National Institute for Health and Care Excellence

Final

Perioperative care in adults

[F] Evidence review for management of anticoagulant medication

NICE guideline NG180

Evidence reviews underpinning recommendation 1.3.9 in the NICE guideline

August 2020

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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1 Management of anticoagulant medication

1.1 Review question: What is the most clinically and cost effective strategy for managing anticoagulant medication?

1.2 Introduction

People taking vitamin K antagonists (VKA), with an international normalised ratio (INR) target greater than 3, are at a particularly high risk of developing deep vein thrombosis, pulmonary embolus or stroke. These are often people with mechanical heart valves and therefore require a greater level of blood thinning than other people using anticoagulant therapies, such as VKA with an INR target lower than 3 or a direct oral anticoagulant (DOAC).

To reduce this risk, it is usual practice to provide 'bridging' therapy in the perioperative period with either unfractionated heparin (UFH) or low molecular heparin (LMWH). Direct Oral Anticoagulants (DOACs) cannot be used in people with mechanical heart valves. UFH requires an intravenous infusion, and is therefore a more complicated therapy to administer than LMWH. The potential harm of bridging therapy is increased postoperative bleeding or wound infections. There is variation in the practice of bridging therapy in hospitals.

It would be useful to know if there is any difference between UFH and LMWH in terms of reducing risk of events, causing harm and costs.

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 who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR >3).
Intervention	Outpatient or self-administered low molecular weight subcutaneous heparin
Comparison	Inpatient intravenous unfractionated heparin
Outcomes	Critical outcomes: • health-related quality of life • mortality • bleeding • thromboembolism • stroke Important outcomes: • length of hospital stay (pre and post-operative)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies comparing outpatient or self-administered low molecular weight subcutaneous heparin with inpatient intravenous unfractionated heparin were identified.

See also the study selection flow chart in appendix C.

Excluded studies

See the excluded studies list in appendix I.

1.4.2 Summary of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.4.3 Quality assessment of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 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:.

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Low molecular weight heparin:

Table 2: UK costs of low molecular weight heparin

Weight	Drug (a)	Dose	Units/ pack	Cost/ pack	Cost/ unit	Units/ day	Total dose	Cost/ day	Cost/ 5 days	Source of dosage
40-43kg										
	Dalteparin sodium	7500 units	10	£42.34	£4.23	1	**7500 units**	£4.23	**£21.17**	GC member
	Enoxaparin sodium	60mg	10	£39.26	£3.93	1	**60mg**	£3.93	**£19.63**	GC member
	Tinzaparin sodium[b]	2500 units	10	£19.80	£1.98	3	**7350 units**	£5.94	**£29.70**	GC member
44-56kg										
	Dalteparin sodium	10000 units	10	£51.22	£5.12	1	**10000 units**	£5.12	**£25.61**	GC member
	Enoxaparin sodium	80mg	10	£55.13	£5.51	1	**80mg**	£5.51	**£27.57**	GC member
	Tinzaparin sodium[b]	4500 units	10	£35.63	£3.56	2	**8750 units**	£7.13	**£35.63**	GC member
57-68kg										
	Dalteparin sodium	12500 units	5	£35.29	£7.06	1	**12500 units**	£7.06	**£35.29**	GC member
	Enoxaparin sodium	100mg	10	£73.20	£7.32	1	**100mg**	£7.32	**£36.60**	GC member
	Tinzaparin sodium[b]	2500 units	10	£19.80	£1.98	5	**11025 units**	£9.90	**£49.50**	GC member
69-84kg										
	Dalteparin sodium	15000 units	5	£42.34	£8.47	1	**15000 units**	£8.47	**£42.34**	GC member
	Enoxaparin sodium	120mg	10	£87.93	£8.79	1	**120mg**	£8.79	**£43.97**	GC member
	Tinzaparin sodium[b]	14000 units	10	£83.30	£8.33	1	**13475 units**	£8.33	**£41.65**	GC member
85-103kg										
	Dalteparin sodium	18000 units	5	£50.82	£10.16	1	**18000 units**	£10.16	**£50.82**	GC member
	Enoxaparin sodium	150mg	10	£99.91	£9.99	1	**150mg**	£9.99	**£49.96**	GC member
	Tinzaparin sodium[b]	2500 units	10	£19.80	£1.98	1	**16450 units**	£10.31	**£51.55**	GC member
		14000 units	10	£83.30	£8.33	1				GC member
104-113kg										
	Dalteparin sodium	18000 units	5	£50.82	£10.16	1	**18000 units**	£10.16	**£50.82**	GC member

Weight	Drug (a)	Dose	Units/ pack	Cost/ pack	Cost/ unit	Units/ day	Total dose	Cost/ day	Cost/ 5 days	Source of dosage
	Enoxaparin sodium	80mg	10	£55.13	£5.51	2	**160mg**	£11.03	**£55.13**	GC member
	Tinzaparin sodium[b]	20000 units	10	£105.66	£10.57	1	**19075 units**	£10.57	**£52.83**	GC member
114-130kg										
	Dalteparin sodium	18,000 units	5	£50.82	£10.16	1	**18000 units**	£10.16	**£50.82**	GC member
	Enoxaparin sodium	100mg	10	£73.20	£7.32	2	**200mg**	£14.64	**£73.20**	GC member
	Tinzaparin sodium[b]	12000	10	£71.40	£7.14	2	**22575 units**	£14.28	**£71.40**	GC member

Source: British National Formulary, August 2019[32]
(a) All drugs are solutions for injection; where less is required the whole pack is costed as wastage is assumed to apply.
(b) Tinzaparin sodium is based on a dose of 175 units/kg; therefore the midpoint of each weight range was used to calculate costs.

Table 3: Costs associated with administering low molecular weight heparin

Staff	Cost per hour[(a)]	Number of hours	Number of visits	Percentage of patients[(b)]	Total cost
Practice nurse	£50.35	0.5	5	10%	£25

Source: PSSRU 2018[14]
(a) These costs include the ratio of direct to indirect time with patients of 1:33 from the PSSRU and include qualification costs.
(b) Percentage of patients requiring assistance administering low-molecular weight heparin was assumed to be 10% by the committee.

Unfractionated heparin:

Table 4: UK costs of unfractionated heparin

Drug	Formulation	Dose	Number of hours	Mg/ units	Units/ pack	Cost/ pack	Cost/ unit	Total cost	Source of dosage
Heparin sodium	Solution for injection	800 – 2,400 units per hour[b]	138[a]	10,000	10	£64.59	£6.45	£77.51 – £219.61	GC member

Source: British National Formulary, August 2019[32]

a) Based on the adult spending 5 days in hospital pre-surgery and the infusion being stopped 6 hours before surgery

b) Based on weight range of 40–130kg

The cost associated with a bed day required for administering unfractionated heparin is presented in Table 5. This is not bundled as part of the surgery they will have.

Table 5: Costs associated with administering unfractionated heparin

Cost of hospital bed day	Cost of 5 days in hospital	Source, assumptions
£407	£2,035	NHS reference costs 2017/18[16] Based on elective inpatient excess bed days, all episodes excluding paediatrics

Cost of downstream events that could be avoided with the correct bridging therapy.

Table 6: Potential downstream costs

HRG code	Description	Cost per unit	Source, assumptions
AA35A - AA35F	Stroke with CC scores 0 to 16+	£6,176	NHS reference costs 2017/18[16] Elective inpatient including excess bed days Weighted average was calculated
YQ51A - YQ51E	Deep Vein Thrombosis with CC Score 0 to 12+	£1,107	NHS reference costs 2017/18[16] Elective inpatient including excess bed days Weighted average was calculated

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant published evidence was identified.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee agreed that the main potential harm of bridging therapy is increased postoperative bleeding. As such, the committee considered critical outcomes for decision making to be health-related quality of life, mortality, bleeding, thromboembolism and stroke. The committee also considered length of hospital stay to be an important outcome towards decision making.

No evidence was identified for any of the outcomes.

1.7.1.2 The quality of the evidence

No evidence was identified.

1.7.1.3 Benefits and harms

No clinical evidence was identified.

In people at high risk of thrombosis, for example, people with mechanical heart valves, bridging therapy with low molecular weight heparin or intravenous unfractionated heparin when warfarin is temporarily discontinued may be beneficial. However, increases in bleeding events have also been reported. No evidence was found to address this issue. The committee concluded that there was insufficient evidence upon which to base a recommendation regarding management strategies for anticoagulant medication in those who require bridging for surgery and therefore made a research recommendation.

1.7.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The committee were presented with some examples of unit costs. There are considerable differences in the upfront costs of the two interventions. Low molecular weight heparin has a lower upfront cost, as adults self-administer their heparin and do not need to be in hospital. The cost of low molecular weight heparin is dependent on the patient's weight; ranging from £20 to £70 for five days. Some patients may require assistance from a district nurse to administer the injections, and it was assumed that this might apply to 10% of patients, which would cost an additional £25 per patient. Adherence may also be lower because of the self-administration required, which could have implications for whether the surgery could go ahead.

Unfractionated heparin involves an infusion, which is more expensive, and also requires up to five days in hospital pre-surgery, which has a high cost. Unfractionated heparin dose is also dependent on the weight of the adult, and ranges from £77 to £219. As adults who

receive unfractionated heparin have to be in hospital, this leads to a high cost for their hospital stay. Based on NHS reference costs the average cost of a hospital bed day is around £365 and the total cost of five days would amount to £2,035.

Potential downstream costs are also of importance and were presented to the committee. The postoperative length of stay could depend on how well the adult has responded to their bridging therapy and can have an impact on their chances of having events such as a stroke, deep vein thrombosis, pulmonary embolism or bleeding events. These events have a high cost associated with them, for example, the average cost of a stroke is £6,176 and the average cost of deep vein thrombosis is £1,107. Also, the intervention that leads to better outcomes will have a positive impact on the adult such as improved quality of life.

As there is uncertainty about which intervention is more effective, the committee agreed to make a research recommendation.

1.7.3 Other factors the committee took into account

The committee noted that people taking vitamin K antagonists (VKA), with an international normalised ratio (INR) target greater than 3 are at a particularly high risk of developing deep vein thrombosis, pulmonary embolus or stroke. These are often people with mechanical heart valves and therefore require a greater level of blood thinning than other people using anticoagulant therapies, such as VKA with an INR target lower than 3 or a direct oral anticoagulant (DOAC).

The committee was aware of other published evidence suggesting that novel oral anticoagulants/direct oral anticoagulants are not licensed and are contraindicated in people with mechanical heart values. Low molecular weight heparin has similar pharmacodynamic properties, so may be equally effective in this population; however, no evidence was identified to support or refute this.

The committee discussed an INR of 2.5 as recommended in some International guidelines. However, it was noted that values are not the ones used in current practice. For example, for people with heart valves the range is between 2.5 and 3.5 and the target is 3.0. For this reason 3.0 was chosen as the INR value for the research recommendation. In addition, the BNF refers to target INR ranges rather than target values, however a target range is generally taken to be within 0.5 of the target (that is, a target value 3.5 equates to a target range of 3 to 4).

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: Management of anticoagulant medication.

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the most clinically and cost effective strategy for perioperative management of anticoagulant medication in patients taking warfarin with target INR >3?
2.	Review question	What is the most clinically and cost effective strategy for perioperative management of anticoagulant medication in patients taking warfarin with target INR >3?
3.	Objective	To determine the most clinically and cost effective strategy for perioperative management of anticoagulant medication in patients taking warfarin with target INR >3 undergoing surgery.
4.	Searches	• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE The searches may be re-run 6 weeks before the 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	Perioperative care
6.	Population	Inclusion: Adults 18 years and over who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR >3). Exclusion: • children and young people aged 17 years and younger • surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	• outpatient or self-administered low molecular weight subcutaneous heparin

8.	Comparator/Reference standard/Confounding factors	• inpatient intravenous unfractionated heparin
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. Observational studies if no RCT evidence is identified.
10.	Other exclusion criteria	Exclusions: • non-English language studies • studies published before 2000
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	• health-related quality of life • mortality • bleeding • thromboembolism • stroke The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
13.	Secondary outcomes (important outcomes)	• length of hospital stay (pre and postoperative) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort

		studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments 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	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for 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. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified. • List any other software planned to be used. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered 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 pooled using random-effects.			
17.	Analysis of sub-groups	Subgroups: • older people (over 60 years) • Chronic Kidney Disease (CKD)			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	[To be added.]			
22.	Anticipated completion date	[To be added.]			
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 perioperativecare@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: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swain Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane
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 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.
29.	Other registration details	n/a
30.	Reference/URL for published protocol	n/a
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	Perioperative care, preoperative, anticoagulant, warfarin, bridging	
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	

Table 8: 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.) • 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. 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).[41] **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 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 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 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. For example, economic evaluations based on observational studies will be excluded, when the clinical review is only looking for RCTs,

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 2014, updated 2018.[41]

For more detailed information, please see the Methodology Review.

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 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Preoperative Care/ or Preoperative Period/
2.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
3.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
7.	5 not 6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/

15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	anticoagulants/ or acenocoumarol/ or coumarins/ or phenindione/ or phenprocoumon/ or warfarin/
28.	warfarin*.ti,ab.
29.	(coumarin* or coumadin or dicoumarol or acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)).ti,ab.
30.	or/27-29
31.	26 and 30
32.	randomized controlled trial.pt.
33.	controlled clinical trial.pt.
34.	randomi#ed.ab.
35.	placebo.ab.
36.	randomly.ab.
37.	clinical trials as topic.sh.
38.	trial.ti.
39.	or/32-38
40.	Meta-Analysis/
41.	Meta-Analysis as Topic/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	Epidemiologic studies/
52.	Observational study/
53.	exp Cohort studies/
54.	(cohort adj (study or studies or analys* or data)).ti,ab.
55.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

56.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	Controlled Before-After Studies/
58.	Historically Controlled Study/
59.	Interrupted Time Series Analysis/
60.	(before adj2 after adj2 (study or studies or data)).ti,ab.
61.	or/51-60
62.	exp case control study/
63.	case control*.ti,ab.
64.	or/62-63
65.	61 or 64
66.	Cross-sectional studies/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/66-67
69.	61 or 68
70.	61 or 64 or 68
71.	39 or 50 or 70
72.	31 and 71
73.	31 and (39 or 50 or 72)

Embase (Ovid) search terms

1.	*preoperative care/ or *preoperative period/
2.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
3.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
7.	5 not 6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22

24.	7 not 23
25.	*anticoagulant agent/ or *acenocoumarol/ or *coumarin derivative/ or *phenindione/ or *phenprocoumon/ or *warfarin/
26.	warfarin*.ti,ab.
27.	(coumarin* or coumadin or dicoumarol or acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)).ti,ab.
28.	or/25-27
29.	24 and 28
30.	random*.ti,ab.
31.	factorial*.ti,ab.
32.	(crossover* or cross over*).ti,ab.
33.	((doubl* or singl*) adj blind*).ti,ab.
34.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
35.	crossover procedure/
36.	single blind procedure/
37.	randomized controlled trial/
38.	double blind procedure/
39.	or/30-38
40.	systematic review/
41.	Meta-Analysis/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	Epidemiologic studies/
52.	Observational study/
53.	exp Cohort studies/
54.	(cohort adj (study or studies or analys* or data)).ti,ab.
55.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
56.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	Controlled Before-After Studies/
58.	Historically Controlled Study/
59.	Interrupted Time Series Analysis/
60.	(before adj2 after adj2 (study or studies or data)).ti,ab.
61.	or/51-60
62.	exp case control study/
63.	case control*.ti,ab.

64.	or/62-63
65.	61 or 64
66.	Cross-sectional studies/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/66-67
69.	61 or 68
70.	61 or 64 or 68
71.	39 or 50 or 70
72.	29 and 71
73.	29 and (39 or 50 or 72)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Preoperative Care] this term only
#2.	MeSH descriptor: [Preoperative Period] this term only
#3.	(pre-operat* or preoperati*or pre-surg* or presurg*):ti,ab
#4.	(before or prior or advance or pre or prepar*) near/3 (surg* or operat* or anaesthes* or anesthes*):ti,ab
#5.	(or #1-#4)
#6.	MeSH descriptor: [Anticoagulants] this term only
#7.	MeSH descriptor: [Acenocoumarol] this term only
#8.	MeSH descriptor: [Coumarins] this term only
#9.	MeSH descriptor: [Phenindione] this term only
#10.	MeSH descriptor: [Phenprocoumon] this term only
#11.	MeSH descriptor: [Warfarin] this term only
#12.	(or #6-#11)
#13.	warfarin*:ti,ab
#14.	(coumarin* or coumadin or dicoumarol or acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)):ti,ab
#15.	#12 or #13 or #14
#16.	#5 and #15

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the perioperative care population 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 health economics searches were run on Medline and Embase.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 May 2019	Exclusions Health economics studies
Embase	2014 – 30 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 02 May 2019 NHSEED - Inception to 02 May	None

Database	Dates searched	Search filter used
	2019	

Medline (Ovid) search terms

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	1 or 2 or 3 or 4 or 5
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	7 or 8
10.	postoperative care/ or exp Postoperative Period/ or exp Perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp Preoperative Care/ or Preoperative Period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	6 or 9 or 14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.

37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
41.	39 not 40
42.	economics/
43.	value of life/
44.	exp "costs and cost analysis"/
45.	exp Economics, Hospital/
46.	exp Economics, medical/
47.	Economics, nursing/
48.	economics, pharmaceutical/
49.	exp "Fees and Charges"/
50.	exp budgets/
51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/42-57
59.	41 and 58

Embase (Ovid) search terms

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
5.	1 or 2 or 3 or 4
6.	peroperative care/ or exp peroperative care/ or exp perioperative nursing/
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	6 or 7 or 8
10.	postoperative care/ or exp postoperative period/ or perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp preoperative care/ or preoperative period/

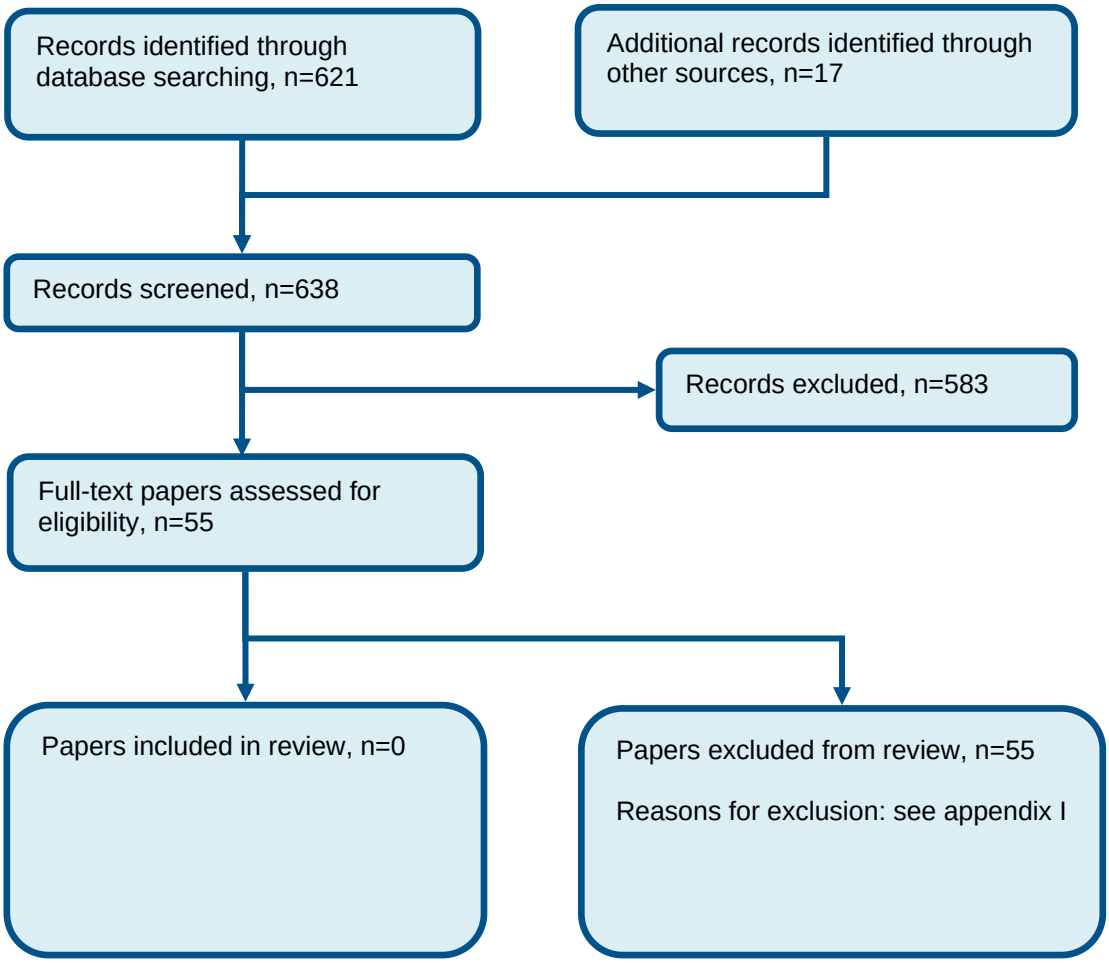
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	5 or 9 or 14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/
33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
39.	37 not 38
40.	health economics/
41.	exp economic evaluation/
42.	exp health care cost/
43.	exp fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	39 and 53

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Preoperative Care EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Perioperative Care EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Perioperative Period EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Perioperative Nursing EXPLODE ALL TREES
#5.	(((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#6.	(((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#7.	(((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#8.	(((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(* IN HTA)
#11.	(* IN NHSEED)
#12.	#9 AND #10
#13.	#9 AND #11
#14.	MeSH DESCRIPTOR Intraoperative Care EXPLODE ALL TREES
#15.	#1 OR #2 OR #3 OR #4 OR #14
#16.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*))
#17.	(((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#18.	((postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*))
#19.	((after adj3 (surg* or operat* or anaesthes* or anesthes*)))
#20.	((post adj3 (operat* or anaesthes* or anesthes*)))
#21.	((pre-operat* or preoperat* or pre-surg* or presurg*))
#22.	(((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#23.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24.	#10 AND #23
#25.	#11 AND #23
#26.	#12 OR #13 OR #24 OR #25

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of management of anticoagulant medication



Appendix D: Clinical evidence tables

No relevant clinical studies were identified.

Appendix E: Forest plots

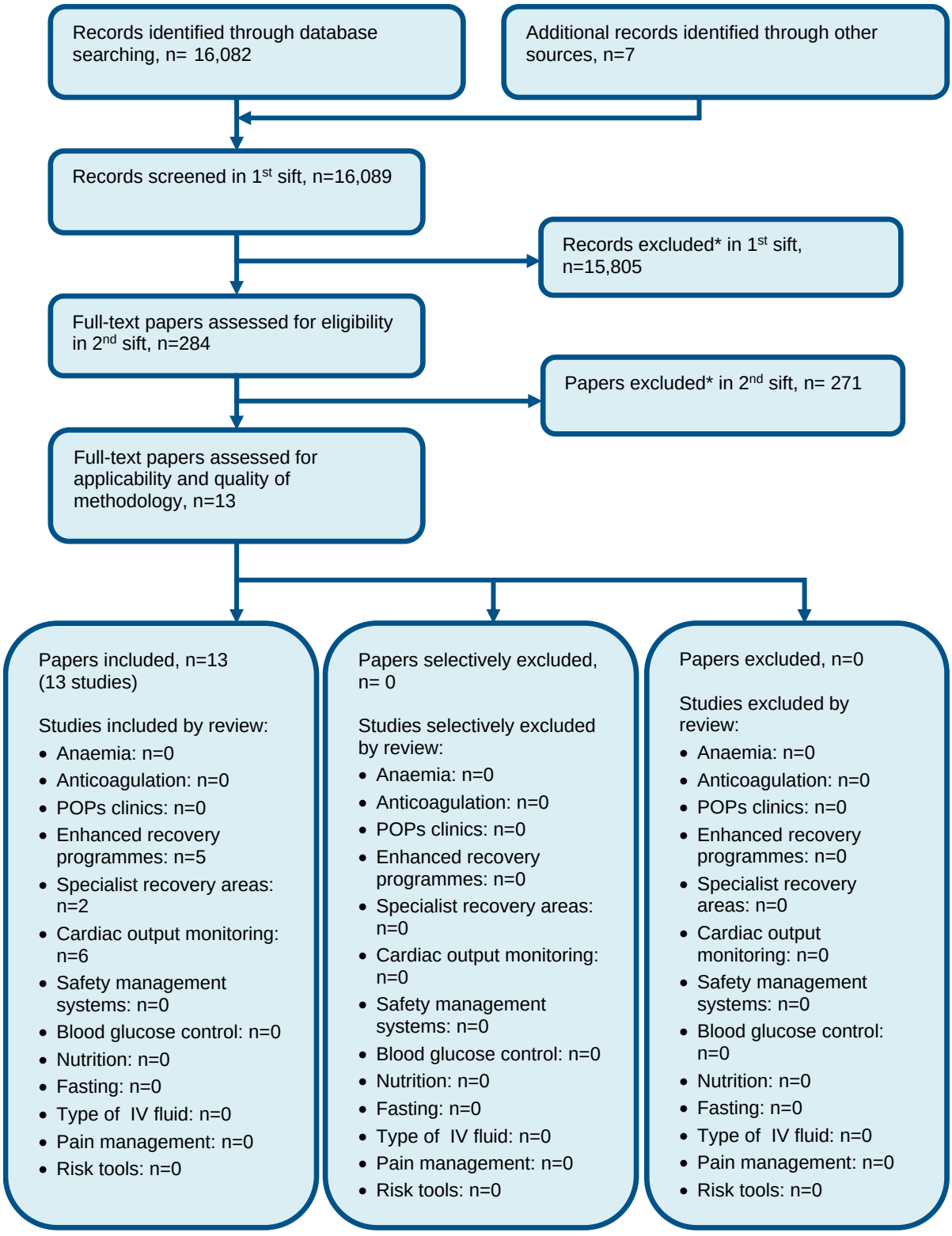
No relevant clinical studies were identified.

Appendix F: GRADE tables

No relevant clinical studies were identified.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 11: Studies excluded from the clinical review

Study	Exclusion reason
Akl 2008[3]	Not review population
Akl 2011[2]	Not review population
Akl 2014[1]	Not review population
Anon 1988[13]	Not review population
Anonymous 1997[4]	Not review population
Attanasio 2001[5]	Incorrect interventions
Bani-hani 2008[6]	Incorrect interventions
Baykal 2001[7]	Not review population. Incorrect interventions
Bergqvist 1990[8]	Not review population. Incorrect interventions
Boncinelli 2001[9]	Not review population
Chen 2013[10]	Not review population
Cheng 2012[11]	Incorrect interventions
Cohen 2005[12]	Incorrect interventions
Dahan 1990[15]	Incorrect study design (narrative report)
Dixon 2011[17]	Incorrect interventions
Ederhy 2006[18]	Not in English
Eriksson 1996[19]	Incorrect interventions
Eriksson 1997[20]	Incorrect interventions
Eriksson 1997[21]	Incorrect interventions
Forster 2016[22]	Incorrect interventions
Fricker 1988[23]	Not review population
Gallus 1993[24]	Not review population
Godwin 1993[25]	Study abstract
Guo 2017[26]	Incorrect interventions
Haas 2005[28]	Not review population. Incorrect interventions
Haas 2006[27]	Not review population
Handoll 2002[29]	Not review population
Heilmann 1998[30]	Not review population
Jamula 2009[31]	Incorrect interventions
Junqueira 2017[33]	Not review population
Kakkar 1997[34]	Not review population
Kakkar 2000[35]	Not review population
Lastoria 2006[36]	Not review population
Lereun 2011[37]	Incorrect interventions
Matar 2018[38]	Not review population
Mcleod 2001[39]	Not review population
Monreal 1989[40]	Not review population. Incorrect interventions
Onarheim 1986[42]	Not review population
Ono 2015[43]	Article not in English

Study	Exclusion reason
Pini 1989[44]	Not review population. Incorrect interventions
Platz 1993[45]	Article not in English
Rader 1997[46]	Conference abstract
Ramos 2008[47]	Incorrect interventions
Renda 2007[48]	Not review population
Senaran 2006[49]	Incorrect interventions
Shaw 2018[50]	Incorrect interventions
Speziale 1988[51]	Not review population. Incorrect interventions
Swedenborg 1996[52]	Not review population
Von tempelhoff 1997[53]	Not review population
Von tempelhoff 2000[54]	Not review population
Wang 2004[55]	Incorrect interventions
Watanabe 2011[56]	Incorrect interventions. incorrect study design
Zee 2017[57]	Not guideline condition

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 12: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 Anticoagulant medication

Research question: What is the most clinically and cost effective strategy for managing anticoagulant medication?

Why this is important:

The search criteria revealed no evidence comparing the different strategies for bridging anticoagulation in the perioperative period for patients requiring an INR >3.0. Evidence is required to compare the use of unfractionated heparin as an inpatient and LMWH as an outpatient in terms of clinical and cost effective outcomes.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults 18 years and over who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR >3). This is often people with mechanical heart valves. This refers to target INR ranges rather than target values, however a target range is generally taken to be within 0.5 of the target (that is, a target value 3.5 equates to a target range of 3 to 4). Components: Outpatient or self-administered low molecular weight subcutaneous heparin or Inpatient intravenous unfractionated heparin Outcome(s): Health-related quality of life, mortality, bleeding, thromboembolism, stroke and length of hospital stay (pre and postoperative)
Importance to patients or the population	We need to know which strategy is most effective based on group consensus terms of providing safe prevention of clinical events and the impact on patient quality of life as well as service costs.
Relevance to NICE guidance	Currently Trusts adopt different strategies based on no evidence.
Relevance to the NHS	Consensus based recommendations would change practice. The potential to reduce length of hospital admission might be significant.
National priorities	None identified
Current evidence base	No studies that met the review criteria were identified.
Equality	None identified
Study design	Dephi survey of haematologists
Feasibility	There are no feasibility issues but a good response to the survey is required if it to be representative
Other comments	There is uncertainty that either method is equivalent to the use of VKA antagonists in patients who are high risk. The majority of patients will have mechanical heart valves
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.