Vitamin K antagonists versus low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism

Vitamin K antagonists versus low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism

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What's new

Date	Event	Description
11 November 2016	New citation: conclusions not changed	Searches rerun, one new included study identified. Review text updated and 'Summary of findings' table added. New author joined review team. No changes to conclusions.
11 November 2016	Updated	Searches rerun. One new included study identified.

History

Date	Event	Description
29 March 2012	Updated	New authors have taken over this review, searches re-run, eight new included studies added and long-term follow-up from one study added. Risk of bias assessed for all included studies.
29 March 2012	New citation: conclusions not changed	New authors have taken over this review, review updated, conclusions not changed.
14 February 2011	Amended	Link to anticoagulant feed-back added
28 August 2008	Amended	Converted to new review format.
14 May 2003	Updated	Two new studies added to included and three to ongoing.

Abstract

Background

People with venous thromboembolism (VTE) are generally treated for five days with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) followed by three months of vitamin K antagonist treatment. Treatment with vitamin K antagonists (VKA) requires regular laboratory measurements, carries a risk of bleeding and some patients have contraindications to treatment. Treatment with LMWH has been proposed for minimising the risk of bleeding complications. This is the second update of a review first published in 2001.

Objectives

The purpose of this review was to evaluate the efficacy and safety of long term treatment (three months) of symptomatic VTE with LMWH compared to long term (three months) treatment with vitamin K antagonists.

Search methods

For this update the Cochrane Vascular Information Specialist searched the Specialised Register (last searched November 2016) and CENTRAL (2016, Issue 10). Clinical trials registries were also searched for ongoing studies.

Selection criteria

Randomised controlled trials comparing LMWH with VKA for the long treatment (three months) of symptomatic VTE. Two review authors independently evaluated trials for inclusion and methodological quality.

Data collection and analysis

The review authors independently extracted data and assessed the risk of bias. Any disagreements were resolved by discussion. Meta-analysis was performed using fixed-effect models with Peto odds ratios (Peto ORs) and 95% confidence intervals (CIs). The outcomes of interest were recurrent VTE major bleeding and mortality. We used GRADE to assess the overall quality of the evidence supporting these outcomes.

Main results

All 16 trials, with a combined total of 3299 participants, fulfilling our inclusion criteria were combined in a meta-analysis. The quality of the evidence according to GRADE was moderate for recurrent VTE, low for major bleeding and moderate for mortality. The quality of the evidence was downgraded for imprecision (recurrent VTE, mortality) and for risk of bias and inconsistency (major bleeding).

We found no clear difference in recurrent VTE between LMWH and VKA (Peto OR 0.83, 95% confidence interval (CI) 0.60 to 1.15; P = 0.27; 3299 participants; 16 studies; moderate quality evidence). We found less bleeding with LMWH compared with VKA (Peto OR 0.51, 95% CI 0.32 to 0.80; P = 0.004; 3299 participants; 16 studies; low quality evidence). However, when only high quality studies were compared for bleeding no clear difference was observed between LMWH and VKA (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08; 1872 participants; 7 studies). We found no clear difference between LMWH and VKA in mortality (Peto OR 1.08, 95% CI 0.75 to 1.56; P = 0.68; 3299 participants; 16 studies; moderate quality evidence).

Authors' conclusions

Moderate quality evidence shows there is no clear difference between LMWH and VKA in preventing symptomatic VTE and mortality after an episode of symptomatic DVT. Low quality evidence shows fewer cases of major bleeding with LMWH compared with VKA. However, when only high quality studies are compared for bleeding, no clear difference was observed between LMWH and VKA. LMWH may be an alternative in some patients, for example those in geographically inaccessible areas, who are unable or reluctant to visit the thrombosis service regularly, or with contraindications to VKA.

Plain language summary

Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic blood clots

Background

Blood clots (venous thromboembolism) sometimes cause blockages in veins after surgery, bed rest, or spontaneously. These clots can be fatal when they travel to the lungs. Vitamin K antagonists (VKAs), 99% of which are warfarin, are effective in preventing renewed blood clot formation, because they thin the blood. Low-molecular-weight heparins (LMWHs) are drugs that also thin the blood and are used for people who are at greater risk of major bleeding, people who cannot take vitamin K antagonists, and pregnant women.

Purpose of the review

To assess the benefits and harms of long term treatment (three months) of venous thromboembolism with LMWH compared to long term treatment with vitamin K antagonists.

Key results

This systematic review of 16 trials with a combined total of 3299 participants (current until November 2016) found no clear difference in recurrent blood clots and deaths between LMWH and VKA; and fewer bleeding episodes with LMWH when compared with VKA. However, when only high quality studies were compared for bleeding no clear differences were observed between LMWH and VKA.

Quality of the evidence

The quality of the evidence for the outcomes recurrent blood clots and deaths was moderate. The quality of this evidence

was downgraded because of the small number of events, leading to imprecision. For the outcome bleeding, the quality of the evidence was low because of inconsistency between the studies and risk of bias. More research into the long term treatment of blood clots in the veins with LMWH and VKA is needed.

Authors conclusion

This review found no clear difference in recurrent blood clots and deaths between LMWH and VKA; and fewer bleeding episodes with LMWH when compared with VKA. However, when only high quality studies were compared for bleeding no clear differences were observed between LMWH and VKA. LMWH may be an alternative in some patients, for example those in geographically inaccessible areas, who are unable or reluctant to visit the thrombosis service regularly, or those for whom it may be harmful to take VKA.

Background

Description of the condition

Venous thromboembolism (VTE) describes the formation of thrombus in the deep veins, most commonly in the legs, (deep vein thrombosis or DVT), and/or the subsequent embolisation of all or part of the thrombus to the pulmonary circulation (pulmonary embolization or PE). DVT of the lower limbs may be associated with localised pain, swelling and erythema as well as the development of pulmonary emboli (PE), and the later occurrence of post thrombotic syndrome (persistent swelling, erythema and ulceration). PE presents acutely with shortness of breath, pain on inspiration, tachycardia and right heart overload, and if untreated, can lead to circulatory collapse and death and in the longer term it can also cause chronic post-thrombotic pulmonary hypertension. Increasingly DVT may involve the upper extremities in the era of more liberal central venous catheterisation. Rarely other venous circulation (cerebral veins, portal and mesenteric veins, etc.) can be affected.

In addition to DVT and PE, thrombus can also form in the superficial veins, where it is associated with local pain and inflammation (superficial venous thrombosis). This tends to be associated with lower mortality and morbidity rates than DVT, although some patients may be at a higher risk of DVT formation depending on the location of the clot (Chengelis 1996; Nasr 2015).

Venous thromboembolism (VTE), is comprised of DVT and PE and can occur spontaneously. However there are many risk factors for VTE, including periods of inactivity, dehydration, hospitalisation, trauma, clotting disorders and previous thrombosis, varicose veins with phlebitis, pregnancy, oral combined hormonal contraceptives, malignancy, obesity, smoking and age (Anderson 2003; NICE 2010).

The incidence of VTE in mostly Caucasian populations is between 100 and 200 per 100,000 person years (Heit 2015; White 2003). Of these, it is estimated that 45 to 117, per 100,000 person years are due to DVT (without PE) and 29 to 78 per 100,000 person years are due to PE (with or without DVT) (Heit 2015). Recurrent VTE occurs in approximately 7.4% of patients at one year, rising to 30.4% of patients by 10 years (Cushman 2007; Heit 2015; White 2003).

Description of the intervention

The primary aim of treatment of symptomatic VTE is to prevent its recurrence, including preventing potentially fatal PE. Clinical guidelines provide recommendations for treatment of VTE in different settings (Kearon 2016; NICE 2012). In general, anticoagulation is the recommended treatment of choice. The recommended initial treatment is with either a direct oral anticoagulant (with or without initial parenteral anticoagulation as indicated) or a parenteral anticoagulant in conjunction with a vitamin K antagonist. Long-term therapy (for usually a minimum duration of three months anticoagulation) is indicated to treat acute VTE.

The prolonged use of a vitamin K antagonist has proven efficacy in comparison to placebo and low dose heparin (unfractionated heparin) (Hull 1979; Lagerstedt 1985). The use of adjusted doses of subcutaneous unfractionated heparin in therapeutic doses is as effective as a vitamin K antagonist in preventing recurrence of symptomatic VTE, but both require regular laboratory monitoring (Hull 1982b). Normal practice is to use vitamin K antagonists to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 (Hull 1982a). However, with the use of vitamin K antagonists there remains a considerable risk of major bleeding (approximately 3% to 4%) in the first three months of treatment (Hutten 1999). Moreover, in some patients it is difficult to achieve a stable INR in the therapeutic range, which leads to an increased risk of bleeding complications.

How the intervention might work

Long term treatment of symptomatic VTE with low-molecular-weight heparin (LMWH) has been proposed for minimising the risk of bleeding complications. LMWHs have been compared to unfractionated heparin in the initial treatment of symptomatic VTE, and are associated with a reduction in major bleeding (Hettiarachchi 1998). Moreover, use of LMWH is less frequently complicated by thrombocytopaenia (Warkentin 1995) and osteoporosis (Kelton 1995; Monreal 1994) than use of unfractionated heparin, and these compounds do not require laboratory monitoring.

Why it is important to do this review

If the efficacy and safety of LMWHs are found to be comparable to VKA, they could be used in the long term treatment of symptomatic VTE. This would be especially important for patients in whom VKA are contraindicated or impractical, for example pregnant women or those living in geographically inaccessible places.

Objectives

The purpose of this review was to evaluate the efficacy and safety of long term treatment (three months) of symptomatic VTE with LMWH compared to long term (three months) treatment with vitamin K antagonists.

Methods

Criteria for considering studies for this review

Types of studies

We included trials which randomly allocated participants to long term (three months) treatment with vitamin K antagonists or LMWH.

Types of participants

We included trials involving participants with symptomatic venous thromboembolism (VTE). We excluded trials if they exclusively included participants with active malignancy and symptomatic VTE, because this is the subject of another Cochrane review (Akl 2014). In addition, we excluded trials if objective tests were not used to confirm the diagnosis of deep venous thrombosis (DVT) (such as venography, ultrasound or any sequence of tests that results in a high positive predictive value for the diagnosis of symptomatic DVT) or the diagnosis of pulmonary embolism (PE) (such as high probability ventilation-perfusion lung scan or pulmonary angiography).

Types of interventions

We included trials comparing vitamin K antagonists with LMWH for the long term (three months) treatment of symptomatic VTE. Trials were included if the initial treatment for symptomatic VTE consisted of LMWH or unfractionated heparin for five to 10 days.

Types of outcome measures

Primary outcomes

- the incidence of recurrent symptomatic VTE during three months of allocated treatment
- the occurrence of major bleeding complications during three months of allocated treatment
- mortality during three months of allocated treatment

To confirm an episode of suspected recurrent VTE the following criteria were considered as constituting a positive diagnosis of recurrent symptomatic DVT:

- an extension of an intraluminal filling defect on a venogram, or
- a new intraluminal filling defect, or
- an extension of non-visualisation of proximal veins in the presence of a sudden cut-off defect on a venogram seen on at least two projections

Where no previous venogram was available for comparison, an intraluminal filling defect was considered sufficient. Where no venogram was available, abnormal results of compression ultrasonography in an area where compression had previously been normal, or a substantial increase in the diameter of the thrombus during full compression at the popliteal or femoral vein (Koopman 1996; Levine 1996) were accepted. Where neither a venogram nor an ultrasonographic trial was available, a change in the results of impedance plethysmography from normal to abnormal accompanied by a change from a negative to positive result on a D-dimer test were acceptable.

To confirm an episode of suspected recurrent PE the following criteria were accepted:

- a new intraluminal filling defect,
- an extension of an existing defect, or
- the sudden cut-off of vessels more than 2.5 mm in diameter on a pulmonary angiogram.

Where no prior pulmonary angiogram was available, an intraluminal filling defect or sudden cut-off of vessels more than 2.5 mm in diameter on a pulmonary angiogram was sufficient. Where no pulmonary angiogram was available, a defect of at least 75% of a segment on the perfusion scan with normal ventilation was accepted. Where the ventilation-perfusion scan was non-diagnostic (and no pulmonary angiogram was available), satisfaction of the above criteria for DVT was acceptable. Pulmonary embolism demonstrated at autopsy was also acceptable.

Haemorrhages were classified as major if they were: clinically overt and associated with a fall in the haemoglobin level of 2 g/dL (1.6 mM) or more; clinically overt and leading to a transfusion of two or more units of packed cells; intracranial; retroperitoneal; leading directly to death; leading to interruption of antithrombotic treatment; or (re)operation.

Studies were excluded for the evaluation of bleeding if the definitions of major and minor bleeding were unclear.

Secondary outcomes

- the incidence of recurrent symptomatic VTE during additional six to nine months after cessation of the allocated three months treatment of symptomatic VTE
- the occurrence of major bleeding complications during additional six to nine months after cessation of the allocated three months treatment of symptomatic VTE
- mortality during additional six to nine months after cessation of the allocated three months treatment of symptomatic VTE

Additional long term outcomes were considered for inclusion in the review where these were available.

Search methods for identification of studies

We did not apply any language restrictions on publications or any restrictions regarding publications status.

Electronic searches

For this update the Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- The Cochrane Vascular Specialised Register (11 November 2016);
- The Cochrane Central Register of Controlled Trials (CENTRAL (2016, Issue 10)) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, EMBASE Ovid, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular module in The Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial registries for details of ongoing and unpublished studies (11 November 2016).

- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch)
- ISRCTN Register (www.isrctn.com/)

See Appendix 2.

Searching other resources

We searched the reference lists of articles retrieved by electronic searches for additional citations. We contacted trialists for further information in cases where there were missing data or doubts about whether to include trials in the review.

Data collection and analysis

Selection of studies

Potentially eligible trials were scrutinised for eligibility independently by at least two members of the current review team (AA, AST, MS). Disagreements were resolved by discussion. We obtained full versions of articles that potentially met the inclusion criteria based on the title or abstract and assessed these independently against the inclusion criteria. The reason for each study's exclusion is presented in the Characteristics of excluded studies table.

Data extraction and management

Eligible articles were reviewed and summary information extracted and recorded on forms developed by Cochrane Vascular. The following information was sought: participant characteristics (age, gender, co-morbidities); number of participants in each treatment arm; duration of therapy; type of anticoagulant (vitamin K antagonist and LMWH); and the incidence and timing of recurrent VTE, major bleeding complications, and mortality. In situations where important information was not reported we contracted the trial authors.

Assessment of risk of bias in included studies

Two review authors working independently (AA, MS) used the 'Risk of bias tool' as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias, judging each item of bias to be at low, unclear or high risk of bias according to the Handbook guidance.

Trials were then classified into two categories. Category I trials were those trials with a high methodological quality, that is clearly concealed randomisation and double-blind treatment or blinded assessment of the outcome measures. Category II trials were those trials with a lower level of methodological quality, that is unclear or clearly not concealed randomisation or blind outcome assessment was not used. All information regarding the adequacy of the randomisation process, allocation concealment, blinding, intention-to-treat analysis and completeness of the follow-up were sought.

Measures of treatment effect

We used Review Manager 5.3 provided by Cochrane to analyse data. For dichotomous outcomes, statistical analysis was presented as Peto odds ratios (Peto OR) with 95% confidence intervals (CI).

Unit of analysis issues

Participating individuals were the unit of analysis.

Dealing with missing data

Where necessary, we contacted the authors of included trials to clarify data and provide missing values.

Assessment of heterogeneity

All analyses were conducted on an intention-to-treat basis. When the individual trials did not use intention-to-treat analyses, the analyses in this review were on the basis of the data (absolute numbers) provided in the included trial report.

We assessed trial heterogeneity using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Where heterogeneity was identified ($I^2 > 50\%$), we investigated the reason for heterogeneity.

Assessment of reporting biases

We used asymmetry in funnel plots to assess reporting bias when more than ten studies were included in the meta-analysis (Higgins 2011).

Data synthesis

The calculated Peto OR from the individual trials were combined across trials, giving weight to the number of events in each of the two treatment groups in each separate trial, using the Mantel-Haenszel procedure. This assumes a fixed treatment effect (Mantel 1959; Collins 1987).

We performed separate analyses for all trials combined and for trials of high methodological quality (Category I) (see Assessment of risk of bias in included studies).

Subgroup analysis and investigation of heterogeneity

Separate analyses were performed for trials that used similar initial treatment in both trial arms and those that used different treatment regimes during the initial treatment for PE or DVT (that is LMWH versus unfractionated heparin in the initial treatment of symptomatic VTE, a potential source of confounding). In addition, we performed analyses for symptomatic PE and symptomatic DVT. This way we explored the effect of vitamin K antagonists for these two different disease components of symptomatic VTE.

Sensitivity analysis

The primary analysis included data from all participants in the trials during the period of randomly allocated treatment. We performed sensitivity analyses to explore the effect that risk of bias had on estimates of treatment effects by excluding those studies that were classed as category II trials (those trials with a lower level of methodological quality, that is unclear or clearly not concealed randomisation or blind outcome assessment was not used, see Assessment of risk of bias in included studies).

Summary of Findings

We presented the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the primary outcomes (Types of outcome measures) in a 'Summary of findings' table, according to the GRADE principles as described by Higgins 2011 and Atkins 2004.
We developed a 'Summary of findings' table for the comparison 'LMWH versus VKA during allocated treatment (category I and II studies)' and used the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/) to assist in the preparation of the 'Summary of findings' table.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See Figure 1

We identified one new study eligible for inclusion for this update (Perez-de-Llano 2010).

Included studies

In total 16 trials describing the long term treatment of symptomatic venous thromboembolism (VTE) fulfilled our inclusion criteria (Beckman 2003; Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Kakkar 2003; Kucher 2005; Lopaciuk 1999; Lopez 2001; Massicotte 2003; Perez-de-Llano 2010; Pini 1994; Romera 2009; Veiga 2000). Three trials (Beckman 2003; Kucher 2005; Perez-de-Llano 2010) included only participants with symptomatic pulmonary embolism (PE). One trial included participants with both symptomatic DVT and symptomatic PE (Massicotte 2003). The 12 remaining trials included participants with symptomatic DVT. See the table Characteristics of included studies for a detailed description of the trials.

The breakdown of trials according to the countries in which they were performed is as follows:

- Canada (Hull 2007; Hull 2009; Massicotte 2003);
- Germany (Hamann 1998);
- Greece (Daskalopoulos 2005);
- Italy (Pini 1994);
- Poland (Lopaciuk 1999);
- Spain (Gonzalez 1999; Lopez 2001; Perez-de-Llano 2010; Romera 2009; Veiga 2000);
- USA (Beckman 2003; Kakkar 2003; Kucher 2005);
- UK (Das 1996).

A total of 3299 participants were recruited into the 16 included trials. The number of participants in each trial ranged from 40 (Kucher 2005) to 737 (Hull 2007). In seven trials similar treatments were used in both arms (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Perez-de-Llano 2010; Pini 1994). In the remaining nine trials participants were allocated to different treatments in the trial arms (Beckman 2003; Hamann 1998; Kakkar 2003;

Kucher 2005; Lopaciuk 1999; Lopez 2001; Massicotte 2003; Romera 2009; Veiga 2000). The 16 included trials were published between 1994 and 2010 (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Kakkar 2003; Lopaciuk 1999; Lopez 2001; Massicotte 2003; Perez-de-Llano 2010; Pini 1994; Romera 2009; Veiga 2000).

Category I trials were those trials with a high methodological quality, that is clearly concealed randomisation and double-blind treatment or blinded assessment of the outcome measures. Category II trials were those trials with a lower level of methodological quality, that is unclear or clearly not concealed randomisation or blind outcome assessment was not used. Seven trials were deemed category I trials (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003; Pini 1994) and the remaining nine trials were deemed category II trials (Beckman 2003; Hamann 1998; Kakkar 2003; Kucher 2005; Lopaciuk 1999; Lopez 2001; Perez-de-Llano 2010; Romera 2009; Veiga 2000). For more details on methodological quality see section Risk of bias in included studies.

Seven of the 16 trials included only participants with symptomatic DVT and used similar initial treatment in both treatment arms. These included two category I trials (Das 1996; Pini 1994) and five category II trials (Hamann 1998; Lopaciuk 1999; Lopez 2001; Romera 2009; Veiga 2000). The category II trial by Kakkar 2003 randomised participants between three treatment arms, in one arm the initial treatment was intravenous unfractionated heparin followed by three months of treatment with vitamin K antagonist. In the other two treatment arms participants were initially treated with LMWH followed by either a vitamin K antagonist or LMWH for 12 weeks. In the category I trials by Gonzalez 1999, Daskalopoulos 2005 and Hull 2007, the initial treatment in the LMWH arm consisted of subcutaneous LMWH while the initial treatment in the vitamin K antagonist arm consisted of a course of intravenous unfractionated heparin. Category I trial Hull 2009 included only participants with acute proximal DVT; the initial treatment was either subcutaneous LMWH or subcutaneous LMWH plus warfarin. In trials including only patients with symptomatic PE (Beckman 2003; Kucher 2005; Perez-de-Llano 2010), Beckman 2003 compared different initial treatments but for the participants in Kucher 2005 and Perez-de-Llano 2010 the same initial treatment was used, that is subcutaneous LMWH. One trial included participants with both symptomatic DVT and symptomatic PE (Massicotte 2003), and the initial treatment was different in the two treatment groups.

Pini 1994 followed all participants for the entire follow-up period and intention-to-treat analysis was performed. Das 1996 reported that a total of 19 participants (18%) did not complete the trial according to the protocol; six participants in the LMWH group did not complete the three months of follow-up (one death, one severe illness, two PE, one loss to follow-up, one inadequate venogram). Thirteen participants in the vitamin K antagonist group did not complete the three months of follow-up (three deaths, three severe illness, one PE, three losses to follow-up, three inadequate venograms). The analyses of these participants were based on an intention-to-treat analysis. Gonzalez 1999 excluded 20 (11%) participants from the analysis, eight participants in the LMWH arm and 12 in the vitamin K antagonist arm. Intention-to-treat analysis was not provided and nor were outcome data provided (in total 12 participants had no second venogram, in five participants treatment was not conducted properly, and three participants were lost to follow-up). Lopaciuk 1999 excluded a total of nine participants after randomisation and intention-to-treat analyses were not conducted. Three participants in the LMWH group (one sudden death during initial treatment, one PE (day three) and vena caval filter insertion (day 14), one initial treatment changed to unfractionated heparin) and six participants in the vitamin K antagonist group (two an exclusion criterion overlooked (vein compression by arterial aneurysm), three consent withdrawal, one initial treatment changed to thrombectomy) did not complete the trial according to the protocol. Kakkar 2003 reported 54 participants not included in the intention-to-treat analysis (evenly divided over the three treatment arms), six participants did not have a baseline venography and in 48 participants symptomatic DVT was not confirmed independently at the baseline venogram. Daskalopoulos 2005 reported a total of six participants excluded before commencement of treatment (five in the LMWH arm and one in the vitamin K antagonist arm). Hull 2007 reported that a total of six participants did not complete the trial according to the protocol, and intention-to-treat analysis was provided for these participants. In the vitamin K antagonist arm four participants did not complete the trial (one lost to follow-up and three withdrew consent), in the LMWH arm two participants did not complete the trial (one lost to follow-up and one withdrew consent). Hull 2009 reported that 3/480 participants were lost to follow up at 12 months (1 heparin and 2 usual care group). Perez-de-Llano 2010 reported that eight participants did not complete the study protocol successfully. Five participants (9.7%) randomised to heparin (metastatic cancer, allergy to heparin, vein thrombosis and two unknown reasons) and three (6%) to the vitamin K antagonist arm (metastatic cancer, inability to reach therapeutic INR and one unknown reason). Hamann 1998, Veiga 2000, Lopez 2001, Beckman 2003, Kucher 2005 and Romera 2009 reported that all trial participants were followed-up. Massicotte 2003 reported use of intention-to-treat analyses but two participants, one from each group, who did not receive study medications were excluded from the intention-to-treat analyses. There were also two participants who failed the inclusion criteria and two who failed the exclusion criteria but who did receive study medications. These four participants were left in the intention-to-treat analyses. Massicotte 2003 also reported that eight participants (including one death) in the LMWH group and 14 (including 4 deaths) in the UFH group withdrew from the study.

All included studies had a minimum of three months treatment. Three studies reported a treatment period of six months (Daskalopoulos 2005; Perez-de-Llano 2010; Romera 2009), while in a further three studies some of the participants had three months treatment and others had six months treatment (Hamann 1998; Lopez 2001; Veiga 2000). Additional follow up after the treatment period was reported in 12 studies ranging from 28 days to nine months (Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Kakkar 2003; Lopaciuk 1999; Lopez 2001; Massicotte 2003; Pini 1994; Romera 2009; Veiga 2000).

Quality of treatment with vitamin K antagonists, defined as an INR between 2.0 and 3.0, was provided in seven trials (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Lopez 2001; Perez-de-Llano 2010; Pini 1994; Veiga 2000); the percentages are given in the Characteristics of included studies. Beckman 2003 and Hull 2007 provided the INRs for the participants who had a major bleeding complication. Romera 2009 partly provided the INRs for participants with bleeding complications.

Excluded studies

In total four studies were excluded. The reasons for exclusion were:

- non-randomised trial (Vorobyeva 2009);
- composite end-point trial (Ghirarduzzi 2009);
- subjective reporting (Hull 2001; Hull 2001a).

Risk of bias in included studies

See Figure 2 and Figure 3 for a graphical presentation of the risk of bias. A lack of detail was the main reason for the 'unclear' rating for most trials.

Allocation (selection bias)

In nine trials the method used to generate the random allocation sequence was given in sufficient detail, indicating a low risk of bias (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Kucher 2005; Massicotte 2003; Perez-de-Llano 2010; Pini 1994). The randomisation method was unclear in seven trials (Beckman 2003; Hamann 1998; Kakkar 2003; Lopaciuk 1999; Lopez 2001; Romera 2009; Veiga 2000).

Allocation was adequately concealed only in three trials (Das 1996; Lopaciuk 1999; Veiga 2000). An unclear risk of bias was given for the remaining 13 trials (Beckman 2003; Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Kakkar 2003; Kucher 2005; Lopez 2001; Massicotte 2003; Perez-de-Llano 2010; Pini 1994; Romera 2009).

Blinding (performance bias and detection bias)

All included trials were at high risk of performance bias because they were open label trials.

Eleven trials were at low risk of detection bias because of adequate blinding of the outcome assessments (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Kakkar 2003; Lopez 2001; Massicotte 2003; Pini 1994; Romera 2009; Veiga 2000). Two trials were at high risk of detection bias because blinded outcome assessment was not reported (Kucher 2005; Lopaciuk 1999); and three trials were at unclear risk of bias because it was unclear as to whether those collecting the outcomes were aware of the allocation (Beckman 2003; Hamann 1998; Perez-de-Llano 2010).

Incomplete outcome data (attrition bias)

The risk of bias was low for 15 trials as they followed-up and reported on all the participants (Beckman 2003; Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Kucher 2005; Lopaciuk 1999; Lopez 2001; Massicotte 2003; Perez-de-Llano 2010; Pini 1994; Romera 2009; Veiga 2000). Only Kakkar 2003 was classed as high risk of bias, as 33% of the randomised participants were not followed-up as described in the trial design.

Selective reporting (reporting bias)

Fourteen trials were at low risk of bias and two trials (Das 1996; Hamann 1998), had an unclear risk of bias due to insufficient information provided in the trial reports.

Other potential sources of bias

Nine of the trials were free of other sources of bias (Beckman 2003; Das 1996; Kakkar 2003; Kucher 2005; Lopez 2001; Perez-de-Llano 2010; Pini 1994; Romera 2009; Veiga 2000). However, one trial had an unclear risk as insufficient information was provided (Hamann 1998). Lopaciuk 1999 was deemed unclear risk of other bias because three fatal peripheral or cardiovascular events in the acenocoumarol group are not discussed and the follow-up treatments after the planned three month outcomes differed in both groups. A further five (category I) trials had an unclear risk as they may have been confounded by differences in the initial treatment (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003).

Effects of interventions

The incidence of recurrent venous thromboembolism during active treatment

All 16 trials reported the occurrence of recurrent symptomatic venous thromboembolism (VTE) during the first three months after randomisation.

A total of 86 of the 1702 participants (5.1%) in the vitamin K antagonist group had recurrent symptomatic VTE versus 70 of the 1597 participants (4.4%) in the LMWH group. The pooled analysis showed no clear difference between the two treatment modalities for recurrent symptomatic VTE (Peto OR 0.83, 95% CI 0.60 to 1.15; P = 0.27; 3299 participants; 16 studies; moderate quality evidence) for participants with symptomatic VTE. Heterogeneity was I^2 = 9% (Analysis 1.1; Figure 4).

Although 15 trials showed no clear differences in recurrent VTE between LMWH and vitamin K antagonist treatment, one (Gonzalez 1999), did find a difference in favour of LMWH treatment (Peto OR 0.38, 95% CI 0.17 to 0.86; 185 participants).

Twelve trials included only participants with symptomatic DVT. In these trials a total of 82 of the 1572 participants (5.2%) in the vitamin K antagonist group had recurrent symptomatic VTE versus 63 of the 1449 participants (4.3%) in the LMWH group, showing no clear difference between the two treatment modalities for recurrent symptomatic VTE (Peto OR 0.79, 95% CI 0.57 to 1.11; P = 0.18; 3021 participants; 12 studies) in participants with symptomatic DVT. Heterogeneity was I^2

= 8% (Analysis 2.1).

In contrast, in the three trials including only participants with symptomatic PE none of the 90 participants (0%) in the vitamin K antagonist group had recurrent symptomatic VTE versus five of the 112 participants (4.5%) in the LMWH group, resulting in no clear difference between treatments for episodes of recurrent symptomatic VTE (Peto OR 5.70, 95% CI 0.91 to 35.60; P = 0.06; 202 participants; 3 studies) in participants with symptomatic PE. Heterogeneity was I^2 = 0% (Analysis 3.1).

When considering category I trials (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003; Pini 1994), six trials only included participants with symptomatic DVT while the remaining Massicotte 2003 included participants diagnosed with both symptomatic DVT and PE. A total of 61 of the 941 participants (6.5%) had recurrent symptomatic VTE in the vitamin K antagonist arm versus 49 of the 931 participants (5.3%) allocated to LMWH treatment in the three months of treatment. Analysis of the pooled data showed no clear difference between the two treatment modalities for recurrent symptomatic VTE (Peto OR 0.80, 95% CI 0.54 to 1.18; P = 0.26; 1872 participants; 7 studies). Heterogeneity was I^2 = 16% (Analysis 4.1).

Five category I trials may have been confounded by a difference in the initial treatment (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003). Analysing these trials separately showed no clear difference between treatment groups with a Peto OR of 0.68 (95% CI 0.44 to 1.03; P = 0.07; 1580 participants; 5 studies). Heterogeneity was I^2 = 0%) (Analysis 6.1). The two category I trials that compared a vitamin K antagonist against LMWH for the long term treatment of symptomatic VTE, using the same initial treatment in both arms, were considered in a separate analysis (Das 1996; Pini 1994). Analysis of the pooled data showed no clear difference in recurrent symptomatic VTE between treatments (Peto OR 1.95, 95% CI 0.74 to 5.19; P = 0.18; 292 participants; 2 studies). Heterogeneity was I^2 = 0% (Analysis 5.1).

The incidence of recurrent symptomatic venous thromboembolism during the additional period of follow-up after cessation of active treatment

Five category I (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Pini 1994), and five category II trials (Hamann 1998; Lopaciuk 1999; Lopez 2001; Romera 2009; Veiga 2000), evaluated a period of six to nine months after cessation of the allocated treatment. A total of 53 of the 1296 participants (4.1%) in the vitamin K antagonist group versus a total of 59 of the 1296 participants (4.6%) in the arm allocated to LMWH treatment experienced an episode of recurrent symptomatic VTE. Combined analysis showed no clear difference in recurrent symptomatic VTE between the two treatment arms (Peto OR 1.12, 95% CI 0.77 to 1.64; P = 0.56; 2592 participants; 10 studies). Heterogeneity was I^2 = 28% (Analysis 7.1).

A separate analysis for the category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Pini 1994), evaluating an additional period of nine months after cessation of the allocated treatment, resulted in a total of 36 of the 846 participants (4.3%) in the vitamin K antagonist arm versus a total of 45 of the 845 participants (5.3%) in the LMWH arm experiencing an episode of recurrent symptomatic VTE. Combined analysis showed no clear difference in thromboembolic complications between the two treatment modalities (Peto OR 1.26, 95% CI 0.81 to 1.98; P = 0.30; 1691 participants; 5 studies). Heterogeneity was I^2 = 14%) (Analysis 8.1). It should be noted that in Pini 1994, 34 of the 94 participants used the vitamin K antagonist during an additional three months and 14 of the 94 participants used the vitamin K antagonist for an additional nine months, whereas in the LMWH group all 93 participants stopped their assigned treatment after three months. Furthermore, in Hull 2007, 250 of the 368 participants in the vitamin K antagonist allocated treatment arm were treated with LMWH beyond the three months of allocated treatment, while in the LMWH group 146 of the 369 participants continued with the allocated treatment beyond the three months of allocated treatment. Hull 2009 also reported that some participants in both treatment groups received ongoing warfarin after the initial three months of allocated treatment.

The total period of 12 month follow-up (combining the 3-month period of active treatment and 9 months of follow up) in five category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Pini 1994), included a total of 91 of the 846 participants (10.8%) in the vitamin K antagonist group that had recurrent symptomatic VTE versus 87 of the 845 participants (10.3%) in the LMWH group, showing no clear difference between the two treatment modalities for the risk of recurrent symptomatic VTE (Peto OR 0.95, 95% CI 0.70 to 1.30; P = 0.75; 1691 participants; 5 studies) for participants with symptomatic PE. Heterogeneity was I^2 = 58% (Analysis 10.1).

Analysis of the pooled data in 10 category I and category II trials (Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Lopaciuk 1999; Lopez 2001; Pini 1994; Romera 2009; Veiga 2000), showed no clear difference between LMWH and vitamin K antagonist treatment for the total period of 12 months' follow-up (Peto OR 0.88, 95% CI 0.67 to 1.15; P = 0.34, 2592 participants; 10 studies). Heterogeneity was I^2 = 41% (Analysis 9.1).

The incidence of major bleeding during active treatment

All 16 category I and II trials reported the incidence of major bleeding during allocated treatment. Thirteen trials did not find a clear difference between the two groups. Only two trials found differences between the groups (Beckman 2003; Lopez 2001). Lopez 2001 found a difference in favour of the LMWH group (Peto OR 0.12, 95% CI 0.02 to 0.89). This trial included only participants with DVT. Beckman 2003 also found a difference in favour of the LMWH group (Peto OR 0.05, 95% CI 0.00 to 0.92). This trial included only participants with symptomatic PE.

Analysis of the pooled trials showed major bleeding complications in 50 of the 1702 participants (2.9%) in the vitamin K antagonist arm versus 25 of the 1597 participants (1.6%) in the LMWH group. This difference was in favour of LMWH therapy for the outcome of major bleeding (Peto OR 0.51, 95% CI 0.32 to 0.80; P = 0.004; 3299 participants; 16 studies; low quality evidence). Heterogeneity was I^2 = 0% (Analysis 1.2; Figure 5).

Analysing the 12 trials including only participants with symptomatic DVT, a total of 42 of the 1572 participants (2.7%) in the vitamin K antagonist group had major bleeding versus 22 of the 1449 participants (1.5%) in the LMWH group, showing a

difference between the two treatment modalities in favour of LMWH for the outcome of major bleeding (Peto OR 0.54, 95% CI 0.33 to 0.88; P = 0.01; 3021 participants; 12 studies) for participants treated with symptomatic DVT. Heterogeneity was I^2 = 0% (Analysis 2.2).

The three trials (Beckman 2003; Kucher 2005; Perez-de-Llano 2010), including only participants with symptomatic PE observed a total of three of the 90 participants (3.3%) in the vitamin K antagonist group with major bleeding versus one of the 112 participants (0.9%) in the LMWH group, showing no clear differences between treatments for the outcome of major bleeding (Peto OR 0.23, 95% CI 0.03 to 1.78; P = 0.16; 202 participants; 3 studies) for participants treated with symptomatic PE. Heterogeneity was I^2 = 52% (Analysis 3.2).

When considering only category I trials (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003; Pini 1994), a total of 34 of the 941 participants (3.6%) experienced major bleeding in the vitamin K antagonist arm versus 21 of the 931 participants (2.3%) allocated to LMWH treatment in the three months of treatment. Analysis of the pooled data showed no clear difference between the two treatment modalities for the outcome of major bleeding (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08; 1872 participants; 7 studies). Heterogeneity was I^2 = 0% (Analysis 4.2).

We performed post-hoc analyses assessing the subsets of fatal haemorrhage and intracranial haemorrhage in order to assess how LMWH and VKA differ with respect to severe bleeds. We found no clear differences between LMWH and VKA with the combined category I and category II studies and category I studies only (results not shown).

For two category I trials with the same initial treatment in both groups (Das 1996; Pini 1994), and five category I trials with different initial treatments in the two groups (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003), analysis of data showed no evidence of a difference in major bleeding incidence between the two treatment modalities (Peto OR 1.01, 95% CI 0.20 to 5.12; P = 0.99; 292 participants; 2 studies; I^2 = not applicable) (Analysis 5.2); and no clear difference between the two treatment modalities (Peto OR 0.59, 95% CI 0.33 to 1.04; P = 0.07; 1580 participants; 5 studies; I^2 = 0%) (Analysis 6.2) respectively.

The incidence of major bleeding during the additional period of follow-up after cessation of active treatment

No major bleeding occurred in the additional nine months of follow-up (Analysis 7.2; Analysis 8.2).

Analysis of the pooled data in nine category I and category II trials (Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Lopaciuk 1999; Lopez 2001; Pini 1994; Romera 2009; Veiga 2000), for the total of 12 months' follow-up showed major bleeding complications in 36 of the 1056 participants (3.4%) in the vitamin K antagonist arm versus 20 of the 1056 participants (1.9%) in the LMWH group. This difference was in favour of LMWH therapy (Peto OR 0.56, 95% CI 0.33 to 0.95; P = 0.03; 2112 participants; 9 studies). Heterogeneity was I^2 = 0% (Analysis 9.2).

The total period of 12 months' follow-up in four category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Pini 1994), included a total of 25 of the 606 participants (4.1%) in the vitamin K antagonist group that had a major bleeding incident versus 18 of the 605 participants (3.0%) in the LMWH group, showing no clear difference between the two treatment modalities (Peto OR 0.72, 0.95% CI 0.39 to 1.32; P = 0.28; 1211 participants; 4 studies). Heterogeneity was I^2 = 0% (Analysis 10.2).

Mortality during active treatment

All 16 trials reported mortality during the allocated treatment but no clear differences between the two treatment groups were observed. Fifty-nine of the 1702 participants (3.5%) died in the vitamin K antagonist treatment group versus 62 of the 1597 participants (3.9%) in the LMWH group, which produced a pooled Peto OR of 1.08 (95% CI 0.75 to 1.56; P = 0.68; 3299 participants; 16 studies, moderate quality evidence). Heterogeneity was I^2 = 0% (Analysis 1.3; Figure 6). Similar results were obtained when only category I trial data were pooled (Peto OR 0.92, 95% CI 0.61 to 1.41; P = 0.71; 1872 participants; 7 studies). Heterogeneity was I^2 = 0% (Analysis 4.3).

For two category I trials with the same initial treatment in both groups (Das 1996; Pini 1994), and five category I trials with different initial treatments in the two groups (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003), pooled analyses did not show a clear difference in mortality between the two treatment modalities (Peto OR 0.89, 95% CI 0.29 to 2.68; P = 0.83; 292 participants; 2 studies; I^2 = 0% (Analysis 5.3); and Peto OR 0.93, 95% CI 0.59 to 1.46; P = 0.76; 1580 participants; 5 studies; I^2 = 0% (Analysis 6.3)).

For the 12 trials that considered participants with DVT and for the three trials that considered participants with PE no clear difference in mortality was detected between the two treatment modalities (Peto OR 1.10, 95% CI 0.75 to 1.60; P = 0.64; 3021 participants; 12 studies; I^2 = 0% (Analysis 2.3); and Peto OR 5.39, 95% CI 0.51 to 57.36; P = 0.16; 202 participants; 3 studies; I^2 = 0% (Analysis 3.3)).

Mortality during the additional period of follow-up after cessation of active treatment

Five category I and five category II trials (Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Hull 2009; Lopaciuk 1999; Lopez 2001; Pini 1994; Romera 2009; Veiga 2000), reported an extended follow-up period for an additional six to nine months and found that 72 of the 1296 participants (5.6%) in the vitamin K antagonist arm died versus 72 of the 1296 participants (5.6%) in the LMWH group (Peto OR 1.00, 95% CI 0.71 to 1.40; P = 1.00; 2592 participants; 10 studies). Heterogeneity was I^2 = 0% (Analysis 7.3). Similar results were obtained when only category I trials were considered (Peto OR 1.06, 95% CI 0.72 to 1.55; P = 0.77; 1691 participants; 5 studies; I^2 = 0%) (Analysis 8.3).

An analysis of mortality for the total 12 month follow-up period did not detect a clear difference between the two treatment modalities for the 10 category I and category II trials (Peto OR 1.09, 95% CI 0.84 to 1.43; P = 0.51; 2592 participants; 10

studies; I = 0% (Analysis 9.3)) or the five category I trials (Peto OR 1.05, 95% CI 0.78 to 1.42; P = 0.76; 1691 participants; 5 studies; I^2 = 0% (Analysis 10.3)).

Discussion

Summary of main results

In this review no clear differences were detected between LMWH and vitamin K antagonists for two of the three primary outcomes (recurrent symptomatic venous thromboembolism (VTE) and overall mortality). For the third outcome, major bleeding, a reduction in favour of LMWH was found (Peto OR 0.51, 95% CI 0.32 to 0.80; P = 0.004). However, when the category I trials alone (clearly concealed randomisation, double blind or blinded outcome assessment) were pooled, no clear difference in major bleeding was observed between the treatment groups (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08). Therefore, the review found no evidence that LMWH treatment has greater efficacy than vitamin K antagonists in the long term treatment of VTE, but long term treatment of symptomatic VTE with LMWH may be safer with respect to major bleeding than long term treatment with vitamin K antagonists. The largest trial (Hull 2007), did not observe any clear differences for any of the three outcomes. Similar results were found for recurrent symptomatic VTE, major bleeding and mortality during additional six to nine months after cessation of the allocated three months treatment of symptomatic VTE.

In interpreting the findings of the review there are several worthwhile considerations. Five category I trials did not use the same initial treatment in both treatment arms, and these differences may threaten the validity of the data from these trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003). A previous report suggests that the inferior quality of initial unfractionated heparin treatment may be associated with higher recurrence of VTE during follow-up (Hull 1997), and two trials included in the review did not report the quality of the unfractionated heparin treatment (Daskalopoulos 2005; Gonzalez 1999). In the largest trial Hull 2007, the initial treatment with unfractionated heparin was adequate but this produced no effect between the two treatment modalities. Doses of the various low-molecular-weight compounds used in the individual trials ranged from 100 IU/kg reviparin sodium to 175 anti-Xa IU/kg tinzaparin and 4000 anti-Xa IU enoxaparin. Daskalopoulos 2005 and Hull (Hull 2007; Hull 2009) used the same dose of LMWH for both the initial and long term treatment of symptomatic VTE. Massicotte 2003 recruited only children and the dose was adjusted accordingly. These five category I trials found no clear difference in the incidence of recurrent VTE between LMWH and vitamin K antagonists (Peto OR 0.68, 95% CI 0.44 to 1.03; P = 0.07).

In contrast, the two category I trials with the same initial treatment in both treatment arms that observed a trend in favour of vitamin K antagonists for the prevention of recurrent symptomatic VTE used relatively low doses of LMWH during long term treatment of DVT (Das 1996; Pini 1994), which were approximately twice the dosage normally used in prophylaxis of symptomatic VTE and not weight-adjusted. The relatively low dose used is reflected in the very low levels of anti-Xa activity found after 22 hours (0.04 U/mL after the injection of 4000 anti-Xa IU enoxaparin) (Pini 1994).

Lopez 2001 included 25 participants (14 participants in the LMWH treatment group and 11 participants in the vitamin K antagonists treatment group; n = 158) with infrapopliteal DVT (calf vein thrombosis) diagnosed by duplex ultrasonography. A sensitivity analysis excluding these data from the analysis did not affect the findings. Two considerations are of interest here. Firstly, duplex ultrasonography is not as sensitive and specific for distal thrombosis as it is for proximal DVT (Mitchell 1991). Secondly, the natural history of distal DVT is unclear. It is estimated, from trials of diagnosis, that approximately only 20% of calf vein thrombi develop into a proximal DVT within two weeks of presentation whereas the remainder, which are probably small and self-limiting, do not (Heijboer 1993; Huisman 1986; Huisman 1989; Hull 1985).

The difference in major bleeding complications in favour of LMWH during the allocated treatment of three months has to be considered with caution. Different LMWH compounds and relatively low doses of the medication were used, as previously mentioned. While a difference in bleeding incidence in favour of LMWH was found when all trials were combined (Peto OR 0.51, 95% CI 0.32 to 0.80; P = 0.004), when only the category I trials were considered no clear difference between LMWH and VKA was observed (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08). These trials used higher dosages of LMWH. On the other hand, the only trial that found a difference in favour of LMWH treatment used the same dose of LMWH for initial treatment as well as for long term treatment of symptomatic DVT (Peto OR 0.12, 95% CI 0.02 to 0.89) (Lopez 2001). Post-hoc analyses showed no clear differences between LMWH and VKA when subsets of fatal and intracranial haemorrhage were assessed.

Overall, there is no substantial difference in efficacy in the long term treatment of patients with DVT with LMWH or vitamin K antagonists, but long-term treatment with LMWH may cause fewer episodes of major bleeding than vitamin K antagonist therapy.

Currently many patients are treated at home with a course of subcutaneous LMWH administered by the patients themselves. After this initial treatment patients will continue with a three month course of vitamin K antagonist with the dose adjusted to achieve an INR between 2.0 and 3.0. The trials by Das 1996 and Daskalopoulos 2005 do not represent current practice.

Important practical considerations also influence the choice between LMWH and vitamin K antagonists. These are mainly based on patient and local preferences. The major disadvantage of vitamin K antagonist treatment, compared to LMWH treatment, is the need for regular laboratory monitoring. Furthermore, vitamin K antagonist compounds have some major drug interactions but drug interactions of LMWH, on the other hand, are uncommon. In addition, LMWH is relatively safe during pregnancy (Sanson 1999). A major disadvantage of the treatment with LMWH is that the patient has to self-administer subcutaneous injections on a daily basis. In the included trials, only a few patients stopped the treatment with LMWH and that was mainly due to problems other than the administration of subcutaneous injections. Das

1996 reported that 8% of patients refused to participate in the trial because of reluctance to administer subcutaneous injections by themselves.

Overall completeness and applicability of evidence

The participants with symptomatic VTE that were included in these trials were a representative mix of people with this disease. All trials included approximately similar participants, therefore these data are generalisable to the wider population. Several trials have been published which exclusively included only participants with a diagnosis of cancer and who have symptomatic VTE. We did not include these trials in our review because the participants are not the normal cohort of patients suffering from symptomatic VTE and because this is the subject of another Cochrane review (Akl 2014).

There was only a small amount of data available for patients suffering from symptomatic PE. This review includes data from only 202 people with PE and the review findings should be interpreted with caution.

Direct oral anticoagulants (DOACs) are changing the manner in which patients are being managed (Robertson 2015; Robertson 2015b). Therefore, in the future, as more and more patients are prescribed with DOACs instead of VKA and LMWH, the analysis of this review may become outdated. We will reconsider the focus and future of this review when the review is due to be updated.

Quality of the evidence

Fifty-nine per cent of the included patients (1872/3299) were included in trials with category I classification, the highest quality of evidence, and the review only included direct comparisons of the two treatments.

All randomised controlled trials included in this systematic review were conducted in an unblinded manner because the two different interventions were delivered in different settings (hospital and home), making participant blinding impossible. Where the participant outcomes were collected by individuals who were blind to the treatment allocation we considered the threats to the validity of the trial's conclusion to be reduced. Where it was not reported that those collecting the outcome measures were unaware of the treatment allocation it is possible that the trial's findings are compromised. Trials where the allocation is not concealed and the outcomes are not collected in a blind manner are essentially observational in nature rather than experimental. Analysis for category I trials (clearly concealed randomisation, double blind or blinded outcome assessment) only, show similar results to those analyses combining all studies except for bleeding where no clear difference between treatment groups was observed.

The quality of the evidence for recurrent VTE and mortality was downgraded to moderate due to imprecision as a result of small number of events and a relatively large confidence interval. We decided not to downgrade for risk of bias due to blinding because a sensitivity analysis excluding studies deemed of low methodological quality confirmed the results of no clear difference between LMWH and VKA.

The quality of the evidence for major bleeding was downgraded to low due to risk of bias and inconsistency: a sensitivity analysis analysing only category I trials (clearly concealed randomisation, double blind or blinded outcome assessment) showed no clear difference between VKA and LMWH. Bleeding outcomes are more susceptible to biased outcome reporting than outcomes such as VTE and mortality and only two studies (studies of low methodological quality) report lower bleeding for LMWH, the remainder showed no clear difference due to confidence intervals crossing line of no effect. See Summary of findings table 1.

Potential biases in the review process

The methods used to conduct the review are described in detail in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and particular strengths are the independent application of the review eligibility criteria, independent data extraction and assessment of the risk of bias and assessment of the quality of the evidence according to GRADE. The search strategies were devised and conducted by the Cochrane Vascular Information Specialist who is highly skilled in the identification of randomised controlled trials. The potential biases in the review process are the missing information in three trials regarding aspects of their conduct (Massicotte 2003; Pini 1994; Romera 2009).

Agreements and disagreements with other studies or reviews

Three published systematic reviews have previously evaluated vitamin K antagonists versus LMWH (Bochenek 2012; Ferretti 2006; Iorio 2003). Two did not find a clear difference between LMWH and oral anticoagulants (Ferretti 2006; Iorio 2003).

Iorio 2003 reviewed the efficacy and safety of long term treatment of VTE with LMWH compared with oral anticoagulants and did not find a clear difference between the two types of treatment in the assessment of recurrent VTE (OR 0.66, 95% CI 0.41 to 1.07), for major bleeding (OR 0.45, 95% CI 0.18 to 1.11) or in total mortality (OR 1.19, 95% CI 0.78 to 1.83). This meta-analysis included six trials (Das 1996; Gonzalez 1999; Lopaciuk 1999; Lopez 2001; Pini 1994; Veiga 2000) and an abstract (Hull 2000). All were included in our review except Hull 2000, which is a duplicate report (conference abstract) of the included trial Hull 2007.

Ferretti 2006 reviewed only recurrent VTE after treatment with LMWH compared with oral anticoagulants for people with VTE and did not find a clear difference between the two treatments in the assessment of recurrent symptomatic VTE (OR 1.29, 95% CI 0.82 to 2.02). This meta-analysis included three trials in patients with cancer, which were excluded for the purpose of this Cochrane review, three other trials which we judged to be of high methodological quality (Das 1996; Gonzalez 1999; Pini 1994), four we considered to be of lower methodological quality (Kakkar 2003; Lopaciuk 1999; Lopez

2001; Veiga 2000), and an abstract (Hull 2002) of the included trial Hull 2007.

The third systematic review did detect a difference between the two treatments. Bochenek 2012 reviewed the efficacy and safety of long term treatment of VTE with LMWH compared with oral anticoagulants and found a reduction in episodes of VTE (OR 0.75, 95% CI 0.59 to 0.97) and the outcome major bleeding (OR 0.59, 95% CI 0.47 to 0.74). The review did not evaluate mortality as an outcome. The Bochenek 2012 review also included six trials which we judged to be high methodological quality trials (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Massicotte 2003; Pini 1994), and six trials which we judged to be lower methodological quality trials (Beckman 2003; Kakkar 2003; Kucher 2005; Lopaciuk 1999; Lopez 2001; Veiga 2000). This meta-analysis by Bochenek 2012 included two trials that considered only cancer patients, which were excluded for the purpose of this Cochrane review. One of these studies showed a significant effect of LMWH and heavily influenced the overall outcome contributing approximately one third of the overall weight and was likely to be the reason for the difference with the Cochrane review.

Authors' conclusions

Implications for practice

Moderate quality evidence shows there is no clear difference between LMWH and VKA in preventing symptomatic VTE and mortality after an episode of symptomatic DVT. Low quality evidence shows fewer cases of major bleeding with LMWH compared with VKA. However, when only high quality studies are compared for bleeding, no clear difference was observed between LMWH and VKA. LMWH may be an alternative in some patients, for example those in geographically inaccessible areas, who are reluctant or unable to visit the thrombosis service regularly, or with contraindications to vitamin K antagonists. Only a limited amount of data exist for patients with symptomatic PE.

Implications for research

To draw more definite conclusions there is a need for more adequately-designed randomised controlled clinical trials, especially in the field of symptomatic PE. There is a need for more adequately-designed trials in patients with contraindications for vitamin K antagonists (e.g. pregnant women), patients who are unable or reluctant to go to the thrombosis service on a regular basis, or patients living in geographically inaccessible areas.

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Contributions of authors

A Andras (AA) assessed trials for inclusion, extracted data, assessed risk of bias, analysed data, drafted manuscript.
A Sala Tenna (AST) drafted the manuscript.
Marlene Stewart (MS): assessed trials for inclusion, extracted data, assessed risk of bias, analysed data, drafted manuscript.

Declarations of interest

AA: none known
AST: none known
MS: none known. MS is a member of Cochrane Vascular's editorial staff. To prevent any conflict of interest issues editorial decisions and activities related to this review were carried out by other editorial staff members where appropriate

Differences between protocol and review

The original protocol was modified as follows for the update published in 2012:

- trials that randomised only cancer patients were excluded, as patients with malignancy are the subject of a different review (Akl 2014);
- secondary outcomes were added and were the same as primary outcomes but in a different time frame. Primary outcomes now are measured during the initial treatment covering three months, while secondary outcomes are considered for an additional nine months, or longer if data are available.

The assessment of the methodological quality of the included trials was changed to the updated Cochrane's recommended 'Risk of bias' tool (Higgins 2011).

For the 2017 update, a 'Summary of findings' table was added according to current Cochrane guidelines.

Published notes

The 'Description of the condition' section are based on a standard background section established by Cochrane Vascular.

Characteristics of studies

Characteristics of included studies

Beckman 2003

Methods	Randomised, parallel-design, single institution treatment trial.
Participants	Patients (40 allocated to LMWH (20 patients 1.5 mg/kg daily and 20 patients 1.0 mg/kg daily) and 20 to vitamin K antagonist treatment) with PE confirmed with high probability ventilation perfusion scanning, a positive spiral chest computed tomogram or a conventional pulmonary angiogram or an intermediate ventilation/perfusion lung scan in the presence of high clinical suspicion of PE. Age (mean ± SD years): LMWH 55 ± 13 / VKA 56 ± 11 Gender (%F): LMWH 75 / VKA 70 Location: one centre in USA
Interventions	The warfarin arm started with a course of unfractionated heparin for 5 days with warfarin continued for 90 days. Compared with the enoxaparin arm starting with a course of 14 days with 1 mg/kg twice daily, followed either a course of 1.5 mg/kg once daily subcutaneous enoxaparin (20 patients) or a course of 1.0 mg/kg of 3 months (20 patients).
Outcomes	Recurrent VTE: DVT: loss of vein compressibility demonstrated by ultrasound. PE: a positive spiral computed tomogram. Major bleeding: clinically overt and associated with a fall in haemoglobin of 2 g/dL or more, intracranial, or pericardial. Mortality data were not provided.
Notes	The patients with major bleeding during vitamin K antagonist treatment had an INR of 8.2 and 3.2 respectively. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the method used to generate the randomisation schedule; Brigham and Women's Hospital (BWH) Investigational Drug Service randomised subjects
Allocation concealment (selection bias)	Unclear risk	BWH Investigational Drug Service randomised subjects but how the allocation was concealed is not revealed
Blinding of participants and personnel (performance bias)	High risk	Open label trial not blind: participants receiving standard therapy had their drug regimen administered at principal investigators office while those receiving LMWH were managed at a different site and underwent echocardiography
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear as to whether those collecting the outcomes were aware of the allocation
Incomplete outcome data (attrition bias)	Low risk	The authors provide a table detailing the reason why 7 patients dropped out
Selective reporting (reporting bias)	Low risk	All intended outcomes are reported
Other bias	Low risk	None observed

Das 1996

Methods	Prospective open single-centre randomised clinical trial.
Participants	105 patients (50 allocated to LMWH and 55 to vitamin K antagonist treatment) over the age of 40 years with DVT, confirmed with venography. Age (mean ± SD years): LMWH 65.3 ± 14.9 / VKA 58.6 ± 16.4 Gender (M/F): LMWH 24/26 / VKA 23/32 Location: one centre in UK
Interventions	Warfarin-sodium for 3 months (INR of 2.0 to 3.0), compared with a 3 month course of subcutaneous Fragmin 5000 anti-Xa units (Kabi 2165 heparin fragment) once daily. Both treatment arms started with 10 days of subcutaneous unfractionated heparin therapy.
Outcomes	Recurrent VTE: DVT: an intraluminal filling defect in a deep vein, demonstrated on repeat venography at a site not previously involved and demonstrated on two views. PE was confirmed on ventilation perfusion scanning, and eventually pulmonary angiography in case of doubt. Major bleeding: overt bleeding associated with a drop in the Hb level of 2 g/dL or more, if it required transfusion of two blood units or more, intracranial, others were classified as minor. Mortality data were provided. Blinded outcome assessment was provided by radiologists unaware of treatment allocation.
Notes	3 months of randomised treatment without additional follow-up. The mean INR achieved in the warfarin group was 2.65, with 68.6% between 2.0 and 3.0, 22.8% between 3.1 and 4.0, and 8.6% between 1.7 and 1.9. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A restricted randomisation list using permuted blocks was prepared using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed and sequentially numbered¬envelopes
Blinding of participants and personnel (performance bias)	High risk	Open trial, not blind. Compliance of patients randomised to LMWH was monitored
Blinding of outcome assessment (detection bias)	Low risk	Independent and blind outcome assessment by radiologists unaware of treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Reasons are given for each of the patients who did not complete the trial
Selective reporting (reporting bias)	Unclear risk	All intended outcomes are reported, but timing of outcomes at 2, 4, 8 weeks are not presented
Other bias	Low risk	None observed

Daskalopoulos 2005

Methods	Prospective, open label randomised clinical trial.
Participants	102 patients (50 allocated to LMWH and 52 to vitamin K antagonist treatment) with an episode of DVT confirmed with colour duplex ultrasound. Age (mean (range) years): LMWH 59.0 (25 - 91)/ VKA 58.2 (23 - 95) Gender (M/F) : LMWH 19/31 / VKA 22/30 Location: one centre in Greece
Interventions	The acenocoumarol arm started with a 5 to 7 day course of unfractionated heparin followed by acenocoumarol for 6 months (INR 2.0 to 3.0). The tinzaparin group started with a 7-day course of once daily subcutaneous tinzaparin 175 anti-Xa IU continued for 6 months.
Outcomes	Recurrent VTE: DVT: presence of new thrombus in a venous segment not found affected at the baseline duplex ultrasound scan. PE was confirmed on ventilation perfusion scanning, and eventually pulmonary angiography in case of doubt. In case of a fatal event, presence of pulmonary artery emboli at autopsy. Major bleeding: overt bleeding associated with a drop in the Hb level of 2 g/dL or more, if it required transfusion of two blood units or more, intracranial, intraspinal, intraocular, pericardial, retroperitoneal or associated with death or if the treatment had to be permanently discontinued. Mortality data were provided. Blinded outcome assessment was provided by specialists not involved in the trial who interpreted all objective diagnostic tests.
Notes	6 months of randomised treatment with 6 months of additional follow-up. The INR values in the acenocoumarol arm were: 67.2% between 2.0 and 3.0, 13.6% above 3.0 and 19.1% below 2.0. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived treatment schedule
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	High risk	Open label not blind
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessment was provided by specialists not involved in the trial who interpreted all objective diagnostic tests
Incomplete outcome data (attrition bias)	Low risk	No drop outs. All data described
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Differences in the initial treatment regimens between the groups

Gonzalez 1999

Methods	Prospective, open single-centre randomised clinical trial.
Participants	185 patients (93 allocated to LMWH and 92 to vitamin K antagonist treatment) with a first or second episode of DVT confirmed with contrast venography (20 excluded from analysis by trialists (8 LMWH, 12 VKA)). Age (mean (range), years): LMWH 62.7 (19 - 83) / VKA 28.3 (20 - 82) Gender (M/F): LMWH 41/44 / VKA 46/34 Location: one centre in Spain
Interventions	The coumarin arm started with a 5-day course of unfractionated heparin followed by coumarin for 3 months (INR 2.0 to 3.0). The enoxaparin group started with a 7-day course of twice daily subcutaneous enoxaparin 40 mg (4000 anti-Xa IU), and continued with a 3 month course of once daily enoxaparin 40 mg.
Outcomes	Recurrent VTE: DVT: a constant intraluminal filling defect in a deep vein not present on the first day. PE: at least one segmental defect not seen on the preceding scan and no abnormality on the chest radiograph area, or pulmonary angiogram. Major bleeding: intracranial or retroperitoneal or producing a decrease in the Hb level of at least 2 g/dL, sufficient to necessitate discontinuation of treatment or the transfusion of two or more units of blood. Mortality from all causes. Blinded outcome assessment was provided by two blinded observers who assessed the outcome of venograms.
Notes	3 months of randomised treatment and an additional 9 months of follow-up. All patients stopped after 3 months of treatment. The intensity of vitamin K antagonist therapy was 15% INR < 2.0, 64% INR between 2.0 to 3.0 and 21% INR > 3.0. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived treatment schedule
Allocation concealment (selection bias)	Unclear risk	Computer-derived treatment schedule, no other information provided
Blinding of participants and personnel (performance bias)	High risk	Open label trial – not blind. Patients in the LMWH group were not hospitalised
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessment was provided by two blinded observers who assessed the outcome of venograms
Incomplete outcome data (attrition bias)	Low risk	Outcomes presented, no lost to follow-up, one patient died of a PE
Selective reporting (reporting bias)	Low risk	All outcomes are reported
Other bias	Unclear risk	Differences in the initial treatment regimens between the groups

Hamann 1998

Methods	Prospective, open randomised clinical trial.
Participants	200 patients (100 allocated to LMWH and 100 to vitamin K antagonist treatment) with DVT confirmed with venography. Age (mean (range) years): 58 (18 - 92) Gender (M/F): 82 / 118 Location, one centre, Germany
Interventions	Phenprocoumon for 3 or 6 months (INR 2.0 - 3.0) compared with 3 or 6 month course of subcutaneous dalteparin-sodium 5000 IU anti-Xa once daily.
Outcomes	Recurrent VTE. Major bleeding. Blinded outcome assessment was not provided.
Notes	Different initial therapies were used: 17 patients venous thrombectomy, 18 patients systemic lysis, 28 patients regional lysis and 137 patients received i.v. unfractionated heparin as initial treatment. Furthermore, 44 patients were treated for 3 months and 156 patients were treated for 6 months for the long-term prevention of recurrent VTE. All the interventions were evenly divided between both groups. 3 or 6 months of randomised treatment and an additional 9 months of follow-up. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	High risk	Open label trial
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	All outcomes reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hull 2007

Methods	Multicentre, randomised, open label clinical trial.
Participants	737 patients (369 allocated to LMWH and 368 to vitamin K antagonist treatment) with DVT confirmed with venography or compression ultrasonography. Age (< 60 years old/ ≥ 60 years old): LMWH 187/182, VKA 152/217 Gender (M/F): LMWH 207/162, VKA 188/180 Location: 30 centres across Canada
Interventions	The warfarin arm started with a 6-day course of unfractionated heparin followed by warfarin for 3 months (INR 2.0 to 3.0). The tinzaparin group received once daily subcutaneous tinzaparin 175 anti-Xa IU/kg of body weight, continued for 3 months.
Outcomes	Recurrent VTE: DVT: (a) a previously compressible proximal vein segment not compressible on repeat ultrasonography or venography demonstrating a constant intraluminal filling defect in the deep veins not present on the baseline venogram. Recurrent PE: (a) high probability lung-scan finding; (b) a non diagnostic lung scan with documented new DVT; (c) spiral computed tomography showing thrombus in the central pulmonary arteries; (d) pulmonary angiography revealing a constant intraluminal filling defect or cut-off of a vessel > 2.5 mm in diameter or (e) PE found at autopsy. Major bleeding: clinically overt and (a) associated with a fall in Hb of 2 grams/dL or more, (b) the transfusion of two or more units of blood or intracranial, retroperitoneal or occurring in a major joint. Mortality data were provided. Blinded outcome assessment is provided by a central, independent adjudication committee.
Notes	3 months of randomised treatment and an additional 9 months of follow-up. In the tinzaparin arm 146 patients continued with warfarin treatment after the 3 months of treatment with tinzaparin for a mean of 202 days (median 258 days). In the warfarin arm 250 patients continued warfarin treatment after the 3 months of allocated treatment for a mean of 156 days (median 147 days). Patients with major bleeding complications: 1 patient INR between 3.1 and 3.9, 2 patients INR above 4.0 on the day of the bleeding complication. Furthermore a figure is given providing the data of the INR values throughout the trial. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Derived by computer
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	An open label trial – not blind
Blinding of outcome assessment (detection bias)	Low risk	A central independent adjudication committee interpreted the events
Incomplete outcome data (attrition bias)	Low risk	All patients included in analysis
Selective reporting (reporting bias)	Low risk	All data presented
Other bias	Unclear risk	Differences in the initial treatment regimens between the groups

Hull 2009

Methods	Multicentre, open label randomised clinical trial.
Participants	480 patients (240 allocated to LMWH and 240 to vitamin K antagonist treatment) with documented, acute, proximal DVT. Age (< 60 years old/ ≥ 60 years old): LMWH 118/122, VKA 122/118 Gender (M/F): LMWH 139/101, VKA 138/102 Location: 22 centres across Canada
Interventions	Patients received tinzaparin 175 IU/kg subcutaneously once daily for 12 weeks, or tinzaparin for 5 days plus oral warfarin, commenced on day 1, INR-adjusted, and continued for 12 weeks ('usual care'). Patients received 1 in-clinic injection, then home treatment.
Outcomes	The primary efficacy outcome measure was the occurrence of objectively documented, symptomatic, recurrent VTE at 12 weeks and 1 year. Other efficacy outcomes were: death rates at 12 weeks and 1 year; patients' self-reported treatment satisfaction during the treatment period; symptoms of PTS; and the incidence of venous leg ulcers as reported by patients. The primary safety outcome measure was the occurrence of bleeding (all, major or minor) during the 12-week treatment period. Additional safety outcomes were the incidence of thrombocytopenia and of bone fractures. Blinded outcome assessment is provided by a central, independent adjudication committee.
Notes	3 months of randomised treatment and an additional 9 months of follow-up. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived treatment schedule
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind
Blinding of outcome assessment (detection bias)	Low risk	Outcomes judged by a blinded central independent adjudication committee
Incomplete outcome data (attrition bias)	Low risk	All outcomes presented. 3 patients lost to follow up at 12 months
Selective reporting (reporting bias)	Low risk	All outcomes presented
Other bias	Unclear risk	Differences in the initial treatment regimens between the groups

Kakkar 2003

Methods	Multicentre, randomised, open label, parallel-group trial.
Participants	297 patients (Group A: 98 patients allocated to 7±2 days of unfractionated heparin followed by a 3 month course of vitamin K antagonists, Group B: 105 patients allocated to 7 ± 2 days of LMWH followed by a 3 month course of vitamin K antagonists and Group C: 94 patients allocated to 3 months of treatment with LMWH) with DVT confirmed by venography. Age (years (range)): Group A 61.2 (49.9 - 70.5), Group B 61.2 (44.4 - 69.5), Group C 63.2 (45.1 - 70.8) Gender (M, %): Group A 63, 64.3%, Group B 61, 58.1%, Group C 58, 61.7% Location: 27 centres in three countries (Poland, Spain, UK)
Interventions	Group A: The first coumarin arm started with a 7 ± 2 day course of unfractionated heparin followed by warfarin for 3 months (INR 2.0 to 3.0). Group B: The second coumarin arm started with a 7 ± 2 day course of bemiparin 115 anti-Xa IU/kg once daily, followed by warfarin for 3 months (INR 2.0 to 3.0). Group C: The bemiparin received once daily subcutaneous tinzaparin 115 anti-Xa IU/kg of body weight for 10 days, followed by a fixed dose of 3500 anti-Xa IU for 90 days.
Outcomes	Recurrent VTE: DVT: venography. PE: high probability lung-scan finding. Major bleeding: clinically overt and associated with a fall in Hb of 2g/dL or more, the transfusion of two or more units of blood or intracranial, retroperitoneal. Mortality data were provided. Blinded outcome assessment is provided.
Notes	3 months of randomised treatment and an additional 28 days of follow-up. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about the generation of the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	No information about the concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Open label trial – not blind
Blinding of outcome assessment (detection bias)	Low risk	Blinded assessment of outcomes
Incomplete outcome data (attrition bias)	High risk	Drop outs are only partially explained
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	None observed

Kucher 2005

Methods	Randomised, controlled, open label, single institution treatment trial.
Participants	40 patients (20 allocated to LMWH and 20 to vitamin K antagonist treatment) with PE confirmed with high probability ventilation perfusion scanning, a positive contrast chest computed tomogram or a conventional pulmonary angiogram. Age (years, mean ± SD): LMWH 52 ± 17/ VKA 51 ± 18 Gender (F: n,%): LMWH 15, 75% / VKA 14, 70% Location: one centre in USA
Interventions	The warfarin arm started with a course of enoxaparin (1 mg/kg) twice daily for at least 10 doses overlapping 4 days with warfarin continued for 90 days. Compared with the enoxaparin arm starting with a course of 10-18 days with 1 mg/kg twice daily, followed by a 3 month course of once daily subcutaneous enoxaparin (1.5 mg/kg). 10 patients were treated with thrombolysis because of right ventricular failure.
Outcomes	Recurrent VTE: DVT: a filling defect by conventional venography or loss of vein compressibility demonstrated by ultrasound. PE: high probability lung-scan finding, a positive contrast chest computed tomogram, or a conventional pulmonary angiogram. Major bleeding: clinically overt and associated with a fall in Hb of 3 g/dL or more, intracranial, intraocular, retroperitoneal or pericardial. Mortality data were provided. Blinded outcome assessment is not provided.
Notes	3 months of randomised treatment and thereafter treatment at the discretion of the treating physician. No follow-up after 3 months is provided. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked computer randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open label trial – not blind
Blinding of outcome assessment (detection bias)	High risk	Independent outcome collection not reported
Incomplete outcome data (attrition bias)	Low risk	There were no trial withdrawals
Selective reporting (reporting bias)	Low risk	Prospectively stated outcomes reported
Other bias	Low risk	None observed

Lopaciuk 1999

Methods	Prospective, open, multicentre randomised clinical trial.
Participants	202 patients (101 allocated to LMWH and 101 to vitamin K antagonist treatment) with proximal DVT confirmed with contrast phlebography. Evaluable data available for 98 LMWH and 95 VKA participants. Age (mean ± SD, years) : LMWH 56.6 ± 16.2 / VKA 57.8 ± 14.6 Gender (M/F): LMWH 45/53 / VKA 49/46 Location: 11 centres in Poland
Interventions	Acenocoumarol for 3 months (INR of 2.0 to 3.0), compared with a 3 month course of once daily subcutaneous nadroparin (85 anti-Xa units per kilogram). Both treatment arms started with a 10-day course of twice daily subcutaneous nadroparin 85 anti-Xa units per kilogram.
Outcomes	Recurrent VTE: DVT: a new constant intraluminal filling defect compared to baseline venography. PE: a new segmental or greater perfusion defect on a lung scan or a positive pulmonary angiogram. Major bleeding: overt bleeding associated with a fall in Hb of 2 g/dL or more with a need for transfusion of two or more units of packed red cells or intracranial or retroperitoneal bleeding. Mortality from all causes. Blinded outcome assessment was not provided.
Notes	3 months of randomised treatment and an additional 9 months of follow-up. 21 patients (22%) used acenocoumarol for an additional 3 months, 5 (5%) to 9 months and 15 (16%) to one year. In the nadroparin group 7 patients (7%) prolonged their treatment to 4 to 5 months, and to 9 months in one patient. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	In sealed envelopes
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind
Blinding of outcome assessment (detection bias)	High risk	Blinded outcome assessment not reported
Incomplete outcome data (attrition bias)	Low risk	Withdrawals accounted for
Selective reporting (reporting bias)	Low risk	Prospectively stated outcomes reported
Other bias	Unclear risk	3 fatal peripheral or cardiovascular events in the acenocoumarol group are not discussed. The follow-up treatments after the planned 3 month outcomes differed in both groups

Lopez 2001

Methods	Prospective, open, single-centre randomised clinical trial.
Participants	158 patients (81 allocated to LMWH and 77 to vitamin K antagonist treatment) with a first DVT episode in this leg confirmed with duplex scan examination. Age (mean (95% CI), years): LMWH 65 (62 - 69) / VKA 66 (63 - 70) Gender (M/F): LMWH 31/50 / VKA 38/39 Location: one centre in Spain
Interventions	Acenocoumarol for 3 or 6 months (INR 2.0 to 3.0), compared to subcutaneous nadroparin adjusted to body weight two times daily (1025 anti-Xa IU / 10 kg). Both treatment arms started with a course of at least 5 days of treatment with subcutaneous nadroparin twice daily (1025 anti-Xa IU / 10 kg).
Outcomes	Recurrent VTE: DVT: the appearance of thrombosis in a previously unaffected venous segment of the ipsilateral or contralateral leg. PE: constant intraluminal filling defect in spiral computed tomography or conventional angiography. Major bleeding: overt bleeding and associated with a decrease of 2 g/dL or more in the Hb level, if it required a blood transfusion of 2 units or more, if it was intracranial or retroperitoneal, or if the treatment had to be permanently discontinued. All other episodes of bleeding were defined as minor.
Notes	3 to 6 months of randomised treatment and an additional 6 to 9 months of follow-up. 44 patients were treated for 6 months in the acenocoumarol group and 34 in the nadroparin group. The remainder were treated for 3 months. Control INR values were less than 2.0 in 22.8%, between 2 and 3 in 67.8% and above 3 in 9.4% of the cases. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of the allocation sequence not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind
Blinding of outcome assessment (detection bias)	Low risk	Blind outcomes collected by independent panel of physicians
Incomplete outcome data (attrition bias)	Low risk	Withdrawals explained
Selective reporting (reporting bias)	Low risk	All prospectively started outcomes reported
Other bias	Low risk	None observed

Massicotte 2003

Methods	Multicentre, open label, randomised clinical trial.
Participants	78 patients (all children) (37 allocated to reviparin and 41 to unfractionated heparin plus anticoagulant) with DVT confirmed by either venography or compression ultrasound, or PE confirmed by ventilation perfusion scan or pulmonary angiogram. Age (mean ± SD, years): LMWH 9.4 ± 6.6 / VKA 8.7 ± 5.9 Gender (M/F): LMWH 17/20 / VKA 19/22 Location: 37 centres in 6 countries (Australia, Canada, Germany, The Netherlands, UK, USA)
Interventions	Interventions started within 48 hours of randomisation. 3 months of 100 IU/kg reviparin sodium (Knoll, Germany), compared with 3 months of UFH followed by oral anticoagulants.
Outcomes	Recurrent VTE during the 3 months of treatment and subsequent 3 month follow-up or death due to DVT. Other outcomes included: - safety outcomes; - major bleeding defined as clinically significant overt bleeding which required immediate transfusion of red blood cells or any retroperitoneal, intracranial or intra-articular bleeding; - minor bleeding defined as bruising, oozing around intravenous sites and surgical wounds, small amount of blood from suctioning endotracheal tubes, small amounts of blood in urine or stool, and minor nose bleeds.
Notes	3 months of randomised treatment and an additional 3 months of follow-up. Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived protocol
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind
Blinding of outcome assessment (detection bias)	Low risk	An independent and blinded, central adjudication committee assessed all outcomes
Incomplete outcome data (attrition bias)	Low risk	Out of the 78 patients, 66 completed the trial, 17 withdrawn, 5 deaths
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes are presented
Other bias	Unclear risk	Differences in the initial treatment regimens between the groups

Perez-de-Llano 2010

Methods	Randomised, multicentre open-label trial.
Participants	102 patients (52 allocated to LMWH monotherapy and 50 to LMWH followed by chronic vitamin K antagonist treatment) with objectively confirmed PE (perfusion lung scan or chest computed tomogram). Age (year (range)): LMWH 72.4 (25 - 93) / VKA 72.1 (24 - 91) Gender (male, %): LMWH 25, 50% / VKA 28, 53.9% Location: four centres in Spain
Interventions	Participants received tinzaparin 175 IU/kg subcutaneously once daily for 6 months, or tinzaparin plus oral acenocoumarol, commenced within 48 hours of the first dose of tinzaparin, INR-adjusted, and continued for 6 months. In this latter group tinzaparin was continued until the INR was above 2 on two consecutive days.
Outcomes	Symptomatic, recurrent VTE at 1 month, 3 months and 6 months (by compression ultrasonography or helical computed tomography). Composite of major and minor clinically relevant bleeding during treatment. Bleeding was defined as major if it was clinically and associated with a decrease in Hb levels of at least 2 g/dL or required a transfusion of at least 2 units of red blood cells, or if it was intracranial or retroperitoneal. Other adverse reactions were also reported. Blinded outcome assessment was not provided.
Notes	Category II trial. The INR values after discharge were: 51.7% of measurements were within therapeutic range, 41.5% below it and 6.8% above it. LEO Pharma provided indemnity and grants to support study and two study authors reported either lecturing or working for LEO Pharma.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We stratified randomization through a central computer-generated list"
Allocation concealment (selection bias)	Unclear risk	Randomisation through a central computer-generated list - no other information regarding allocation concealment provided
Blinding of participants and personnel (performance bias)	High risk	Open label trial
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	"Eight patients did not complete the 6-month protocol successfully: five (9.7%) randomized to tinzaparin (metastatic cancer, allergy to tinzaparin, vein thrombosis and for two patients the reason was unknown) and three (6%) to VKA (metastatic cancer, inability to reach therapeutic INR and for one patents the reason was unknown)" All withdrawals and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Prospectively stated outcomes reported
Other bias	Low risk	None observed

Pini 1994

Methods	Prospective, open single-centre randomised clinical trial.
Participants	187 patients (93 allocated to LMWH and 94 to vitamin K antagonist treatment) with a first or second episode of symptomatic DVT confirmed with strain-gauge plethysmography combined with a positive D-dimer latex test most of the time confirmed with contrast venography. Age (years, mean): LMWH 65.4 / VKA 65.0 Gender (M/F): LMWH 47/46 / VKA 54/40 Location: one centre in Italy
Interventions	3 months of conventional treatment with warfarin (INR 2.0 - 3.5), compared to a 3 month course of enoxaparin 4000 anti-Xa units once daily. All patients were initially treated with a 10-day course of subcutaneous UFH adjusted to an APTT of about 1.3 to 1.9 times the patient's basal value.
Outcomes	Recurrent VTE, DVT: a new intraluminal filling defect in the deep veins by repeated venography or, if marked reduction of strain-gauge plethysmography was coupled with a positive D-dimer test that followed a negative one. PE: was defined by a single or multiple segmental defects at perfusion scan with no abnormalities on the chest radiograph in that area, by positive pulmonary angiogram, or by autopsy. Major bleeding: clinically overt bleeding associated with a fall in haemoglobin of 2g/dL, led to a blood transfusion, or was intracranial or retroperitoneal bleeding. All other episodes were defined as minor. Mortality from all causes. Blinded outcome assessment was provided by an independent panel of physicians who were unaware of treatment allocation.
Notes	3 months of randomised treatment and an additional 9 months of follow-up. Anticoagulation was graded good in 38% of patients (at least 67% of INR values within the therapeutic range), intermediate in 43% (34 - 66% of values in the therapeutic range), and poor in 19% of cases (< 34% of values in the therapeutic range). Category I trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind
Blinding of outcome assessment (detection bias)	Low risk	Final adjudication of the outcome measures conducted by an independent panel of physicians, one of whom was not involved in the trial
Incomplete outcome data (attrition bias)	Low risk	Patients exclusions explained and no enrolled patients dropped out
Selective reporting (reporting bias)	Low risk	All 3 outcomes reported (recurrent VTE, PE and bleeding); deaths also reported
Other bias	Low risk	None observed

Romera 2009

Methods	Open label, prospective, randomised clinical trial.
Participants	241 patients (119 allocated to LMWH and 122 to vitamin K antagonist treatment) with an episode of symptomatic DVT confirmed with duplex ultrasonography. Age (mean ± SD years): LMWH 58.9 ±17.6 / VKA: 61.3 ± 16.2 Gender (male, %): LMWH 64, 53.8% / VKA: 70, 57.4% Location: two centres in Spain
Interventions	The warfarin arm started with a course of tinzaparin 175 anti-Xa IU/kg of body weight followed by warfarin for 6 months (INR 2.0 to 3.0). The tinzaparin group received once daily subcutaneous tinzaparin 175 anti-Xa IU/kg of body weight, continued for 6 months.
Outcomes	Recurrent VTE: DVT: a previously compressible proximal vein segment was no longer compressible on ultrasonography. PE: high-probability lung scan with clinical suspicion, an abnormal perfusion scan with documented new DVT or a spiral CT showing thrombus in the pulmonary arteries. Major bleeding: clinically overt bleeding associated with a fall in Hb of 2 g/dL or more, led to a blood transfusion of two or more units, or was intracranial, retroperitoneal bleeding, or in a major joint. Mortality of all causes. Blinded outcome assessment was provided.
Notes	6 months of randomised treatment and an additional 6 months of follow-up. One note was made of the adequateness of anticoagulation during vitamin K antagonist treatment. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	High risk	Open label not blind
Blinding of outcome assessment (detection bias)	Low risk	Independently collected outcomes
Incomplete outcome data (attrition bias)	Low risk	All outcome data presented
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes reported
Other bias	Low risk	None observed

Veiga 2000

Methods	Prospective, open, single-centre randomised clinical trial
Participants	100 patients (50 allocated to LMWH and 50 to vitamin K antagonist treatment) over the age of 75 years with a symptomatic proximal DVT confirmed with phlebography. Age: (mean, years): LMWH 80.9 / VKA 79.6 Gender (M/F): LMWH 17/33 / VKA 24/26 Location: one centre in Spain
Interventions	Acenocoumarol for 3 or 6 months (INR 2.0 to 3.0), compared to once daily subcutaneous enoxaparin 40 mg (4000 International Factor Xa Inhibitory Units). Both treatment arms started with a course of at least 10 days of intravenous UFH. Starting with a bolus of 5000 IU and followed with 4000 IU administered every 4 hours, with a target APTT of 1.5 to 2.0 times the baseline APTT.
Outcomes	Recurrent VTE: DVT: a new filling defect was observed in the phlebography. PE: pulmonary scintigraphy and/or pulmonary arteriography. Necropsy was performed when necessary. Major bleeding: overt bleeding and associated with a decrease of 2g/dL or more in the Hb, if it required a blood transfusion, was retroperitoneal, intracranial or intra-articular, or led to death. All other episodes of bleeding were defined as minor.
Notes	3 to 6 months of randomised treatment and an additional 6 to 9 months of follow-up. 7 patients were treated for 6 months in the acenocoumarol group and 5 in the enoxaparin group. The remainder were treated for 3 months. Therapeutic compliance was graded as good in 15 (30%) patients (within the desired INR range in more than 75% of occasions), acceptable in 28 (56%) patients (within INR target range in 50 - 75% of occasions), and poor in 7 (14%) of the patients (less than 50% of occasions in within the target range). In the enoxaparin group four patients reported slight irregularities, in five others, the number of vials returned did not correspond exactly with the doses needed for that time period. Category II trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Closed envelopes used but no further information provided
Allocation concealment (selection bias)	Low risk	Closed envelopes
Blinding of participants and personnel (performance bias)	High risk	Open label trial - not blind: LMWH administered to hospitalised patient versus acenocoumarol outpatients
Blinding of outcome assessment (detection bias)	Low risk	Outcomes collected by independent specialists
Incomplete outcome data (attrition bias)	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes are accounted for
Other bias	Low risk	None observed

Footnotes

APTT: activated partial thromboplastin time
CI: confidence interval
DVT: deep venous thrombosis
Hb: haemoglobin

INR: international normalised ratio
IU: international units
LMWH: low molecular weight heparin
PE: pulmonary embolism
PTS: post-thrombotic syndrome
SD: standard deviation
UFH: unfractionated heparin
VKA; vitamin K antagonist
VTE: venous thromboembolism

Characteristics of excluded studies

Ghirarduzzi 2009

Reason for exclusion	Composite end-point trial

Hull 2001

Reason for exclusion	Subjective patient reported outcomes

Hull 2001a

Reason for exclusion	Subjective patient reported outcomes

Vorobyeva 2009

Reason for exclusion	Non-randomised trial

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 LMWH compared to VKA for the long term treatment of symptomatic VTE

LMWH compared to VKA for the long term treatment of symptomatic VTE

Patient or population: patients with symptomatic VTE requiring long term treatment (three months) for symptomatic VTE
Setting: hospital and outpatient
Intervention: LMWH
Comparison: VKA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with VKA	Risk with LMWH				
Incidence of recurrent VTE (treatment duration 3 months)	Study population 51 per 1,000	42 per 1,000 (31 to 58)	Peto OR 0.83 (0.60 to 1.15)	3299 (16 RCTs)	⊕⊕⊕⊖ MODERATE[1, 2]	
Incidence of major bleeding (treatment duration 3 months)	Study population 29 per 1,000	15 per 1,000 (10 to 24)	Peto OR 0.51 (0.32 to 0.80)	3299 (16 RCTs)	⊕⊕⊖⊖ LOW [3, 4]	
Mortality (treatment duration 3 months)	Study population 35 per 1,000	37 per 1,000 (26 to 53)	Peto OR 1.08 (0.75 to 1.56)	3299 (16 RCTs)	⊕⊕⊕⊖ MODERATE [1, 2]	

* The basis for the **assumed risk** with VKA for 'Study population' was the average risk in the VKA group (i.e. total number of participants with events divided by the total number of participants in the VKA group included in the meta-analysis. **The risk in the LMWH group** (and its 95% confidence interval) is based on the assumed risk in the VKA group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **LMWH:** Low molecular weight heparin; **OR:** Odds ratio; **VKA:** Vitamin K antagonist; **VTE:** Venous thromboembolism

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] High risk of bias due to no blinding but not downgraded as analysis excluding studies deemed of low methodological quality confirms the results of no clear difference between LMWH and VKA
[2] Downgraded by one level due to imprecision; small number of events, relatively large confidence interval
[3] Downgraded by one level for risk of bias as sensitivity analysis analysing only category I trials (clearly concealed randomisation, double blind or blinded outcome assessment) shows no clear difference between VKA and LMWH. Bleeding outcomes are more susceptible to biased outcome reporting than outcomes such as VTE and mortality
[4] Downgraded by one level for inconsistency: only two studies (studies of low methodological quality) report lower bleeding for LMWH, the remainder showed no clear difference with confidence intervals crossing line of no effect

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Classification pending references

Data and analyses

1 LMWH versus VKA during allocated treatment (category I and II trials) in participants with VTE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Incidence of recurrent VTE	16	3299	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.83 [0.60, 1.15]
1.2 Incidence of major bleeding	16	3299	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.51 [0.32, 0.80]
1.3 Mortality	16	3299	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.08 [0.75, 1.56]

2 LMWH versus VKA during allocated treatment (category I and II trials) in participants with DVT

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Incidence of recurrent VTE	12	3021	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.79 [0.57, 1.11]
2.2 Incidence of major bleeding	12	3021	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.54 [0.33, 0.88]
2.3 Mortality	12	3021	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.10 [0.75, 1.60]

3 LMWH versus VKA during allocated treatment (category I and II trials) in participants with PE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Incidence of recurrent VTE	3	202	Peto Odds Ratio(Peto, Fixed, 95% CI)	5.70 [0.91, 35.60]
3.2 Incidence of major bleeding	3	202	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.23 [0.03, 1.78]
3.3 Mortality	3	202	Peto Odds Ratio(Peto, Fixed, 95% CI)	5.39 [0.51, 57.36]

4 LMWH versus VKA during allocated treatment (category I trials) in participants with VTE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Incidence of recurrent VTE	7	1872	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.80 [0.54, 1.18]
4.2 Incidence of major bleeding	7	1872	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.62 [0.36, 1.07]
4.3 Mortality	7	1872	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.92 [0.61, 1.41]

5 Category I trials and the same initial treatment in both groups (UFH or LMWH)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Incidence of recurrent VTE	2	292	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.95 [0.74, 5.19]
5.2 Incidence of major bleeding	2	292	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.01 [0.20, 5.12]
5.3 Mortality	2	292	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.89 [0.29, 2.68]

6 Category I trials and initial treatment is not the same in both groups (UFH compared to LMWH)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

6.1 Incidence of recurrent VTE	5	1580	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.68 [0.44, 1.03]
6.2 Incidence of major bleeding	5	1580	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.59 [0.33, 1.04]
6.3 Mortality	5	1580	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.93 [0.59, 1.46]

7 LMWH versus VKA during additional follow-up (category I and II trials)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Incidence of recurrent VTE	10	2592	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.12 [0.77, 1.64]
7.2 Incidence of major bleeding	9	2112	Peto Odds Ratio(Peto, Fixed, 95% CI)	Not estimable
7.3 Mortality	10	2592	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.00 [0.71, 1.40]

8 LMWH versus VKA in the additional nine months of follow-up (category I trials)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Incidence of recurrent VTE	5	1691	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.26 [0.81, 1.98]
8.2 Incidence of major bleeding	4	1211	Peto Odds Ratio(Peto, Fixed, 95% CI)	Not estimable
8.3 Mortality	5	1691	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.06 [0.72, 1.55]

9 LMWH versus VKA for the total period of 12 months of follow-up (category I and II trials)

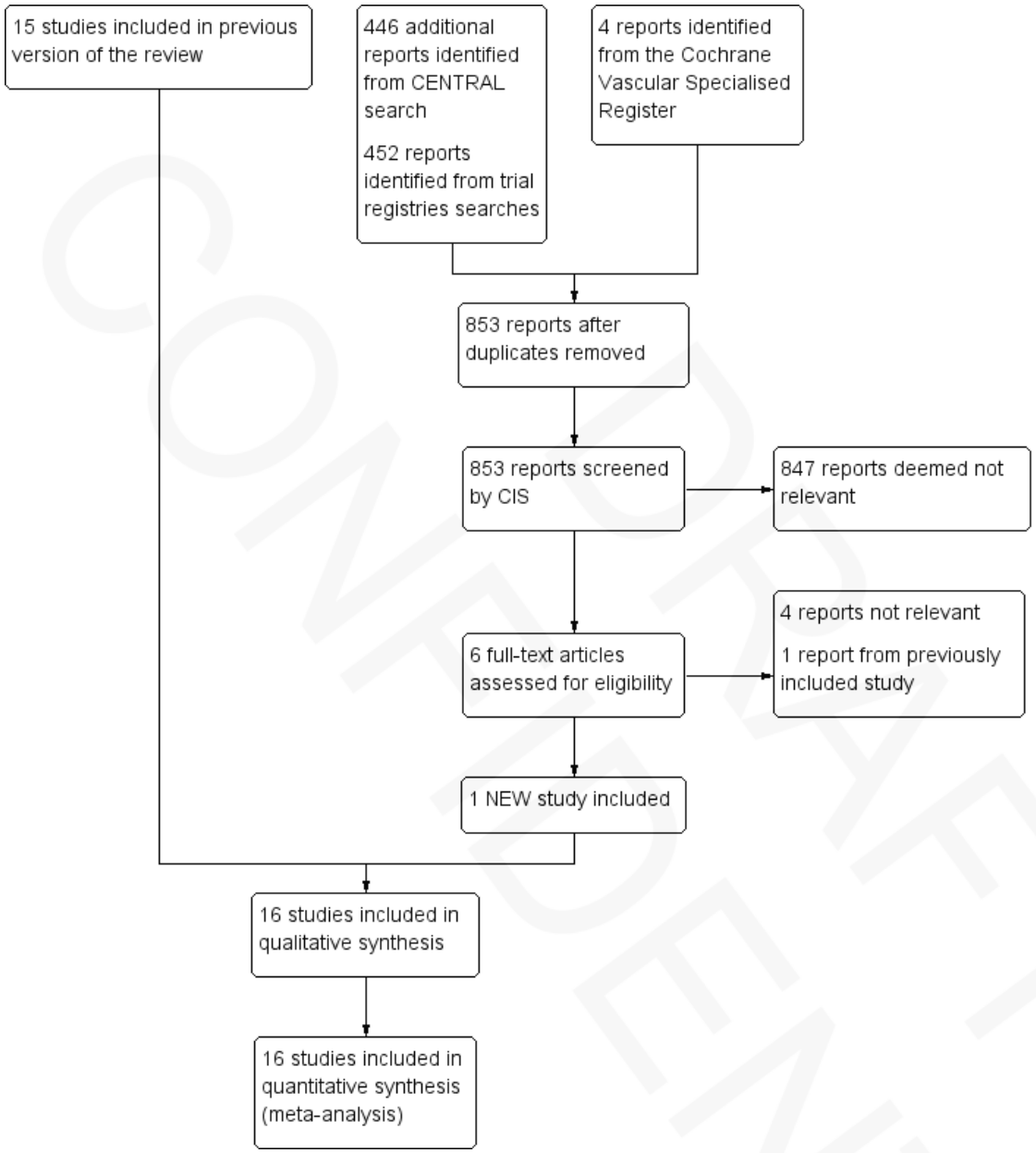
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Incidence of recurrent VTE	10	2592	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.88 [0.67, 1.15]
9.2 Incidence of major bleeding	9	2112	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.56 [0.33, 0.95]
9.3 Mortality	10	2592	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.09 [0.84, 1.43]

10 LMWH versus VKA for the total period of 12 months of follow-up (category I trials)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 Incidence of recurrent VTE	5	1691	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.95 [0.70, 1.30]
10.2 Incidence of major bleeding	4	1211	Peto Odds Ratio(Peto, Fixed, 95% CI)	0.72 [0.39, 1.32]
10.3 Mortality	5	1691	Peto Odds Ratio(Peto, Fixed, 95% CI)	1.05 [0.78, 1.42]

Figures

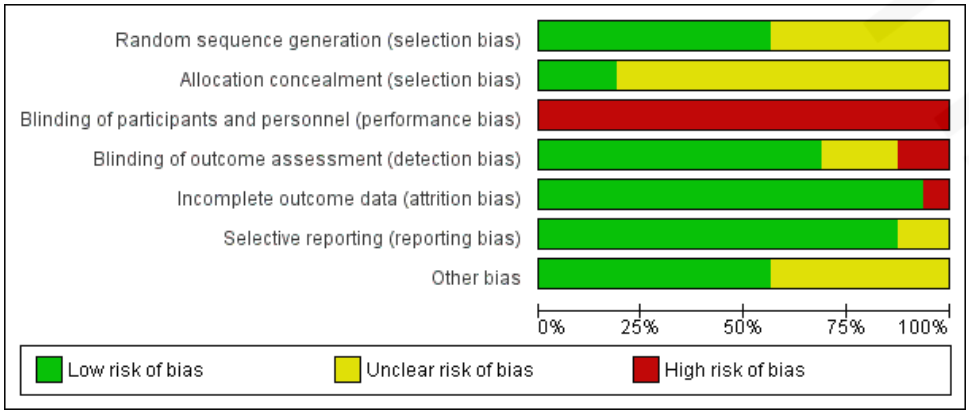
Figure 1



Caption

Study flow diagram.

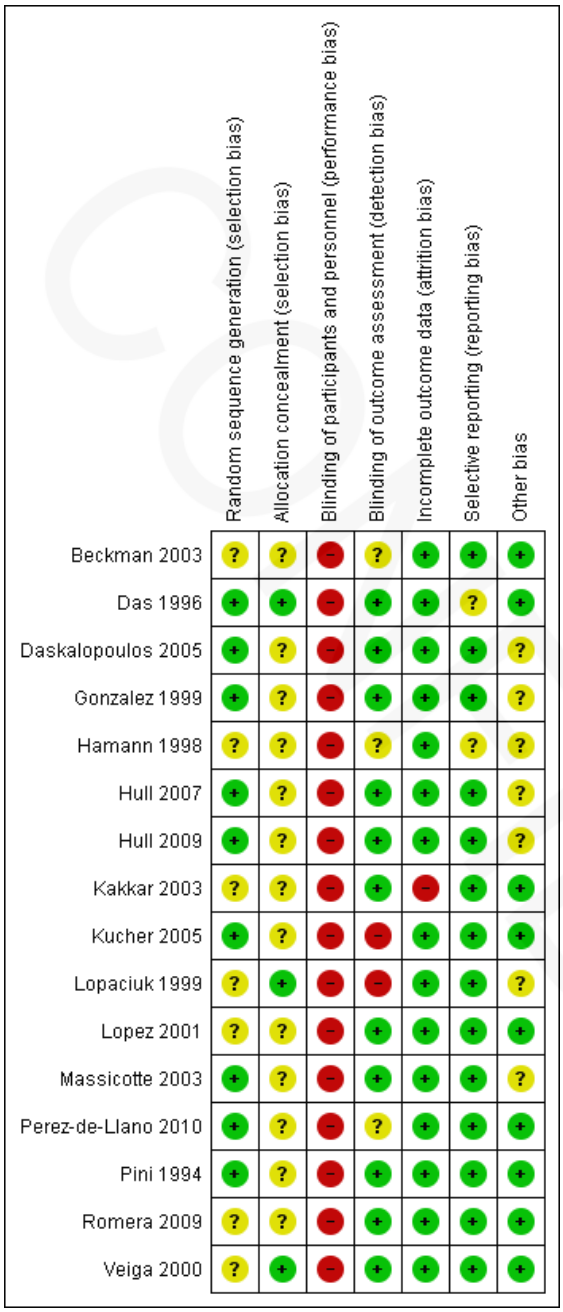
Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

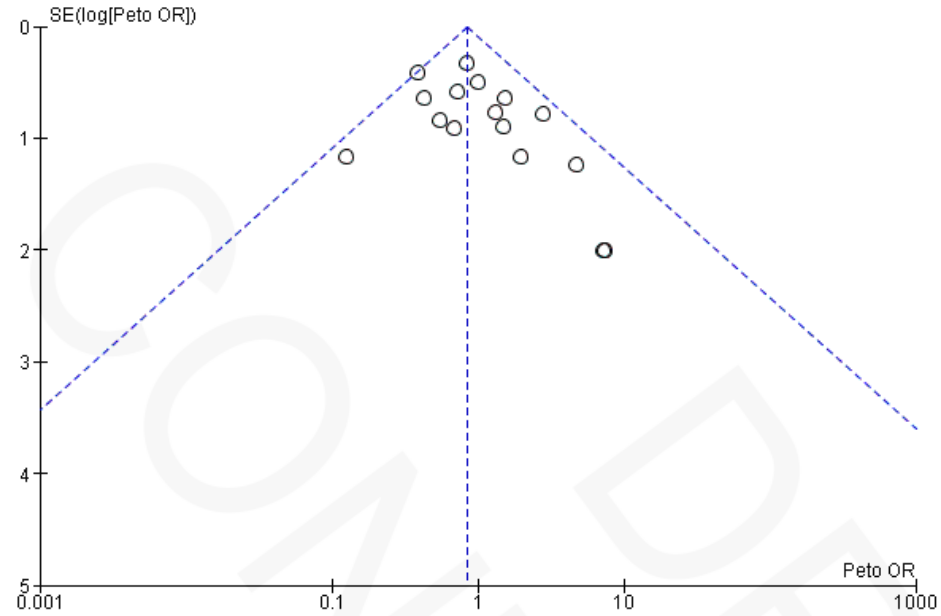
Figure 3



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

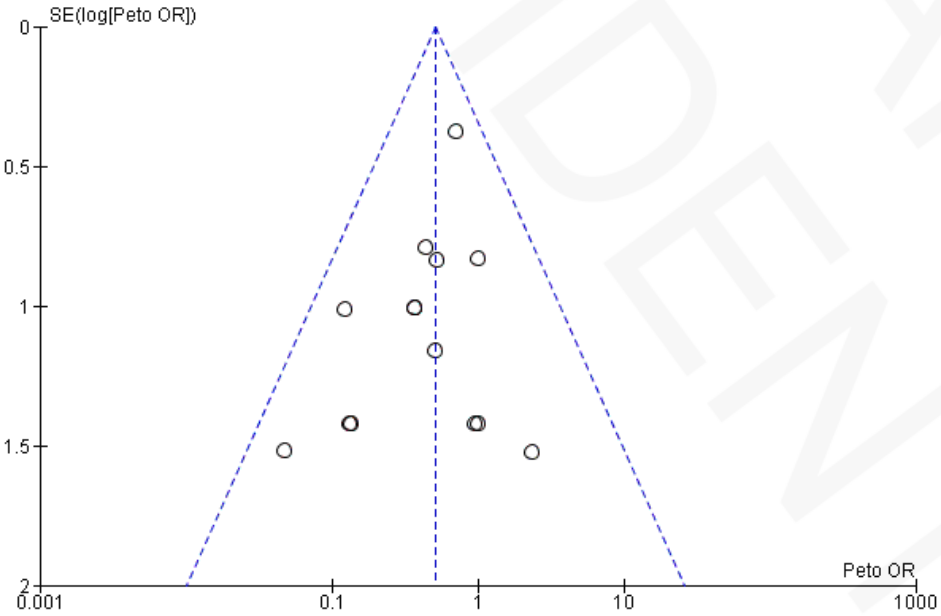
Figure 4 (Analysis 1.1)



Caption

Funnel plot of comparison: 2 LMWH versus VKA during three months of allocated treatment (category I and II trials), outcome: 2.1 incidence of recurrent VTE.

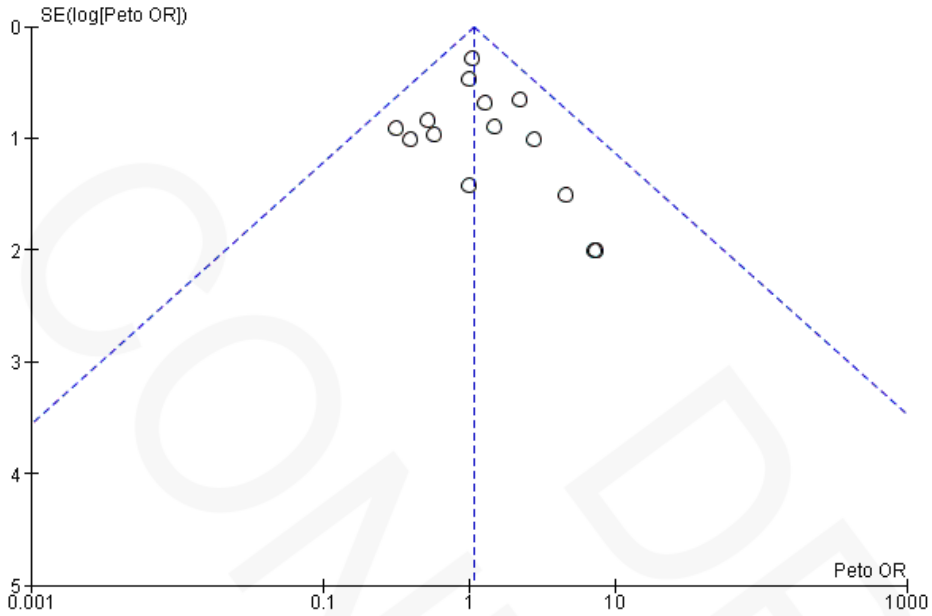
Figure 5 (Analysis 1.2)



Caption

Funnel plot of comparison: 2 LMWH versus VKA during three months of allocated treatment (category I and II trials), outcome: 2.2 incidence of major bleeding.

Figure 6 (Analysis 1.3)



Caption

Funnel plot of comparison: 2 LMWH versus VKA during three months of allocated treatment (category I and II trials), outcome: 2.3 Mortality.

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK
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- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK
  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

Feedback

1 Anticoagulant feedback, 14 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at http://www.editorial-unit.cochrane.org/anticoagulants-feedback.

Reply

Contributors

Appendices

1 CENTRAL search strategy

#1	MESH DESCRIPTOR Thrombosis	1234
#2	MESH DESCRIPTOR Thromboembolism	896
#3	MESH DESCRIPTOR Venous Thromboembolism	239
#4	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	2001
#5	(thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI, AB,KY	17573
#6	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	734
#7	(PE or DVT or VTE):TI,AB,KY	4603
#8	(((vein* or ven*) near thromb*)):TI,AB,KY	6271

#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	20979
#10	MESH DESCRIPTOR Anticoagulants	3271
#11	MESH DESCRIPTOR Coumarins EXPLODE ALL TREES	1618
#12	(((vitamin k or vit k) near3 antagon*)):TI,AB,KY	370
#13	VKA:TI,AB,KY	140
#14	anticoagula*:TI,AB,KY	7493
#15	anti-coagula*:TI,AB,KY	146
#16	warfarin*:TI,AB,KY	2809
#17	*coum* :TI,AB,KY	834
#18	(Jantoven or Marevan or Lawarin or Waran or Warfant or Dindevan):TI,AB,KY	4
#19	phenindione:TI,AB,KY	33
#20	(Sinthrome or Sintrom):TI,AB,KY	8
#21	(Marcumar or Falithrom):TI,AB,KY	10
#22	(aldocumar or tedicumar):TI,AB,KY	0
#23	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	9306
#24	MESH DESCRIPTOR Heparin, Low-Molecular-Weight EXPLODE ALL TREES	1488
#25	(low near4 hepar*):TI,AB,KY	3132
#26	(LMWH or LMH):TI,AB,KY	802
#27	(nadroparin* or fraxiparin* or enoxaparin):TI,AB,KY	1620
#28	(Clexane or klexane or lovenox):TI,AB,KY	42
#29	(dalteparin or Fragmin or ardeparin):TI,AB,KY	561
#30	(normiflo or tinzaparin or logiparin):TI,AB,KY	182
#31	(Innohep or certoparin or sandoparin or reviparin):TI,AB,KY	134
#32	(clivarin* or danaproid or danaparoid):TI,AB,KY	56
#33	(antixarin or ardeparin* or bemiparin*):TI,AB,KY	42
#34	(Zibor or cy 222 or embolex or monoembolex):TI,AB,KY	38
#35	(parnaparin* or rd 11885 or RD1185):TI,AB,KY	27
#36	(tedelparin or Kabi-2165 or Kabi 2165):TI,AB,KY	42
#37	(emt-966 or emt-967 or pk-10 169 or pk-10169 or pk10169):TI,AB,KY	8
#38	(fr-860 or cy-216 or cy216):TI,AB,KY	51
#39	(seleparin* or tedegliparin or seleparin* or tedegliparin*):TI,AB,KY	1
#40	("kb 101" or kb101 or lomoparan or orgaran):TI,AB,KY	31
#41	(parnaparin or fluxum or lohepa or lowhepa):TI,AB,KY	33
#42	(op 2123 or parvoparin):TI,AB,KY	1
#43	calciparin*:TI,AB,KY	22
#44	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	4570
#45	#9 AND #23 AND #44	1187
#46	15/02/2012 TO 31/10/2016:DL	308891
#47	#45 AND #46	446

2 Trials registries searches

ClinicalTrials.gov

44 studies found for: Thromboembolism OR thrombosis OR DVT in Condition AND

(vitamin k antagonist OR warfarin OR coumadin OR phenprocoumon OR acenocoumarol OR dicoumarol) AND heparin in

Interventions

World Health Organization International Clinical Trials Registry Platform

496 records for 138 trials for: Thromboembolism OR thrombosis OR DVT in Condition AND

(warfarin OR coumadin OR phenprocoumon OR acenocoumarol OR dicoumarol) AND heparin in Intervention

ISRCTN Register

3 results found for (warfarin OR coumadin OR phenprocoumon OR acenocoumarol OR dicoumarol) AND (thromboembolism or thrombosis or DVT)

3 Glossary

anticoagulant: medicine that help prevent blood clots

intravenous: into the vein(s)

oral anticoagulant: anticoagulant taken by mouth

parenteral anticoagulant: administration of anticoagulant by injection or infusion

subcutaneous: under the skin