

## Perioperative care in adults

### [F] Management of anticoagulant medication

*NICE guideline*

*Intervention evidence review*

*November 2019*

*Draft for Consultation*

*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.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#), [Scottish Government](#), and [Northern Ireland Executive](#). All NICE guidance is subject to regular review and may be updated or withdrawn.

## **Copyright**

© NICE 2019. All rights reserved. Subject to [Notice of rights](#).

# Contents

<b>1</b>	<b>Management of anticoagulant medication.....</b>	<b>5</b>
1.1	Review question: What is the most clinically and cost effective strategy for managing anticoagulant medication? .....	5
1.2	Introduction .....	5
1.3	PICO table.....	5
1.4	Clinical evidence .....	5
1.4.1	Included studies .....	5
1.4.2	Summary of clinical studies included in the evidence review.....	6
1.4.3	Quality assessment of clinical studies included in the evidence review .....	6
1.5	Economic evidence .....	6
1.5.1	Included studies .....	6
1.5.2	Excluded studies .....	6
1.5.3	Unit costs .....	6
1.6	Evidence statements .....	10
1.6.1	Clinical evidence statements.....	10
1.6.2	Health economic evidence statements.....	10
1.7	The committee’s discussion of the evidence.....	10
1.7.1	Interpreting the evidence.....	10
1.7.2	Cost effectiveness and resource use .....	10
1.7.3	Other factors the committee took into account .....	11
	<b>Appendices.....</b>	<b>17</b>
	Appendix A: Review protocols .....	17
	Appendix B: Literature search strategies .....	24
	B.1 Clinical search literature search strategy .....	24
	B.2 Health Economics literature search strategy.....	29
	Appendix C: Clinical evidence selection.....	34
	Appendix D: Clinical evidence tables .....	35
	Appendix E: Forest plots.....	36
	Appendix F: GRADE tables .....	37
	Appendix G: Health economic evidence selection .....	38
	Appendix H: Health economic evidence tables .....	39
	Appendix I: Excluded studies.....	40
	I.1 Excluded clinical studies.....	40
	I.2 Excluded health economic studies.....	41
	Appendix J: Research recommendations .....	42

# 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

<b>Population</b>	Adults 18 years and over who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR >3).
<b>Intervention</b>	Outpatient or self-administered low molecular weight subcutaneous heparin
<b>Comparison</b>	Inpatient intravenous unfractionated heparin
<b>Outcomes</b>	Critical outcomes: <ul style="list-style-type: none"><li>• health-related quality of life</li><li>• mortality</li><li>• bleeding</li><li>• thromboembolism</li><li>• stroke</li></ul> Important outcomes: <ul style="list-style-type: none"><li>• length of hospital stay (pre and post-operative)</li></ul>
<b>Study design</b>	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.

1 Excluded studies

2 See the excluded studies list in appendix I.

3 **1.4.2 Summary of clinical studies included in the evidence review**

4 No relevant clinical studies were identified.

5 **1.4.3 Quality assessment of clinical studies included in the evidence review**

6 No relevant clinical studies were identified.

7 **1.5 Economic evidence**

8 **1.5.1 Included studies**

9 No health economic studies were included.

10 **1.5.2 Excluded studies**

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

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

14 **1.5.3 Unit costs**

15 Relevant unit costs are provided below to aid consideration of cost effectiveness.  
16  
17  
18

## 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
<b>40-43kg</b>										
	Dalteparin sodium	7500 units	10	£42.34	£4.23	1	<b>7500 units</b>	£4.23	<b>£21.17</b>	GC member
	Enoxaparin sodium	60mg	10	£39.26	£3.93	1	<b>60mg</b>	£3.93	<b>£19.63</b>	GC member
	Tinzaparin sodium <sup>b</sup>	2500 units	10	£19.80	£1.98	3	<b>7350 units</b>	£5.94	<b>£29.70</b>	GC member
<b>44-56kg</b>										
	Dalteparin sodium	10000 units	10	£51.22	£5.12	1	<b>10000 units</b>	£5.12	<b>£25.61</b>	GC member
	Enoxaparin sodium	80mg	10	£55.13	£5.51	1	<b>80mg</b>	£5.51	<b>£27.57</b>	GC member
	Tinzaparin sodium <sup>b</sup>	4500 units	10	£35.63	£3.56	2	<b>8750 units</b>	£7.13	<b>£35.63</b>	GC member
<b>57-68kg</b>										
	Dalteparin sodium	12500 units	5	£35.29	£7.06	1	<b>12500 units</b>	£7.06	<b>£35.29</b>	GC member
	Enoxaparin sodium	100mg	10	£73.20	£7.32	1	<b>100mg</b>	£7.32	<b>£36.60</b>	GC member
	Tinzaparin sodium <sup>b</sup>	2500 units	10	£19.80	£1.98	5	<b>11025 units</b>	£9.90	<b>£49.50</b>	GC member
<b>69-84kg</b>										
	Dalteparin sodium	15000 units	5	£42.34	£8.47	1	<b>15000 units</b>	£8.47	<b>£42.34</b>	GC member
	Enoxaparin sodium	120mg	10	£87.93	£8.79	1	<b>120mg</b>	£8.79	<b>£43.97</b>	GC member
	Tinzaparin sodium <sup>b</sup>	14000 units	10	£83.30	£8.33	1	<b>13475 units</b>	£8.33	<b>£41.65</b>	GC member
<b>85-103kg</b>										
	Dalteparin sodium	18000 units	5	£50.82	£10.16	1	<b>18000 units</b>	£10.16	<b>£50.82</b>	GC member
	Enoxaparin sodium	150mg	10	£99.91	£9.99	1	<b>150mg</b>	£9.99	<b>£49.96</b>	GC member
	Tinzaparin sodium <sup>b</sup>	2500 units	10	£19.80	£1.98	1	<b>16450 units</b>	£10.31	<b>£51.55</b>	GC member
		14000 units	10	£83.30	£8.33	1				GC member
<b>104-113kg</b>										
	Dalteparin sodium	18000 units	5	£50.82	£10.16	1	<b>18000 units</b>	£10.16	<b>£50.82</b>	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	<b>160mg</b>	£11.03	<b>£55.13</b>	GC member
	Tinzaparin sodium <sup>b</sup>	20000 units	10	£105.66	£10.57	1	<b>19075 units</b>	£10.57	<b>£52.83</b>	GC member
<b>114-130kg</b>										
	Dalteparin sodium	18,000 units	5	£50.82	£10.16	1	<b>18000 units</b>	£10.16	<b>£50.82</b>	GC member
	Enoxaparin sodium	100mg	10	£73.20	£7.32	2	<b>200mg</b>	£14.64	<b>£73.20</b>	GC member
	Tinzaparin sodium <sup>b</sup>	12000	10	£71.40	£7.14	2	<b>22575 units</b>	£14.28	<b>£71.40</b>	GC member

Source: British National Formulary, August 2019<sup>32</sup>

(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 <sup>(a)</sup>	Number of hours	Number of visits	Percentage of patients <sup>(b)</sup>	Total cost
Practice nurse	£50.35	0.5	5	10%	£25

Source: PSSRU 2018<sup>14</sup>

(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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19

**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 <sup>b</sup>	138 <sup>a</sup>	10,000	10	£64.59	£6.45	£77.51 – £219.61	GC member

Source: British National Formulary, August 2019<sup>32</sup>

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 <sup>16</sup> 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 <sup>16</sup> 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 <sup>16</sup> Elective inpatient including excess bed days Weighted average was calculated

## 1 1.6 Evidence statements

### 2 1.6.1 Clinical evidence statements

3 No relevant published evidence was identified.

### 4 1.6.2 Health economic evidence statements

- 5 • No relevant economic evaluations were identified.

## 6 1.7 The committee's discussion of the evidence

### 7 1.7.1 Interpreting the evidence

#### 8 1.7.1.1 The outcomes that matter most

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

14 No evidence was identified for any of the outcomes.

#### 15 1.7.1.2 The quality of the evidence

16 No evidence was identified.

#### 17 1.7.1.3 Benefits and harms

18 No clinical evidence was identified.

19 In people at high risk of thrombosis, for example, people with mechanical heart valves,  
20 bridging therapy with low molecular weight heparin or intravenous unfractionated heparin  
21 when warfarin is temporarily discontinued may be beneficial. However, increases in bleeding  
22 events have also been reported. No evidence was found to address this issue

### 23 1.7.2 Cost effectiveness and resource use

24 No economic evidence was identified for this question.

25 The committee were presented with some examples of unit costs. There are considerable  
26 differences in the upfront costs of the two interventions. Low molecular weight heparin has a  
27 lower upfront cost, as adults self-administer their heparin and do not need to be in hospital.  
28 The cost of low molecular weight heparin is dependent on the patient's weight; ranging from  
29 £20 to £70 for five days. Some patients may require assistance from a district nurse to  
30 administer the injections, and it was assumed that this might apply to 10% of patients, which  
31 would cost an additional £25 per patient. Adherence may also be lower because of the self-  
32 administration required, which could have implications for whether the surgery could go  
33 ahead.

34 Unfractionated heparin involves an infusion, which is more expensive, and also requires up  
35 to five days in hospital pre-surgery, which has a high cost. Unfractionated heparin dose is  
36 also dependent on the weight of the adult, and ranges from £77 to £219. As adults who  
37 receive unfractionated heparin have to be in hospital, this leads to a high cost for their  
38 hospital stay. Based on NHS reference costs the average cost of a hospital bed day is  
39 around £365 and the total cost of five days would amount to £2,035.

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

8 The committee stated that there is variation in current practice, emphasising the need to  
9 establish which form of heparin is more effective. They felt that although low molecular  
10 weight heparin is being used more widely for this group of adults, there is a lack of  
11 substantial evidence as to whether it is as effective as unfractionated heparin. Conversely, as  
12 unfractionated heparin is more resource intensive, there is also evidence needed to confirm  
13 its cost effectiveness compared to low molecular weight heparin.

14 As there was no relevant clinical or cost effectiveness evidence, there is uncertainty about  
15 which intervention is more effective, therefore the committee made a research  
16 recommendation.

### 17 **1.7.3 Other factors the committee took into account**

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

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

29 The committee discussed an INR of 2.5 as recommended in some International guidelines.  
30 However, it was noted that values are not the ones used in current practice. For example,  
31 for people with heart valves the range is between 2.5 and 3.5 and the target is 3.0. For this  
32 reason 3.0 was chosen as the INR value for the research recommendation. In addition, the  
33 BNF refers to target INR ranges rather than target values, however a target range is  
34 generally taken to be within 0.5 of the target (that is, a target value 3.5 equates to a target  
35 range of 3 to 4).  
36

## References

1. Akl EA, Kahale L, Sperati F, Neumann I, Labedi N, Terrenato I et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: 24966161. DOI: <https://dx.doi.org/10.1002/14651858.CD009447.pub2>.
2. Akl EA, Labedi N, Terrenato I, Barba M, Sperati F, Sempos EV et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: 22071865. DOI: <https://dx.doi.org/10.1002/14651858.CD009447>.
3. Akl EA, Terrenato I, Barba M, Sperati F, Sempos EV, Muti P et al. Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Archives of Internal Medicine*. 2008; 168(12):1261-9
4. Anonymous. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. *British Journal of Surgery*. 1997; 84(8):1099-103
5. Attanasio E, Russo P, Carunchio G, Caprino L. Dermatan sulfate versus unfractionated heparin for the prevention of venous thromboembolism in patients undergoing surgery for cancer. A cost-effectiveness analysis. *Pharmacoeconomics*. 2001; 19(1):57-68
6. Bani-Hani M, Titi MA, Jaradat I, Al-Khaffaf H. Interventions for preventing venous thromboembolism following abdominal aortic surgery. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD005509. DOI: [10.1002/14651858.CD005509.pub2](https://dx.doi.org/10.1002/14651858.CD005509.pub2).
7. Baykal C, Al A, Demirtas E, Ayhan A. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind clinical study. *European Journal of Gynaecological Oncology*. 2001; 22(2):127-30
8. Bergqvist D, Burmark US, Frisell J, Guilbaud O, Hallbook T, Horn A et al. Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. *Seminars in Thrombosis and Hemostasis*. 1990; 16(Suppl):19-24
9. Boncinelli S, Marsili M, Lorenzi P, Fabbri LP, Pittino S, Filoni M et al. Haemostatic molecular markers in patients undergoing radical retropubic prostatectomy for prostate cancer and submitted to prophylaxis with unfractionated or low molecular weight heparin. *Minerva Anestesiologica*. 2001; 67(10):693-703
10. Chen YC, Chi CC, Chan FC, Wen YW. Low molecular weight heparin for prevention of microvascular occlusion in digital replantation. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: 23836382. DOI: <https://dx.doi.org/10.1002/14651858.CD009894.pub2>.
11. Cheng SS, Nordenholz K, Matero D, Pearlman N, McCarter M, Gajdos C et al. Standard subcutaneous dosing of unfractionated heparin for venous thromboembolism prophylaxis in surgical ICU patients leads to subtherapeutic factor Xa inhibition. *Intensive Care Medicine*. 2012; 38(4):642-8
12. Cohen AT, Hirst C, Sherrill B, Holmes P, Fidan D. Meta-analysis of trials comparing ximelagatran with low molecular weight heparin for prevention of venous

- 1 thromboembolism after major orthopaedic surgery. *British Journal of Surgery*. 2005;  
2 92(11):1335-44
- 3 13. Comparison of a low molecular weight heparin and unfractionated heparin for the  
4 prevention of deep vein thrombosis in patients undergoing abdominal surgery. The  
5 European Fraxiparin Study (EFS) Group. *British Journal of Surgery*. 1988;  
6 75(11):1058-63
- 7 14. Curtis L, Burns A. Unit costs of health and social care 2018. Canterbury. Personal  
8 Social Services Research Unit University of Kent, 2018. Available from:  
9 <https://kar.kent.ac.uk/70995/>
- 10 15. Dahan M, Boneu B, Renella J, Berjaud J, Bogaty J, Durand J. Prevention of deep  
11 venous thromboses in cancer thoracic surgery with a low-molecular-weight heparin:  
12 fraxiparine. *Fraxiparine: Second International Symposium Recent Pharmacological  
13 and Clinical Data*. New York, NY: John Wiley & Sons Inc., 1990. p. 27-31.
- 14 16. Department of Health. NHS reference costs 2017-18. 2017. Available from:  
15 <https://improvement.nhs.uk/resources/reference-costs/#rc1718> Last accessed:  
16 02/08/2019
- 17 17. Dixon B, Opeskin K, Stamaratis G, Nixon I, Yi M, Newcomb AE et al. Pre-operative  
18 heparin reduces pulmonary microvascular fibrin deposition following cardiac surgery.  
19 *Thrombosis Research*. 2011; 127(1):e27-30
- 20 18. Ederhy S, Di Angelantonio E, Meuleman C, Janewer S, Boccara F, Cohen A. Low  
21 molecular weight heparin and non valvular atrial fibrillation. *Archives des Maladies du  
22 Coeur et des Vaisseaux*. 2006; 99(12):1210-1214
- 23 19. Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P. Prevention of deep-  
24 vein thrombosis after total hip replacement: direct thrombin inhibition with  
25 recombinant hirudin, CGP 39393. *Lancet*. 1996; 347(9002):635-9
- 26 20. Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C et al. Prevention of  
27 thromboembolism with use of recombinant hirudin. Results of a double-blind,  
28 multicenter trial comparing the efficacy of desirudin (Revasc) with that of  
29 unfractionated heparin in patients having a total hip replacement. *Journal of Bone &  
30 Joint Surgery - American Volume*. 1997; 79(3):326-33
- 31 21. Eriksson BI, Wille-Jorgensen P, Kalebo P, Mouret P, Rosencher N, Bosch P et al. A  
32 comparison of recombinant hirudin with a low-molecular-weight heparin to prevent  
33 thromboembolic complications after total hip replacement. *New England Journal of  
34 Medicine*. 1997; 337(19):1329-35
- 35 22. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous  
36 thromboembolism following total hip or knee replacement or hip fracture repair.  
37 *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD004179. DOI:  
38 10.1002/14651858.CD004179.pub2.
- 39 23. Fricker JP, Vergnes Y, Schach R, Heitz A, Eber M, Grunebaum L et al. Low dose  
40 heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis  
41 of thromboembolic complications of abdominal oncological surgery. *European Journal  
42 of Clinical Investigation*. 1988; 18(6):561-7
- 43 24. Gallus A, Cade J, Ockelford P, Hepburn S, Maas M, Magnani H. Orgaran (Org  
44 10172) or heparin for preventing venous thrombosis after elective surgery for  
45 malignant disease? A double-blind, randomised, multicentre comparison. ANZ-  
46 Organon Investigators' Group. *Thrombosis and Hemostasis*. 1993; 70(4):562-7

- 1 25. Godwin JE, Comp.P., Davidson B, Rossi M. Comparison of the efficacy and safety of  
2 subcutaneous Rd heparin vs subcutaneous unfractionated heparin for the prevention  
3 of deep-vein thrombosis in patients undergoing abdominal or pelvic-surgery for  
4 cancer. *Thrombosis and Haemostasis*. 1993; 69(6):647
- 5 26. Guo Q, Huang B, Zhao J, Ma Y, Yuan D, Yang Y et al. Perioperative pharmacological  
6 thromboprophylaxis in patients with cancer: A systematic review and meta-analysis.  
7 *Annals of Surgery*. 2017; 265(6):1087-93
- 8 27. Haas S, Breyer HG, Bacher HP, Fareed J, Misselwitz F, Victor N et al. Prevention of  
9 major venous thromboembolism following total hip or knee replacement: a  
10 randomized comparison of low-molecular-weight heparin with unfractionated heparin  
11 (ECHOS Trial). *International Angiology*. 2006; 25(4):335-42
- 12 28. Haas S, Wolf H, Kakkar AK, Fareed J, Encke A. Prevention of fatal pulmonary  
13 embolism and mortality in surgical patients: a randomized double-blind comparison of  
14 LMWH with unfractionated heparin. *Thrombosis and Haemostasis*. 2005; 94(4):814-9
- 15 29. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong GM, Milne AA, Gillespie WJ.  
16 Heparin, low molecular weight heparin and physical methods for preventing deep vein  
17 thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane*  
18 *Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD000305. DOI:  
19 10.1002/14651858.CD000305.
- 20 30. Heilmann L, Von Tempelhoff GF, Kirkpatrick CJ, Schneider D, Hommel G, Pollow K.  
21 Comparison of unfractionated versus low molecular weight heparin for deep vein  
22 thrombosis prophylaxis during breast and pelvic cancer surgery: efficacy, safety, and  
23 follow-up. *Clinical and Applied Thrombosis-Hemostasis*. 1998; 4(4):268-73
- 24 31. Jamula E, Woods K, Verhovsek M, Douketis JD, McDonald E. Comparison of pain  
25 and ecchymosis with low-molecular-weight heparin vs. unfractionated heparin in  
26 patients requiring bridging anticoagulation after warfarin interruption: a randomized  
27 trial. *Journal of Thrombosis and Thrombolysis*. 2009; 28(3):266-8
- 28 32. Joint Formulary Committee. *British National Formulary* (online). Available from:  
29 <http://www.medicinescomplete.com> Last accessed: 04/04/19
- 30 33. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular  
31 weight heparins for avoiding heparin-induced thrombocytopenia in postoperative  
32 patients. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.:  
33 CD007557. DOI: 10.1002/14651858.CD007557.pub3.
- 34 34. Kakkar VV, Boeckl O, Boneu B, Bordenave L, Brehm OA, Brücke P et al. Efficacy  
35 and safety of a low-molecular-weight heparin and standard unfractionated heparin for  
36 prophylaxis of postoperative venous thromboembolism: European multicenter trial.  
37 *World Journal of Surgery*. 1997; 21(1):2-9
- 38 35. Kakkar VV, Howes J, Sharma V, Kadziola Z. A comparative double-blind, randomised  
39 trial of a new second generation LMWH (bemiparin) and UFH in the prevention of  
40 post-operative venous thromboembolism. The Bemiparin Assessment group.  
41 *Thrombosis and Haemostasis*. 2000; 83(4):523-9
- 42 36. Latoria S, Rollo HA, Yoshida WB, Giannini M, Moura R, Maffei FH. Prophylaxis of  
43 deep-vein thrombosis after lower extremity amputation: comparison of low molecular  
44 weight heparin with unfractionated heparin. *Acta Cirurgica Brasileira*. 2006;  
45 21(3):184-6
- 46 37. Lereun C, Wells P, Diamantopoulos A, Rasul F, Lees M, Sengupta N. An indirect  
47 comparison, via enoxaparin, of rivaroxaban with dabigatran in the prevention of

- 1                   venous thromboembolism after hip or knee replacement. *Journal of Medical*  
2                   *Economics*. 2011; 14(2):238-44
- 3           38.       Matar C, Kahale L, Hakoum M, Tsoiakian I, Etxeandia-Ikobaltzeta I, Yosucio V et al.  
4                   Anticoagulation for perioperative thromboprophylaxis in people with cancer. *Cochrane*  
5                   *Database of Systematic Reviews* 2018, Issue 7. Art. No.: CD009447. DOI:  
6                   10.1002/14651858.CD009447.pub3.
- 7           39.       McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM et al.  
8                   Subcutaneous heparin versus low-molecular-weight heparin as  
9                   thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian  
10                   colorectal DVT prophylaxis trial: a randomized, double-blind trial. *Annals of Surgery*.  
11                   2001; 233(3):438-44
- 12           40.       Monreal M, Lafoz E, Navarro A, Granero X, Caja V, Caceres E et al. A prospective  
13                   double-blind trial of a low molecular weight heparin once daily compared with  
14                   conventional low-dose heparin three times daily to prevent pulmonary embolism and  
15                   venous thrombosis in patients with hip fracture. *Journal of Trauma*. 1989; 29(6):873-5
- 16           41.       National Institute for Health and Care Excellence. *Developing NICE guidelines: the*  
17                   *manual*, updated 2018. London. National Institute for Health and Care Excellence,  
18                   2014. Available from: [https://www.nice.org.uk/process/pmg20/chapter/introduction-](https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview)  
19                   and-overview
- 20           42.       Onarheim H, Lund T, Heimdal A, Arnesjo B. A low molecular weight heparin (KABI  
21                   2165) for prophylaxis of postoperative deep venous thrombosis. *Acta Chirurgica*  
22                   *Scandinavica*. 1986; 152:593-6
- 23           43.       Ono K, Hidaka H, Koyama Y, Ishii K. Effects of heparin bridging anticoagulation on  
24                   perioperative bleeding and thromboembolic risks. *Anesthesia and Analgesia*. 2015;  
25                   120(3S\_Suppl):S301
- 26           44.       Pini M, Tagliaferri A, Manotti C, Lasagni F, Rinaldi E, Dettori AG. Low molecular  
27                   weight heparin (Alfa LHWH) compared with unfractionated heparin in prevention of  
28                   deep-vein thrombosis after hip fractures. *International Angiology*. 1989; 8(3):134-9
- 29           45.       Platz A, Hoffmann R, Kohler A, Bischof T, Trentz O. [Prevention of thromboembolism  
30                   in hip fracture: unfractionated heparin versus low molecular weight heparin ( a  
31                   prospective, randomized study)]. *Zeitschrift für Unfallchirurgie und*  
32                   *Versicherungsmedizin*. 1993; 86(3):184-8
- 33           46.       Rader CP, Kramer C, König A, Gohlke F, Eulert J. Comparison between low-  
34                   molecular and unfractionated heparin in the prevention of thrombosis in patients with  
35                   total endoprosthetic replacement of hip and knee joint. *Zeitschrift für Orthopädie und*  
36                   *Ihre Grenzgebiete*. 1997; 135(1):52-7
- 37           47.       Ramos J, Perrotta C, Badariotti G, Berenstein G. Interventions for preventing venous  
38                   thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database of*  
39                   *Systematic Reviews* 2008, Issue 4. Art. No.: CD005259. DOI:  
40                   10.1002/14651858.CD005259.pub3.
- 41           48.       Renda G, Di Pillo R, D'Alleva A, Sciartilli A, Zimarino M, De Candia E et al. Surgical  
42                   bleeding after pre-operative unfractionated heparin and low molecular weight heparin  
43                   for coronary bypass surgery. *Haematologica*. 2007; 92(3):366-73
- 44           49.       Senaran H, Acaroglu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of  
45                   deep vein thrombosis prophylaxis in total hip replacement patients. *Archives of*  
46                   *Orthopaedic and Trauma Surgery*. 2006; 126(1):1-5

- 1 50. Shaw JR, Woodfine JD, Douketis J, Schulman S, Carrier M. Perioperative interruption of  
2 direct oral anticoagulants in patients with atrial fibrillation: A systematic review and  
3 meta-analysis. *Research and Practice in Thrombosis and Haemostasis*. 2018;  
4 2(2):282-290
- 5 51. Speziale F, Verardi S, Taurino M, Nicolini G, Rizzo L, Fiorani P et al. Low molecular  
6 weight heparin prevention of post-operative deep vein thrombosis in vascular surgery.  
7 *Pharmatherapeutica*. 1988; 5(4):261-8
- 8 52. Swedenborg J, Nydahl S, Egberg N. Low molecular mass heparin instead of  
9 unfractionated heparin during infrainguinal bypass surgery. *European Journal of*  
10 *Vascular and Endovascular Surgery*. 1996; 11(1):59-64
- 11 53. von Tempelhoff GF, Dietrich M, Niemann F, Schneider D, Hommel G, Heilmann L.  
12 Blood coagulation and thrombosis in patients with ovarian malignancy. *Thrombosis*  
13 *and Haemostasis*. 1997; 77(3):456-61
- 14 54. von Tempelhoff GF, Harenberg J, Niemann F, Hommel G, Kirkpatrick CJ, Heilmann  
15 L. Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin  
16 on cancer survival following breast and pelvic cancer surgery: A prospective  
17 randomized double-blind trial. *International Journal of Oncology*. 2000; 16(4):815-24
- 18 55. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Yu PC. Prevention of deep-vein  
19 thrombosis after total knee arthroplasty in Asian patients. Comparison of low-  
20 molecular-weight heparin and indomethacin. *Journal of Bone & Joint Surgery -*  
21 *American Volume*. 2004; 86-A(1):136-40
- 22 56. Watanabe T, Matsubara S, Usui R, Izumi A, Kuwata T, Suzuki M. No increase in  
23 hemorrhagic complications with thromboprophylaxis using low-molecular-weight  
24 heparin soon after cesarean section. *Journal of Obstetrics and Gynaecology*  
25 *Research*. 2011; 37(9):1208-11
- 26 57. Zee AA, van LK, van dHM, Janssen L, Janzing HM. Low molecular weight heparin for  
27 prevention of venous thromboembolism in patients with lower-limb immobilization.  
28 *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD006681. DOI:  
29 10.1002/14651858.CD006681.pub4.
- 30
- 31

1 **Appendices**  
 2 **Appendix A: Review protocols**

3 **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	<ul style="list-style-type: none"> <li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li> <li>• Cochrane Database of Systematic Reviews (CDSR)</li> <li>• Embase</li> <li>• MEDLINE</li> </ul> <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies will be published in the final review.</p>
5.	Condition or domain being studied	Perioperative care
6.	Population	<p>Inclusion: Adults 18 years and over who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR &gt;3).</p> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• children and young people aged 17 years and younger</li> <li>• surgery for burns, traumatic brain injury or neurosurgery</li> </ul>
7.	Intervention/Exposure/Test	<ul style="list-style-type: none"> <li>• outpatient or self-administered low molecular weight subcutaneous heparin</li> </ul>

8.	Comparator/Reference standard/Confounding factors	<ul style="list-style-type: none"> <li>inpatient intravenous unfractionated heparin</li> </ul>
9.	Types of study to be included	<p>Randomised controlled trials (RCTs), systematic reviews of RCTs.</p> <p>Observational studies if no RCT evidence is identified.</p>
10.	Other exclusion criteria	<p>Exclusions:</p> <ul style="list-style-type: none"> <li>non-English language studies</li> <li>studies published before 2000</li> </ul>
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> <li>health-related quality of life</li> <li>mortality</li> <li>bleeding</li> <li>thromboembolism</li> <li>stroke</li> </ul> <p>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.</p>
13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> <li>length of hospital stay (pre and postoperative)</li> </ul> <p>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.</p>
14.	Data extraction (selection and coding)	<p>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.</p> <p>Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <ul style="list-style-type: none"> <li>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)</li> <li>Randomised Controlled Trial: Cochrane RoB (2.0)</li> <li>Non randomised study, including cohort</li> </ul>

		<p>studies: Cochrane ROBINS-I</p> <ul style="list-style-type: none"> <li>• Case control study: CASP case control checklist</li> <li>• Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool</li> <li>• Cross sectional study: JBI checklist for cross sectional study</li> <li>• Case series: Institute of Health Economics (IHE) checklist for case series</li> </ul> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> <li>• papers were included /excluded appropriately</li> <li>• a sample of the data extractions</li> <li>• correct methods are used to synthesise data</li> <li>• a sample of the risk of bias assessments</li> </ul> <p>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.</p>
16.	Strategy for data synthesis	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p> <p>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.</p> <p>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 <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a></p> <ul style="list-style-type: none"> <li>• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.</li> <li>• CERQual will be used to synthesise data from qualitative studies.</li> <li>• WinBUGS will be used for network meta-analysis, if possible given the data identified.</li> <li>• List any other software planned to be used.</li> </ul> <p>Heterogeneity between the studies in effect measures will be assessed using the I<sup>2</sup> statistic and visually inspected. An I<sup>2</sup> value greater than 50% will be considered indicative of substantial</p>

		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: <ul style="list-style-type: none"> <li>• older people (over 60 years)</li> <li>• Chronic Kidney Disease (CKD)</li> </ul>		
18.	Type and method of review	<input checked="" type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
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 <a href="#">Developing NICE guidelines: the manual</a> . 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:

		<ul style="list-style-type: none"> <li>• notifying registered stakeholders of publication</li> <li>• publicising the guideline through NICE's newsletter and alerts</li> <li>• 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.</li> </ul>
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	<input type="checkbox"/> Ongoing
		<input type="checkbox"/> Completed but not published
		<input type="checkbox"/> Completed and published
		<input type="checkbox"/> Completed, published and being updated
		<input type="checkbox"/> Discontinued
35..	Additional information	n/a
36.	Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>

1

2

**Table 8: Health economic review protocol**

Review question	All questions – health economic evidence
<b>Objectives</b>	To identify health economic studies relevant to any of the review questions.
<b>Search criteria</b>	<ul style="list-style-type: none"> <li>• Populations, interventions and comparators must be as specified in the clinical review protocol above.</li> <li>• 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).</li> <li>• 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.)</li> <li>• Unpublished reports will not be considered unless submitted as part of a call for evidence.</li> <li>• Studies must be in English.</li> </ul>
<b>Search strategy</b>	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
<b>Review strategy</b>	<p>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.</p> <p>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).<sup>41</sup></p> <p><b>Inclusion and exclusion criteria</b></p>

- 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.<sup>41</sup>

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/

1

14.	exp Preoperative Care/ or Preoperative Period/
15.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
16.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
17.	or/1-3
18.	limit 4 to English language
19.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
20.	5 not 6
21.	letter/
22.	editorial/
23.	news/
24.	exp historical article/
25.	Anecdotes as Topic/
26.	comment/
27.	case report/
28.	(letter or comment*).ti.
29.	or/8-15
30.	randomized controlled trial/ or random*.ti,ab.
31.	16 not 17
32.	animals/ not humans/
33.	exp Animals, Laboratory/
34.	exp Animal Experimentation/
35.	exp Models, Animal/
36.	exp Rodentia/
37.	(rat or rats or mouse or mice).ti.
38.	or/18-24
39.	7 not 25
40.	anticoagulants/ or acenocoumarol/ or coumarins/ or phenindione/ or phenprocoumon/ or warfarin/
41.	warfarin*.ti,ab.
42.	(coumarin* or coumadin or dicoumarol or acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)).ti,ab.
43.	or/27-29
44.	26 and 30
45.	randomized controlled trial.pt.
46.	controlled clinical trial.pt.
47.	randomi#ed.ab.
48.	placebo.ab.
49.	randomly.ab.
50.	clinical trials as topic.sh.
51.	trial.ti.
52.	or/32-38
53.	Meta-Analysis/
54.	Meta-Analysis as Topic/

55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(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.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/40-49
64.	Epidemiologic studies/
65.	Observational study/
66.	exp Cohort studies/
67.	(cohort adj (study or studies or analys* or data)).ti,ab.
68.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
69.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	Controlled Before-After Studies/
71.	Historically Controlled Study/
72.	Interrupted Time Series Analysis/
73.	(before adj2 after adj2 (study or studies or data)).ti,ab.
74.	or/51-60
75.	exp case control study/
76.	case control*.ti,ab.
77.	or/62-63
78.	61 or 64
79.	Cross-sectional studies/
80.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
81.	or/66-67
82.	61 or 68
83.	61 or 64 or 68
84.	39 or 50 or 70
85.	31 and 71
86.	31 and (39 or 50 or 72)

1

**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)

1

### 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

1

## 2 B.2 Health Economics literature search strategy

3 Health economic evidence was identified by conducting a broad search relating to the  
4 perioperative care population in NHS Economic Evaluation Database (NHS EED – this  
5 ceased to be updated after March 2015) and the Health Technology Assessment database  
6 (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for  
7 Research and Dissemination (CRD). Additional health economics searches were run on  
8 Medline and Embase.

9 **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 2019	None

10

11

### 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

1

**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

1

#### 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

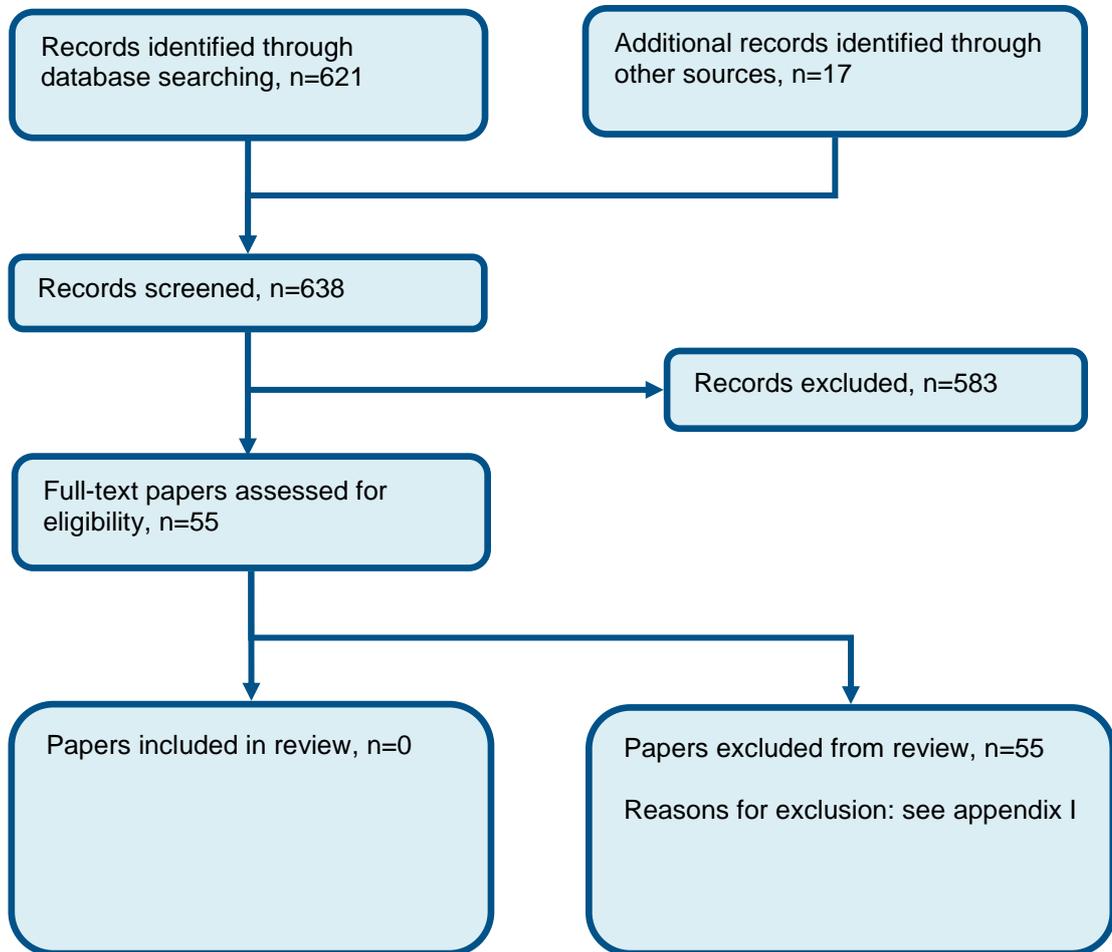
1

2

1

## Appendix C: Clinical evidence selection

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



2

## Appendix D: Clinical evidence tables

No relevant clinical studies were identified.

1  
2  
3  
4

## **Appendix E: Forest plots**

No relevant clinical studies were identified.

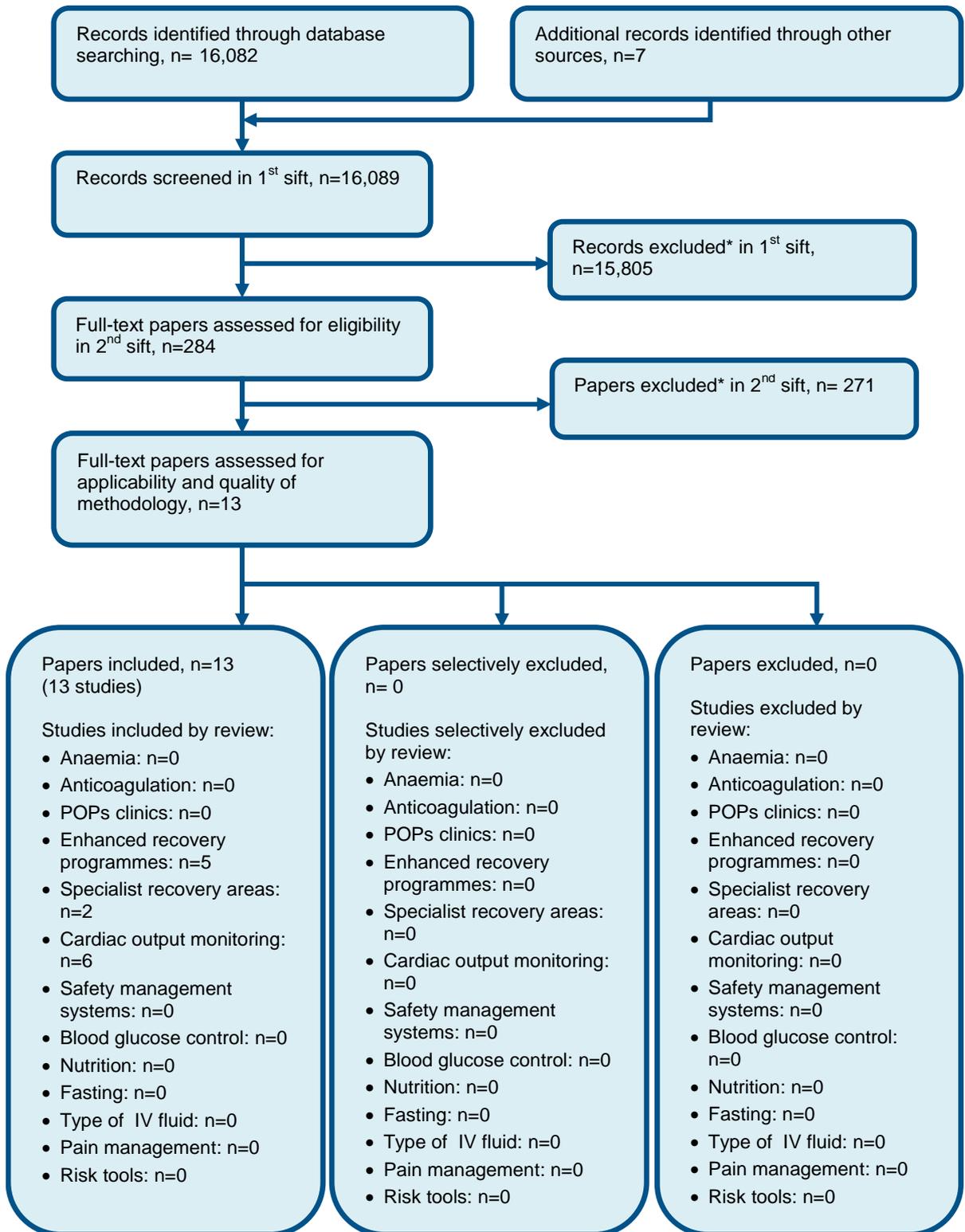
## Appendix F: GRADE tables

No relevant clinical studies were identified.

1  
2

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

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

1

## 2 I.2 Excluded health economic studies

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

7 **Table 12: Studies excluded from the health economic review**

Reference	Reason for exclusion
None	

8

# 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:**

<b>PICO question</b>	<p>Population: Adults 18 years and over who require bridging of anticoagulant medication (warfarin) for surgery due to high risk (target INR &gt;3). This is often people with mechanical heart valves.</p> <p>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).</p> <p>Intervention(s): Outpatient or self-administered low molecular weight subcutaneous heparin</p> <p>Comparison: Inpatient intravenous unfractionated heparin</p> <p>Outcome(s): Health-related quality of life, mortality, bleeding, thromboembolism, stroke and length of hospital stay (pre and postoperative)</p>
<b>Importance to patients or the population</b>	We need to know which strategy is most effective in terms of providing safe prevention of clinical events and the impact on patient quality of life as well as service costs.
<b>Relevance to NICE guidance</b>	Currently Trusts adopt different strategies based on no evidence.
<b>Relevance to the NHS</b>	Knowing if one strategy is superior in clinical or cost effective terms would change practice. The potential to reduce length of hospital admission might be significant.
<b>National priorities</b>	None identified
<b>Current evidence base</b>	No studies that met the review criteria were identified.
<b>Equality</b>	None identified
<b>Study design</b>	RCT comparing the two commonly used strategies. There is uncertainty about the quality of provision of unfractionated heparin in terms of Trust protocols and training for staff.
<b>Feasibility</b>	There are no feasibility issues as both methods are used in current clinical practice.
<b>Other comments</b>	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.

1