ClinicalEvidence

Thromboembolism

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ABSTRACT

INTRODUCTION: Deep venous thrombosis (DVT) or pulmonary embolism may occur in almost 2 in 1000 people each year, with up to 25% of those having a recurrence. Around 5% to 15% of people with untreated DVT may die from pulmonary embolism. Risk factors for DVT include immobility, surgery (particularly orthopaedic), malignancy, pregnancy, older age, and inherited or acquired prothrombotic clotting disorders. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for proximal DVT? What are the effects of treatments for isolated calf DVT? What are the effects of treatments for pulmonary embolism? What are the effects of interventions on oral anticoagulation management in people with thromboembolism? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 45 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticoagulation; compression stockings; low molecular weight heparin (short and long term, once or twice daily, and home treatment); oral anticoagulants (short and long term, high intensity, abrupt discontinuation, and computerised decision support); prolonged duration of anticoagulation; thrombolysis; vena cava filters; and warfarin.

QUESTIONS

INTERVENTIONS

PROXIMAL DVT

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

ISOLATED CALF DVT

Likely to be beneficial

Unlikely to be beneficial

PULMONARY EMBOLISM

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

ORAL ANTICOAGULATION MANAGEMENT FOR THROMBOEMBOLISM

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Hip fracture: the effects of perisurgical medical interventions on surgical outcome and prevention of complications

To be covered in future updates

Oral antithrombotic agents (such as glycoprotein IIb/IIIa antagonists)

Footnote

*Clinical consensus based on observational data

Key points

- Deep venous thrombosis (DVT) or pulmonary embolism may occur in almost 2 in 1000 people each year, with up to 25% of those having a recurrence.

  About 5% to 15% of people with untreated DVT may die from pulmonary embolism.

  The risk of recurrence of thromboembolism falls over time, but the risk of bleeding from anticoagulation remains constant.

- Oral anticoagulants are considered effective in people with proximal DVT compared with no treatment, although we found few trials.

  In people with proximal DVT or pulmonary embolism, long-term anticoagulation reduces the risk of recurrence, but high-intensity treatment has shown no benefit. Both approaches increase the risk of major bleeding.

  Low molecular weight heparin (LMWH) is more effective than unfractionated heparin, and may be as effective as oral anticoagulants, although all are associated with some adverse effects.

  We don't know how effective tapering off of oral anticoagulant agents is compared with stopping abruptly.

  We don't know whether once-daily LMWH is as effective as twice-daily administration at preventing recurrence.

  Home treatment may be more effective than hospital-based treatment at preventing recurrence, and equally effective in reducing mortality.

  Vena cava filters reduce the short-term rate of pulmonary embolism, but they may increase the long-term risk of recurrent DVT.

  Elastic compression stockings reduce the incidence of post-thrombotic syndrome after a DVT compared with placebo or no treatment.

- In people with isolated calf DVT, anticoagulation with warfarin may reduce the risk of proximal extension, although prolonged treatment seems no more beneficial than short-term treatment.

- Anticoagulation may reduce mortality compared with no anticoagulation in people with a pulmonary embolus, but it increases the risk of bleeding. We found few studies that evaluated treatments for pulmonary embolism.

  LMWH may be as effective and safe as unfractionated heparin.

  Thrombolysis seems as effective as heparin in treating people with major pulmonary embolism, but it is also associated with adverse effects.

  The use of computerised decision support may increase the time spent adequately anticoagulated, and reduce thromboembolic events or major haemorrhage, compared with manual dosage calculation.

DEFINITION

Venous thromboembolism is any thromboembolic event occurring within the venous system, including deep venous thrombosis (DVT) and pulmonary embolism. **DVT** is a radiologically confirmed partial or total thrombotic occlusion of the deep venous system of the legs sufficient to produce symptoms of pain or swelling. **Proximal DVT** affects the veins above the knee (popliteal, superficial femoral, common femoral, and iliac veins). **Isolated calf DVT** is confined to the deep veins of the calf and does not affect the veins above the knee. **Pulmonary embolism** is radiologically confirmed partial or total thromboembolic occlusion of pulmonary arteries, sufficient to cause symptoms of breathlessness, chest pain, or both. **Post-thrombotic syndrome** is oedema, ulceration, and impaired viability of the subcutaneous tissues of the leg occurring after DVT. **Recurrence** refers to symptomatic deterioration due to a further (radiologically confirmed) thrombosis, after a previously confirmed thromboembolic event, where there had been an initial partial or total symptomatic improvement. **Extension** refers to a radiologically confirmed, new, constant, symptomatic intraluminal filling defect extending from an existing thrombosis. **Self-testing** is where the patient is responsible

for testing their international normalised ratio (INR) at home using capillary sampling and a point-of-care (POC) device. Dosing of warfarin and frequency of testing is advised by a health professional clinically responsible for their management. **Self-management** is where the patient is responsible for testing their INR at home using capillary sampling and a POC device. Dosing of warfarin and frequency of testing is also managed by the patient with support from the health professional clinically responsible according to an agreed contract.

INCIDENCE/ PREVALENCE

We found no reliable study of the incidence or prevalence of DVT or pulmonary embolism in the UK. A prospective Scandinavian study found an annual incidence of 1.6 to 1.8 per 1000 people in the general population. [1] [2] A more recently published retrospective study from Norway found the incidence of DVT between 1995 and 2001 to be 0.93 per 1000 person-years (95% CI 0.85 per 1000 person-years to 1.02 per 1000 person-years), and of pulmonary embolism to be 0.50 per 1000 person-years (95% CI 0.44 per 1000 person-years to 0.56 per 1000 person-years). [3] A further Australian study found a standardised annual incidence per 1000 residents of 0.57 (95% CI 0.47 to 0.67) for all venous thromboembolism, 0.35 (95% CI 0.26 to 0.44) for DVT, and 0.21 (95% CI 0.14 to 0.28) for pulmonary embolism. [4] Ethnic origin may affect incidence, with one study reporting increased incidence in African-Americans. [5] One postmortem study estimated that 600,000 people develop pulmonary embolism each year in the USA, of whom 60,000 die as a result. [6]

AETIOLOGY/ RISK FACTORS

Risk factors for DVT include immobility, surgery (particularly orthopaedic), malignancy, pregnancy, older age, and inherited or acquired prothrombotic clotting disorders. [7] The oral contraceptive pill is associated with increased risk of death from venous thromboembolism (absolute risk increase [ARI] with any combined oral contraception: 1–3 deaths/million women/year). [8] The principal cause of pulmonary embolism is a DVT. [9]

PROGNOSIS

The annual recurrence rate of symptomatic calf DVT in people without recent surgery is over 25%. [10] [11] The rate of fatal recurrent venous thromboembolism after anticoagulation has been estimated at 0.3 per 100 patient-years. [12] Proximal extension develops in 40% to 50% of people with symptomatic calf DVT. [13] Proximal DVT may cause fatal or non-fatal pulmonary embolism, recurrent venous thrombosis, and post-thrombotic syndrome. One case series (462 people) published in 1946 found 5.8% mortality from pulmonary emboli in people in a maternity hospital with untreated DVT. [14] More recent cohorts of treated people have reported mortality of 4.4% at 15 days [15] and 10% at 30 days. [16] One non-systematic review of observational studies found that, in people after recent surgery who have an asymptomatic deep calf vein thrombosis, the rate of fatal pulmonary embolism was 13% to 15%. [17] The incidence of other complications without treatment is not known. The risk of recurrent venous thrombosis and complications is increased by thrombotic risk factors and is more common in men. [18] [19]

AIMS OF INTERVENTION

To reduce acute symptoms of DVT and to prevent morbidity and mortality associated with thrombus extension, post-thrombotic syndrome, and pulmonary embolisation; to reduce recurrence; to minimise any adverse effects of treatment.

OUTCOMES

Mortality, **rates of symptomatic recurrence**, **post-thrombotic syndrome**, **symptomatic pulmonary embolism**, and **adverse effects**. Proxy outcomes include **radiological evidence of clot extension or pulmonary embolism**. For oral anticoagulation management: **time spent in the target international normalised range**.

METHODS

Clinical Evidence search and appraisal June 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2010, Embase 1980 to June 2010, and The Cochrane Database of Systematic Reviews, May 2010 (online; searched 13 May 2010; 1966 to date of issue). When editing this review we used The Cochrane Database of Systematic Reviews 2010, Issue 2. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Additional studies were identified by the authors through searches of their own files. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to be at least single blinded where possible to blind, containing 20 or more individuals, of whom 80% or more were followed up. RCTs were included only if participants were included and outcomes defined on the basis of objective tests, and if the trial provided dose ranges (with adjusted dosing schedules for oral anticoagulation and unfractionated heparin) and independent, blinded outcome assessment. There was no minimum length of follow-up required to include studies, with the exception of the question: What are the effects of treatments for pulmonary embolism? Here, at least a 1-year follow-up was required. We excluded all studies described as "open",

"open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. If we found multiple systematic reviews for a treatment option, we included only the highest quality review, selecting on the basis of strength of methods, currency, and depth of coverage. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 21). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for proximal DVT?

OPTION COMPRESSION STOCKINGS FOR PROXIMAL DVT

Rates of symptomatic recurrence
Compared with placebo or no treatment Compression stockings are no more effective at reducing symptomatic recurrence of venous thromboembolism at 36 to 76 months (high-quality evidence).

Post-thrombotic syndrome
Compared with placebo or no treatment Compression stockings are more effective at reducing post-thrombotic syndrome at 3 to 76 months (high-quality evidence).

Different durations of stockings compared with each other Prolonged treatment for around 4 years with compression stockings may reduce symptoms of post-thrombotic syndrome at 3 months and 1 year compared with no further treatment (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of different types of compression stockings.

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits:

Compression stockings versus no treatment:
We found one systematic review (search date 2006; 4 RCTs, 537 people after DVT) comparing elastic compression stockings versus placebo stockings or no intervention. [20] It found that compression stockings significantly reduced post-thrombotic syndrome compared with control at 36 to 76 months (3 RCTs, 490 people; AR: 53/210 [25%] with stockings *v* 114/210 [54%] with control; RR 0.47, 95% CI 0.36 to 0.61). It found no significant difference in recurrent symptomatic DVT between groups at 36 to 76 months (3 RCTs, 421 people; 28/239 [12%] with stockings *v* 37/251 [15%] with placebo/no intervention; RR 0.79, 95% CI 0.50 to 1.26).

Different types of stockings versus each other:
We found no systematic review or RCTs.

Duration of treatment with stockings:
We found one RCT (169 people with proximal DVT). [21] The people were randomised after wearing a compression stocking for 6 months (standard treatment) to the prolonged treatment group (continue to wear compression stockings for a mean of 3.7 years) versus no further treatment (no compression stockings) to assess the efficacy of prolonged treatment for the prevention of post-thrombotic signs and symptoms. [21] The RCT found that prolonged treatment significantly reduced symptoms of post-thrombotic syndrome at 3 months (OR 0.35, 95% CI 0.17 to 0.73) and at 1 year (OR 0.46, 95% CI 0.23 to 0.90) compared with no further treatment, but no significant reduction of symptoms was seen thereafter (no further data reported). [21]

Harms:

Compression stockings versus no treatment:
The systematic review and included RCTs gave no information on harms. [20]

Different types of stockings versus each other:
We found no RCTs.

Duration of treatment with stockings:
The RCT gave no information on adverse effects. [21]

Comment: The systematic reviews analysed data on thigh- and knee-high stockings together, because previous studies had found no difference in venous pressure measurements or foot volume between different stocking lengths.

Clinical guide:
Stockings are cheap and effective in preventing thrombotic syndrome, although they are not particularly popular with patients. The data from the review suggest possible benefit from wearing stockings for 1 year after proximal DVT but not thereafter.

OPTION LOW MOLECULAR WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN FOR PROXIMAL DVT

Mortality
Compared with unfractionated heparin Low molecular weight heparin (LMWH) is more effective at reducing mortality at 3 to 6 months (high-quality evidence).

Rate of symptomatic recurrence
Compared with unfractionated heparin LMWH is more effective at reducing both recurrence of pulmonary embolus and DVT (moderate-quality evidence).

Adverse effects
LMWH is associated with reduced risk of major haemorrhage compared with unfractionated heparin.

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits:

Low molecular weight heparin (LMWH) versus unfractionated heparin:
We found one systematic review [22] and one subsequent RCT. [23]

The systematic review (search date 2004, 9 RCTs, 4451 people) compared low molecular weight heparin (LMWH) versus unfractionated heparin (variable dose) in people with proximal DVT. [22] It found that LMWH significantly reduced mortality at 3 to 6 months compared with unfractionated heparin (AR: 70/2094 [3%] with LMWH *v* 110/2063 [5%] with unfractionated heparin; OR 0.62, 95% CI 0.46 to 0.84). LMWH also significantly reduced recurrent venous thromboembolism (combined DVT and pulmonary embolism) at 3 to 6 months compared with unfractionated heparin (AR: 80/2192 [4%] with LMWH *v* 143/2259 [6%] with unfractionated heparin; OR 0.57, 95% CI 0.44 to 0.75). When analysed separately, it found that LMWH reduced both DVT and pulmonary embolism at 3 to 6 months compared with unfractionated heparin (pulmonary embolism: 6 RCTs, 2803 people; AR: 18/1400 [1%] with LMWH *v* 44/1403 [3%] with unfractionated heparin; OR 0.42, 95% CI 0.26 to 0.70; DVT: 6 RCTs, 2460 people; AR: 37/1233 [3%] with LMWH *v* 58/1227 [5%] with unfractionated heparin; OR 0.63, 95% 0.42 to 0.95). [22]

The subsequent RCT (708 people; 81% with DVT, 19% with pulmonary embolism) compared LMWH versus unfractionated heparin (given at a fixed dose subcutaneously, according to participant's weight). It found no significant difference in recurrence of thromboembolism at 3 months between LMWH and unfractionated heparin (AR: 13/345 [3.8%] with unfractionated heparin *v* 12/352 [3.4%] with LMWH; absolute difference +0.4%, 95% CI –2.6% to +3.3%). Activated prothrombin time (APTT) was not routinely monitored. [23]

Oral anticoagulation versus LMWH:
See benefits of long-term LMWH versus long-term oral anticoagulation, p 8 .

Harms:

Low molecular weight heparin (LMWH) versus unfractionated heparin:
Haemorrhage:
The systematic review found that LMWH was associated with significantly lower rates of major haemorrhage compared with variable-dose unfractionated heparin (AR: 18/1804 [1%] with LMWH *v* 37/1785 [2%] with unfractionated heparin; OR 0.50, 95% CI 0.29 to 0.85). [22] The subsequent RCT comparing unmonitored fixed-dose weight-adjusted unfractionated heparin with LMWH found no significant difference in major haemorrhage at 10 days (AR: 4/345 [1.1%] with unfractionated heparin *v* 5/352 [1.4%] with LMWH; absolute difference –0.3%, 95% CI –2.3% to +1.7%). [23] APTT was measured after an average of 2.8 days, but it was not used to adjust the unfractionated heparin dose. The RCT found no correlation between either short-term APTT and recurrent venous thromboembolism, or prolonged APTT and major haemorrhage.

Thrombocytopenia:
The systematic review [22] and subsequent RCT [23] gave no information on thrombocytopenia. We found one further systematic review (search date 2005, 7 studies, 5447 people), which included prospective studies of the incidence of heparin-associated thrombocytopenia (HAT) in people with venous thromboembolism (DVT and pulmonary embolism). [24] It found no significant difference between LMWH and unfractionated heparin in the incidence of HAT (18/3126 [0.6%] with LMWH *v* 22/2321 [0.9%] with unfractionated heparin; RR 0.69, 95% CI 0.38 to 1.23; P = 0.206). [24]

Comment:

Prospective studies assessing harm:
These varied in their diagnostic criteria and definitions of adverse events, making interpretation difficult.

Clinical guide:
The systematic review comparing LMWH with traditionally administered unfractionated heparin found LMWH to be safer and more effective in the initial treatment of proximal DVT. [22] However, the authors of the subsequent RCT comparing unmonitored fixed-dose, weight-adjusted unfractionated heparin with LMWH found similar effectiveness, and noted that unfractionated heparin is almost 20 times cheaper than LMWH, at least until LMWH comes off patent. [23]

OPTION ORAL ANTICOAGULATION (VITAMIN K ANTAGONISTS SUCH AS ACENOCOUMAROL, FLUTAMIDE, AND WARFARIN) FOR PROXIMAL DVT

Mortality
Compared with low molecular weight heparin (LMWH) Long-term oral anticoagulation is as effective as long-term LMWH at reducing mortality at 3 months (moderate-quality evidence).

Rate of symptomatic recurrence
Oral anticoagulation plus heparin compared with acenocoumarol alone Acenocoumarol plus intravenous unfractionated heparin may be no more effective at reducing recurrence of thromboembolism (low-quality evidence).

Compared with LMWH Long-term oral anticoagulation is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of oral anticoagulation compared with placebo in people with thromboembolism.

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits:

Oral anticoagulation versus placebo:
We found one systematic review (search date 2008, 2 RCTs, 114 people) comparing oral anticoagulation versus placebo or non-steroidal anti-inflammatory drugs (NSAIDs) in people with uncomplicated DVT. [25] Data were not meta-analysed owing to heterogeneity, and the two studies did not have sufficient power to determine differences in mortality or venous thromboembolism between those treated with anticoagulation or placebo/NSAID. [25]

Acenocoumarol (nicoumalone) plus intravenous unfractionated heparin versus acenocoumarol alone:
One RCT (120 people with proximal DVT) found that fewer people had recurrence at interim analysis at 6 months with combined intravenous unfractionated heparin plus acenocoumarol than with acenocoumarol alone; as a result, the trial was stopped. [26] The difference in recurrence did not quite reach significance (4/60 [7%] with combined treatment *v* 12/60 [20%] with acenocoumarol alone; P = 0.058; see comment). [26]

Oral anticoagulation versus low molecular weight heparin (LMWH):
See benefits of long-term LMWH versus long-term oral anticoagulation, p 8 .

Harms:

Oral anticoagulation versus placebo:
Neither of the two included RCTs within the systematic review showed a significant difference in terms of major haemorrhage, but both were underpowered in this respect. [25] We found one additional systematic review of cohort studies. [27] The review (search date 2003, 29 RCTs, 4 cohort studies) evaluated 10,757 people with any type of venous thromboembolism. [27] In total, participants had received 4373 person-years of coumarin derivatives, mainly warfarin. The review found a major bleeding rate of 7.22 per 100 person-years (95% CI 7.19/100 person-years to 7.24/100 person-years), a fatal bleeding rate of 1.31 per 100 person-years (95% CI 1.30/100 person-years to 1.32/100 person-years), and an intracranial bleeding rate of 1.15/100 person-years (95% CI 1.14/100 person-years to 1.16/100 person-years). The event rates for control groups were not re-

ported. Major bleeding rates were similar for 3 months of anticoagulation treatment compared with anticoagulation for up to 1 year (major bleeding rate: 2.06/100 person-years with 3 months of anticoagulation treatment *v* 2.74/100 person-years with 3–12 months of anticoagulation treatment).

Importance of therapeutic range:
One systematic review (search date 2006, 13 cohort studies and 6 RCTs, 80,713 people) assessed anticoagulation intensity and outcomes among people prescribed oral anticoagulants with a range of indications. The review found that there are increased risks of complications with an international normalised ratio (INR) outside the range of 2 to 3. [28] The review reported that the risk of thromboembolism was significantly increased when INR was <2 (RR 3.5, 95% CI 2.8 to 4.4; P <0.01). The review also found that the risk of haemorrhage significantly increased with an INR of 3 to 5 compared with 2 to 3 (RR 2.7, 95% CI 1.8 to 3.9; P <0.01). Further significant increased risks were seen with an INR of >5 compared with INR of 2 to 3 (RR 21.8, 95% CI 12.1 to 39.4; P <0.01). [28]

Acenocoumarol plus intravenous unfractionated heparin versus acenocoumarol alone:
In the RCT comparing acenocoumarol plus heparin versus acenocoumarol alone, one person in the combined treatment group committed suicide at 6 months, and there were two cancer-related deaths, confirmed by postmortem examination, in the group treated with warfarin alone (one in week 11 and one in week 12). [26]

Oral anticoagulation versus low molecular weight heparin (LMWH):
See harms of LMWH, p 5 .

Comment:

Direct oral thrombin inhibitors are a novel alternative option for oral anticoagulation that do not require laboratory monitoring for dose. To date, no trial has reported specific data for the subgroups reported in this review — namely proximal DVT, isolated DVT, and pulmonary embolism. One RCT has reported similar effectiveness and safety profile between direct oral thrombin inhibitors and warfarin in undifferentiated venous thromboembolism. [29]

Oral anticoagulation versus placebo:
The authors of the systematic review estimated that an RCT including 8000 people would be needed to definitively detect potential differences in mortality from pulmonary embolism between anticoagulation and placebo in DVT. They judged this unlikely to take place, both for logistical reasons and because of the ethical difficulties of a placebo-controlled trial of a widely accepted treatment in a potentially life-threatening illness. [25]

Acenocoumarol plus intravenous unfractionated heparin versus acenocoumarol alone for initial treatment:
It is unclear why the RCT was stopped early when it found no significant difference in recurrence between groups. [26] The lower recurrence rates with combined intravenous unfractionated heparin plus acenocoumarol compared with acenocoumarol alone suggest that it may have been considered unethical to continue the trial.

Clinical guide:
Consensus based on observational data regards oral anticoagulants as effective for people with proximal DVT. The issue of therapeutic range with respect to risk/benefit is pertinent to all treatment with oral anticoagulation. In the future, direct oral thrombin inhibitors may be an alternative, but to date no trial has reported specific data for the subgroups reported in this review — namely proximal DVT, isolated DVT, and pulmonary embolism.

OPTION LONG-TERM ORAL ANTICOAGULATION VERSUS SHORT-TERM ORAL ANTICOAGULATION FOR PROXIMAL DVT

Mortality
Compared with short-term anticoagulation Long-term oral anticoagulation may be no more effective at reducing mortality (low-quality evidence).

Rate of symptomatic recurrence
Compared with short-term anticoagulation Long-term oral anticoagulation may be more effective during treatment but may be no more effective at preventing recurrent venous thromboembolism after treatment (low-quality evidence).

Adverse effects
Although the risk of recurrence drops over time, the risk of bleeding remains stable while anticoagulant treatment continues.

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits: We found one systematic review [30] and one subsequent RCT. [31]

The systematic review (search date 2005, 8 RCTs, 2994 people) compared short-term versus long-term oral anticoagulation. Most of the RCTs identified by the review evaluated people with a first episode of pulmonary embolism or proximal DVT, although the proportion of people with a proximal DVT was not reported. The RCTs compared various durations of oral anticoagulation: the short-duration treatment groups ranged from 4 weeks to 6 months, and the prolonged-treatment groups from 12 weeks to 4 years. The review found no significant difference in mortality between prolonged and short anticoagulation at 11 months to 4 years (AR: 71/1498 [4.7%] with long treatment *v* 75/1496 [5.0%] with short treatment; OR 0.93, 95% CI 0.67 to 1.30). The overall rate of venous thromboembolism recurrence was not reported owing to heterogeneity of studies. During the period in which the prolonged group alone was treated, the review found that prolonged treatment significantly reduced recurrent venous thromboembolism compared with short treatment (8 RCTs, 2994 people; AR: 14/1499 [1%] with prolonged treatment *v* 116/1495 [8%] with short treatment; OR 0.18, 95% CI 0.13 to 0.26). However, during the period after prolonged treatment had ceased, it found no significant difference in recurrent venous thromboembolism between short and prolonged treatment (6 RCTs, 2605 people; AR: 96/1304 [7%] with prolonged treatment *v* 76/1301 [6%] with short treatment; OR 1.24, 95% CI 0.91 to 1.69).

The subsequent RCT (810 people, 70% with DVT only, 30% with pulmonary embolism or both pulmonary embolism and DVT) compared giving warfarin for 3 months versus 6 months. [31] Both groups received heparin initially, and had a target international normalised ratio (INR) of 2.0 to 3.5. People with cancer, clotting disorders, or previous DVT or pulmonary embolism within the previous 3 years were excluded. It found no significant difference in recurrent thromboembolic events at 1 year between 3 months' and 6 months' treatment (AR: 31/369 [8.4%] with 3 months' treatment *v* 29/380 [7.6%] with 6 months' treatment; P = 0.80; 95% CI for difference –3.1% to +4.7%). The study may have been underpowered to detect smaller differences, as it did not reach its planned recruitment target of 2400 people.

Harms: The systematic review identified RCTs with different periods of treatment, and their populations had different types of venous thromboembolism (see benefits). The review found a significant increase in major haemorrhage with prolonged compared with shorter periods of anticoagulation (36/1499 [2%] with prolonged treatment *v* 13/1495 [1%] with shorter-term treatment; OR 2.61, 95% CI 1.48 to 4.61). The subsequent RCT found that, at 12 months, 6 months of warfarin significantly increased major haemorrhage compared with 3 months' treatment (AR: 0/369 [0%] with 3 months' treatment *v* 8/380 [2%] with 6 months' treatment; 95% CI for difference –3.5% to –0.7%; P = 0.008). [31] See harms of oral anticoagulation, p 6 .

Comment: **Clinical guide:**
The authors of the review [30] point out that the absolute risk of recurrent venous thromboembolism decreases with time, whereas the harms associated with treatment remain constant and are therefore more likely with longer periods of anticoagulation, as demonstrated by the subsequent RCT. [31] Individuals have different risk profiles, and it is likely that the optimal duration of anticoagulation will vary.

OPTION LONG-TERM LOW MOLECULAR WEIGHT HEPARIN VERSUS LONG-TERM ORAL ANTICOAGULATION FOR PROXIMAL DVT

Mortality
Compared with long-term oral anticoagulation Long-term low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (high-quality evidence).

Rate of symptomatic recurrence
Compared with long-term oral anticoagulation Long-term LMWH is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence).

Adverse effects: major haemorrhage
Long-term LMWH and long-term unfractionated heparin may be equally likely to cause major haemorrhage (very low-quality evidence).

For GRADE evaluation of interventions for thromboembolism, see table , p 21 .

Benefits: We found two systematic reviews [32] [33] and one additional RCT. [34] The first review considered mortality, recurrence, and major haemorrhage, while the second review examined recurrence only.

The first systematic review (search date 2001, 7 RCTs, 1137 people) compared low molecular weight heparin (LMWH) versus oral anticoagulation in people with proximal DVT. All participants

were treated initially with either LMWH or unfractionated heparin for 5 to 10 days, followed by the randomised treatment of LMWH or vitamin K antagonists for 3 to 12 months. [32] It found no significant difference between LMWH and oral anticoagulation in mortality or recurrent symptomatic venous thromboembolism at 3 to 6 months (mortality: AR: 21/568 [4%] with LMWH *v* 14/569 [2%] with oral anticoagulants; OR 1.51, 95% CI 0.77 to 2.97; recurrence: 27/568 [5%] with LMWH *v* 38/569 [7%] with oral anticoagulants; OR 0.70, 95% CI 0.42 to 1.16). [32]

The second systematic review (search date 2003, 11 RCTs [including 6 from the first review], 2907 people with DVT, pulmonary embolism, or both) compared LMWH versus oral anticoagulants, both given for 3 to 6 months. [33] The proportion of people with DVT was not specified. It found that LMWH significantly reduced the recurrence of venous thromboembolism compared with oral anticoagulants at 3 to 6 months (AR: 78/1526 [5%] with LMWH *v* 118/1381 [9%] with oral anticoagulants; RR 0.63, 95% CI 0.47 to 0.83; P = 0.001). [33] When cancer patients and non-cancer patients were analysed separately, the review found a significant difference in recurrence at the end of the treatment period for cancer patients only (4 RCTs with cancer patients; 37/569 [7%] recurrence with LMWH *v* 69/546 [13%] recurrence with oral anticoagulants; RR 0.52, 95% CI 0.35 to 0.76; P = 0.001; 8 RCTs with non-cancer patients; 41/957 [4%] recurrence with LMWH *v* 49/835 [6%] recurrence with oral anticoagulants; RR 0.79, 95% CI 0.52 to 1.21; P = 0.29). There was no significant difference in long-term venous thromboembolism recurrence overall with LMWH compared with oral anticoagulants at 6 to 12 months (44/806 [5%] with LMWH *v* 33/806 [4%] with oral anticoagulants; RR 1.29, 95% CI 0.87 to 3.14; P = 0.11). [33]

The additional RCT (108 people with proximal DVT) compared treatment with oral anticoagulation (participants received initial intravenous unfractionated heparin in hospital) versus outpatient treatment with subcutaneous LMWH, both for 6 months. [34] It found no significant difference in recurrent DVT at 1 year between LMWH and oral anticoagulation (AR: 3/50 [6%] with LMWH *v* 5/52 [10%] with oral anticoagulation; reported as not significant; P value and CI not reported).

Harms:

The first systematic review found that LMWH significantly reduced major haemorrhage compared with long-term oral anticoagulation (7 RCTs; 5/568 [1%] with LMWH *v* 14/569 [2%] with oral anticoagulation; OR 0.38, 95% CI 0.15 to 0.94). However, the review performed a separate analysis of RCTs that clearly concealed randomisation and that were double blinded, or where the assessor was blinded to outcome measures. When only these RCTs were included, it found no significant difference in major haemorrhage between long-term LMWH and oral anticoagulation (3 RCTs; 4/236 [1.7%] with long-term LMWH *v* 5/241 [2.1%] with anticoagulation; OR 0.80, 95% CI 0.21 to 3.00). [32]

The second systematic review gave no information on harms. [33]

The additional RCT found no significant difference in major bleeding between subcutaneous LMWH and intravenous unfractionated heparin followed by oral anticoagulation, but it was underpowered to detect a difference (AR: 2/50 [4%] with LMWH *v* 4/52 [8%] with oral anticoagulation; reported as not significant; P value and CI not reported). [34] See also harms of long-term oral anticoagulation versus short-term oral anticoagulation, p 7 .

Comment:

Trials assessing harm:
These varied in their diagnostic criteria and definitions of adverse events, making interpretation difficult.

Clinical guide:
LMWH and oral anticoagulation have similar long-term risks and benefits. Choice of treatment modality is likely to be influenced by patient choice and by cost. LMWH may reduce rates of recurrence of venous thromboembolism compared with vitamin K antagonists during active treatment in cancer patients. However, this benefit has not been shown to be sustained after anticoagulation has been discontinued.

OPTION VENA CAVA FILTERS FOR PROXIMAL DVT

Mortality
Compared with no filters Vena cava filters are no more effective at reducing mortality at 8 years (moderate-quality evidence).

Pulmonary embolism
Compared with no filters Vena cava filters are more effective at preventing pulmonary embolism at 12 days, and at 8 years (low-quality evidence).

Rate of symptomatic recurrence

Compared with no filters Vena cava filters increase the risk of recurrent DVT at 8 years (moderate-quality evidence).

For GRADE evaluation of interventions for thromboembolism, **see table, p 21 .**

Benefits: We found one systematic review (search date 2009), [35] which identified one RCT. The RCT (400 adults with venography-confirmed proximal DVT considered at high risk of pulmonary embolism) compared vena cava filters (4 different types) versus no filters. Each group was further randomised to be given either unfractionated heparin or low molecular weight heparin (LMWH) for 8 to 12 days. A total of 49% of participants had concurrent pulmonary embolism diagnosed within 48 hours of admission. [36] [37] All participants received oral anticoagulation with warfarin or acenocoumarol for at least 3 months. The RCT found that vena cava filters significantly reduced the incidence of pulmonary embolism compared with no filters at 12 days (2/200 [1%] with filters *v* 9/200 [5%] without filters; OR 0.22, 95% CI 0.05 to 0.90). A further follow-up outside of trial conditions (with previously randomised patients after 8 years; 19 people in the control group had, by this time, also had filters inserted) [38] found that filters significantly reduced pulmonary embolism compared with no filters at 8 years (AR: 9/200 [6%] with filters *v* 24/200 [12%] with no filters; P = 0.008). However, the follow-up study found that vena cava filters significantly increased overall recurrent venous thromboembolism (DVT or pulmonary embolism) at 8 years (AR: 57/200 [36%] with filters *v* 41/200 [28%] with no filters; P = 0.04). The study found no significant difference in mortality between filters and control at 8 years (AR: 98/200 [48%] with filters *v* 103/200 [51%] with no filters; P = 0.83). [38]

Harms: The RCT found no significant difference between vena cava filters and no filters in major bleeding (17/200 [9%] with filters *v* 22/200 [11%] with no filters; OR 0.77, 95% CI 0.41 to 1.45). [37]

Comment: **Clinical guide:**
The decision to use a vena cava filter needs to be made on a patient-by-patient basis.

OPTION ABRUPT DISCONTINUATION OF ORAL ANTICOAGULATION FOR PROXIMAL DVT

Rate of symptomatic recurrence
Compared with additional warfarin for 1 month Abrupt discontinuation is no more likely to cause recurrence of thromboembolism compared with tapered dose for 1 month (low-quality evidence).

For GRADE evaluation of interventions for thromboembolism, **see table , p 21 .**

Benefits: One RCT (41 people with proximal DVT who had received intravenous heparin for 3 to 5 days followed by warfarin for 3 to 6 months) compared abrupt withdrawal of warfarin versus an additional month of warfarin at a fixed low dose of 1.25 mg daily. [39] It found similar recurrence with abrupt compared with gradual discontinuation (3 people with abrupt withdrawal *v* 1 person with gradual withdrawal; CI not reported). [39]

Harms: The RCT gave no information on adverse effects. [39]

Comment: **Clinical guide:**
Evidence from this one small study suggests that, in terms of recurrence of venous thromboembolism, there is no advantage to tapered withdrawal of warfarin over abrupt cessation; however, this study did not have enough power to discount small differences in efficacy. [39]

OPTION HOME TREATMENT WITH SHORT-TERM LOW MOLECULAR WEIGHT HEPARIN FOR PROXIMAL DVT

Mortality
Compared with hospital treatment Mortality may be no higher with home treatment compared with hospital treatment with short-term low molecular weight heparin (LMWH) (low-quality evidence).

Rate of symptomatic recurrence
Compared with hospital treatment Home treatment with short-term LMWH may be more effective at reducing recurrence of thromboembolism compared with hospital treatment with short-term LMWH (low-quality evidence).

For GRADE evaluation of interventions for thromboembolism, **see table , p 21 .**

Benefits: We found one systematic review. [40]

The systematic review (search date 2007, 6 RCTs, 1708 people) compared low molecular weight heparin (LMWH) at home versus hospital treatment with either unfractionated heparin or LMWH for initial treatment of people with DVT. [40] The RCTs identified by the review had methodological problems, including high exclusion rates and partial hospital treatment in the home treatment arms.

The review did not report times of outcome assessments for all RCTs. The review found that home treatment significantly reduced recurrence of venous thromboembolism compared with hospital treatment (AR: 39/857 [5%] with home treatment *v* 63/851 [7%] with hospital treatment; RR 0.61, 95% CI 0.42 to 0.90). It found no significant difference in mortality between groups (AR: 28/857 [3%] with home treatment *v* 39/851 [5%] with hospital treatment; RR 0.72, 95% CI 0.45 to 1.15; outcome times not reported).

Harms: The systematic review found no significant difference between home and hospital treatment in major or minor bleeding (major bleeding: AR: 12/857 [1%] with home treatment *v* 18/851 [2%] with hospital treatment; RR 0.67, 95% CI 0.33 to 1.36; minor bleeding: AR: 80/857 [9%] with home treatment *v* 61/851 [7%] with hospital treatment; RR 1.29, 95% CI 0.94 to 1.78). [40]

Comment: **Clinical guide:**
Home treatment with LMWH is becoming widespread. The limited evidence suggests that initial home management may be more effective than hospital treatment at preventing recurrence, as well as being equally safe.

OPTION ONCE-DAILY VERSUS TWICE-DAILY LOW MOLECULAR WEIGHT HEPARIN FOR PROXIMAL DVT

Mortality
Compared with twice-daily low molecular weight heparin (LMWH) Once-daily LMWH is as effective at reducing mortality at 10 days and at 3 months (high-quality evidence).

Rate of symptomatic recurrence
Compared with twice-daily LMWH Once-daily LMWH is as effective at reducing recurrence of thromboembolism at 10 days and at 3 months (high-quality evidence).

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits: We found two systematic reviews (search dates 1999 [41] and 2005, [42] 5 RCTs, 1522 adults with symptomatic proximal DVT) comparing once-daily versus twice-daily low molecular weight heparin (LMWH) for 5 to 10 days. Both systematic reviews included the same 5 RCTs and found similar results. However, the first review [41] included more RCTs in its meta-analyses, so we report these results here. The reviews found no significant difference between once-daily and twice-daily LMWH in the proportion of people with symptomatic or asymptomatic venous thromboembolism at 10 days or at 3 months (at 10 days: 5 RCTs; 7/742 [0.9%] with once daily *v* 9/766 [1.2%] with twice daily; OR 0.82, 95% CI 0.26 to 2.49; at 3 months: 3 RCTs; 26/614 [4%] with once daily *v* 32/642 [5%] with twice daily; OR 0.85, 95% CI 0.48 to 1.49). [41] They also found no significant difference in mortality at 10 days or at 3 months between once-daily and twice-daily LMWH, although mortality at 10 days was higher in people taking once-daily LMWH (at 10 days: 5 RCTs; 7/750 [0.9%] with once daily *v* 1/772 [0.1%] with twice daily; OR 6.73, 95% CI 0.85 to 30.5; at 3 months: 2 RCTs; 20/614 [3.3%] with once daily *v* 20/646 [3.1%] with twice daily; OR 1.05, 95% CI 0.53 to 2.09). The reviews may have been underpowered to detect a clinically important difference between once-daily and twice-daily LMWH because of low rates of recurrent venous thromboembolism and mortality in the trials.

Harms: The first review found no significant difference in rates of major bleeding between once-daily and twice-daily LMWH (10/750 [1.3%] with once daily *v* 9/772 [1.2%] with twice daily; OR 1.16, 95% CI 0.42 to 3.24). [41]

Comment: **Clinical guide:**
When choosing between once-daily or twice-daily regimens, increased convenience needs to be balanced against potentially lower efficacy.

OPTION HIGH-INTENSITY ORAL ANTICOAGULATION FOR PROXIMAL DVT

Rate of symptomatic recurrence
Compared with lower intensity oral anticoagulation High-intensity oral anticoagulation is no more effective at reducing the risk of thromboembolic events (moderate-quality evidence).

Adverse effects: haemorrhagic events
Compared with low-intensity oral anticoagulation High-intensity oral anticoagulation increases the risk of haemorrhagic events (high-quality evidence).

For GRADE evaluation of interventions for thromboembolism, see table , p 21 .

Benefits: We found one RCT (96 people with a first episode of idiopathic venous thromboembolism) comparing international normalised ratio (INR) targets of 2.0 to 3.0 (low-intensity treatment) versus 3.0 to 4.5 (high-intensity treatment) over 12 weeks' treatment with warfarin after an initial course of intravenous heparin. [43] It found similar recurrence rates of venous thromboembolism at 10 months for both INR target ranges (1/47 [2.1%] with lower range *v* 1/49 [2.0%] with higher range; P >0.05).

Harms: The RCT found significantly more haemorrhagic events with the higher target range (2/47 [4%] with lower range *v* 11/49 [22%] with higher range; ARR 18%, 95% CI 5% to 32%; RR 0.19, 95% CI 0.04 to 0.81; NNT 6, 95% CI 4 to 23). [43]

See harms of oral anticoagulation, p 6 .

Comment: **Clinical guide:**
Current clinical guidelines recommend a target INR of 2.0 to 3.0 for the treatment of DVT. [44]

QUESTION What are the effects of treatments for isolated calf DVT?

OPTION ANTICOAGULATION FOR CALF DVT

Proximal extension of clot
Compared with heparin alone Warfarin plus heparin is more effective at reducing proximal extension of clot at 1 year (high-quality evidence).

Note
We found no direct information from RCTs about whether anticoagulation is better than no active treatment in people with isolated calf DVT.

For GRADE evaluation of interventions for thromboembolism, see table , p 21 .

Benefits: **Warfarin or heparin versus placebo:**
We found no RCTs comparing heparin versus placebo, warfarin versus placebo, or heparin plus warfarin versus placebo.

Warfarin plus heparin versus heparin alone:
We found one RCT (51 people) comparing intravenous unfractionated heparin (international normalised ratio [INR] 2.5–4.2) for at least 5 days with or without 3 months of warfarin. [10] All participants also wore compression stockings. It found that heparin plus warfarin significantly reduced proximal extension of clot at 1 year compared with heparin alone (1/23 [4%] people with heparin plus warfarin *v* 9/28 [32%] people with heparin alone; ARR 28%, 95% CI 9% to 47%).

Harms: **Warfarin plus heparin versus heparin alone:**
The RCT found that two people taking warfarin plus heparin had clinically important bleeding. [10] No one taking heparin alone had clinically important bleeding. See harms of anticoagulation under treatments for proximal DVT, p 6 .

Comment: Direct oral thrombin inhibitors are a novel alternative option for oral anticoagulation that do not require laboratory monitoring for dose. To date, no trial has reported specific data for the subgroups reported in this review — namely proximal DVT, isolated DVT, and pulmonary embolism. One RCT has reported similar effectiveness and safety profile between direct oral thrombin inhibitors and warfarin in undifferentiated venous thromboembolism. [29]

Clinical guide:
Many reported cases of isolated calf DVT are asymptomatic, but they are detected radiologically for research purposes. We found limited evidence about the clinical importance of asymptomatic calf DVT. Similarly, studies into the incidence of pulmonary embolism associated with isolated calf DVT detected asymptomatic embolism by ventilation–perfusion scanning, and the clinical relevance of these findings is unclear.

OPTION PROLONGED DURATION OF ANTICOAGULATION FOR CALF DVT

Rate of recurrence
Compared with shorter duration of anticoagulation Longer (12 weeks) anticoagulation may not reduce recurrence of DVT compared with shorter (6 weeks) anticoagulation (very low-quality evidence).

Adverse effects

Harms of treatment — including major haemorrhage — continue during prolonged treatment. Individuals have different risk profiles, and it is likely that the optimal duration of anticoagulation will vary.

For GRADE evaluation of interventions for thromboembolism, **see table, p 21 .**

Benefits: We found one open-label RCT (736 people with proximal DVT, pulmonary embolism, or isolated calf DVT; 197 with isolated calf DVT) comparing 6 weeks versus 12 weeks of warfarin. [45] A pre-planned subgroup analysis in people with isolated calf DVT found no significant difference in recurrence of venous thromboembolism (AR: 2/105 [2%] with 6 weeks *v* 3/92 [3%] with 12 weeks; RR 0.58, 95% CI 0.10 to 3.36). However, the study may have lacked power to exclude a clinically important effect. [45]

Harms: The RCT found no significant difference in rates of haemorrhage between 6 weeks and 12 weeks of warfarin in people with isolated calf DVT (AR: 13/105 [12%] with 6 weeks *v* 19/92 [21%] with 12 weeks; RR 0.59, 95% CI 0.31 to 1.26). [45]

Comment: **Clinical guide:**
Many reported cases of isolated calf DVT are asymptomatic, but they are detected radiologically for research purposes. We found limited evidence about the clinical importance of asymptomatic calf vein thrombosis. Similarly, studies into the incidence of pulmonary embolism associated with isolated calf DVT detected asymptomatic embolism by ventilation–perfusion scanning, and the clinical relevance of these findings is unclear (see also comment in long-term oral anticoagulation under proximal DVT, p 7).

QUESTION What are the effects of treatments for pulmonary embolism?

OPTION ANTICOAGULATION (WARFARIN AND HEPARIN) FOR PULMONARY EMBOLISM

Mortality
Compared with no anticoagulation Heparin plus warfarin is more effective at reducing mortality at 1 year (moderate-quality evidence).

Adverse effects
Anticoagulants are associated with increased risk of haemorrhage.

Note
We found no direct information from RCTs about anticoagulation compared with no active treatment or about different anticoagulants compared with each other, in people with pulmonary embolism. As with DVT, clinical consensus based on observational studies is that treatment of pulmonary embolism with anticoagulation is effective.

For GRADE evaluation of interventions for thromboembolism, **see table, p 21 .**

Benefits:

Warfarin or heparin versus placebo:
We found no systematic review or RCTs comparing heparin versus placebo or warfarin versus placebo.

Heparin plus warfarin versus no anticoagulation:
We found one RCT (published in 1960; 35 people with pulmonary embolism) comparing heparin plus warfarin versus no anticoagulation. [46] It found that anticoagulation significantly reduced mortality at 1 year compared with no anticoagulation (0/16 [0%] deaths with anticoagulation *v* 5/19 [26%] deaths with no anticoagulation: NNT 4, 95% CI 2 to 16).

Warfarin plus heparin versus warfarin or heparin alone:
We found no systematic review or RCTs.

Harms:

Warfarin or heparin versus placebo:
We found no RCTs.

Heparin plus warfarin versus no anticoagulation:
The RCT gave no information on adverse effects. [46] See harms of anticoagulation under treatments for proximal DVT, p 6 .

Warfarin plus heparin versus warfarin or heparin alone:
We found no RCTs.

Comment: Direct oral thrombin inhibitors are a novel alternative option for oral anticoagulation that do not require laboratory monitoring for dose. To date, no trial has reported specific data for the subgroups reported

in this review — namely proximal DVT, isolated DVT, and pulmonary embolism. One RCT has reported similar effectiveness and safety profile between direct oral thrombin inhibitors and warfarin in undifferentiated venous thromboembolism. [29]

Clinical guide:
As with DVT, clinical consensus based on observational studies is that treatment of pulmonary embolism with anticoagulation is effective.

OPTION PROLONGED DURATION OF ANTICOAGULATION FOR PULMONARY EMBOLISM

Rate of symptomatic recurrence
Compared with shorter duration of anticoagulation Prolonged anticoagulation (6–9 months) may be no more effective at reducing recurrence of venous thromboembolism compared with shorter anticoagulation (3 months) in pulmonary embolism (moderate-quality evidence).

Adverse effects
Longer duration of anticoagulation has been associated with increased risk of haemorrhage.

For GRADE evaluation of interventions for thromboembolism, see table , p 21 .

Benefits: We found one RCT (326 people with pulmonary embolism and previous anticoagulant treatment for 3 months) comparing continued treatment with oral anticoagulant (warfarin or acenocoumarol to target international normalised ratio 2.0–3.0) for a short duration (3 months) versus a longer duration (6 months for people with transient risk factors or 9 months for people with no identifiable risk factors). It found no significant difference in recurrence of venous thromboembolism at about 3 years (AR: 15/165 [9%] with short duration *v* 18/161 [11%] with longer duration; RR 0.82, 95% CI 0.42 to 1.56). [47] However, the RCT may have lacked power to detect a clinically important effect.

Harms: The RCT found similar major bleeding rates and mortality at about 3 years between short-duration and longer-duration oral anticoagulation (bleeding: AR: 1/161 [1%] with short duration *v* 3/165 [2%] with longer duration; mortality: AR: 7/161 [4%] with short duration *v* 12/165 [7%] with longer duration). [47]

Comment: The RCT reported only one episode of recurrent venous thromboembolism during anticoagulation treatment. Other than this RCT, we found no direct evidence in people with pulmonary embolism. Evidence for intensity and duration of treatment has been extrapolated from RCTs in people with proximal DVT and any venous thromboembolism. These trials found that longer courses of anticoagulation reduced recurrence compared with shorter courses (see benefits of anticoagulation under treatments for proximal DVT, p 6), but they may increase the risk of major haemorrhage.

OPTION LOW MOLECULAR WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN FOR PULMONARY EMBOLISM

Mortality
Compared with unfractionated heparin Low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (moderate-quality evidence).

Rate of symptomatic recurrence
Compared with unfractionated heparin LMWH is as effective at reducing venous thromboembolism at 3 months (moderate-quality evidence).

For GRADE evaluation of interventions for thromboembolism, see table , p 21 .

Benefits: We found two systematic reviews comparing low molecular weight heparin (LMWH) versus intravenous unfractionated heparin. [48] [49]

The first systematic review (search date 2003, 12 RCTs, 1951 people with symptomatic or asymptomatic pulmonary embolism) found no significant difference in recurrent venous thromboembolism at the end of treatment (AR: 14/1023 [1%] with LMWH *v* 22/928 [2%] with unfractionated heparin; OR 0.63, 95% CI 0.33 to 1.18) or at 3 months after treatment (AR: 30/988 [3%] with LMWH *v* 39/895 [4%] with unfractionated heparin; OR 0.68, 95% CI 0.42 to 1.09). [49] It also found no significant difference in deaths from any cause (AR: 14/1023 [1.4%] with LMWH *v* 11/928 [1.2%] with unfractionated heparin; OR 1.20, 95% CI 0.59 to 2.45).

The second systematic review included only three trials (search date 2005, 235 people with pulmonary embolism), two of which were included in the first systematic review, while the third was

excluded from the first review for methodological reasons. It found similar results to the first systematic review, [49] and is not reported further here. [48]

Harms: The first systematic review found no significant difference in major bleeding between LMWH or unfractionated heparin (AR: 14/1023 [1%] with LMWH *v* 21/928 [2%] with unfractionated heparin; OR 0.67, 95% CI 0.36 to 1.27). [49] See harms of anticoagulation under treatments for proximal DVT, p 6 . However, the incidence of major haemorrhage was low, and the number of people is likely to have been too small to detect a clinically important difference.

Comment: The meta-analyses may have lacked power to detect clinically important effects of LMWH.

Clinical guide:
LMWH is as effective as unfractionated heparin, with a similar adverse-effects profile.

OPTION THROMBOLYSIS FOR PULMONARY EMBOLISM

Mortality
Compared with heparin Thrombolysis is as effective at reducing mortality (high-quality evidence).

Rate of symptomatic recurrence
Compared with heparin Thrombolysis is as effective at reducing recurrence of thromboembolism (high-quality evidence).

For GRADE evaluation of interventions for thromboembolism, see table, p 21 .

Benefits:

Thrombolysis versus placebo or no treatment:
We found no systematic review or RCTs.

Thrombolysis versus heparin:
We found several systematic reviews and report the results of the most recent one here. [50] The systematic review (search date 2009, 8 RCTs, 679 people) compared different types of thrombolytics versus heparin alone or heparin plus placebo. There was no significant difference in all-cause mortality between thrombolytics and heparin (15/335 [4.5%] with thrombolytics *v* 16/344 [4.7%] with heparin; OR 0.89, 95% CI 0.45 to 1.78). Five studies reported recurrence of pulmonary embolism as an end point, and found no difference between people receiving thrombolytics or heparin (17/299 [6%] with thrombolytics *v* 26/312 [8%] with heparin; OR 0.63, 95% CI 0.33 to 1.20). [50]

Different thrombolytics:
We found two systematic reviews comparing different thrombolytic agents versus each other. [51] [52] The first review (search date 1998, 6 RCTs, 491 people) did not perform a meta-analysis. It found no significant difference in mortality or recurrent pulmonary embolism among different thrombolytics in the individual RCTs. [51] The second review included only 4 trials, all of which were included in the first review, and this review is not reported further. [52]

Harms:

Thrombolysis versus placebo or no treatment:
We found no RCTs.

Thrombolysis versus heparin:
The systematic review found no significant difference in major haemorrhage between those receiving thrombolytics compared with those receiving heparin, although the rate in the thrombolysis group was greater (35/335 [10%] with thrombolytics *v* 22/344 [6%] with heparin; OR 1.61, 95% CI 0.91 to 2.86). [50] There was also no significant difference in minor haemorrhage (OR 1.98, 95% CI 0.68 to 5.75).

Different thrombolytics:
The systematic review found insufficient evidence to compare harms of different thrombolytics. [51]

Comment: The inclusion criteria for the systematic review required definitive diagnosis of pulmonary embolus, which meant that it included only haemodynamically stable people — a group for whom treatments with more substantial safety data, such as anticoagulation with warfarin or low molecular weight heparin (LMWH), are usually preferred. Although data from RCTs and systematic reviews are sparse, bleeding has been estimated to occur in 13% of people who receive thrombolysis, and life-threatening or cerebral bleeding in 2%. [53] Owing to this risk, guidelines recommend that thrombolysis is used only in people with high-risk pulmonary embolism: that is, those with cardiogenic shock or persistent arterial hypotension. [53] One very small RCT (8 people with high-risk pulmonary embolism), which did not meet our inclusion criteria, did find a significant reduction in mortality in this group. [54]

OPTION HIGH-INTENSITY ANTICOAGULATION FOR PULMONARY EMBOLISM

We found no clinically important results from RCTs about the effects of high-intensity oral anticoagulation in people with pulmonary embolism.

For GRADE evaluation of interventions for thromboembolism, **see table , p 21 .**

Benefits: We found no direct evidence (see comment).

Harms: We found no direct evidence (see comment).

Comment: Evidence for intensity of treatment has been extrapolated from RCTs in people with proximal DVT (see high-intensity oral coagulation under proximal DVT, p 11) and any venous thromboembolism. [43] These trials found that recurrence rates were not significantly different with higher international normalised ratio (INR) target ranges (INR 3.0–4.5) compared with a lower range (INR 2.0–3.0), but that higher INR target ranges increased bleeding rates.

QUESTION What are the effects of interventions on oral anticoagulation management in people with thromboembolism?

OPTION COMPUTERISED DECISION SUPPORT FOR THROMBOEMBOLISM

Rate of symptomatic recurrence
Compared with manual dosage Computer-assisted oral anticoagulation dosage may reduce the risk of clinical events (thrombotic and bleeding events) in people with established DVT/pulmonary embolism (moderate-quality evidence).

For GRADE evaluation of interventions for thromboembolism, **see table, p 21 .**

Benefits:

Clinical outcomes:
We found no systematic review but found two RCTs. [55] [56]

The first RCT compared two computer-assisted oral anticoagulation dosage systems (PARMA5 and DAWN) versus manual dosage (32 treatment centres, 18,617 patient-years of follow-up). [55] The RCT included people with a variety of indications for oral anticoagulation including atrial fibrillation, mechanical valves, and venous thromboembolism, but included a subgroup analysis of people with established DVT/pulmonary embolism. The subgroup (3209 people) found that computer-assisted dosage significantly reduced clinical events (thrombotic and bleeding events) compared with the manual dosage group (115 events [6.1 per 100 patient-years] with computer-assisted dosage *v* 152 events [9.1 per 100 patient-years] with manual dosage; RR 0.67, 95% CI 0.52 to 0.85; P = 0.001).

The second RCT (10,421 people with a variety of indications for oral anticoagulation) compared the PARMA5 software alone versus manual dosage. [56] The RCT included a subgroup analysis of people with established DVT/pulmonary embolism. The subgroup (2542 people) found that computer-assisted dosage significantly reduced the risk of clinical event (thrombotic and bleeding events) compared with manual dosage (106 events [6.7 per 100 patient-years] with computer-assisted dosage *v* 134 events [9.7 per 100 patient-years] with manual dosage; RR 0.69, 95% CI 0.53 to 0.89; P = 0.005). It should be noted that these events were primarily major bleeds within the first 3 weeks of treatment (11 with computer-assisted dosage *v* 27 with manual dosage; absolute figures or significance assessment not reported). [56]

Laboratory outcomes:
We found one systematic review [57] and 7 subsequent RCTs. [58] [59] [60] [61] [62] [63] [64]

The review (search date 1997, 9 RCTs, 1336 people) included 8 RCTs using warfarin and one using heparin. [57] The computer systems advised the doses for initiation of anticoagulation (2 RCTs) and for maintenance of anticoagulation (6 RCTs). Follow-up was short (15 days to 12 months). Indications for treatment included cardiac diseases and venous thrombosis. The outcome reported by 7 RCTs (693 people) in the systematic review was the proportion of days within the target range of anticoagulation. The review found that computerised decision support increased the time that the international normalised ratio (INR) was in the target range compared with usual care (OR 1.29, 95% CI 1.12 to 1.49). Reanalysis excluding one trial that introduced significant heterogeneity found similar results (OR for remaining RCTs 1.25, 95% CI 1.08 to 1.45).

The first subsequent RCT (285 people) compared a computerised decision-support dosing system versus physician-adjusted dosing in 5 hospitals. [58] People who were taking warfarin for at least

6 days were selected and followed for at least 3 months (results not analysed by intention to treat; results from 254 people [89%] analysed). People managed by computerised decision support spent significantly more time with their INR in the target range than people managed conventionally (63% with computerised decision support *v* 53% with conventional management; P <0.05). [58]

The second subsequent RCT (244 people) compared a package of care that included computerised decision support versus traditional hospital outpatient management. [59] The intervention was based in primary care — a practice nurse clinic that included near-patient INR testing and computerised decision support. It found significantly more time spent in the target range after 12 months with packaged care compared with traditional outpatient management (69% with packaged care *v* 57% with traditional care; P <0.001). It found no significant difference in the proportion of tests in range (61% with packaged care *v* 51% with traditional care; reported as not significant; no further data reported) or in the point prevalence of tests in range (71% with packaged care *v* 62% with traditional care; reported as not significant; no further data reported). [59]

The third subsequent RCT (101 people receiving oral anticoagulation after heart valve replacement) compared a computerised decision-support system versus standard manual monitoring of INR over 315 days. [60] It found no significant difference in the proportion of INRs in the target range, or in time spent in the target range (no further data and no mean follow-up time reported). It found that people had significantly fewer dose changes with computerised than with standard manual monitoring (31% with computerised *v* 47% with manual; P = 0.02).

The fourth subsequent RCT (335 people receiving initiation, 916 people receiving maintenance anticoagulation treatment for a variety of indications) compared a computerised decision-support system for both dosing and appointment scheduling versus standard manual monitoring by "expert physicians". [61] It found that significantly more people managed by computerised decision support achieved a stable INR in the first month, and spent more time with their INR in the target range over 3 months compared with people managed by standard monitoring (achieved stable range: 39% with computerised decision support *v* 27% with standard monitoring; P <0.01; remained in range: 71% with computerised decision support *v* 68% with standard monitoring; P <0.001).

The fifth subsequent RCT (122 people on warfarin after hip replacement) compared usual care versus computerised decision support. [62] Only initiation of warfarin was studied. The RCT found that computerised decision support significantly reduced the mean time taken to reach therapeutic levels of anticoagulation compared with usual care (2.8 days with computerised decision support *v* 4.7 days with usual care; P = 0.002).

The sixth subsequent RCT (crossover design; 1880 people attending an anticoagulation clinic and receiving oral anticoagulants for at least 4 weeks) found that computerised decision support significantly increased the percentage of time in the target INR range compared with standard monitoring over 10 weeks (AR: 65% with computerised decision support *v* 67% with standard monitoring; P <0.002). [63]

The seventh subsequent RCT found that computerised decision support significantly increased the proportion of time spent in the target INR range compared with physician dosing in hospital inpatients (30 people in hospital already receiving warfarin for a variety of indications; mean length of stay 35 days; target INR 2.0–3.0; time spent in target INR range: 62% with computerised decision support *v* 44% with physician dosing; P <0.05). [64] Physicians performed worse in this RCT than in many of the other studies quoted above.

Harms:

Clinical outcomes:

One systematic review (search date 1997, 9 RCTs, 1336 people) found major haemorrhage in 14/700 (2%) people with computerised decision support compared with 25/636 (4%) in the standard monitoring group. [57] Most of the events occurred in one study, making meta-analysis inappropriate. One RCT found no significant difference in overall mortality or serious adverse events with computerised decision support compared with usual care. [58]

The RCTs gave no information on adverse effects. [55] [56]

Comment:

Computerised decision support for oral anticoagulation seems at least as effective as human performance in terms of both clinical outcome and time spent in the target international normalised ratio range from the limited evidence available. Further larger and longer trials that measure clinical outcomes (particularly harms) are needed.

OPTION SELF-TESTING AND SELF-MANAGEMENT OF ORAL ANTICOAGULATION FOR THROMBOEMBOLISM

We found no clinically important results from RCTs about the effects of self-management on mortality or recurrence in people with thromboembolism.

For GRADE evaluation of interventions for thromboembolism, **see table, p 21 .**

Benefits:

Clinical outcomes:
We found no systematic review or RCTs with sufficient participants with thromboembolic disease to draw conclusions about clinical outcomes. Most people included in such studies have atrial fibrillation as their indication for anticoagulation.

Laboratory outcomes:
We found two systematic reviews, [65] [66] the most recent of which (search date 2007, 18 RCTs, 4723 people) [66] included trials of both self-testing and self-management. The people included in the review had a variety of indications for long-term anticoagulation, including venous thromboembolism. [66] People who self-managed their anticoagulation self-tested their international normalised ratio (INR) using a point-of-care coagulometer, and adjusted their own medication dose. There were substantial clinical differences between studies in follow-up, frequency of tests, and type of control used. Eleven trials reported the percentage time within range of which three studies reported a significant improvement in the time in therapeutic range in the self-testing and self-management groups. [66]

Harms:

Clinical outcomes:
The systematic review, which included people with any indication for oral anticoagulation, found that self-testing significantly reduced major haemorrhages (RR 0.56, 95% CI 0.35 to 0.91) whereas self-management did not (RR 1.12, 95% CI 0.78 to 1.61). [66]

Comment:

Variability in quality of care in the routine-care groups could affect the significant benefits for self-monitoring shown in the reviews. Careful training is required for self-management, and there are cost implications of testing strips and increased frequency of testing. The reliability and quality control of coagulometers is also an important consideration. Finally, withdrawal rates from self-management can be as high as 24% in some studies, despite patients being carefully chosen. [67]

GLOSSARY

Major haemorrhage Exact definitions vary between studies, but a major haemorrhage is usually one involving intracranial, retroperitoneal, joint, or muscle bleeding leading directly to death, or requiring admission to hospital to stop the bleeding or provide a blood transfusion. All other haemorrhages are classified as minor.

Computerised decision support system A computer program that provides advice on the significance and implications of clinical findings or laboratory results.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

International normalised ratio (INR) A value derived from a standardised laboratory test that measures the effect of an anticoagulant. The laboratory materials used in the test are calibrated against internationally accepted standard reference preparations, so that variability between laboratories and different regions is minimised. Normal blood has an international normalised ratio of 1.0. Therapeutic anticoagulation often aims to achieve an international normalised ratio value of 2.0 to 3.5.

Low molecular weight heparin (LMWH) This is made from heparin using chemical or enzymatic methods. The various formulations of LMWH differ in mean molecular weight, composition, and anticoagulant activity. As a group, LMWHs have distinct properties, and it is not yet clear if one LMWH will behave exactly like another. Some LMWHs given subcutaneously do not require monitoring.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Self-management of oral anticoagulation The patient is responsible for testing their INR at home using capillary sampling and a point-of-care (POC) device. Dosing of warfarin and frequency of testing are also managed by the patient with support from the health professional clinically responsible according to an agreed contract.

Self-testing of INR The patient is responsible for testing their INR at home using capillary sampling and a point-of-care (POC) device. Dosing of warfarin and frequency of testing is advised by a health professional clinically responsible for their management. Internal Quality Control (IQC) and External Quality Assurance (EQA) and general

maintenance of the POC can be the responsibility of either the patient or the health professional, but this has to be agreed before patient self-management commences.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Low molecular weight heparin versus unfractionated heparin for proximal DVT New evidence added to harms. [24] Categorisation unchanged (Beneficial).

Self-testing and self-management of oral anticoagulation for thromboembolism New evidence added. [66] Categorisation unchanged (Unknown effectiveness).

Vena cava filters for proximal DVT One systematic review updated. [35] Categorisation unchanged (Trade-off between benefits and harms).

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Competing interests: DAF has been reimbursed by LEO labs for speaking at symposia and is a co-author of two RCTs and a systematic review referenced in this review. EM is the author of two studies and a systematic review referenced in this review. The department where RJM, DAF, EM, and CT work at the University of Birmingham produces a commercially available software package.
We would like to acknowledge the previous contributor to this review: Richard Hobbs.

Disclaimer

TABLE **GRADE evaluation of interventions for thromboembolism**

Important outcomes	Mortality, rates of symptomatic recurrence, post-thrombotic syndrome, symptomatic pulmonary embolism, proxy radiological evidence of clot extension or pulmonary embolism; time spent in the target international normalised range								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for proximal DVT?									
3 (421) [20]	Rates of symptomatic recurrence	Compression stockings *v* placebo or no treatment	4	0	0	0	0	High	
3 (490) [20]	Post-thrombotic syndrome	Compression stockings *v* placebo or no treatment	4	0	0	0	0	High	
1 (169) [21]	Post-thrombotic syndrome	Different durations of stockings *v* each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor reporting of data
8 (4157) [22]	Mortality	LMWH *v* unfractionated heparin	4	0	0	0	0	High	
10 (5159) [22] [23]	Venous thromboembolism	LMWH *v* unfractionated heparin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (120) [26]	Rate of symptomatic recurrence (venous thromboembolism)	Acenocoumarol plus iv unfractionated heparin *v* acenocoumarol alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up
9 (3804) [30]	Mortality	Long-term *v* short-term anticoagulation	4	0	0	–2	0	Low	Directness points deducted for wide inclusion criteria and assessment periods
9 (3804) [30] [31]	Rate of symptomatic recurrence (during treatment)	Long-term *v* short-term anticoagulation	4	0	0	–2	0	Low	Directness points deducted for wide inclusion criteria and assessment periods
7 (1137) [32]	Mortality	Long-term LMWH *v* long-term oral anticoagulation	4	0	0	0	0	High	
14 (at least 2907) [33] [32] [34]	Rate of symptomatic recurrence	Long-term LMWH *v* long-term oral anticoagulation	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for variation in study duration
8 (1239) [32] [34]	Adverse effects (haemorrhage)	Long-term LMWH *v* long-term oral anticoagulation	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Consistency point deducted for conflicting results
1 (400) [35]	Mortality	Vena cava filters *v* no filters	4	–1	0	0	0	Moderate	Quality point deducted for lack of blinding
1 (400) [35] [38]	Pulmonary embolism	Vena cava filters *v* no filters	4	–1	–1	0	0	Low	Quality point deducted for lack of blinding. Consistency point deducted for conflicting results
1 (400) [35] [38]	Rate of symptomatic recurrence (thromboembolism)	Vena cava filters *v* no filters	4	–1	0	0	0	Moderate	Quality point deducted for lack of blinding
1 (41) [39]	Rate of symptomatic recurrence (thromboembolism)	Abrupt withdrawal of heparin *v* additional warfarin for 1 month	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Important outcomes	Mortality, rates of symptomatic recurrence, post-thrombotic syndrome, symptomatic pulmonary embolism, proxy radiological evidence of clot extension or pulmonary embolism; time spent in the target international normalised range								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
6 (1708) [40]	Mortality	Home treatment with LMWH *v* hospital treatment with LMWH	4	–1	0	–1	0	Low	Quality point deducted for reported methodological problems. Directness point deducted for inclusion of different comparators
6 (1708) [40]	Rate of symptomatic recurrence (thromboembolism)	Home treatment with LMWH *v* hospital treatment with LMWH	4	–1	0	–1	0	Low	Quality point deducted for reported methodological problems. Directness point deducted for inclusion of different comparators
5 (1522) [41] [42]	Mortality	Once-daily LMWH *v* twice-daily LMWH	4	0	0	0	0	High	
5 (1522) [41] [42]	Rate of symptomatic recurrence (thromboembolism)	Once-daily LMWH *v* twice-daily LMWH	4	0	0	0	0	High	
1 (96) [43]	Rate of symptomatic recurrence (thromboembolism)	High-intensity oral anticoagulation *v* lower-intensity oral anticoagulation	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (96) [43]	Adverse effects (haemorrhagic events)	High-intensity oral anticoagulation *v* lower-intensity oral anticoagulation	4	–1	0	0	+2	High	Quality point deducted for sparse data. Effect-size points added for RR <0.2
What are the effects of treatments for isolated calf DVT?									
1 (51) [10]	Proximal extension of clot	Warfarin plus heparin *v* heparin alone	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR >2
1 (197) [45]	Rate of symptomatic recurrence (thromboembolism)	6 weeks' warfarin *v* 12 weeks' warfarin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no blinding, and inclusion of other populations in randomisation
What are the effects of treatments for pulmonary embolism?									
1 (35) [46]	Mortality	Heparin plus warfarin *v* no anticoagulation	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (326) [47]	Rate of symptomatic recurrence (thromboembolism)	3 months' oral anticoagulation *v* 6–9 months' oral anticoagulation	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria and length of treatment in the comparison
13 (at least 1951) [48] [49]	Mortality	LMWH *v* unfractionated heparin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
13 (at least 1951) [48] [49]	Rate of symptomatic recurrence (thromboembolism)	LMWH *v* unfractionated heparin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
8 (679) [50]	Mortality	Thrombolysis *v* heparin	4	0	0	0	0	High	
5 (611) [50]	Rate of symptomatic recurrence (thromboembolism)	Thrombolysis *v* heparin	4	0	0	0	0	High	
What are the effects of computerised decision support on oral anticoagulation management?									
2 (5751) [55] [56]	Rate of symptomatic recurrence	Computer-assisted dosage *v* manual dosage	4	–1	0	0	0	Moderate	Quality point deducted because data are subgroup analyses of 2 RCTs

Important outcomes	Mortality, rates of symptomatic recurrence, post-thrombotic syndrome, symptomatic pulmonary embolism, proxy radiological evidence of clot extension or pulmonary embolism; time spent in the target international normalised range								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of patient self-management of oral anticoagulation?									
1 (18,617) [55]	Rate of symptomatic recurrence	Computerised decision support *v* manual dosage	4	–1	0	0	0	Moderate	Quality point deducted because data are subgroup analysis of a larger RCT

Type of evidence: 4 = RCT; 2 = observational; 1 = non-analytical/expert opinion. LMWH, low molecular weight heparin.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.