heparin dose based on previous guideline (CG94) and confirmed by guideline committee member.

(d) Costs are based on 80kg person. Costs are calculated using average NHS costs from the eMIT database (based on average of costs March to June 2017)[14] where available and list prices from the BNF (11th July 2018) where not[26]. It is assumed that wastage is discarded with pre-filled syringes and there is no wastage with multiuse vials.

1.7 Evidence statements

1.7.1 Clinical evidence statements

- There was a clinically important benefit of fondaparinux compared to heparin in patients with UA/NSTEMI for all-cause mortality at 30 days (6938 participants in 3 studies, very low quality evidence) and at 6 months (6938 participants in 3 studies, low quality evidence).

- There was no clinically important difference of fondaparinux compared to heparin for MI at 30 days (6938 participants in 3 studies, moderate quality evidence) and at 6 months (6938 participants in 3 studies, low quality evidence) and for stroke at 30 days and at 6 months (6938 participants in 3 studies, very low quality evidence).

- There was no clinically important benefit of fondaparinux compared to heparin for major bleeding at 30 days and at 6 months (6938 participants in 3 studies, moderate quality evidence) or for TIMI major bleeding at 30 days and 6 months (6177 participants in 1 study, low quality evidence)

- There was a clinically important benefit of fondaparinux compared to heparin for minor bleeding minor bleeding at 30 days and at 6 months (6938 participants in 3 studies, moderate quality evidence)

- There was no clinically important difference of fondaparinux compared to heparin for catheter thrombosis neither with UFH before PCI (916 participants in 3 studies, very low quality evidence) nor without UFH before PCI (1603 participants in 1 study, very low quality evidence).

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

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1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee agreed that outcomes critical for decision making were all-cause mortality, cardiac mortality, new myocardial infarction, catheter thrombosis and complications related to bleeding including haemorrhagic stroke at up to 30 days. Health related quality of life was also considered critical for decision making.

Repeat revascularisation, stent thrombosis and stroke at up to 30 days were considered as important outcomes for decision making. Length of hospital stay was also considered to be an important outcome.

1.8.1.2 The quality of the evidence

There were three randomised controlled studies included in this review. Two studies compared fondaparinux with enoxaparin, and one study compared fondaparinux with nadroparin.

GRADE assessments for all outcomes ranged from very low to moderate. This was mainly due to imprecision, selection, performance and for some outcomes blinding resulting in a high risk of bias rating.

1.8.1.3 Benefits and harms

There was a small clinical benefit of fondaparinux for all-cause mortality at both 30 days and 6 months when compared to heparin. However, there was uncertainty around the results with a confidence interval which does not exclude the possibility of an increase in mortality at 6 months and therefore the committee interpreted these results with caution. The committee noted that although the clinical benefit was relatively small and based on low and very low quality evidence, it was still a reassuring signal that there was no significant increase in mortality.

There was no clinical benefit of fondaparinux compared to LMWH for myocardial infarction and stroke.

There was a clinical benefit in minor bleeding when using fondaparinux and although the absolute risks for major bleeding didn't reach the agreed threshold for clinical benefit, the committee noted that the relative effects were halved (for both major and minor bleeding).

Only 1 event of catheter thrombosis was recorded in a total population of 916 across 3 studies where UFH was given in addition to fondaparinux before PCI. The authors had noted that the patient in which this event occurred had actually received a suboptimal dose of UFH. Therefore, the evidence did not show any increase in risk of catheter thrombosis providing intravenous heparin is given during the procedure.

There was no evidence available for cardiac mortality, health related quality of life, repeat revascularisation, stent thrombosis or length of hospital stay.

Fondaparinux was judged to be more beneficial to LMWH in the detailed analysis performed for CG94, in particular because of the marked reduction in bleeding risk. This was confirmed by the present analysis which looked only at people in whom unfractionated heparin was given in addition to fondaparinux in the peri-angiography period. No adverse effects of fondaparinux were found when compared to LMWH.

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1.8.2 Cost effectiveness and resource use

No economic evaluations were identified specifically for people with UA/NSTEMI undergoing coronary angiography within 24 hours.

Unit costs were presented to aid committee consideration of cost effectiveness. Fondaparinux costs approximately £5.97 to £6.28 per day. Enoxaparin and unfractionated heparin dosing is weight-based and so costs will vary however drug costs are higher than fondaparinux assuming an average weight of 80kg with enoxaparin costing approximately £8.82 to £11.38 per day and unfractionated heparin costing £1.29 for the initial bolus and then £8.88 per day. The committee highlighted that there may also be additional costs associated with unfractionated heparin as it requires activated partial thromboplastin time (APTT) monitoring which can lead to additional resource use as it requires additional staff time and consumables. It is also noted that fondaparinux is administered once daily, while enoxaparin is twice daily and fondaparinux dosing is not weight-based and so is simpler.

The clinical review showed that fondaparinux resulted in a reduction in major and minor bleeding compared to heparin. The committee highlighted that this could result in cost-savings as bleeding may result in additional length of stay in hospital. Avoiding bleeding may also result in higher QALYs. Previously there had been uncertainty regarding the safety of fondaparinux in those undergoing coronary angiography within 24 hours in relation to catheter thrombosis, which led to unfractionated heparin being recommended for these patients. However, the committee considered the evidence reviewed in this update as evidence to support use of fondaparinux being safe in these people when UFH is used during angiography/PCI as well. In is noted that the previous guideline included economic evaluations which showed that enoxaparin was cost-effective when compared to unfractionated heparin and that fondaparinux was dominant (cost saving with improved health outcomes) in comparison to enoxaparin in a broader UA/NSTEMI population.

Given the above the committee agreed that fondaparinux was likely to be a dominant strategy (cost saving with improved health outcomes) for people with UA/NSTEMI undergoing angiography within 24 hours in line with previous conclusions about cost effectiveness in the broader UA/NSTEMI population.

The committee agreed that this recommendation would not lead to a change in practice as the majority of centres in England are currently administering fondaparinux to those undergoing coronary angiography within 24 hours with unfractionated heparin being administered during the angiogram or PCI procedure.

1.8.3 Other factors the committee took into account

The specific problem which prompted this review was that of catheter thrombosis. To some extent this had already been resolved at the time of publication of CG94 as the OASIS-5 investigators had amended their protocol toward the end of their study so that patients receiving fondaparinux also received unfractionated heparin during angiography, and shown that this reduced the risk of catheter blockage. The 2 further studies available to the current GC, albeit small, confirmed that unfractionated heparin negates the excess risk of catheter thrombosis with fondaparinux.

In addition to the formal evidence reviewed, the GC were aware that many Centres in the UK have followed the procedures of the last phase of OASIS-5 and used fondaparinux up to the time of angiography, covering the procedure with unfractionated heparin. The experience in such centres is that this practice does not lead to an increase in catheter thrombosis.

The GC also noted that using one agent throughout is less likely to lead to drug administration errors than swapping agents 24 hours before a procedure.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: antithrombins in UA/NSTEMI

ID	Field	Content
0.	PROSPERO registration number	CRD42019147579
1.	Review title	What is the clinical and cost effectiveness of fondaparinux, with or without intra-procedural i.v. heparin compared to LMWH/UFH in the management of patients with UA or NSTEMI undergoing coronary angiography?
2.	Review question	What is the clinical and cost effectiveness of fondaparinux, with or without intra-procedural i.v. heparin compared to LMWH/UFH in the management of patients with UA or NSTEMI undergoing coronary angiography?
3.	Objective	To determine the efficacy of fondaparinux compared to heparin in patients with UA/NSTEMI undergoing coronary angiography and whether addition of intra-procedural UFH reduces the incidence of catheter thrombosis Rationale: When the need to update CG94 was formally assessed, no substantial new evidence addressing the recommendations on use of anti-thrombins in UA/NSTEMI was identified. However, expert advice was that in practice the recommendation suggesting that fondaparinux should not be given if coronary angiography is planned in the following 24 hours (because of concerns about catheter thrombosis) is inappropriate, since there is no increase in the incidence of catheter thrombosis as long as additional intravenous heparin is given during the procedure. The original question is therefore couched in more general terms than is required to answer the question we need to address (this was our oversight). A more focussed question is appropriate.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Cinahl Searches will be restricted by: English language Human studies Letters and comments are excluded.

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ID	Field	Content
		Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Acute coronary syndrome
6.	Population	Inclusion: Adults 18 years and over with unstable angina or non ST-segment elevation myocardial infarction being considered for percutaneous coronary intervention. Exclusion: None
7.	Intervention/Exposure/Test	Fondaparinux in combination with dual antiplatelet therapy with or without additional intra-procedural heparin and with or without Glycoprotein IIb/IIIa Inhibitors
8.	Comparator/Reference standard/Confounding factors	Unfractionated or low molecular weight heparin in combination with dual antiplatelet therapy with or without additional intra-procedural heparin and with or without Glycoprotein IIb/IIIa Inhibitors
9.	Types of study to be included	Randomised Controlled Trials (RCT) Systematic Reviews (SR) of RCTs Non-randomised studies will be excluded.
10.	Other exclusion criteria	Studies with mixed populations (STEMI and UA/NSTEMI) where UA/NSTEMI patients results are not reported separately Studies where participants are already on anticoagulants for indications other than ACS Non-English language studies Abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	All-cause mortality – up to 30 days (or nearest time point but less than 1 year)_(specify if in hospital) Cardiac mortality – up to 30 days New myocardial infarction – up to 30 days

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ID	Field	Content
		Catheter related thrombosis (during the procedure) Complications related to bleeding including haemorrhagic stroke – up to 30 days (access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: BARC Author's definition TIMI GUSTO Where possible, bleeding outcomes will be categorised into: Major bleeding (including BARC 3-5 and as reported by author) Minor bleeding (including BARC 2, TIMI and as reported by author) Health-related quality of life including EQ5D and SF-36.
13.	Secondary outcomes (important outcomes)	Repeat revascularisation- up to 30 days Stent thrombosis (acute, early or late, probably or definite) up to 30 days Stroke - up to 30 days Length of hospital stay
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be

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ID	Field	Content	
		used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
17.	Analysis of sub-groups	Patients who have a PCI GPI use Age > < 75 years Type of heparin (LMWH vs UFH)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

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ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	19/06/18		
22.	Anticipated completion date	14/05/20		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Acutecoronarysyndromes@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Dr Bernard Higgins [Guideline lead] Dr Saoussen Ftouh/Miss Sedina Lewis/Miss Sophie Carlisle [Senior Systematic Reviewers] Ms Annabelle Davies/Ms Kate Lovibond [Health economist; Health economists lead] Ms Agnes Cuyas/Ms Jill Cobb [Information specialists]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee		

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ID	Field	Content	
		meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=147579	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Acute coronary syndrome, anti-platelets, NSTEMI, unstable angina, STEMI	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

1

2 **Table 6: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)

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	• Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[42] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded

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	before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. • The following will be rated as 'Very serious limitations' and excluded: economic analyses undertaken as part of clinical studies that are excluded from the clinical review; economic models where relative treatment effects are based entirely on studies that are excluded from the clinical review.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[42]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2008 – 22 July 2018	Exclusions
Embase (OVID)	01 January 2008 – 22 July 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews 2008 to 2019 Issue 7 of 12 CENTRAL 2008 to 2019 Issue 7 of 12	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.

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5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	antithrombins/
39.	(fondaparinux or arixtra).ti,ab.
40.	38 or 39
41.	37 and 40

1 **Embase (Ovid) search terms**

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.

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7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	*antithrombin/
37.	fondaparinux/
38.	(fondaparinux or arixtra).ti,ab.
39.	36 or 37 or 38
40.	35 and 39

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Acute Coronary Syndrome] this term only
#2.	MeSH descriptor: [Angina Pectoris] this term only
#3.	MeSH descriptor: [Angina, Unstable] this term only
#4.	MeSH descriptor: [Coronary Thrombosis] this term only
#5.	MeSH descriptor: [Myocardial Infarction] explode all trees
#6.	(or #1-#5)
#7.	MeSH descriptor: [Heart Arrest] this term only
#8.	(acute coronary near/2 syndrome*):ti,ab
#9.	((myocardial or heart) next infarct*):ti,ab
#10.	(heart next (attack* or event*)):ti,ab

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#11.	((heart or cardiac) next arrest*):ti,ab
#12.	(coronary near/2 thrombos*):ti,ab
#13.	(stemi or st-segment or st segment or st-elevation or st elevation):ti,ab
#14.	non-ST-segment elevation:ti,ab
#15.	(non-STEMI or NSTEMI or nonSTEMI):ti,ab
#16.	Q wave myocardial infarction:ti,ab
#17.	non Q wave MI:ti,ab
#18.	(NSTE-ACS or STE-ACS):ti,ab
#19.	(subendocardial near/3 infarct*):ti,ab
#20.	((unstable or variant) near/2 angina*):ti,ab
#21.	(unstable near/2 coronary):ti,ab
#22.	(or #6-#21)
#23.	MeSH descriptor: [Antithrombins] explode all trees
#24.	(fondaparinux or arixtra).ti,ab
#25.	#23 or #24
#26.	#22 and #25

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a search relating to acute coronary syndromes population combined with terms for interventions in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase using a filter for health economics studies.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Embase	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.

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8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	Economics/
39.	Value of life/
40.	exp "Costs and Cost Analysis"/
41.	exp Economics, Hospital/
42.	exp Economics, Medical/
43.	Economics, Nursing/
44.	Economics, Pharmaceutical/
45.	exp "Fees and Charges"/
46.	exp Budgets/
47.	budget*.ti,ab.

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48.	cost*.ti.
49.	(economic* or pharmaco?economic*).ti.
50.	(price* or pricing*).ti,ab.
51.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
52.	(financ* or fee or fees).ti,ab.
53.	(value adj2 (money or monetary)).ti,ab.
54.	or/38-53
55.	37 and 54
56.	*Angiography/
57.	Angiocardiography/
58.	Coronary Angiography/
59.	Angiograph*.ti.
60.	Arteriograph*.ti.
61.	Angiocardiograph*.ti,ab.
62.	Coronary Angiograph*.ti,ab.
63.	Angiogram*.ti,ab.
64.	Cardioangiograph*.ti,ab.
65.	Angiocardiogram.ti,ab.
66.	Angio Cardiograph*.ti,ab.
67.	Coronary Arteriogra*.ti,ab.
68.	Coronarograph*.ti,ab.
69.	*Myocardial Revascularization/
70.	Angioplasty, Balloon, Coronary/
71.	(Myocardial adj revasculari?ation).ti,ab.
72.	PCI.ti,ab.
73.	Percutaneous coronary intervention.ti,ab.
74.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
75.	PTCA.ti,ab.
76.	exp Angioplasty/
77.	Blunt microdissection.ti,ab.
78.	((laser or patch) adj angioplasty).ti,ab.
79.	Percutaneous Transluminal Angioplasty.ti,ab.
80.	Transluminal Coronary Angioplasty.ti,ab.
81.	(Balloon adj3 coronary).ti,ab.
82.	(Balloon adj3 angioplasty).ti,ab.
83.	exp STENTS/
84.	stent*.ti,ab.
85.	Or/56-84
86.	aspirin/
87.	(aspirin or acetylsalicylic acid).ti,ab.
88.	(clopidogrel or plavix).ti,ab.
89.	(ticagrelor or brilique).ti,ab.
90.	(prasugrel or efient or effient or prasita).ti,ab.
91.	Prasugrel Hydrochloride/

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92.	platelet aggregation inhibitors/
93.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
94.	exp Platelet Glycoprotein GPIIb-IIIa Complex/
95.	exp Receptors, Fibrinogen/
96.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
97.	exp adrenergic beta-antagonists/
98.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
99.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/
100.	(beta adj3 block*).ti,ab.
101.	(b adj3 block*).ti,ab.
102.	(beta adj2 antagonist*).ti,ab.
103.	Antithrombins/
104.	Antithrombin*.ti,ab.
105.	(thrombin adj3 inhibitor*).ti,ab.
106.	Hirudins/
107.	Hirudin*.ti,ab.
108.	Hirulog.ti,ab.
109.	Bivalirudin.ti,ab.
110.	Or/86-109
111.	55 and (85 or 110)

1 **Embase (Ovid) search terms**

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.

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16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49
51.	angiography/
52.	angiocardiography/
53.	coronary angiography/
54.	Angiograph*.ti.
55.	Arteriograph*.ti.

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56.	Angiocardiograph*.ti,ab.
57.	Coronary Angiograph*.ti,ab.
58.	Angiogram*.ti,ab.
59.	Cardioangiograph*.ti,ab.
60.	Angiocardiogram.ti,ab.
61.	Angio Cardiograph*.ti,ab.
62.	Coronary Arteriogra*.ti,ab.
63.	Coronarograph*.ti,ab.
64.	*heart muscle revascularization/
65.	transluminal coronary angioplasty/
66.	(Myocardial adj revasculari?ation).ti,ab.
67.	PCI.ti,ab.
68.	Percutaneous coronary intervention.ti,ab.
69.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
70.	PTCA.ti,ab.
71.	*angioplasty/
72.	Blunt microdissection.ti,ab.
73.	((laser or patch) adj angioplasty).ti,ab.
74.	Percutaneous Transluminal Angioplasty.ti,ab.
75.	Transluminal Coronary Angioplasty.ti,ab.
76.	(Balloon adj3 coronary).ti,ab.
77.	(Balloon adj3 angioplasty).ti,ab.
78.	exp STENTS/
79.	stent*.ti,ab.
80.	Or/51-79
81.	acetylsalicylic acid/
82.	(aspirin or acetylsalicylic acid).ti,ab.
83.	(clopidogrel or plavix).ti,ab.
84.	(ticagrelor or brilique).ti,ab.
85.	(prasugrel or efient or effient or prasita).ti,ab.
86.	prasugrel/
87.	antithrombocytic agent/
88.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
89.	exp fibrinogen receptor/
90.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
91.	abciximab/ or eptifibatide/ or tirofiban/
92.	exp beta adrenergic receptor blocking agent/
93.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or

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	tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
94.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or bisoprolol fumarate/ or carvedilol/ or celiprolol/ or esmolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/ or timolol maleate/
95.	(beta adj3 block*).ti,ab.
96.	(b adj3 block*).ti,ab.
97.	(beta adj2 antagonist*).ti,ab.
98.	antithrombin/
99.	Antithrombin*.ti,ab.
100.	(thrombin adj3 inhibitor*).ti,ab.
101.	hirudin derivative/
102.	Hirudin*.ti,ab.
103.	Hirulog.ti,ab.
104.	Bivalirudin.ti,ab.
105.	Or/81-104
106.	50 and (80 or 105)

1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute coronary adj2 syndrome*))
#9.	(((myocardial or heart) adj infarct*))
#10.	((heart adj (attack* or event*)))
#11.	(((heart or cardiac) adj arrest*))
#12.	((coronary adj2 thrombos*))
#13.	((stemi or st-segment or st segment or st-elevation or st elevation))
#14.	("non-ST-segment elevation")
#15.	((non-STEMI or NSTEMI or nonSTEMI))
#16.	("Q wave myocardial infarction")
#17.	("non Q wave MI")
#18.	(NSTE-ACS)
#19.	(STE-ACS)
#20.	(((subendocardial adj3 infarct*)))
#21.	(((((unstable or variant) adj2 angina*)))
#22.	(((unstable adj2 coronary)))
#23.	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24.	(MeSH DESCRIPTOR Angiography)

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#25.	(MeSH DESCRIPTOR Angiocardiography)
#26.	((MeSH DESCRIPTOR Coronary Angiography))
#27.	((Angiograph*))
#28.	((Arteriograph*))
#29.	((Angiocardiograph*))
#30.	((Coronary Angiograph*))
#31.	((Angiogram*))
#32.	((Cardioangiograph*))
#33.	((Angiocardiogram))
#34.	((Angio Cardiograph*))
#35.	((Coronary Arteriogra*))
#36.	((Coronarograph*))
#37.	(MeSH DESCRIPTOR Myocardial Revascularization)
#38.	(MeSH DESCRIPTOR Angioplasty, Balloon, Coronary)
#39.	(((Myocardial adj revasculari?ation)))
#40.	((PCI))
#41.	((Percutaneous coronary intervention))
#42.	((Percutaneous Transluminal Coronary Angioplasty))
#43.	((PTCA))
#44.	(MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES)
#45.	((Blunt microdissection))
#46.	((((laser or patch) adj angioplasty)))
#47.	((Percutaneous Transluminal Angioplasty))
#48.	((Transluminal Coronary Angioplasty))
#49.	(((Balloon adj3 coronary)))
#50.	((Balloon adj3 angioplasty))
#51.	(MeSH DESCRIPTOR Stents EXPLODE ALL TREES)
#52.	((stent*))
#53.	(#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
#54.	(MeSH DESCRIPTOR Aspirin)
#55.	((aspirin or acetylsalicylic acid))
#56.	((clopidogrel or plavix))
#57.	((ticagrelor or brilique))
#58.	((prasugrel or efient or effient or prasita))
#59.	MeSH DESCRIPTOR Prasugrel Hydrochloride
#60.	MeSH DESCRIPTOR Platelet Aggregation Inhibitors
#61.	((Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA))
#62.	MeSH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES
#63.	MeSH DESCRIPTOR Receptors, Fibrinogen EXPLODE ALL TREES
#64.	((Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat))
#65.	MeSH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES
#66.	((propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or

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	emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim))
#67.	(MeSH DESCRIPTOR propranolol)
#68.	(MeSH DESCRIPTOR acebutolol)
#69.	(MeSH DESCRIPTOR atenolol)
#70.	(MeSH DESCRIPTOR bisoprolol)
#71.	(MeSH DESCRIPTOR celiprolol)
#72.	(MeSH DESCRIPTOR labetalol)
#73.	(MeSH DESCRIPTOR metoprolol)
#74.	(MeSH DESCRIPTOR nadolol)
#75.	(MeSH DESCRIPTOR nebivolol)
#76.	(MeSH DESCRIPTOR oxprenolol)
#77.	(MeSH DESCRIPTOR pindolol)
#78.	(MeSH DESCRIPTOR sotalol)
#79.	(MeSH DESCRIPTOR timolol)
#80.	((beta adj3 block*))
#81.	((b adj3 block*))
#82.	((beta adj2 antagonist*))
#83.	MeSH DESCRIPTOR Antithrombins
#84.	(Antithrombin*)
#85.	((thrombin adj3 inhibitor*))
#86.	MeSH DESCRIPTOR Hirudins
#87.	(Hirudin*)
#88.	(Hirulog)
#89.	(Bivalirudin)
#90.	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
#91.	(#23 AND (#53 OR #90))

1

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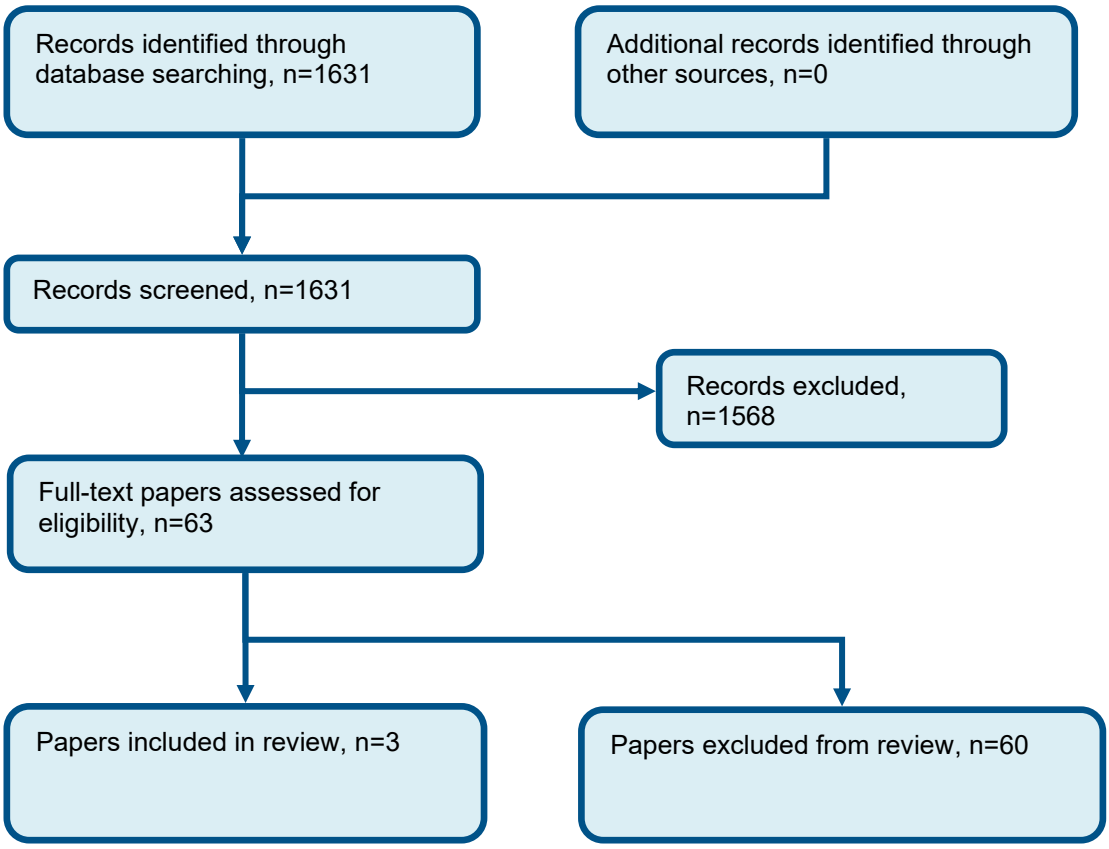
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of antithrombins in UA/NSTEMI



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Appendix D: Clinical evidence tables

Study	OASIS 5 trial: Mehta 2007[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20078)
Countries and setting	Conducted in Canada, France, Netherlands, Poland, Sweden, United Kingdom, USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with unstable angina or non–ST-segment elevation MI and age ≤60 years, positive cardiac biomarkers, or electrocardiographic changes compatible with ischemia. Only people undergoing early PCI were included in the present OASIS-5 substudy
Exclusion criteria	Contraindication to low-molecular-weight heparin, hemorrhagic stroke within the last 12 months, an indication for anticoagulation other than ACS, revascularization procedure already performed for the qualifying event, and severe renal insufficiency (i.e., serum creatinine ≥3 mg/dl or 265 mol/l)
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Fondaparinux group 64.6; Enoxaparin group 64.5 (SD not reported). Gender (M:F): 4392/1846. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear 2. Patients who undergo PCI: PCI
Indirectness of population	No indirectness
Interventions	(n=3134) Intervention 1: Fondaparinux. 2.5 mg once daily subcutaneously. The dose of study drug administered at PCI was determined by the time that had elapsed since administration of the last subcutaneous injection of study drug, and by whether concurrent glycoprotein (GP) IIb/IIIa inhibitors were to be used. Duration Maximum 8 days. Concurrent medication/care: Standard doses of unfractionated heparin (UFH) were used. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: Unfractionated heparin 4. Use of GpIIb/IIIa : Planned for selected patients (Used in 40%).

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	(n=3104) Intervention 2: Heparin - LMWH. Subcutaneous enoxaparin 1 mg/kg twice daily (dose reduced to 1 mg/kg once daily in patients with creatinine clearance 30 ml/min). The dose of study drug administered at PCI was determined by the time that had elapsed since administration of the last subcutaneous injection of study drug, and by whether concurrent glycoprotein (GP) IIb/IIIa inhibitors were to be used. Duration Maximum 8 days. Concurrent medication/care: Standard doses of unfractionated heparin (UFH) were used. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: Unfractionated heparin 4. Use of GpIIb/IIIa : Planned for selected patients
Funding	Academic or government funding (Drs. Mehta, Granger, Eikelboom, Bassand, Faxon, Peters, Budaj, Fox, and Yusuf have received honoraria and consulting fees from GlaxoSmithKline, Sanofi-Aventis, and Bristol-Myers Squibb. Dr. Mehta was supported by a New Investigator Award from the Canadian Institutes of Health Research. Prof. Wallentin receives institutional research grants from Uppsala Clinical Research Centre)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX versus LMWH

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: Death at 30 days; Group 1: 62/3105, Group 2: 65/3072
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: Myocardial infarction at 30 days; Group 1: 177/3105, Group 2: 168/3072
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding at up to 30 days
- Actual outcome: Major bleeding at 30 days; Group 1: 88/3105, Group 2: 166/3072
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: TIMI major bleeding at 30 days; Group 1: 25/3105, Group 2: 46/3072
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome: Minor bleeding at 30 days; Group 1: 53/3105, Group 2: 139/3072
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

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Protocol outcome 4: Catheter related thrombosis at up to 30 days - Actual outcome: Catheter thrombosis (UFH before PCI subgroup) at 30 days; Group 1: 1/75, Group 2: 0/80 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Catheter thrombosis (no UFH before PCI subgroup) at 30 days; Group 1: 9/793, Group 2: 4/810 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Stroke at up to 30 days - Actual outcome: Stroke at 30 days; Group 1: 17/3105, Group 2: 22/3072 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Mortality at 1 year at at 1 year - Actual outcome: Death at 6 months; Group 1: 99/3105, Group 2: 107/3072 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis used but number with outcomes doesn't match number at baseline; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Cardiac mortality at up to 30 days ; Quality of life at Define; Repeat revascularisation at up to 30 days; Probable or definite stent thrombosis at up to 30 days; Length of hospital stay at Define

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Study	Yan 2011[65]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in China; Setting: Single centre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were randomly assigned to a study group within 48 hours after the onset of symptoms of angina at rest lasting at least 10 minutes and were eligible if they met at least one of the following four criteria: (1) an elevated level of troponin I or CK-MB, (2) electrocardiographic (ECG) changes indicative of ischemia (ST-segment depression, transient ST-segment elevation, or T-wave changes in at least two contiguous leads), (3) a documented previous MI, typical exertional angina or revascularization procedure, or (4) the diagnosis of ischemia heart disease through invasive or noninvasive testing
Exclusion criteria	Patients were excluded under the following conditions: age <21 years or >75 years, body weight <50 kg, having received UFH or LMWHs within 1 week before randomization, hemorrhagic stroke within 12 months or ischemic stroke within 1 month, indications for anticoagulation other than ACS, uncontrolled hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg), serum creatinine level more than 20 mg/L, platelet 100×109/L or a counts history of heparin less than induced thrombocytopenia, inherited or acquired haemostasis abnormality, pregnancy, or refusal to participate
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Fondaparinux group: 60.2±9.3; Nadroparin group: 59.9±8.4. Gender (M:F): 214/86. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Patients who undergo PCI: PCI (88% had PCI during initial hospitalisation).
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Fondaparinux. 2.5 mg subcutaneously once daily. Fondaparinux could be given until hospital discharge or for up to 8 days (whichever occurred first). The dose of fondaparinux remained unchanged if the glycoprotein IIb/IIIa inhibitor tirofiban was used. Duration up to 8 days. Concurrent medication/care: all patients received aspirin 100–300 mg/d and clopidogrel 75 mg/d, preceded by a loading

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	dose if indicated. Patients received other standard treatments at the investigators' discretion. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: LMWH 4. Use of GpIIb/IIIa : Not stated / Unclear (Used for some but not specified who for). (n=150) Intervention 2: Heparin - LMWH. Nadroparin 0.1 ml/10 kg subcutaneously twice daily, 0.075 ml/10 kg twice daily if serum creatinine clearance was between 60 and 30 ml/min, or 0.1 ml/10 kg once daily if serum creatinine clearance was below 30 ml/min. Nadroparin was to be given for 2–8 days or until the patient was in clinically stable condition. The dose of nadroparin was reduced by half if the glycoprotein IIb/IIIa inhibitor tirofiban was used.. Duration 2-8 days or until stable. Concurrent medication/care: all patients received aspirin 100–300 mg/d and clopidogrel 75 mg/d, preceded by a loading dose if indicated. Patients received other standard treatments at the investigators' discretion. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: LMWH 4. Use of GpIIb/IIIa : Not stated / Unclear (Used but doesn't specify who for).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX versus LMWH

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: Death at 30 days; Group 1: 0/150, Group 2: 0/150
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: Myocardial infarction at 30 days; Group 1: 4/150, Group 2: 6/150
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding at up to 30 days
- Actual outcome: Bleeding at 30 days; Group 1: 7/150, Group 2: 11/150
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Catheter related thrombosis at up to 30 days
- Actual outcome: Catheter related thrombosis at 30 days; Group 1: 0/150, Group 2: 0/150
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 5: Stroke at up to 30 days - Actual outcome: Stroke at 30 days; Group 1: 0/150, Group 2: 0/150 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Mortality at 1 year at at 1 year - Actual outcome: Death at 180 days; Group 1: 0/150, Group 2: 0/150 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Cardiac mortality at up to 30 days ; Quality of life at Define; Repeat revascularisation at up to 30 days; Probable or definite stent thrombosis at up to 30 days; Length of hospital stay at Define

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Study	Zhao 2015[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=461)
Countries and setting	Conducted in China; Setting: Henan Provincial People's Hospital (Zhengzhou, Henan, China)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 180 days follow up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were included if they had ischaemic symptoms; electrocardiographic changes indicative of ischaemia; elevated levels of troponin I and creatine kinase–myocardial band (CK-MB) isoenzyme; a significant stenosis or occlusion requiring placement of at least 1 intracoronary stent; and successful PCI performed within 72 h after admission, with a myocardial ischaemia flow grade of 2–3
Exclusion criteria	The exclusion criteria were as follows: age <18 years or >80 years; UFH or LMWH received within 1 week before randomization; haemorrhagic stroke within 12 months or ischaemic stroke within 1 month before randomization; indications for anticoagulation other than ACS; STEMI; uncontrolled hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg); serum creatinine level >20 mg/L; platelet count <100 9 109/L; a history of heparin-induced thrombocytopenia, inherited or acquired haemostasis abnormality, or pregnancy; or refusal to participate. Patients were also excluded if GPIIb/IIIa inhibitors were deemed not to be necessary, according to the discretion of the treating physician
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Fondaparinux group: 60.1 (11.); enoxaparin group: 59.8 (11.4). Gender (M:F): 346/115. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear 2. Patients who undergo PCI: PCI
Indirectness of population	No indirectness
Interventions	(n=229) Intervention 1: Fondaparinux. fondaparinux administered subcutaneously at a dose of 2.5mg once daily, for 2–8 days or (if sooner) until hospital discharge. Duration 2-8 days. Concurrent medication/care: All patients also received intravenous injection of tirofiban immediately after PCI (10 lg/kg for 3 min, then 0□15 lg/kg/min for 36 h), as well as administration of aspirin (100–300 mg/day) and clopidogrel (75 mg/day), preceded by a loading dose (300 mg in both groups) if indicated. All participants received a dose of UFH was 7000–10 000 U if tirofiban was not used during PCI or 5000–7000 U if tirofiban was used. Patients were also given other standard treatments as needed. Indirectness: No indirectness

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	Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: LMWH 4. Use of GpIIb/IIIa : Not stated / Unclear (n=232) Intervention 2: Heparin - LMWH. enoxaparin for 2–8 days until the patient was deemed clinically stable. Dosing of enoxaparin was 0.1 mL/10 kg subcutaneously twice daily, 0□075 mL/10 kg twice daily if the serum creatinine clearance was between 60 and 30 mL/min, or 0□1 mL/10 kg once daily if the serum creatinine clearance was below 30 mL/min.. Duration 2-8 days. Concurrent medication/care: All patients also received intravenous injection of tirofiban immediately after PCI (10 lg/kg for 3 min, then 0□15 lg/kg/min for 36 h), as well as administration of aspirin (100–300 mg/day) and clopidogrel (75 mg/day), preceded by a loading dose (300 mg in both groups) if indicated. All participants received a dose of UFH was 7000–10 000 U if tirofiban was not used during PCI or 5000–7000 U if tirofiban was used. Patients were also given other standard treatments as needed. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Type of antiplatelet: Clopidogrel 3. Type of heparin: LMWH 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Academic or government funding (Henan Provincial People's Hospital)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FONDAPARINUX versus LMWH

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: Death at 30 days; Group 1: 2/229, Group 2: 4/232
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: Myocardial infarction at 30 days; Group 1: 4/229, Group 2: 6/232
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding at up to 30 days
- Actual outcome: Major bleeding at 30 days; Group 1: 3/229, Group 2: 6/232
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Minor bleeding at 30 days; Group 1: 13/229, Group 2: 22/232
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Catheter related thrombosis at up to 30 days
- Actual outcome: Catheter related thombosis at 30 days; Group 1: 0/229, Group 2: 0/232

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Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Stroke at up to 30 days - Actual outcome: Stroke at 30 days; Group 1: 0/229, Group 2: 0/232 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Mortality at 1 year at at 1 year - Actual outcome: Death at 180 days; Group 1: 4/229, Group 2: 5/232 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Cardiac mortality at up to 30 days ; Quality of life at Define; Repeat revascularisation at up to 30 days; Probable or definite stent thrombosis at up to 30 days; Length of hospital stay at Define

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Appendix E: Forest plots

E.1 Fondaparinux vs heparin

Figure 2: All-cause mortality (30 days)

Study or Subgroup	Fondaparinux Events	Fondaparinux Total	Heparin Events	Heparin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Mehta 2007	62	3105	65	3072	89.0%	-0.00 [-0.01, 0.01]
Yan 2011	0	150	0	150	4.3%	0.00 [-0.01, 0.01]
Zhao 2015	2	229	4	232	6.6%	-0.01 [-0.03, 0.01]
Total (95% CI)		**3484**		**3454**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	64		69			

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)

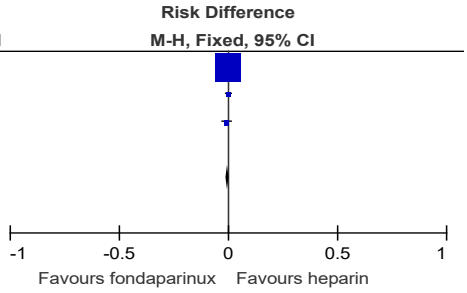

Figure 3: All-cause mortality (6 months)

Study or Subgroup	Fondaparinux Events	Fondaparinux Total	Heparin Events	Heparin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Mehta 2007	99	3105	107	3072	89.0%	-0.00 [-0.01, 0.01]
Yan 2011	0	150	0	150	4.3%	0.00 [-0.01, 0.01]
Zhao 2015	4	229	5	232	6.6%	-0.00 [-0.03, 0.02]
Total (95% CI)		**3484**		**3454**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	103		112			

Heterogeneity: Chi² = 0.20, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)

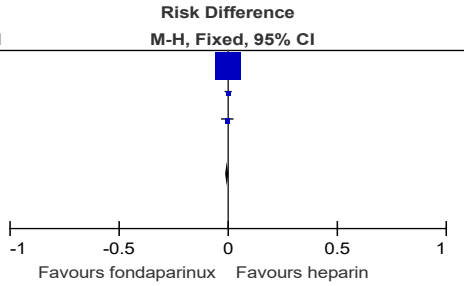

Figure 4: Myocardial infarction (30 days)

Study or Subgroup	Fondaparinux Events	Fondaparinux Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	177	3105	168	3072	93.4%	1.04 [0.85, 1.28]
Yan 2011	4	150	6	150	3.3%	0.67 [0.19, 2.31]
Zhao 2015	4	229	6	232	3.3%	0.68 [0.19, 2.36]
Total (95% CI)		**3484**		**3454**	**100.0%**	**1.02 [0.83, 1.24]**
Total events	185		180			

Heterogeneity: Chi² = 0.91, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)

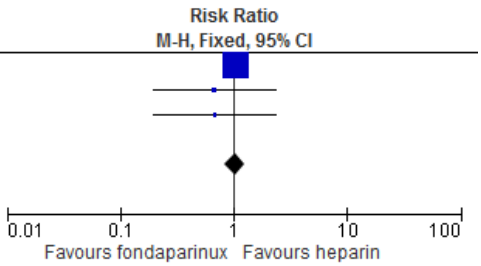

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Figure 5: Myocardial infarction (6 months)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	230	3105	210	3072	93.4%	1.08 [0.90, 1.30]
Yan 2011	5	150	6	150	2.7%	0.83 [0.26, 2.67]
Zhao 2015	7	229	9	232	4.0%	0.79 [0.30, 2.08]
Total (95% CI)		**3484**		**3454**	**100.0%**	**1.07 [0.89, 1.27]**
Total events	242		225			

Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)

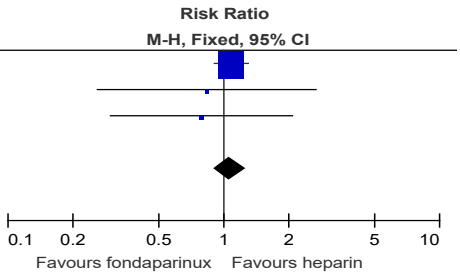

Figure 6: Stroke (30 days)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Mehta 2007	17	3105	22	3072	89.0%	-0.00 [-0.01, 0.00]
Yan 2011	0	150	0	150	4.3%	0.00 [-0.01, 0.01]
Zhao 2015	0	229	0	232	6.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**3484**		**3454**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	17		22			

Heterogeneity: Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

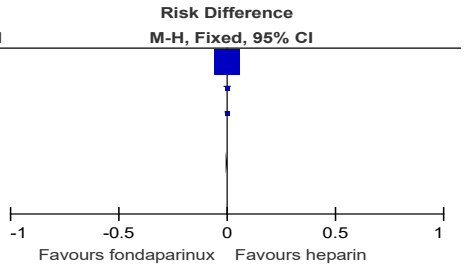

Figure 7: Stroke (6 months)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Mehta 2007	25	3105	35	3072	89.0%	-0.00 [-0.01, 0.00]
Yan 2011	0	150	0	150	4.3%	0.00 [-0.01, 0.01]
Zhao 2015	1	229	1	232	6.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**3484**		**3454**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	26		36			

Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

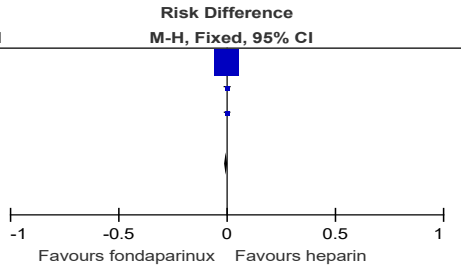

Figure 8: Major bleeding (30 days)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	88	3105	166	3072	94.9%	0.52 [0.41, 0.68]
Yan 2011	3	150	3	150	1.7%	1.00 [0.21, 4.88]
Zhao 2015	3	229	6	232	3.4%	0.51 [0.13, 2.00]
Total (95% CI)		**3484**		**3454**	**100.0%**	**0.53 [0.42, 0.68]**
Total events	94		175			

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 5.03 (P < 0.00001)

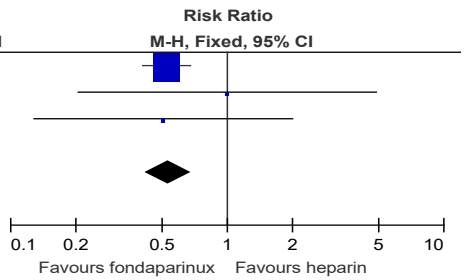

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Figure 9: Major bleeding (6 months)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	104	3105	190	3072	94.1%	0.54 [0.43, 0.68]
Yan 2011	3	150	3	150	1.5%	1.00 [0.21, 4.88]
Zhao 2015	5	229	9	232	4.4%	0.56 [0.19, 1.65]
Total (95% CI)		**3484**		**3454**	**100.0%**	**0.55 [0.44, 0.69]**
Total events	112		202			

Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 5.20 (P < 0.00001)

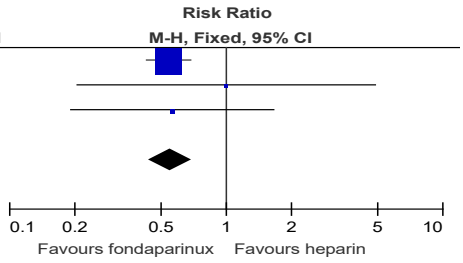

Figure 10: Minor bleeding (30 days)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	53	3105	139	3072	82.4%	0.38 [0.28, 0.52]
Yan 2011	4	150	8	150	4.7%	0.50 [0.15, 1.63]
Zhao 2015	13	229	22	232	12.9%	0.60 [0.31, 1.16]
Total (95% CI)		**3484**		**3454**	**100.0%**	**0.41 [0.31, 0.54]**
Total events	70		169			

Heterogeneity: Chi² = 1.64, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 6.35 (P < 0.00001)

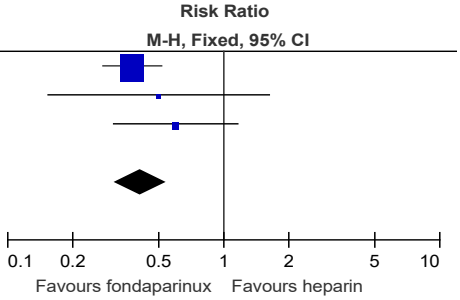

Figure 11: Minor bleeding (6 months)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	56	3105	142	3072	78.6%	0.39 [0.29, 0.53]
Yan 2011	4	150	8	150	4.4%	0.50 [0.15, 1.63]
Zhao 2015	19	229	31	232	17.0%	0.62 [0.36, 1.07]
Total (95% CI)		**3484**		**3454**	**100.0%**	**0.43 [0.34, 0.56]**
Total events	79		181			

Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 6.32 (P < 0.00001)

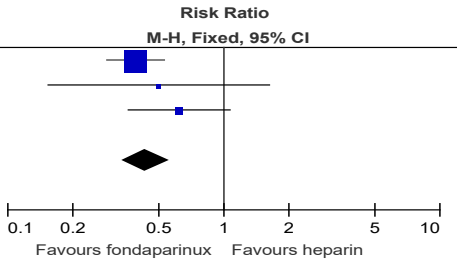

Figure 12: TIMI major bleeding (30 days)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	25	3105	46	3072	0.54 [0.33, 0.87]

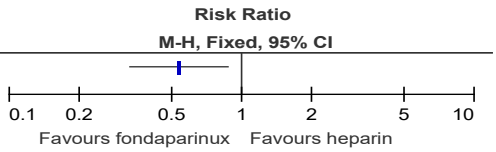

Figure 13: TIMI minor bleeding (6 months)

Study or Subgroup	Fondaparinux Events	Total	Heparin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	28	3105	53	3072	0.52 [0.33, 0.82]

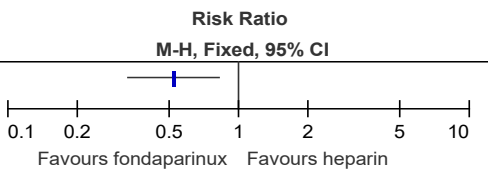

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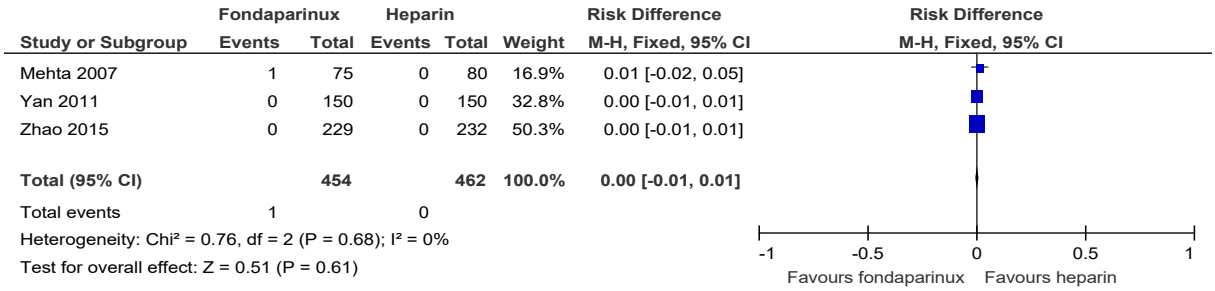
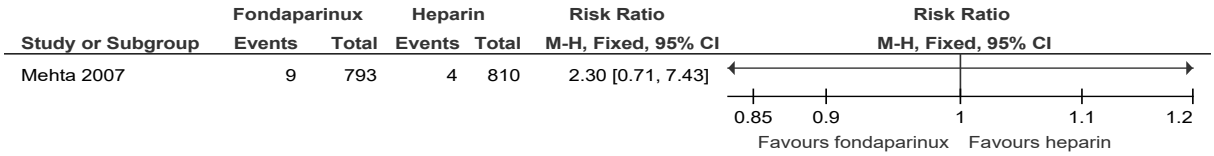
Figure 14: Catheter thrombosis (UFH before PCI)



Mehta 2007 - This 1 patient received a suboptimal dose of UFH before PCI

Figure 15: Catheter thrombosis (UFH after PCI)



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Appendix F: GRADE tables

Table 9: Clinical evidence profile: Fondaparinux versus heparin for UA/NSTEMI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fondaparinux	Heparin	Relative (95% CI)	Absolute		
All-cause mortality (30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	64/3484 (1.8%)	1.7%	See comment 3	1 fewer per 1000 (from 9 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality (6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	103/3484 (3%)	2.2%	See comment 3	2 fewer per 1000 (from 7 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/3484 (5.3%)	4%	RR 1.02 (0.83 to 1.24)	1 more per 1000 (from 7 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Myocardial infarction (6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	242/3484 (6.9%)	4%	RR 1.07 (0.89 to 1.27)	3 more per 1000 (from 4 fewer to 11	⊕⊕OO	CRITICAL

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										more)	LOW	
Stroke (30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	17/3484 (0.49%)	0%	See comment 3	-	⊕OOO VERY LOW	IMPORTANT
Stroke (6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	26/3484 (0.75%)	0.4%	See comment 3	1 fewer per 1000 (from 4 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
Major bleeding (30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94/3484 (2.7%)	2.6%	RR 0.53 (0.42 to 0.68)	12 fewer per 1000 (from 8 fewer to 15 fewer)	⊕⊕OO LOW	CRITICAL
Major bleeding (6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/3484 (3.2%)	3.9%	RR 0.55 (0.44 to 0.69)	18 fewer per 1000 (from 12 fewer to 22 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor bleeding (30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/3484 (2%)	5.3%	RR 0.41 (0.31 to 0.54)	31 fewer per 1000 (from 24 fewer to 37 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor bleeding (6 months)												

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3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/3484 (2.3%)	5.3%	RR 0.43 (0.34 to 0.56)	30 fewer per 1000 (from 23 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
TIMI Major bleeding (30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/3105 (0.81%)	1.5%	RR 0.54 (0.33 to 0.87)	7 fewer per 1000 (from 2 fewer to 10 fewer)	⊕⊕OO LOW	CRITICAL
TIMI Major bleeding (6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/3105 (0.9%)	1.7%	RR 0.52 (0.33 to 0.82)	8 fewer per 1000 (from 3 fewer to 11 fewer)	⊕⊕OO LOW	CRITICAL
Catheter thrombosis (UFH before PCI)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/454 (0.22%)	0%	See comment 3	-	⊕OOO VERY LOW	
Catheter thrombosis (UFH after PCI)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/793 (1.1%)	0.5%	RR 2.3 (0.71 to 7.43)	6 more per 1000 (from 1 fewer to 32 more)	⊕OOO VERY LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

[3] No relative effect due to 0 events. Risk difference calculated in Review Manager

[4] Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%– no imprecision

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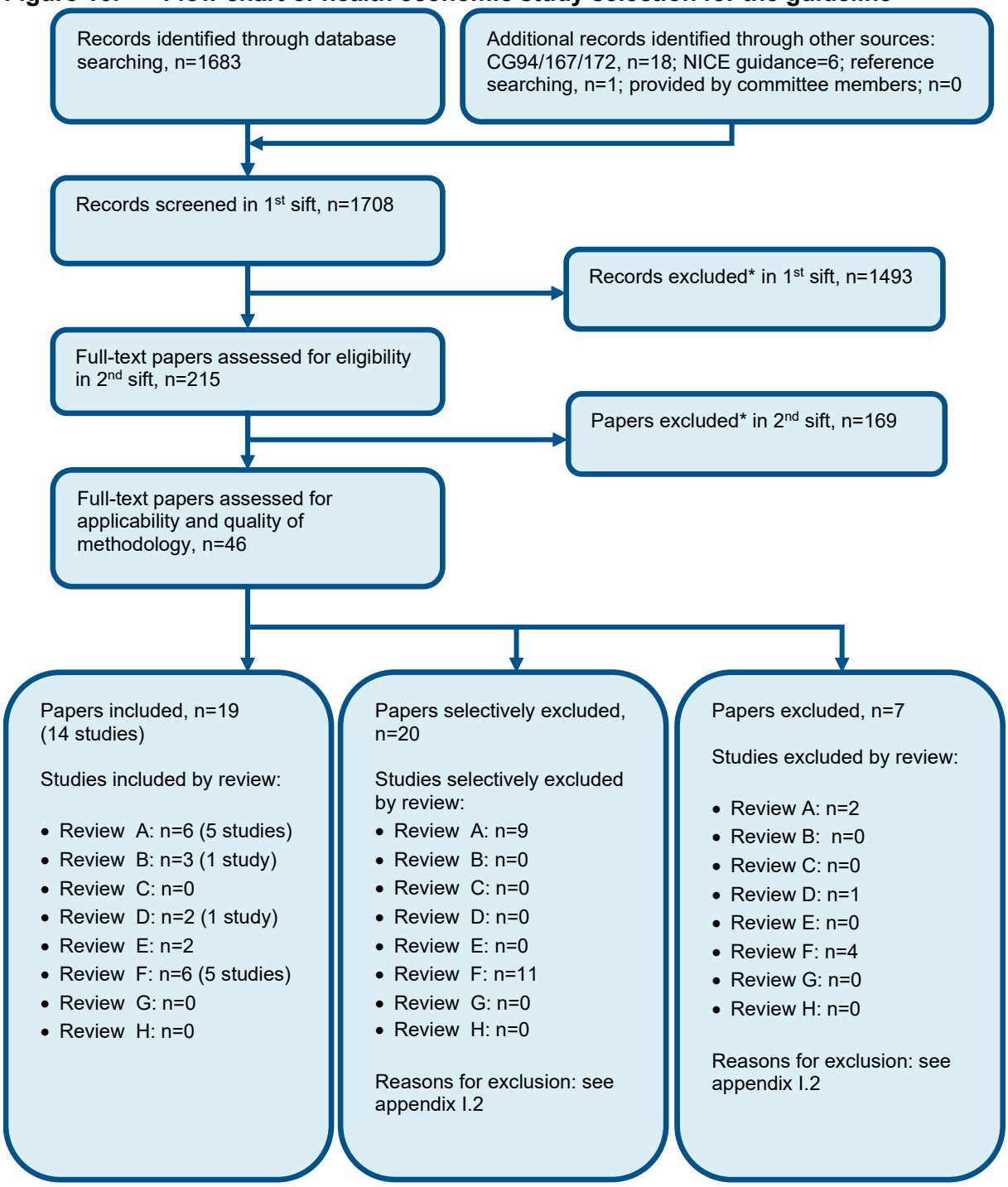
Appendix G: Health economic evidence selection

Figure 16: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Review A = dual-antiplatelet therapy; Review B = early invasive investigation for UA/NSTEMI; Review C = antithrombins in UA/NSTEMI; Review D = bivalirudin in STEMI; Review E = multi-vessel PCI; Review F = drug-eluting stents; Review G = combination of antiplatelets and anticoagulants; Review H = beta-blocker therapy.

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Appendix H: Health economic evidence tables

None

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Abell 2017[1]	Incorrect study design
Alam 2015[2]	Incorrect study design
Anderson 2010[3]	Not review population
Antman 2008[4]	Incorrect study design
Bangalore 2014[5]	Meta-analysis: checked for references
Barantke 2008[6]	Review: checked for references
Belousov 2009[7]	Abstract only
Ben-Hadj-Khalifa 2011[8]	Not guideline condition
Brito 2011[9]	Systematic review: checked for references
Budaj 2009[10]	Not review population
Bundhun 2017[11]	Systematic review: checked for references
Cohen 2015[13]	Not review population
Coons 2008[15]	Meta-analysis: checked for references
De Andrade 2012[16]	Incorrect study design
De Lorenzo-Pinto 2016[17]	Incorrect study design
Ducrocq 2015[18]	Inappropriate comparison
Eikelboom 2008[19]	Meta-analysis: checked for references
Futura Oasis-Trial Group 2010[20]	Inappropriate comparison
Gialama 2014[21]	Meta-analysis: checked for references
Gong 2016[22]	Incorrect study design
Gurbel 2016[23]	Review: checked for references
Hamon 2011[24]	Incorrect study design. Inappropriate comparison
Hamon 2012[25]	Incorrect study design. Inappropriate comparison
Jolly 2009[27]	Not review population
Joyner 2009[28]	Not review population
Karthikeyan 2009[29]	Not review population
Khodabandeh 2019[30]	Incorrect study design
Kossovsky 2012[31]	Incorrect study design
Krasnova 2015[32]	Abstract only
Landenhed 2010[33]	Not review population
Latour-Perez 2009[34]	Incorrect study design
Latour-Perez 2012[35]	Incorrect study design
Maxwell 2009[36]	Incorrect study design
McKeage 2010[37]	Systematic review: checked for references
Mehta 2005[38]	Design and rationale paper only
Mehta 2008[40]	Review: checked for references

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Study	Exclusion reason
Mehta 2008[39]	Not review population
Oldgren 2008[43]	Not review population
Pepe 2012[44]	Incorrect study design
Permsuwan 2015[45]	Incorrect study design
Peters 2008[46]	Not review population
Providencia 2014[47]	Meta-analysis: checked for references
Puymirat 2015[48]	Incorrect study design
Qiao 2016[49]	Meta-analysis: checked for references
Ross Terres 2015[50]	Incorrect study design
Schiele 2010[51]	Review: checked for references
Schiele 2010[52]	Incorrect study design
Schlitt 2008[53]	Not guideline condition
Sculpher 2009[54]	Economic analysis
Shah 2014[55]	Not review population
Sharma 2018[56]	Incorrect study design
Soeiro 2016[57]	Incorrect study design
Steg 2010[58]	Inappropriate comparison
Sun 2011[59]	Not review population
Szummer 2015[60]	Incorrect study design
Trailokya 2015[61]	Review: checked for references
Turpie 2008[62]	Review: checked for references
Van Rees Yellinga 2010[63]	Not review population
Wan Haslindawani 2014[64]	Incorrect study design
Zhao 2016[66]	Incorrect study design

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 11: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

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