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

Andras A, Sala Tenna A, Stewart M

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[Intervention Review]

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

Alina Andras[1], Adriano Sala Tenna[2], Marlene Stewart[3]

[1]Keele University, Keele, UK. [2]Department of Vascular Surgery, Freeman Hospital, Newcastle Upon Tyne, UK. [3]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

Contact address: Alina Andras, Keele University, Keele, Staffordshire, ST5 5BG, UK. alinaro@hotmail.com, a.andras@keele.ac.uk.

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ABSTRACT

Background

People with venous thromboembolism (VTE) generally are treated for five days with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH), followed by three months of vitamin K antagonists (VKAs). Treatment with VKAs requires regular laboratory measurements and carries risk of bleeding; some patients have contraindications to such treatment. Treatment with LMWH has been proposed to minimise 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) with LMWH versus long term treatment (three months) with VKAs for symptomatic VTE.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Specialised Register (last searched November 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10), The Cochrane Vascular Information Specialistalso searched clinical trials registries for ongoing studies.

Selection criteria

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

Data collection and analysis

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

Main results

Sixteen trials, with a combined total of 3299 participants fulfilled our inclusion criteria. According to GRADE, the quality of evidence was moderate for recurrent VTE, low for major bleeding, and moderate for mortality. We downgraded the quality of the evidence for imprecision (recurrent VTE, mortality) and for risk of bias and inconsistency (major bleeding).

We found no clear differences 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 than 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 comparing only high-quality studies for bleeding, we observed no clear differences between LMWH and VKA (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08; 1872 participants; seven studies). We found no clear differences between LMWH and VKA in terms of 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 no clear differences between LMWH and VKA in preventing symptomatic VTE and death after an episode of symptomatic DVT. Low-quality evidence suggests fewer cases of major bleeding with LMWH than with VKA. However, comparison of only high-quality studies for bleeding shows no clear differences between LMWH and VKA. LMWH may represent an alternative for some patients, for example, those residing in geographically inaccessible areas, those who are unable or reluctant to visit the thrombosis service regularly, and those with contraindications to VKA.

PLAIN LANGUAGE SUMMARY

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

Background

Blood clots (venous thromboembolism) sometimes cause blockages in veins after surgery, during bed rest, or spontaneously. These clots can be fatal when they travel to the lungs. Vitamin K antagonists (VKAs), 99% of which consist of warfarin, are effective in preventing renewed blood clot formation, because they thin the blood. Low-molecular-weight heparins (LMWHs) are drugs that thin the blood and are used for people who are at 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 with long term treatment with VKAs.

Key results

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

Quality of the evidence

The quality of evidence for the outcomes recurrent blood clots and death was moderate. The quality of this evidence was downgraded because of the small number of events reported, leading to imprecision. For the outcome bleeding, the quality of evidence was low because of inconsistency between studies and risk of bias. Continued research into long term treatment of blood clots in the veins with LMWH and VKA is needed.

Authors' conclusions

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

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

LMWH compared with VKA for long term treatment of symptomatic VTE

Patient or population: patients with symptomatic VTE requiring long term treatment (3 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		Peto OR 0.83 (0.60 to 1.15)	3299 (16 RCTs)	⊕⊕⊕◯ MODERATE[a,b]	
	51 per 1000	42 per 1000 (31 to 58)				
Incidence of major bleeding (treatment duration 3 months)	Study population		Peto OR 0.51 (0.32 to 0.80)	3299 (16 RCTs)	⊕⊕◯◯ LOW[c,d]	
	29 per 1000	15 per 1000 (10 to 24)				
Mortality (treatment duration 3 months)	Study population		Peto OR 1.08 (0.75 to 1.56)	3299 (16 RCTs)	⊕⊕⊕◯ MODERATE[a,b]	
	35 per 1000	37 per 1000 (26 to 53)				

* 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 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 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

[a] High risk of bias due to no blinding but not downgraded, as analysis excluding studies deemed of low methodological quality confirms no clear differences between LMWH and VKA

[b] Downgraded by one level owing to imprecision, small number of events, and relatively large confidence interval

[c] Downgraded by one level for risk of bias, as sensitivity analysis based on category I trials (clearly concealed randomisation, double-blind or blinded outcome assessment) shows no clear differences between VKA and LMWH. Bleeding outcomes are more susceptible to biased outcome reporting than outcomes such as VTE and mortality

[d] Downgraded by one level for inconsistency: only two studies (studies of low methodological quality) reported less bleeding for LMWH, and the remainder showed no clear differences, with confidence intervals crossing the line of no effect

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is defined as formation of thrombus in the deep veins, most commonly in the legs (deep vein thrombosis, or DVT), and/or subsequent embolisation of all or part of the thrombus to the pulmonary circulation (pulmonary embolisation, or PE). DVT of the lower limbs may be associated with localised pain, swelling, and erythema, as well as with development of pulmonary emboli (PE) and later occurrence of post-thrombotic syndrome (PTS; 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; over the longer term, PE can cause chronic post-thrombotic pulmonary hypertension. In this era of more liberal central venous catheterisation, DVT may more often involve the upper extremities. Rarely, other venous circulation (within cerebral veins, portal and mesenteric veins, etc.) can be affected.

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

Venous thromboembolism (VTE) comprises DVT and PE and can occur spontaneously. However, risk factors for VTE are many and include periods of inactivity, dehydration, hospitalisation, trauma, clotting disorders and previous thrombosis, varicose veins with phlebitis, pregnancy, use of oral combined hormonal contraceptives, malignancy, obesity, smoking, and advanced 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 to PE (with or without DVT) (Heit 2015). Recurrent VTE occurs in approximately 7.4% of patients at one year and in 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 prevention of its recurrence, including prevention of 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 consists of a direct oral anticoagulant (with or without initial parenteral anticoagulation as indicated) or a parenteral anticoagulant given in conjunction with a VKA. Long term therapy (usually for a minimum duration of three months of anticoagulation) is indicated for treatment of acute VTE.

Prolonged use of a VKA has proven efficacy in comparison with placebo and low-dose heparin (unfractionated heparin) for treatment of VTE (Hull 1979; Lagerstedt 1985). Use of adjusted therapeutic doses of subcutaneous unfractionated heparin is as effective as use of a VKA for preventing recurrence of symptomatic VTE, but both require regular laboratory monitoring (Hull 1982b). Usual practice is to administer VKAs to achieve an international normalised ratio (INR) of 2.0 to 3.0 (Hull 1982a). However, use of VKAs continues to present considerable risk of major bleeding (approximately 3% to 4%) during the first three months of treatment (Hutten 1999). Moreover, for some patients, it is difficult to achieve a stable INR in the therapeutic range, and this leads to 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 to minimise risk of bleeding complications. Comparison of LMWH versus unfractionated heparin for initial treatment of symptomatic VTE reveals that LMWH is associated with a reduction in major bleeding (Hettiarachchi 1998), and that treatment with LMWH is less frequently complicated by thrombocytopaenia (Warkentin 1995) and osteoporosis (Kelton 1995; Monreal 1994); also, these compounds do not require laboratory monitoring.

Why it is important to do this review

If the efficacy and safety of LMWH are found to be comparable with those of VKAs, LMWH could be used for long term treatment of symptomatic VTE. This would be especially important for patients in whom VKAs are contraindicated or impractical, for example, pregnant women and 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) with LMWH versus long term treatment (three months) with VKAs for symptomatic VTE.

METHODS

Criteria for considering studies for this review

Types of studies

We included trials that randomly allocated participants to long term (three months) treatment with VKAs or LMWH.

Types of participants

We included trials involving participants with symptomatic venous thromboembolism (VTE). We excluded trials that exclusively included participants with active malignancy and symptomatic VTE because this is the topic of another Cochrane review (Akl 2014). In addition, we excluded trials when investigators did not use objective tests 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 VKAs versus LMWH for 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 5 to 10 days.

Types of outcome measures

Primary outcomes

- Incidence of recurrent symptomatic VTE during three months of allocated treatment
- 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, we considered the following criteria as constituting a positive diagnosis of recurrent symptomatic DVT.

- Extension of an intraluminal filling defect on a venogram.
- New intraluminal filling defect.
- 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.

When no previous venogram was available for comparison, we considered an intraluminal filling defect as sufficient. When no venogram was available, we accepted 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). When 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 a positive result on a D-dimer test, was acceptable.

To confirm an episode of suspected recurrent PE, we accepted the following criteria.

- New intraluminal filling defect.
- Extension of an existing defect.
- Sudden cut-off of vessels > 2.5 mm in diameter on a pulmonary angiogram.

When no prior pulmonary angiogram was available, an intraluminal filling defect or a sudden cut-off of vessels > 2.5 mm in diameter on a pulmonary angiogram was sufficient. When no pulmonary angiogram was available, we accepted a defect of $\geq$ 75% of a segment on the perfusion scan with normal ventilation. When 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.

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

We excluded studies that evaluated bleeding if definitions of major and minor bleeding were unclear.

Secondary outcomes

- Incidence of recurrent symptomatic VTE during additional six to nine months after cessation of allocated three months of treatment for symptomatic VTE
- Occurrence of major bleeding complications during additional six to nine months after cessation of allocated three months of treatment for symptomatic VTE
- Mortality during additional six to nine months after cessation of allocated three months of treatment for symptomatic VTE

We considered additional long term outcomes for inclusion in the review when these were available.

Search methods for identification of studies

We applied no language restrictions on publications and no restrictions regarding status of publications.

Electronic searches

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

- Cochrane Vascular Specialised Register (11 November 2016).
- 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, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED), and through handsearching of 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 when data were missing, or when we had doubts about whether we should include specific trials in the review.

Data collection and analysis

Selection of studies

At least two members of the current review author team (AA, AST, MS) independently scrutinised trials for eligibility and resolved disagreements by discussion. We obtained full versions of articles that potentially met our inclusion criteria upon review of titles or abstracts and assessed these trials independently against the inclusion criteria. We have presented the reason for exclusion of each study in the Characteristics of excluded studies table.

Data extraction and management

We reviewed eligible articles and extracted and recorded summary information on forms developed by Cochrane Vascular. We sought the following information: participant characteristics (age, gender, comorbidities); number of participants in each treatment arm; duration of therapy; type of anticoagulant (vitamin K antagonist/LMWH); and incidence and timing of recurrent VTE, major bleeding complications, and mortality. When important information was not reported, we contacted 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 to be at low, unclear, or high risk of bias according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.

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

Measures of treatment effect

We used Review Manager 5.3 as provided by Cochrane to analyse data. For dichotomous outcomes, we have presented results of statistical analysis as Peto odds ratios (Peto ORs) with 95% confidence intervals (CIs).

Unit of analysis issues

Participating individuals were the unit of analysis.

Dealing with missing data

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

Assessment of heterogeneity

We conducted all analyses on an intention-to-treat basis. When individual trials did not use intention-to-treat analysis, we analysed data (absolute numbers) as provided in the included trial report.

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

Assessment of reporting biases

We used asymmetry in funnel plots to assess reporting bias when we included more than 10 studies in the meta-analysis (Higgins 2011).

Data synthesis

We combined calculated Peto ORs from individual trials across trials, giving weight to the number of events reported in each of the two treatment groups for each separate trial. This approach assumes the use of a fixed-effect analysis model (Collins 1987; Mantel 1959).

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

We performed separate analyses for trials that used similar initial treatment in both trial arms and for those that used different treatment regimens during initial treatment for PE or DVT (i.e. LMWH vs unfractionated heparin for initial treatment of symptomatic VTE - a potential source of confounding). In addition, we performed analyses for symptomatic PE and symptomatic DVT to explore the effects of vitamin K antagonists on these two different disease components of symptomatic VTE.

Sensitivity analysis

The primary analysis included data on all trial participants 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 studies classified as category II trials (trials with low methodological quality, i.e. unclear or clearly not concealed randomisation or no blind outcome assessment; see Assessment of risk of bias in included studies).

'Summary of findings'

We presented the main findings of this review regarding quality of evidence, magnitude of effects of interventions examined, and sum of available data on primary outcomes (Types of outcome measures) in a 'Summary of findings' table, according to 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 GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/) to facilitate preparation of the 'Summary of findings' table.

RESULTS

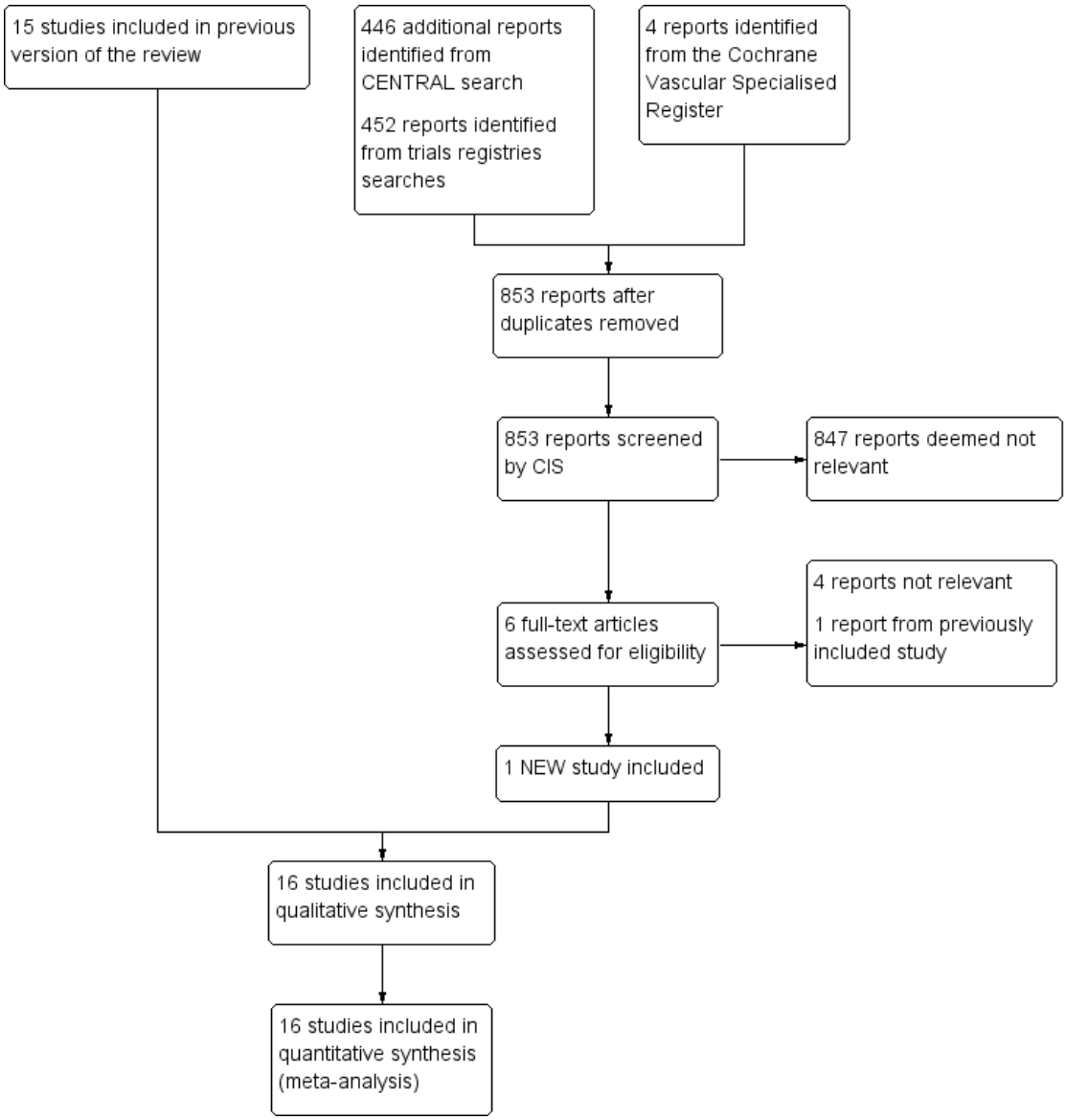
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



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

Included studies

In total, 16 trials that examined long term treatment of symptomatic 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 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 Characteristics of included studies table for a detailed description of these trials.

The trials were performed in the following countries.

- 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).

The 16 included trials recruited a total of 3299 participants. The number of participants in each trial ranged from 40 (Kucher 2005) to 737 (Hull 2007). Seven trials provided similar treatments in both arms (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Perez-de-Llano 2010; Pini 1994); the remaining nine trials allocated participants to different treatments provided in different 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 (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).

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

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 Kakkar 2003 randomised participants between three treatment arms; in one arm, initial treatment was intravenous unfractionated heparin followed by three months of VKA. The other two treatment arms initially treated participants with LMWH followed by a VKA or LMWH for 12 weeks. In the category I trials Gonzalez 1999, Daskalopoulos 2005, and Hull 2007, initial treatment in the LMWH arm consisted of subcutaneous LMWH, and initial treatment in the VKA arm consisted of a course of intravenous unfractionated heparin. Category I trial Hull 2009 included only participants with acute proximal DVT; initial treatment consisted of subcutaneous LMWH or subcutaneous LMWH plus warfarin. Among trials including only participants with symptomatic PE (Beckman 2003; Kucher 2005; Perez-de-Llano 2010), Beckman 2003 compared different initial treatments, but Kucher 2005 and Perez-de-Llano 2010 provided the same initial treatment, that is, subcutaneous LMWH. One trial included participants with both symptomatic DVT and symptomatic PE (Massicotte 2003) and provided different initial treatment for the two treatment groups. Pini 1994 followed all participants for the entire follow-up period and performed intention-to-treat analysis. 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); 13 participants in the VKA 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); and analyses of participant data 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. Investigators did not provide results of intention-to-treat analysis nor outcome data (in total, 12 participants had no second venogram, five participants received treatment that was not conducted properly, and three participants were lost to follow-up). Lopaciuk 1999 excluded a total of nine participants after randomisation and performed no intention-to-treat analyses. Three participants in the LMWH group (one sudden death during initial treatment, one PE (day three) and vena caval filter insertion (day 14), and one initial treatment changed to unfractionated heparin) and six in the VKA group (two with an exclusion criterion overlooked (vein compression by arterial aneurysm), three consent

withdrawals, and one initial treatment changed to thrombectomy) did not complete the trial according to the protocol. Kakkar 2003 reported that 54 participants were 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 by the baseline venogram. Daskalopoulos 2005 reported that a total of six participants were excluded before commencement of treatment (five in the LMWH arm and one in the VKA arm). Hull 2007 reported that a total of six participants did not complete the trial according to the protocol and provided intention-to-treat analysis of data for these participants. In the VKA arm, four participants did not complete the trial (one was lost to follow-up and three withdrew consent); and in the LMWH arm, two participants did not complete the trial (one was lost to follow-up and one withdrew consent). Hull 2009 reported that 3 of 480 participants were lost to follow-up at 12 months (1 in the heparin group and 2 in the 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 VKA (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 excluded two participants - one from each group, who did not receive study medications - from these analyses. Two participants failed to meet inclusion criteria and two failed to meet exclusion criteria, but these participants did receive study medications and were left in the intention-to-treat analyses. Massicotte 2003 reported that eight participants (including one death) in the LMWH group and 14 (including 4 deaths) in the unfractionated heparin group withdrew from the study.

All included studies provided a minimum of three months of treatment. Three studies reported a treatment period of six months (Daskalopoulos 2005; Perez-de-Llano 2010; Romera 2009), and in three other studies some participants received three months of treatment and others six months of treatment (Hamann 1998; Lopez 2001; Veiga 2000). A total of 12 studies reported additional follow-up after cessation of treatment ranging from 28 days to 9 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).

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

Excluded studies

In total, we excluded four studies. Reasons for exclusion included the following.

- Non-randomised trial (Vorobyeva 2009).
- Composite endpoint trial (Ghirarduzzi 2009).
- Subjective reporting (Hull 2001; Hull 2001a).

Risk of bias in included studies

See Figure 2 and Figure 3 for graphical presentations of risk of bias. Lack of detail was the main reason for the 'unclear' rating for most trials.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

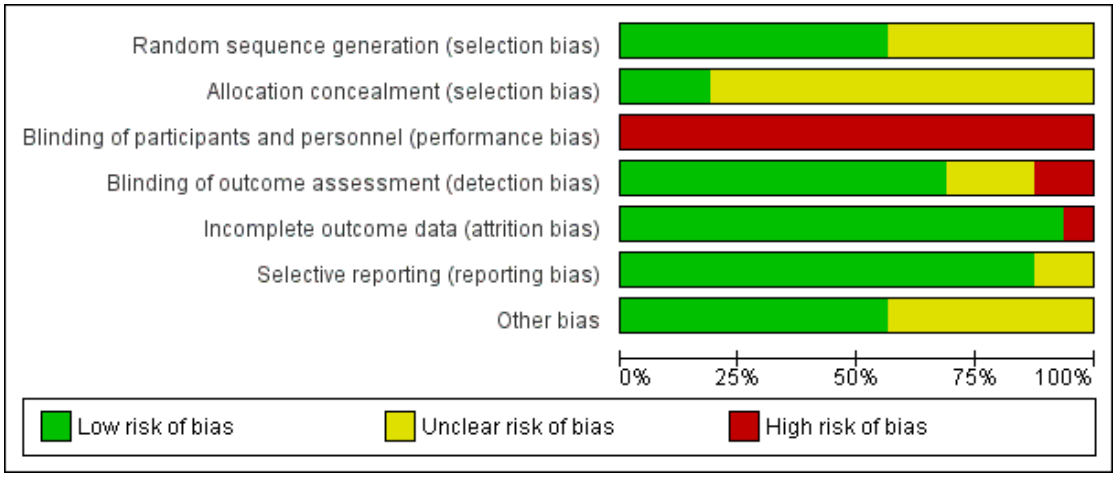
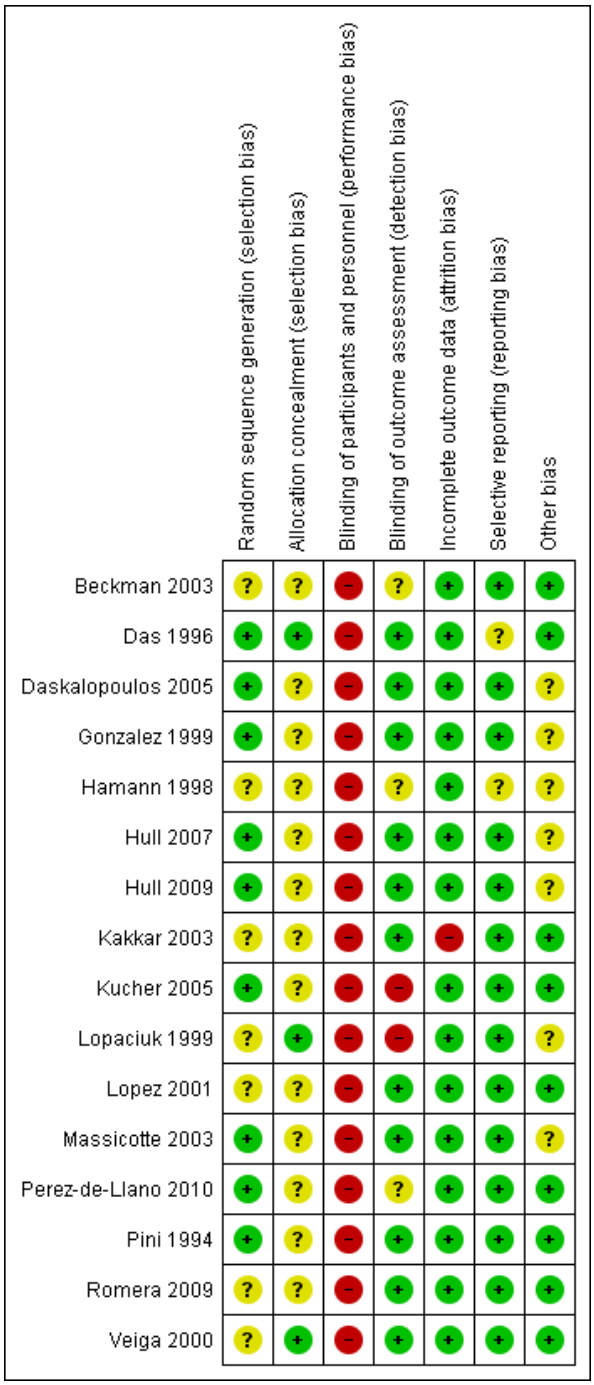


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Allocation

Nine trials described the method used to generate the random allocation sequence in sufficient detail, indicating 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).

Only three trials adequately concealed allocation (Das 1996; Lopaciuk 1999; Veiga 2000). We determined that the remaining 13 trials had unclear risk of bias (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

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 they reported adequate blinding of 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 they did not report blinded outcome assessment (Kucher 2005; Lopaciuk 1999); and three trials were at unclear risk of bias because it was unclear whether those collecting outcomes data were aware of the allocation (Beckman 2003; Hamann 1998; Perez-de-Llano 2010).

Incomplete outcome data

Risk of bias was low for 15 trials, as investigators followed-up and reported on all 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). We classified only Kakkar 2003 as having high risk of bias, as investigators did not follow up on 33% of randomised participants, as was required by the trial design.

Selective reporting

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

Other potential sources of bias

Nine 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 was at unclear risk, as investigators provided insufficient information (Hamann 1998). We deemed Lopaciuk 1999 to be at unclear risk of other bias because study authors did not discuss three fatal peripheral or cardiovascular events in the acenocoumarol group, and because follow-up treatments after planned three-month outcomes differed between groups. Five (category I) trials had unclear risk, as results may have been confounded by differences in the initial treatment (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003).

Effects of interventions

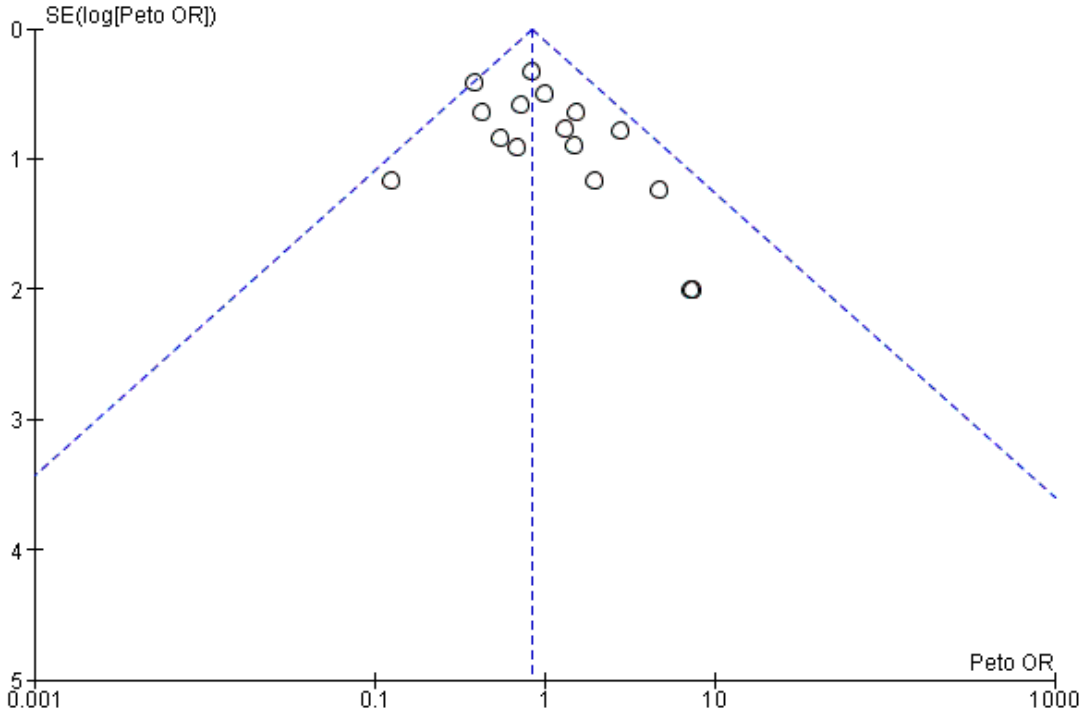
See: **Summary of findings for the main comparison** LMWH compared with VKA for long term treatment of symptomatic VTE

Incidence of recurrent venous thromboembolism during active treatment

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

A total of 86 of 1702 participants (5.1%) in the VKA group had recurrent symptomatic VTE versus 70 of 1597 participants (4.4%) in the LMWH group. Pooled analysis showed no clear differences between 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) among participants with symptomatic VTE. Heterogeneity was assessed as I^2 = 9% (Analysis 1.1; Figure 4).

Figure 4. 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.



Although 15 trials showed no clear differences in recurrent VTE between LMWH and VKA treatment, one trial (Gonzalez 1999) found 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 1572 participants (5.2%) in the VKA group had recurrent symptomatic VTE versus 63 of 1449 participants (4.3%) in the LMWH group, showing no clear differences between treatment modalities for recurrent symptomatic VTE (Peto OR 0.79, 95% CI 0.57 to 1.11; P = 0.18; 3021 participants; 12 studies) among participants with symptomatic DVT. Heterogeneity was assessed as I^2 = 8% (Analysis 2.1).

In contrast, among the three trials including only participants with symptomatic PE, none of 90 participants (0%) in the VKA group had recurrent symptomatic VTE versus 5 of 112 participants (4.5%) in the LMWH group, resulting in no clear differences between treatments for episodes of recurrent symptomatic VTE (Peto OR 5.70, 95% CI 0.91 to 35.60; P = 0.06; 202 participants; three studies) among participants with symptomatic PE. Heterogeneity was assessed as I^2 = 0% (Analysis 3.1).

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

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

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

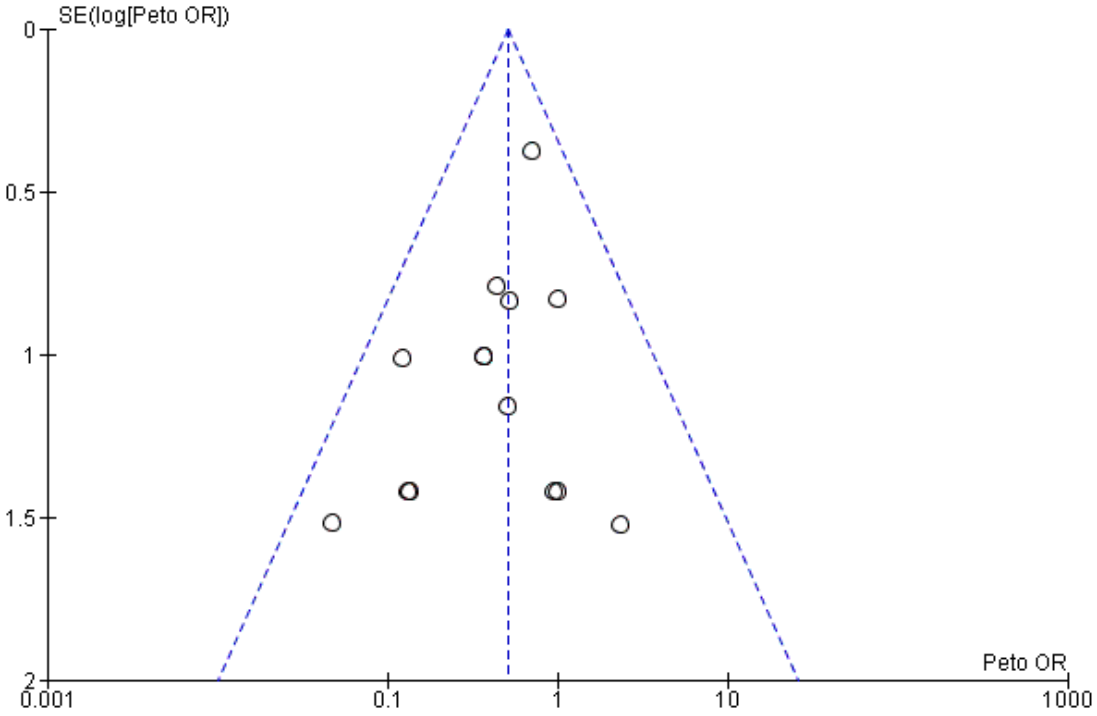
Five category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Pini 1994) and five category II trials (Hamann 1998; Lopaciuk 1999; Lopez 2001; Romera 2009; Veiga 2000) evaluated a period of six to nine months after cessation of the allocated treatment. A total of 53 of 1296 participants (4.1%) in the VKA group versus 59 of 1296 participants (4.6%) in the arm allocated to LMWH treatment experienced an episode of recurrent symptomatic VTE. Combined analysis showed no clear differences in recurrent symptomatic VTE between treatment arms (Peto OR 1.12, 95% CI 0.77 to 1.64; P = 0.56; 2592 participants; 10 studies). Heterogeneity was assessed as 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 846 participants (4.3%) in the VKA arm versus 45 of 845 participants (5.3%) in the LMWH arm experiencing an episode of recurrent symptomatic VTE. Combined analysis showed no clear differences in thromboembolic complications between treatment modalities (Peto OR 1.26, 95% CI 0.81 to 1.98; P = 0.30; 1691 participants; five studies). Heterogeneity was assessed as I^2 = 14% (Analysis 8.1). It should be noted that in Pini 1994, 34 of 94 participants used the VKA during an additional three months and 14 of 94 participants used the VKA for an additional nine months, whereas in the LMWH group all 93 participants stopped assigned treatment after three months. Furthermore, in Hull 2007, 250 of 368 participants in the VKA allocated treatment arm were treated with LMWH beyond the three months of allocated treatment and in the LMWH group 146 of 369 participants continued allocated treatment beyond the three months of allocated treatment. Hull 2009 reported that some participants in both treatment groups received ongoing warfarin after the first three months of allocated treatment.

The total 12-month period of follow-up (combining three months of active treatment and nine months of follow-up) among five category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Pini 1994) included a total of 91 of 846 participants (10.8%) in the VKA group versus 87 of 845 participants (10.3%) in the LMWH group who had recurrent symptomatic VTE and showed no clear differences between treatment modalities for risk of recurrent symptomatic VTE (Peto OR 0.95, 95% CI 0.70 to 1.30; P = 0.75; 1691 participants; five studies) among participants with symptomatic PE. Heterogeneity was assessed as I^2 = 58% (Analysis 10.1).
Analysis of pooled data from 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 differences between LMWH and VKA treatment for the total 12-month period of follow-up (Peto OR 0.88, 95% CI 0.67 to 1.15; P = 0.34; 2592 participants; 10 studies). Heterogeneity was assessed as I^2 = 41% (Analysis 9.1).

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 found no clear differences and only two trials found differences between groups (Beckman 2003; Lopez 2001). Lopez 2001 found a difference that favoured the LMWH group (Peto OR 0.12, 95% CI 0.02 to 0.89). This trial included only participants with DVT. Beckman 2003 found a difference that favoured the LMWH group (Peto OR 0.05, 95% CI 0.00 to 0.92). This trial included only participants with symptomatic PE.
Analysis of pooled trials showed major bleeding complications among 50 of 1702 participants (2.9%) in the VKA arm versus 25 of 1597 participants (1.6%) in the LMWH group. This difference favoured 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 assessed as I^2 = 0% (Analysis 1.2; Figure 5).

Figure 5. 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.



Analysing the 12 trials that included only participants with symptomatic DVT revealed that a total of 42 of 1572 participants (2.7%) in the VKA group had major bleeding versus 22 of 1449 participants (1.5%) in the LMWH group, showing a difference between treatment modalities that favoured 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) among participants treated with symptomatic DVT. Heterogeneity was assessed as I^2 = 0% (Analysis 2.2).

The three trials (Beckman 2003; Kucher 2005; Perez-de-Llano 2010) that included only participants with symptomatic PE observed major bleeding in a total of 3 of 90 participants (3.3%) in the VKA group versus 1 of 112 participants (0.9%) in the LMWH group, revealing 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; three studies) among participants treated for symptomatic PE. Heterogeneity was assessed as I^2 = 52% (Analysis 3.2).

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

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

For two category I trials providing the same initial treatment in both groups (Das 1996; Pini 1994) analysis of data showed no evidence of a difference in major bleeding incidence between treatment modalities (Peto OR 1.01, 95% CI 0.20 to 5.12; P = 0.99; 292 participants; two studies; I^2 = not applicable) (Analysis 5.2).

For five category I trials providing different initial treatments in the two groups (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003) analysis of data showed no clear differences between treatment modalities (Peto OR 0.59, 95% CI 0.33 to 1.04; P = 0.07; 1580 participants; five studies; I^2 = 0%) (Analysis 6.2).

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

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

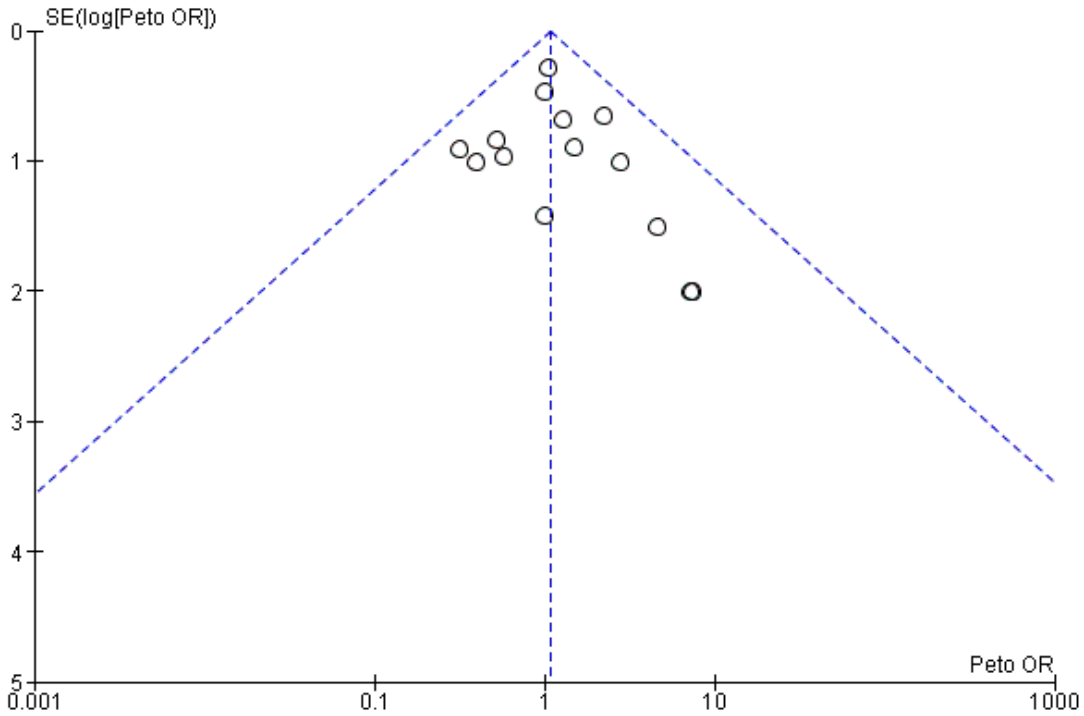
Analysis of pooled data in nine category I and category II trials (Daskalopoulos 2005; Gonzalez 1999; Hamann 1998; Hull 2007; Lopaciuk 1999; Lopez 2001; Pini 1994; Romera 2009; Veiga 2000) for the total 12 months of follow-up showed major bleeding complications in 36 of 1056 participants (3.4%) in the VKA arm versus 20 of 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; nine studies). Heterogeneity was assessed as I^2 = 0% (Analysis 9.2).

The 12-month period of follow-up (combining three months active treatment and nine months follow-up) in four category I trials (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Pini 1994) included a total of 25 of 606 participants (4.1%) in the VKA group versus 18 of 605 participants (3.0%) in the LMWH group who had a major bleeding incident, and showed no clear differences between treatment modalities (Peto OR 0.72, 95% CI 0.39 to 1.32; P = 0.28; 1211 participants; four studies). Heterogeneity was assessed as I^2 = 0% (Analysis 10.2).

Mortality during active treatment

All 16 trials reported mortality during allocated treatment with no clear differences between treatment groups. Fifty-nine of 1702 participants (3.5%) in the VKA treatment group died versus 62 of 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 assessed as I^2 = 0% (Analysis 1.3; Figure 6). We obtained similar results when pooling only category I trial data (Peto OR 0.92, 95% CI 0.61 to 1.41; P = 0.71; 1872 participants; seven studies). Heterogeneity was assessed as I^2 = 0% (Analysis 4.3).

Figure 6. Funnel plot of comparison: 2 LMWH versus VKA during three months of allocated treatment (category I and II trials), outcome; 2.3 mortality.



For two category I trials providing the same initial treatment for both groups (Das 1996; Pini 1994) and five category I trials providing different initial treatments for the two groups (Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Hull 2009; Massicotte 2003), pooled analyses did not show a clear difference in mortality between treatment modalities (Peto OR 0.89, 95% CI 0.29 to 2.68; P = 0.83; 292 participants; two studies; I^2 = 0% (Analysis 5.3); and Peto OR 0.93, 95% CI 0.59 to 1.46; P = 0.76; 1580 participants; five 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, analysis revealed no clear differences in mortality between 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; three 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 1296 participants (5.6%) in the VKA arm versus 72 of 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) died. Heterogeneity was assessed as I^2 = 0% (Analysis 7.3). We obtained similar results when considering only category I trials (Peto OR 1.06, 95% CI 0.72 to 1.55; P = 0.77; 1691 participants; five studies; I^2 = 0%) (Analysis 8.3).

Analysis of mortality for the total 12-month follow-up period did not detect a clear difference between 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^2 = 0% (Analysis 9.3)) nor for the five category I trials (Peto OR 1.05, 95% CI 0.78 to 1.42; P = 0.76; 1691 participants; five studies; I^2 = 0% (Analysis 10.3)).

DISCUSSION

Summary of main results

This review detected no clear differences between low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs) for two of the three primary outcomes (recurrent symptomatic venous thromboembolism (VTE) and overall mortality). For the third outcome, major bleeding, data show a reduction in favour of LMWH (Peto odds ratio (OR) 0.51, 95% confidence interval (CI) 0.32 to 0.80; P = 0.004). However, pooling of data from category I trials alone (clearly concealed randomisation, double-blind or blinded outcome assessment) revealed no clear differences in major bleeding between treatment groups (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08). Although this review found no evidence that LMWH has greater efficacy than VKAs for long term treatment of VTE, evidence shows that long term treatment of symptomatic VTE with LMWH versus long term treatment with VKAs may be safer with respect to major bleeding. The largest trial (Hull 2007) reported no clear differences for any of the three outcomes. Results were similar for recurrent symptomatic VTE, major bleeding, and mortality during an additional six to nine months after cessation of the allocated three months of treatment for symptomatic VTE.

In interpreting the findings of this review, one must consider several points. Five category I trials did not use the same initial treatment in both treatment arms, and these differences may threaten the validity of data derived 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 unfractionated heparin treatment (Daskalopoulos 2005; Gonzalez 1999). In the largest trial (Hull 2007), initial treatment with unfractionated heparin was adequate but produced no differences in effect between treatment modalities. Doses of the various LMWH compounds used in 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 initial and long term treatment of symptomatic VTE. Massicotte 2003 recruited only children and adjusted the dose accordingly. These five category I trials found no clear difference in the incidence of recurrent VTE between LMWH and VKAs (Peto OR 0.68, 95% CI 0.44 to 1.03; P = 0.07).

In contrast, the two category I trials that provided the same initial treatment for both treatment arms observed a trend in favour of VKAs for prevention of recurrent symptomatic VTE when using relatively low doses of LMWH during long term treatment of deep vein thrombosis (DVT) (Das 1996; Pini 1994); dosages were approximately twice those normally used for prophylaxis of symptomatic VTE and were not adjusted for weight. 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 injection of 4000 anti-Xa IU enoxaparin) (Pini 1994).

Lopez 2001 included 25 participants (14 participants in the LMWH treatment group and 11 in the VKA treatment group; n = 158) with infrapopliteal DVT (calf vein thrombosis) diagnosed by duplex ultrasonography. Excluding these data from the sensitivity analysis did not affect findings. Two considerations are of interest here. First, duplex ultrasonography is not as sensitive and specific for distal thrombosis as it is for proximal DVT (Mitchell 1991). Second, 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 probably are small and self-limiting, do not (Heijboer 1993; Huisman 1986; Huisman 1989; Hull 1985).

The difference in major bleeding complications favouring LMWH during allocated treatment of three months has to be considered with caution. Different LMWH compounds and relatively low doses of medication were used, as has been mentioned. Although a difference in bleeding incidence favouring LMWH was found when all trials were combined (Peto OR 0.51, 95% CI 0.32 to 0.80; P = 0.004), no clear difference between LMWH and VKA was observed (Peto OR 0.62, 95% CI 0.36 to 1.07; P = 0.08) when only category I trials were considered. 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 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, the data show no substantial differences in efficacy for long term treatment of patients with DVT with LMWH or VKAs, but long term treatment with LMWH may cause fewer episodes of major bleeding than occur with VKA therapy.

Currently, many patients are treated at home with a course of subcutaneous LMWH administered by the patients themselves. After this initial treatment, patients continue with a three-month course of VKA with the dose adjusted to achieve an international normalised ratio (INR) between 2.0 and 3.0. Treatments used in Das 1996 and Daskalopoulos 2005 do not represent current practice.

Important practical considerations involving mainly patient and local preferences also influence the choice between LMWH and VKAs. The major disadvantage of VKA treatment compared with LMWH treatment is the need for regular laboratory monitoring. Furthermore, VKA compounds have some major drug interactions, but drug interactions of LMWH are uncommon. In addition, treatment with LMWH is relatively safe during pregnancy (Sanson 1999). A major disadvantage of treatment with LMWH is that the patient has to self-administer subcutaneous injections on a daily basis. Among the included trials, only a few participants stopped treatment with LMWH, mainly as the result of problems other than 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

Participants with symptomatic VTE included in these trials constituted a representative mix of people with this disease. All trials included approximately similar participants; therefore, these data can be generalised to the wider population. Several published trials included only participants with a diagnosis of cancer who had symptomatic VTE. We did not include these trials in our review because participants do not represent the normal cohort of patients with a diagnosis of symptomatic VTE, and because this is the topic of another Cochrane review (Akl 2014).

Only scant data have been gathered on patients with symptomatic pulmonary embolisation (PE). This review includes data from only 202 people with PE, and review findings should be interpreted with caution.

Direct oral anticoagulants (DOACs) are changing the ways that patients are treated (Robertson 2015; Robertson 2015b). Therefore, in the future, as more and more patients are prescribed DOACs instead of VKA and LMWH, the analysis performed for this review may become outdated. We will reconsider the focus and future of this review in future updates.

Quality of the evidence

Fifty-nine per cent of included patients (1872/3299) participated in trials with category I classification yielding evidence of highest quality on direct treatment comparisons.

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. When participant outcomes were assessed by individuals who were blind to treatment allocation, we considered threats to the validity of trial conclusions to be reduced. When it was not reported that those collecting outcome measures data were unaware of treatment allocation, trial findings may have been compromised. Trials in which allocation is not concealed and outcomes are not collected in a blind manner are essentially observational rather than experimental in nature. Analysis for only category I trials (clearly concealed randomisation, double-blind or blinded outcome assessment) shows similar results to those of analyses for all studies combined, except for bleeding, which showed no clear differences between treatment groups.

We downgraded the quality of evidence for recurrent VTE and mortality to moderate owing to imprecision resulting from the small number of events and the 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 no clear differences between LMWH and VKA.

We downgraded the quality of evidence for major bleeding to low owing to risk of bias and inconsistency: a sensitivity analysis including only category I trials (clearly concealed randomisation, double-blind or blinded outcome assessment) showed no clear differences 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) have reported less bleeding with LMWH; the remainder showed no clear differences because confidence intervals crossed the line of no effect. See Summary of findings for the main comparison.

Potential biases in the review process

Methods used to conduct this review are described in detail in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011); particular strengths include independent application of review eligibility criteria, independent data extraction and assessment of risk of bias, and assessment of quality of evidence according to GRADE. The Cochrane Vascular Information Specialist, who is highly skilled in identification of randomised controlled trials, devised and conducted the search strategies. We are confident that we have included all relevant studies. However, the possibility remains that some relevant trials, particularly in the 'grey' literature (e.g. conference proceedings), have been missed. Other potential biases in the review process are the missing information from 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 VKAs versus LMWH (Bochenek 2012; Ferretti 2006; Iorio 2003). Two reviews 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 treatment types in terms of assessment of recurrent VTE (odds ratio (OR) 0.66, 95% CI 0.41 to 1.07), major bleeding (OR 0.45, 95% CI 0.18 to 1.11), or 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 one abstract (Hull 2000). We included all trials 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 found no clear differences between treatments when assessing recurrent symptomatic VTE (OR 1.29, 95% CI 0.82 to 2.02). This meta-analysis included three trials of patients with cancer, which we excluded for the purpose of this Cochrane review, three other trials that we judged to be of high methodological quality (Das 1996; Gonzalez 1999; Pini 1994), four that we considered 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 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 in the outcome major bleeding (OR 0.59, 95% CI 0.47 to 0.74). This review did not evaluate mortality as an outcome. The Bochenek 2012 review included six trials that we judged to be of high methodological quality (Das 1996; Daskalopoulos 2005; Gonzalez 1999; Hull 2007; Massicotte 2003; Pini 1994) and six trials that we judged to be of lower methodological quality (Beckman 2003; Kakkar 2003; Kucher 2005; Lopaciuk 1999; Lopez 2001; Veiga 2000). The meta-analysis by Bochenek 2012 included two trials that considered only patients with cancer, who were excluded for the purpose of this Cochrane review. One of these studies showed a significant effect of LMWH heavily influencing the overall outcome and contributing approximately one-third of the overall weight; this was likely the reason for the difference between Bochenek 2012 and the current Cochrane review.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-quality evidence shows no clear differences between LMWH and VKA in preventing symptomatic VTE and mortality after an episode of symptomatic DVT. Low-quality evidence suggests fewer cases of major bleeding with LMWH than with VKA. However, when only high-quality studies are compared for bleeding, no clear difference between LMWH and VKA is evident. LMWH may present an alternative for some patients, for example, those in geographically inaccessible areas, those who are reluctant or unable to visit the thrombosis service regularly, and those with contraindications to VKAs. Only limited data are available for patients with symptomatic PE.

Implications for research

For more definitive conclusions, additional adequately designed randomised controlled clinical trials are needed, especially in the field of symptomatic PE. These trials must include patients with contraindications for VKAs (e.g. pregnant women), patients who are unable or reluctant to go to the thrombosis service on a regular basis, and patients living in geographically inaccessible areas.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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 VKA treatment) with PE confirmed on 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: 1 centre in USA
Interventions	The warfarin arm comprised of a course of continuous infusion intravenous unfractionated heparin for a minimum of 5 days and concomitant warfarin for 90 days. The enoxaparin arm started with a course of 14 days of 1 mg/kg twice-daily, followed by either a course of 1.5 mg/kg once-daily, enoxaparin (20 participants), or a course of 1.0 mg/kg once-daily enoxaparin (20 participants). All participants in the enoxaparin arm received a total of 90 days of enoxaparin. Randomisation into the enoxaparin categories was performed at beginning of trial when participants were initially assigned to enoxaparin or standard/warfarin therapy
Outcomes	Recurrent VTE/DVT: loss of vein compressibility demonstrated on ultrasound PE: positive spiral computed tomogram Major bleeding: clinically overt and associated with a fall in haemoglobin ≥ 2 g/dL, intracranial or pericardial Mortality data were not provided
Notes	Participants with major bleeding during VKA treatment had an INR of 8.2 and 3.2, respectively Category II trial

Risk of bias

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 study participants
Allocation concealment (selection bias)	Unclear risk	BWH Investigational Drug Service randomised participants, but how allocation was concealed is not revealed

Beckman 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial not blinded: Participants receiving standard therapy had drug regimen administered at the principal investigator's office; those receiving LMWH were treated at a different site and underwent echocardiography
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear as to whether those collecting outcomes data were aware of the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors provided a table detailing the reason why 7 participants dropped out
Selective reporting (reporting bias)	Low risk	All intended outcomes were 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 VKA treatment) > 40 years of age with DVT, confirmed on 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: 1 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: intraluminal filling defect in a deep vein, demonstrated on repeat venography at a site not previously involved, and demonstrated on 2 views PE was confirmed on ventilation-perfusion scanning, and eventually on pulmonary angiography in case of doubt Major bleeding: overt bleeding associated with a drop in Hb level $\geq$ 2 g/dL, transfusion of $\geq$ 2 blood units if required, or intracranial haemorrhage; other cases 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 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

Das 1996 (*Continued*)

Risk of bias		
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) All outcomes	High risk	Open trial, not blind. Compliance of participants randomised to LMWH was monitored
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent and blind outcome assessment by radiologists unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons are given for each participant who did not complete the trial
Selective reporting (reporting bias)	Unclear risk	All intended outcomes were reported, but timing of outcomes at 2, 4, and 8 weeks was 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 VKA treatment) with an episode of DVT confirmed on colour duplex ultrasound Age, mean (range), years: LMWH 59.0 (25 to 91)/VKA 58.2 (23 to 95) Gender, M/F: LMWH 19/31/VKA 22/30 Location: 1 centre in Greece
Interventions	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). 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 on baseline duplex ultrasound scan PE: confirmed on ventilation-perfusion scanning, and eventually on 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 Hb level $\geq$ 2 g/dL; transfu-

Daskalopoulos 2005 (*Continued*)

	sion of ≥ 2 blood units, if required; intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, or death; or need for permanent discontinuation of treatment 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 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

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) All outcomes	High risk	Open-label, not blind
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	Low risk	No drop-outs. All data described
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Differences in initial treatment regimens between groups

Gonzalez 1999

Methods	Prospective open single-centre randomised clinical trial
Participants	185 patients (93 allocated to LMWH and 92 to VKA treatment) with a first or second episode of DVT confirmed on contrast venography (20 excluded from analysis by trialists (8 LMWH, 12 VKA)) Age, mean (range), years: LMWH 62.7 (19 to 83)/VKA 28.3 (20 to 82) Gender, M/F: LMWH 41/44/VKA 46/34 Location: 1 centre in Spain

Gonzalez 1999 (*Continued*)

Interventions	Coumarin arm started with a 5-day course of unfractionated heparin followed by coumarin for 3 months (INR 2.0 to 3.0). 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: constant intraluminal filling defect in a deep vein not present on the first day PE: ≥ 1 segmental defect not seen on preceding scan and no abnormality on chest radiograph or pulmonary angiogram Major bleeding: intracranial or retroperitoneal or producing a decrease in Hb level ≥ 2 g/dL, sufficient to necessitate discontinuation of treatment or transfusion of ≥ 2 units of blood Mortality from all causes Blinded outcome assessment was provided by 2 blinded observers, who assessed the outcomes of venograms
Notes	3 months of randomised treatment and an additional 9 months of follow-up. All participants stopped after 3 months of treatment Intensity of VKA therapy was 15% INR < 2.0, 64% INR between 2.0 and 3.0, and 21% INR > 3.0 Category I trial

Risk of bias

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) All outcomes	High risk	Open-label trial, not blind. Participants in the LMWH group were not hospitalised
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment was provided by 2 blinded observers who assessed outcomes of venograms
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes presented; no loss to follow-up; 1 participant died of a PE
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	Differences in initial treatment regimens between groups

Hamann 1998

Methods	Prospective open randomised clinical trial
Participants	200 patients (100 allocated to LMWH and 100 to VKA treatment) with DVT confirmed on venography Age, mean (range), years: 58 (18 to 92) Gender, M/F: 82/118 Location: 1 centre, Germany
Interventions	Phenprocoumon for 3 or 6 months (INR 2.0 to 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 participants underwent venous thrombectomy, 18 systemic lysis, 28 regional lysis, and 137 IV unfractionated heparin as initial treatment Furthermore, 44 participants were treated for 3 months and 156 for 6 months for long term prevention of recurrent VTE. All interventions were evenly divided between groups 3 or 6 months of randomised treatment and an additional 9 months of follow-up Category II trial

Risk of bias

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) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hull 2007

Methods	Multi-centre randomised open-label clinical trial
Participants	737 patients (369 allocated to LMWH and 368 to VKA treatment) with DVT confirmed on 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	Warfarin arm started with a 6-day course of unfractionated heparin followed by warfarin for 3 months (INR 2.0 to 3.0). Tinzaparin group received once-daily subcutaneous tinzaparin 175 anti-Xa IU/kg of body weight, continued for 3 months
Outcomes	Recurrent VTE/ DVT: 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) 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 ≥ 2 grams/dL, or (b) transfusion of ≥ 2 units of blood, or intracranial or retroperitoneal bleeding occurring in a major joint Mortality data were provided Blinded outcome assessment was 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 participants continued with warfarin treatment after 3 months of treatment with tinzaparin for a mean of 202 days (median, 258 days). In the warfarin arm, 250 participants continued warfarin treatment after 3 months of allocated treatment for a mean of 156 days (median, 147 days) Participants with major bleeding complications: 1 participant with INR between 3.1 and 3.9, 2 with INR > 4.0 on the day of the bleeding complication Furthermore, a figure in the study publication provides data on INR values throughout the trial Category I trial

Risk of bias

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) All outcomes	High risk	Open-label trial - not blind

Hull 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central independent adjudication committee interpreted events
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	All data presented
Other bias	Unclear risk	Differences in initial treatment regimens between groups

Hull 2009

Methods	Multi-centre open-label randomised clinical trial
Participants	480 patients (240 allocated to LMWH and 240 to VKA 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	Participants 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'). Participants received 1 in-clinic injection, then home treatment
Outcomes	Primary efficacy outcome measure was occurrence of objectively documented, symptomatic, recurrent VTE at 12 weeks and at 1 year. Other efficacy outcomes were death rates at 12 weeks and 1 year; participants' self-reported treatment satisfaction during the treatment period; symptoms of PTS; and incidence of venous leg ulcers as reported by participants. Primary safety outcome measure was occurrence of bleeding (all, major, or minor) during the 12-week treatment period. Additional safety outcomes included incidence of thrombocytopenia and of bone fracture Blinded outcome assessment was 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

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

Hull 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes judged by a blinded central independent adjudication committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes presented. 3 participants lost to follow-up at 12 months
Selective reporting (reporting bias)	Low risk	All outcomes presented
Other bias	Unclear risk	Differences in initial treatment regimens between groups

Kakkar 2003

Methods	Multi-centre randomised open-label parallel-group trial
Participants	297 patients (Group A: 98 allocated to 7 ± 2 days of unfractionated heparin followed by a 3-month course of VKAs; Group B: 105 allocated to 7 ± 2 days of LMWH followed by a 3-month course of VKAs; Group C: 94 allocated to 3 months of treatment with LMWH, with DVT confirmed on venography Age, years (range): Group A 61.2 (49.9 to 70.5), Group B 61.2 (44.4 to 69.5), Group C 63.2 (45.1 to 70.8) Gender, M, %: Group A 63, 64.3%; Group B 61, 58.1%; Group C 58, 61.7% Location: 27 centres in 3 countries (Poland, Spain, UK)
Interventions	Group A: 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: 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: Bemiparin arm 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 $\geq$ 2 g/dL, transfusion of $\geq$ 2 units of blood, or intracranial or retroperitoneal bleeding Mortality data were provided Blinded outcome assessment was provided
Notes	3 months of randomised treatment and an additional 28 days of follow-up Category II trial

Kakkar 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information about generation of the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	No information about concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessment of outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs were 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 VKA treatment) with PE confirmed on 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: 1 centre in USA
Interventions	Warfarin arm started with a course of enoxaparin (1 mg/kg) twice daily for ≥ 10 doses overlapping 4 days with warfarin continued for 90 days. Enoxaparin arm started with a course of 10 to 18 days at 1 mg/kg twice daily, followed by a 3-month course of once-daily subcutaneous enoxaparin 1.5 mg/kg 10 participants were treated with thrombolysis because of right ventricular failure
Outcomes	Recurrent VTE/DVT: filling defect on conventional venography or loss of vein compressibility demonstrated on ultrasound PE: high-probability lung scan finding, positive contrast chest computed tomogram, or conventional pulmonary angiogram Major bleeding: clinically overt and associated with a fall in Hb ≥ 3 g/dL;or intracranial, intraocular, retroperitoneal, or pericardial bleeding

Kucher 2005 (*Continued*)

	Mortality data were provided Blinded outcome assessment was not provided
Notes	3 months of randomised treatment; thereafter treatment at the discretion of the treating physician. No follow-up was provided after 3 months Category II trial

Risk of bias

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) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Independent outcome collection not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No trial withdrawals
Selective reporting (reporting bias)	Low risk	Prospectively stated outcomes reported
Other bias	Low risk	None observed

Lopaciuk 1999

Methods	Prospective open multi-centre randomised clinical trial
Participants	202 patients (101 allocated to LMWH and 101 to VKA treatment) with proximal DVT confirmed on 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

Lopaciuk 1999 (*Continued*)

Outcomes	Recurrent VTE/DVT: new constant intraluminal filling defect compared with baseline venography PE: new segmental or greater perfusion defect on lung scan or positive pulmonary angiogram Major bleeding: overt bleeding associated with a fall in Hb $\geq$ 2 g/dL with need for transfusion of $\geq$ 2 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 participants (22%) used acenocoumarol for an additional 3 months, 5 (5%) for 9 months, and 15 (16%) for 1 year. In the nadroparin group, 7 participants (7%) prolonged treatment to 4 to 5 months, and 1 participant to 9 months Category II trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinded outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	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. Follow-up treatments after planned 3-month outcomes differed between groups

Lopez 2001

Methods	Prospective open single-centre randomised clinical trial
Participants	158 patients (81 allocated to LMWH and 77 to VKA treatment) with a first DVT episode in this leg confirmed on duplex scan examination Age, mean (95% CI), years: LMWH 65 (62 to 69)/VKA 66 (63 to 70) Gender, M/F: LMWH 31/50/VKA 38/39 Location: 1 centre in Spain
Interventions	Acenocoumarol for 3 or 6 months (INR 2.0 to 3.0) compared with subcutaneous nadroparin adjusted to body weight 2 times daily (1025 anti-Xa IU/10 kg). Both treatment arms started with a course of ≥ 5 days of treatment with subcutaneous nadroparin twice daily (1025 anti-Xa IU/10 kg)
Outcomes	Recurrent VTE/DVT: appearance of thrombosis in a previously unaffected venous segment of the ipsilateral or contralateral leg PE: constant intraluminal filling defect on spiral computed tomography or conventional angiography Major bleeding: overt bleeding associated with a decrease ≥ 2 g/dL in Hb level; requirement for blood transfusion of ≥ 2 units; intracranial or retroperitoneal bleeding; or need for permanent discontinuation of treatment. 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 participants in the acenocoumarol group and 34 in the nadroparin group were treated for 6 months. 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 cases Category II trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind outcomes collected by independent panel of physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals explained

Lopez 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	All prospectively started outcomes reported
Other bias	Low risk	None observed

Massicotte 2003

Methods	Multi-centre open-label randomised clinical trial
Participants	78 patients (all children) (37 allocated to reviparin and 41 to unfractionated heparin plus anticoagulant) with DVT confirmed on venography or compression ultrasound, or PE confirmed on 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 3 months of treatment and subsequent 3-month follow-up or death due to DVT Other outcomes: - Safety outcomes - Major bleeding defined as clinically significant overt bleeding requiring 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 of endotracheal tubes, small amounts of blood in urine or stool, and minor nosebleeds
Notes	3 months of randomised treatment and an additional 3 months of follow-up Category I trial

Risk of bias

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) All outcomes	High risk	Open-label trial - not blind

Massicotte 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent and blinded central adjudication committee assessed all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 78 participants, 66 completed the trial, 17 withdrew, and 5 died
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes were presented
Other bias	Unclear risk	Differences in initial treatment regimens between groups

Perez-de-Llano 2010

Methods	Randomised multi-centre open-label trial
Participants	102 patients (52 allocated to LMWH monotherapy and 50 to LMWH followed by chronic VKA treatment) with objectively confirmed PE (perfusion lung scan or chest computed tomogram) Age, year (range): LMWH 72.4 (25 to 93)/VKA 72.1 (24 to 91) Gender, male, %: LMWH 25, 50%/VKA 28, 53.9% Location: 4 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 INR was > 2 on 2 consecutive days
Outcomes	Symptomatic, recurrent VTE at 1 month, 3 months, and 6 months (on 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 associated with a decrease in Hb levels ≥ 2 g/dL, required a transfusion of ≥ 2 units of red blood cells, or was intracranial or retroperitoneal Other adverse reactions were also reported Blinded outcome assessment was not provided
Notes	Category II trial INR values after discharge were 51.7% of measurements within therapeutic range, 41.5% below, and 6.8% above LEO Pharma provided indemnity and grants to support the study, and 2 study authors reported lecturing or working for LEO Pharma

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Perez-de-Llano 2010 (*Continued*)

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) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	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 VKA treatment) with first or second episode of symptomatic DVT confirmed on strain-gauge plethysmography combined with a positive D-dimer latex test most often confirmed with contrast venography Age, years, mean: LMWH 65.4/VKA 65.0 Gender, M/F: LMWH 47/46/VKA 54/40 Location: 1 centre in Italy
Interventions	3 months of conventional treatment with warfarin (INR 2.0 to 3.5), compared with a 3-month course of enoxaparin 4000 anti-Xa units once daily. All participants were initially treated with a 10-day course of subcutaneous unfractionated heparin adjusted to an APTT of about 1.3 to 1.9 times the participant's basal value

Pini 1994 (*Continued*)

Outcomes	Recurrent VTE/DVT: new intraluminal filling defect in the deep veins by repeated venography or, if marked reduction of strain-gauge plethysmography, coupled with a positive D-dimer test that followed a negative one PE: defined by single or multiple segmental defects at perfusion scan with no abnormalities on chest radiograph in that area, on positive pulmonary angiogram, or at autopsy Major bleeding: clinically overt bleeding associated with a fall in haemoglobin of 2 g/dL leading to a blood transfusion, or 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 as good in 38% of participants (≥ 67% of INR values within therapeutic range), intermediate in 43% (34% to 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

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) All outcomes	High risk	Open-label trial - not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Final adjudication of outcome measures conducted by an independent panel of physicians, 1 of whom was not involved in the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant exclusions explained and no enrolled participants 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 VKA treatment) with an episode of symptomatic DVT confirmed on 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: 2 centres in Spain
Interventions	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). Tinzaparin group received once-daily subcutaneous tinzaparin 175 anti-Xa IU/kg of body weight, continued for 6 months
Outcomes	Recurrent VTE/ DVT: previously compressible proximal vein segment no longer compressible on ultrasonography PE: high-probability lung scan with clinical suspicion, abnormal perfusion scan with documented new DVT or spiral computed tomography showing thrombus in the pulmonary arteries Major bleeding: clinically overt bleeding associated with a fall in Hb $\geq$ 2 g/dL leading to blood transfusion of $\geq$ 2 units; or intracranial or retroperitoneal bleeding, or bleeding 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 VKA treatment Category II trial

Risk of bias

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) All outcomes	High risk	Open-label, not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independently collected outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data presented
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes reported

Romera 2009 (*Continued*)

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 VKA treatment) ≥ 75 years of age with a symptomatic proximal DVT confirmed on phlebography Age, mean, years: LMWH 80.9/VKA 79.6 Gender, M/F: LMWH 17/33/VKA 24/26 Location: 1 centre in Spain
Interventions	Acenocoumarol for 3 or 6 months (INR 2.0 to 3.0) compared with once-daily subcutaneous enoxaparin 40 mg (4000 IU Factor Xa inhibitor). Both treatment arms started with a course of ≥ 10 days of intravenous unfractionated heparin. Starting with a bolus of 5000 IU and followed by 4000 IU administered every 4 hours, with a target APTT of 1.5 to 2.0 times baseline APTT
Outcomes	Recurrent VTE/DVT: new filling defect observed on phlebography PE: pulmonary scintigraphy and/or pulmonary arteriography. Necropsy was performed when necessary Major bleeding: overt bleeding and associated with a decrease in Hb of ≥ 2 g/dLl requiring a blood transfusion; retroperitoneal, intracranial, or intra-articular, or leading 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 participants in the acenocoumarol group and 5 in the enoxaparin group were treated for 6 months. The remainder were treated for 3 months Therapeutic compliance was graded as good in 15 (30%) participants (within desired INR range on more than 75% of occasions), acceptable in 28 (56%) participants (within INR target range on 50% to 75% of occasions), and poor in 7 (14%) participants (< 50% of occasions within the target range). In the enoxaparin group, 4 participants reported slight irregularities; in 5 others, the number of vials returned did not correspond exactly with doses needed for that time period Category II trial

Risk of bias

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) All outcomes	High risk	Open-label trial - not blind: LMWH administered to hospitalised participants vs

Veiga 2000 (*Continued*)

		acenocoumarol outpatient participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes collected by independent specialists
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All prospectively stated outcomes were accounted for
Other bias	Low risk	None observed

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 *[ordered by study ID]*

Study	Reason for exclusion
Ghirarduzzi 2009	Composite endpoint trial
Hull 2001	Subjective participant-reported outcomes
Hull 2001a	Subjective participant-reported outcomes
Vorobyeva 2009	Non-randomised trial

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	16	3299	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.60, 1.15]
2 Incidence of major bleeding	16	3299	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.32, 0.80]
3 Mortality	16	3299	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.75, 1.56]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	12	3021	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.57, 1.11]
2 Incidence of major bleeding	12	3021	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.33, 0.88]
3 Mortality	12	3021	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.75, 1.60]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	3	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.70 [0.91, 35.60]
2 Incidence of major bleeding	3	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.03, 1.78]
3 Mortality	3	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.39 [0.51, 57.36]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	7	1872	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.54, 1.18]
2 Incidence of major bleeding	7	1872	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.36, 1.07]
3 Mortality	7	1872	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.61, 1.41]

Comparison 5. Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	2	292	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [0.74, 5.19]
2 Incidence of major bleeding	2	292	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.20, 5.12]
3 Mortality	2	292	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.29, 2.68]

Comparison 6. Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	5	1580	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.44, 1.03]
2 Incidence of major bleeding	5	1580	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.33, 1.04]
3 Mortality	5	1580	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.59, 1.46]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	10	2592	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.77, 1.64]
2 Incidence of major bleeding	9	2112	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	10	2592	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.71, 1.40]

Comparison 8. LMWH versus VKA during additional nine months of follow-up (category I trials)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	5	1691	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.81, 1.98]
2 Incidence of major bleeding	4	1211	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	5	1691	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.72, 1.55]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	10	2592	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.67, 1.15]
2 Incidence of major bleeding	9	2112	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.33, 0.95]
3 Mortality	10	2592	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.84, 1.43]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of recurrent VTE	5	1691	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.70, 1.30]
2 Incidence of major bleeding	4	1211	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.39, 1.32]
3 Mortality	5	1691	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.78, 1.42]

Analysis 1.1. Comparison 1 LMWH versus VKA during allocated treatment (category I and II trials) in participants with VTE, Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Beckman 2003	3/40	0/20		1.8 %	4.72 [0.41, 54.32]
Das 1996	5/50	2/55		4.5 %	2.75 [0.60, 12.69]
Daskalopoulos 2005	2/50	3/52		3.3 %	0.69 [0.11, 4.11]
Gonzalez 1999	8/93	19/92		16.0 %	0.38 [0.17, 0.86]
Hamann 1998	3/100	2/100		3.4 %	1.50 [0.26, 8.84]
Hull 2007	18/369	21/368		25.5 %	0.85 [0.45, 1.62]
Hull 2009	8/240	8/240		10.7 %	1.00 [0.37, 2.71]
Kakkar 2003	3/103	5/221		4.7 %	1.31 [0.29, 5.89]

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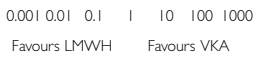
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Kucher 2005	1/20	0/20		0.7 %	7.39 [0.15, 372.38]
Lopaciuk 1999	3/101	7/101		6.6 %	0.43 [0.12, 1.54]
Lopez 2001	0/81	3/77		2.0 %	0.13 [0.01, 1.22]
Massicotte 2003	2/36	4/40		3.8 %	0.55 [0.10, 2.87]
Perez-de-Llano 2010	1/52	0/50		0.7 %	7.11 [0.14, 358.60]
Pini 1994	6/93	4/94		6.5 %	1.54 [0.43, 5.49]
Romera 2009	5/119	7/122		7.9 %	0.72 [0.23, 2.31]
Veiga 2000	2/50	1/50		2.0 %	1.97 [0.20, 19.43]
Total (95% CI)	**1597**	**1702**		**100.0 %**	**0.83 [0.60, 1.15]**

Total events: 70 (LMWH), 86 (VKA)

Heterogeneity: Chi^2 = 16.53, df = 15 (P = 0.35); I^2 =9%

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 LMWH versus VKA during allocated treatment (category I and II trials) in participants with VTE, Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

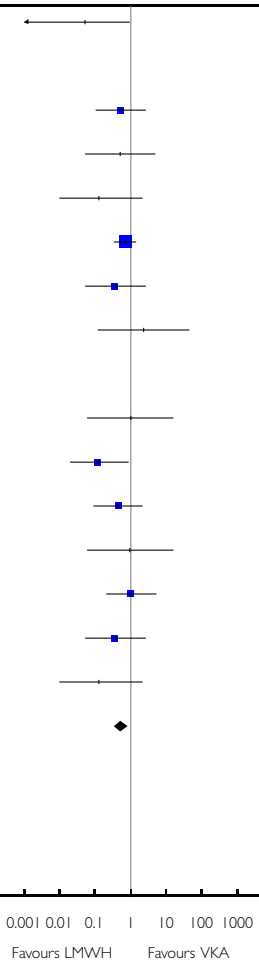
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Beckman 2003	0/40	2/20		2.4 %	0.05 [0.00, 0.92]
Das 1996	0/50	0/55			Not estimable
Daskalopoulos 2005	2/50	4/52		7.9 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	2/92		4.1 %	0.50 [0.05, 4.91]
Hamann 1998	0/100	2/100		2.8 %	0.13 [0.01, 2.16]
Hull 2007	12/369	17/368		38.7 %	0.70 [0.33, 1.46]
Hull 2009	1/240	3/240		5.5 %	0.37 [0.05, 2.61]
Kakkar 2003	1/103	1/221		2.4 %	2.32 [0.12, 45.75]
Kucher 2005	0/20	0/20			Not estimable
Lopaciuk 1999	1/101	1/101		2.8 %	1.00 [0.06, 16.10]
Lopez 2001	0/81	4/77		5.4 %	0.12 [0.02, 0.89]
Massicotte 2003	2/36	5/40		8.9 %	0.44 [0.09, 2.07]
Perez-de-Llano 2010	1/52	1/50		2.7 %	0.96 [0.06, 15.59]
Pini 1994	3/93	3/94		8.1 %	1.01 [0.20, 5.12]
Romera 2009	1/119	3/122		5.5 %	0.37 [0.05, 2.68]
Veiga 2000	0/50	2/50		2.7 %	0.13 [0.01, 2.15]
Total (95% CI)	**1597**	**1702**		**100.0 %**	**0.51 [0.32, 0.80]**

Total events: 25 (LMWH), 50 (VKA)

Heterogeneity: Chi^2 = 9.25, df = 13 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 2.89 (P = 0.0038)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 LMWH versus VKA during allocated treatment (category I and II trials) in participants with VTE, Outcome 3 Mortality.

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

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

Outcome: 3 Mortality

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Beckman 2003	2/40	0/20		1.5 %	4.60 [0.24, 89.21]
Das 1996	1/50	3/55		3.4 %	0.39 [0.05, 2.88]
Daskalopoulos 2005	2/50	4/52		5.0 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	0/92		0.9 %	7.31 [0.15, 368.42]
Hamann 1998	1/100	1/100		1.7 %	1.00 [0.06, 16.10]
Hull 2007	25/369	24/368		40.1 %	1.04 [0.58, 1.86]
Hull 2009	9/240	9/240		15.2 %	1.00 [0.39, 2.56]
Kakkar 2003	1/103	4/221		3.7 %	0.58 [0.09, 3.83]
Kucher 2005	0/20	0/20			Not estimable
Lopaciuk 1999	3/101	2/101		4.3 %	1.50 [0.26, 8.84]
Lopez 2001	7/81	3/77		8.2 %	2.22 [0.62, 7.95]
Massicotte 2003	1/36	4/40		4.1 %	0.31 [0.05, 1.91]
Perez-de-Llano 2010	1/52	0/50		0.9 %	7.11 [0.14, 358.60]
Pini 1994	5/93	4/94		7.5 %	1.28 [0.34, 4.85]
Romera 2009	0/119	0/122			Not estimable
Veiga 2000	3/50	1/50		3.4 %	2.80 [0.38, 20.52]
Total (95% CI)	**1597**	**1702**		**100.0 %**	**1.08 [0.75, 1.56]**

Total events: 62 (LMWH), 59 (VKA)

Heterogeneity: Chi^2 = 9.05, df = 13 (P = 0.77); I^2 =0.0%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 LMWH versus VKA during allocated treatment (category I and II trials) in participants with DVT, Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

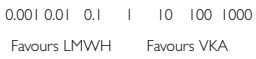
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	5/50	2/55		4.9 %	2.75 [0.60, 12.69]
Daskalopoulos 2005	2/50	3/52		3.6 %	0.69 [0.11, 4.11]
Gonzalez 1999	8/93	19/92		17.2 %	0.38 [0.17, 0.86]
Hamann 1998	3/100	2/100		3.6 %	1.50 [0.26, 8.84]
Hull 2007	18/369	21/368		27.4 %	0.85 [0.45, 1.62]
Hull 2009	8/240	8/240		11.5 %	1.00 [0.37, 2.71]
Kakkar 2003	3/103	5/221		5.0 %	1.31 [0.29, 5.89]
Lopaciuk 1999	3/101	7/101		7.1 %	0.43 [0.12, 1.54]
Lopez 2001	0/81	3/77		2.2 %	0.13 [0.01, 1.22]
Pini 1994	6/93	4/94		7.0 %	1.54 [0.43, 5.49]
Romera 2009	5/119	7/122		8.5 %	0.72 [0.23, 2.31]
Veiga 2000	2/50	1/50		2.2 %	1.97 [0.20, 19.43]
Total (95% CI)	**1449**	**1572**		**100.0 %**	**0.79 [0.57, 1.11]**

Total events: 63 (LMWH), 82 (VKA)

Heterogeneity: Chi^2 = 11.92, df = 11 (P = 0.37); I^2 =8%

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 LMWH versus VKA during allocated treatment (category I and II trials) in participants with DVT, Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	0/50	0/55			Not estimable
Daskalopoulos 2005	2/50	4/52		9.2 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	2/92		4.8 %	0.50 [0.05, 4.91]
Hamann 1998	0/100	2/100		3.2 %	0.13 [0.01, 2.16]
Hull 2007	12/369	17/368		45.0 %	0.70 [0.33, 1.46]
Hull 2009	1/240	3/240		6.4 %	0.37 [0.05, 2.61]
Kakkar 2003	1/103	1/221		2.8 %	2.32 [0.12, 45.75]
Lopaciuk 1999	1/101	1/101		3.2 %	1.00 [0.06, 16.10]
Lopez 2001	0/81	4/77		6.3 %	0.12 [0.02, 0.89]
Pini 1994	3/93	3/94		9.4 %	1.01 [0.20, 5.12]
Romera 2009	1/119	3/122		6.4 %	0.37 [0.05, 2.68]
Veiga 2000	0/50	2/50		3.2 %	0.13 [0.01, 2.15]
Total (95% CI)	**1449**	**1572**		**100.0 %**	**0.54 [0.33, 0.88]**

Total events: 22 (LMWH), 42 (VKA)

Heterogeneity: Chi^2 = 6.51, df = 10 (P = 0.77); I^2 =0.0%

Test for overall effect: Z = 2.44 (P = 0.015)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 LMWH versus VKA during allocated treatment (category I and II trials) in participants with DVT, Outcome 3 Mortality.

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

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

Outcome: 3 Mortality

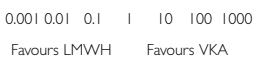
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	1/50	3/55		3.6 %	0.39 [0.05, 2.88]
Daskalopoulos 2005	2/50	4/52		5.3 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	0/92		0.9 %	7.31 [0.15, 368.42]
Hamann 1998	1/100	1/100		1.9 %	1.00 [0.06, 16.10]
Hull 2007	25/369	24/368		42.9 %	1.04 [0.58, 1.86]
Hull 2009	9/240	9/240		16.3 %	1.00 [0.39, 2.56]
Kakkar 2003	1/103	4/221		4.0 %	0.58 [0.09, 3.83]
Lopaciuk 1999	3/101	2/101		4.6 %	1.50 [0.26, 8.84]
Lopez 2001	7/81	3/77		8.8 %	2.22 [0.62, 7.95]
Pini 1994	5/93	4/94		8.1 %	1.28 [0.34, 4.85]
Romera 2009	0/119	0/122			Not estimable
Veiga 2000	3/50	1/50		3.6 %	2.80 [0.38, 20.52]
Total (95% CI)	**1449**	**1572**		**100.0 %**	**1.10 [0.75, 1.60]**

Total events: 58 (LMWH), 55 (VKA)

Heterogeneity: $Chi^2 = 5.43$, df = 10 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 LMWH versus VKA during allocated treatment (category I and II trials) in participants with PE, Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

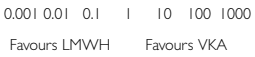
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Beckman 2003	3/40	0/20		56.3 %	4.72 [0.41, 54.32]
Kucher 2005	1/20	0/20		21.9 %	7.39 [0.15, 372.38]
Perez-de-Llano 2010	1/52	0/50		21.8 %	7.11 [0.14, 358.60]
Total (95% CI)	**112**	**90**		**100.0 %**	**5.70 [0.91, 35.60]**

Total events: 5 (LMWH), 0 (VKA)

Heterogeneity: $Chi^2 = 0.05$, df = 2 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 1.86 (P = 0.063)

Test for subgroup differences: Not applicable

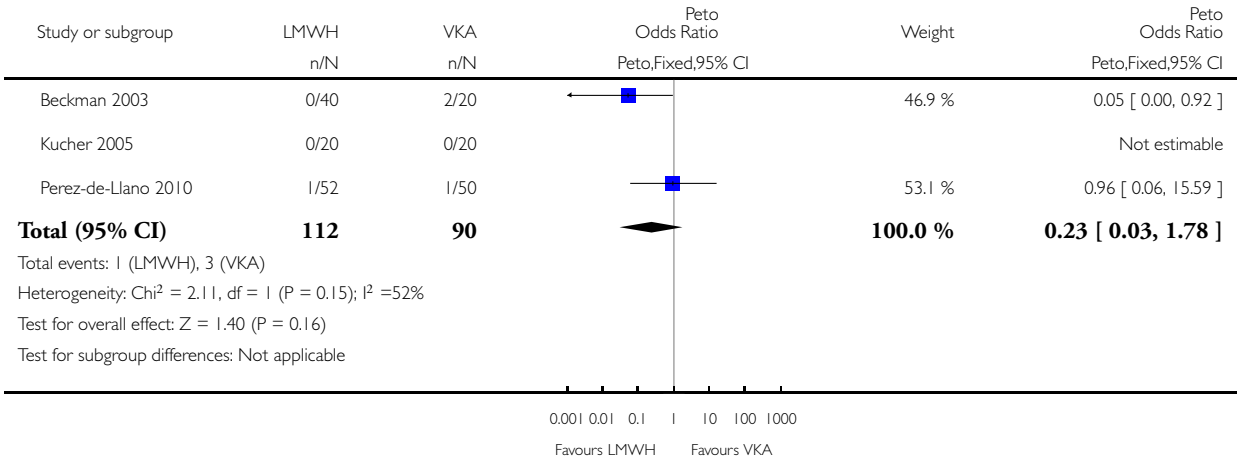


Analysis 3.2. Comparison 3 LMWH versus VKA during allocated treatment (category I and II trials) in participants with PE, Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

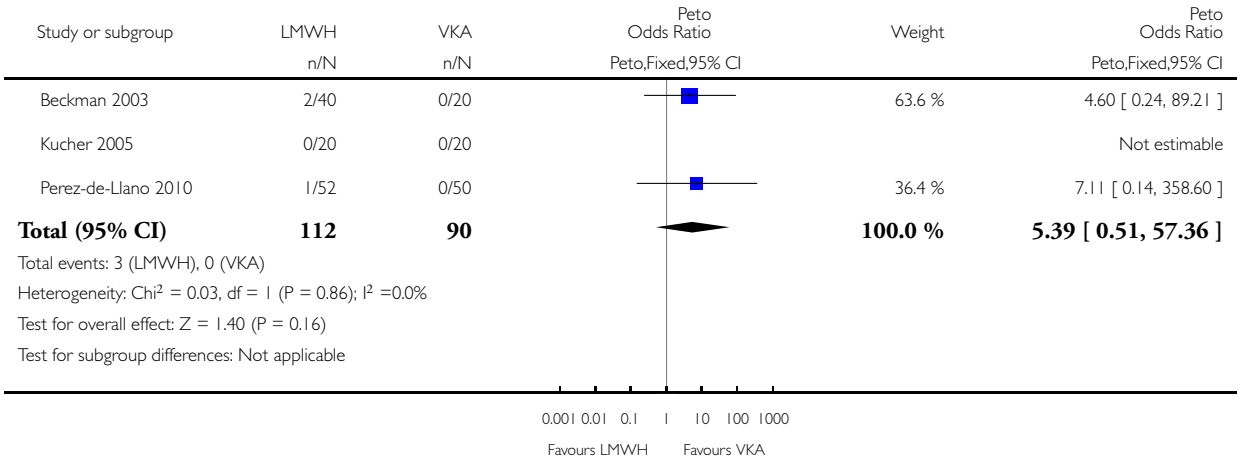


Analysis 3.3. Comparison 3 LMWH versus VKA during allocated treatment (category I and II trials) in participants with PE, Outcome 3 Mortality.

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

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

Outcome: 3 Mortality



Analysis 4.1. Comparison 4 LMWH versus VKA during allocated treatment (category I trials) in participants with VTE, Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

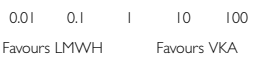
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	5/50	2/55		6.4 %	2.75 [0.60, 12.69]
Daskalopoulos 2005	2/50	3/52		4.7 %	0.69 [0.11, 4.11]
Gonzalez 1999	8/93	19/92		22.7 %	0.38 [0.17, 0.86]
Hull 2007	18/369	21/368		36.2 %	0.85 [0.45, 1.62]
Hull 2009	8/240	8/240		15.2 %	1.00 [0.37, 2.71]
Massicotte 2003	2/36	4/40		5.5 %	0.55 [0.10, 2.87]
Pini 1994	6/93	4/94		9.3 %	1.54 [0.43, 5.49]
Total (95% CI)	**931**	**941**		**100.0 %**	**0.80 [0.54, 1.18]**

Total events: 49 (LMWH), 61 (VKA)

Heterogeneity: $Chi^2 = 7.15$, df = 6 (P = 0.31); $I^2 = 16\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 LMWH versus VKA during allocated treatment (category I trials) in participants with VTE, Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

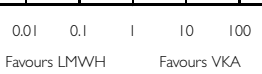
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	0/50	0/55			Not estimable
Daskalopoulos 2005	2/50	4/52		10.8 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	2/92		5.6 %	0.50 [0.05, 4.91]
Hull 2007	12/369	17/368		52.8 %	0.70 [0.33, 1.46]
Hull 2009	1/240	3/240		7.5 %	0.37 [0.05, 2.61]
Massicotte 2003	2/36	5/40		12.2 %	0.44 [0.09, 2.07]
Pini 1994	3/93	3/94		11.1 %	1.01 [0.20, 5.12]
Total (95% CI)	**931**	**941**		**100.0 %**	**0.62 [0.36, 1.07]**

Total events: 21 (LMWH), 34 (VKA)

Heterogeneity: $Chi^2 = 0.99$, df = 5 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 1.73 (P = 0.084)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 LMWH versus VKA during allocated treatment (category I trials) in participants with VTE, Outcome 3 Mortality.

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

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

Outcome: 3 Mortality

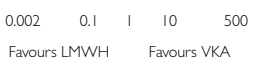
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Das 1996	1/50	3/55		4.5 %	0.39 [0.05, 2.88]
Daskalopoulos 2005	2/50	4/52		6.5 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	0/92		1.1 %	7.31 [0.15, 368.42]
Hull 2007	25/369	24/368		52.6 %	1.04 [0.58, 1.86]
Hull 2009	9/240	9/240		19.9 %	1.00 [0.39, 2.56]
Massicotte 2003	1/36	4/40		5.4 %	0.31 [0.05, 1.91]
Pini 1994	5/93	4/94		9.9 %	1.28 [0.34, 4.85]
Total (95% CI)	**931**	**941**		**100.0 %**	**0.92 [0.61, 1.41]**

Total events: 44 (LMWH), 48 (VKA)

Heterogeneity: $Chi^2 = 4.05$, df = 6 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

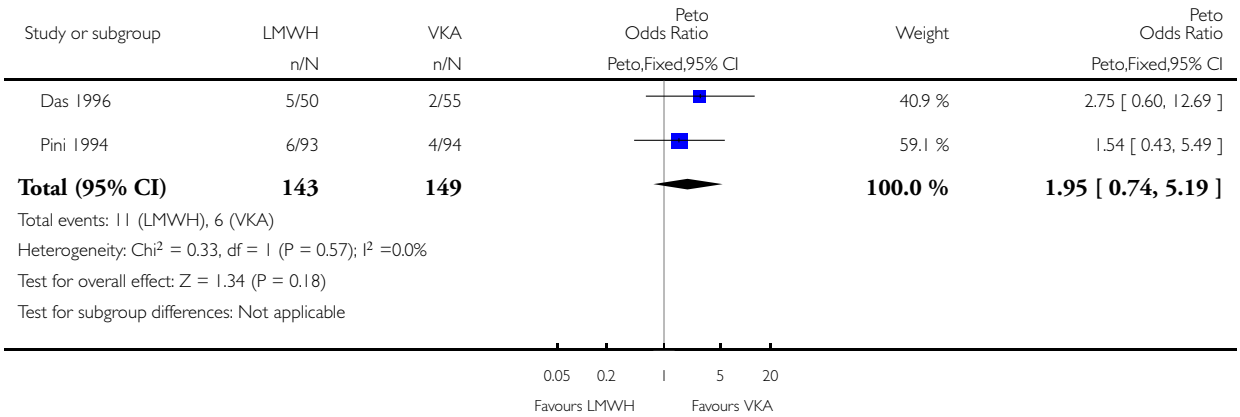


Analysis 5.1. Comparison 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH), Outcome 1 Incidence of recurrent VTE.

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

Comparison: 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH)

Outcome: 1 Incidence of recurrent VTE

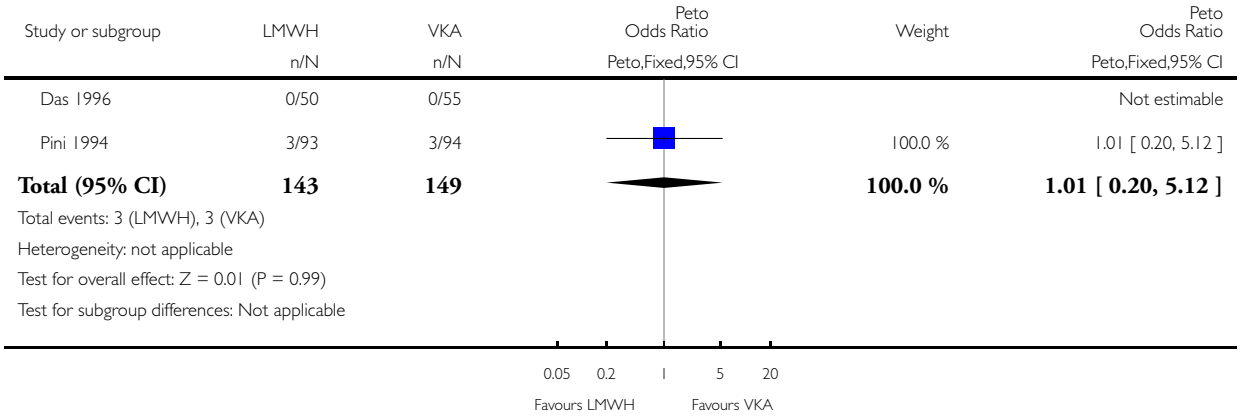


Analysis 5.2. Comparison 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH), Outcome 2 Incidence of major bleeding.

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

Comparison: 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH)

Outcome: 2 Incidence of major bleeding

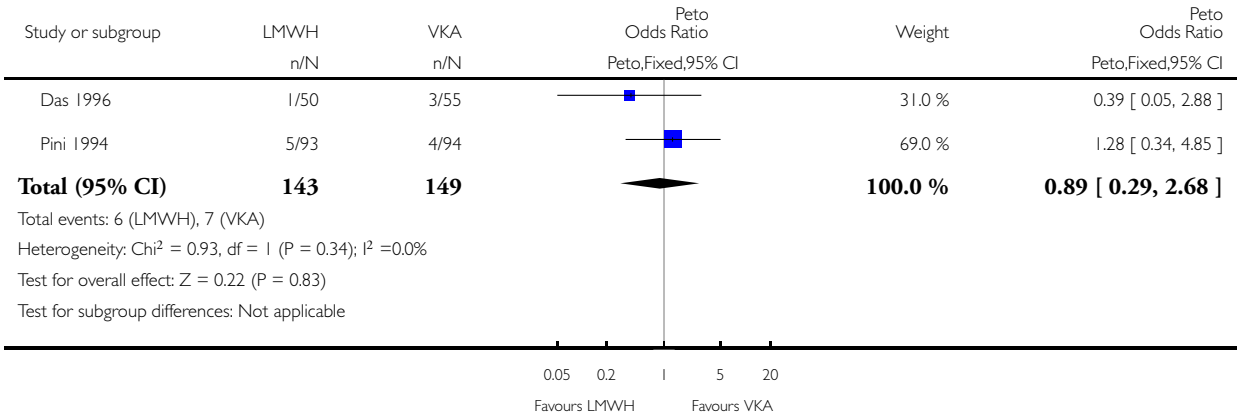


Analysis 5.3. Comparison 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH), Outcome 3 Mortality.

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

Comparison: 5 Category I trials and the same initial treatment in both groups (unfractionated heparin or LMWH)

Outcome: 3 Mortality



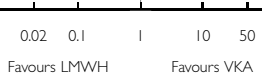
Analysis 6.1. Comparison 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH), Outcome 1 Incidence of recurrent VTE.

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

Comparison: 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH)

Outcome: 1 Incidence of recurrent VTE

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	3/52		5.6 %	0.69 [0.11, 4.11]
Gonzalez 1999	8/93	19/92		26.9 %	0.38 [0.17, 0.86]
Hull 2007	18/369	21/368		43.0 %	0.85 [0.45, 1.62]
Hull 2009	8/240	8/240		18.0 %	1.00 [0.37, 2.71]
Massicotte 2003	2/36	4/40		6.5 %	0.55 [0.10, 2.87]
Total (95% CI)	**788**	**792**		**100.0 %**	**0.68 [0.44, 1.03]**
Total events: 38 (LMWH), 55 (VKA)					
Heterogeneity: Chi^2 = 3.01, df = 4 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 1.81 (P = 0.070)					
Test for subgroup differences: Not applicable					



Analysis 6.2. Comparison 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH), Outcome 2 Incidence of major bleeding.

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

Comparison: 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH)

Outcome: 2 Incidence of major bleeding

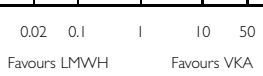
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	4/52		12.1 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	2/92		6.3 %	0.50 [0.05, 4.91]
Hull 2007	12/369	17/368		59.4 %	0.70 [0.33, 1.46]
Hull 2009	1/240	3/240		8.5 %	0.37 [0.05, 2.61]
Massicotte 2003	2/36	5/40		13.7 %	0.44 [0.09, 2.07]
Total (95% CI)	**788**	**792**		**100.0 %**	**0.59 [0.33, 1.04]**

Total events: 18 (LMWH), 31 (VKA)

Heterogeneity: $Chi^2 = 0.60$, df = 4 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH), Outcome 3 Mortality.

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

Comparison: 6 Category I trials and initial treatment not the same in both groups (unfractionated heparin compared with LMWH)

Outcome: 3 Mortality

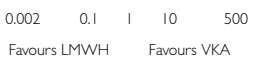
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	4/52		7.6 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	0/92		1.3 %	7.31 [0.15, 368.42]
Hull 2007	25/369	24/368		61.4 %	1.04 [0.58, 1.86]
Hull 2009	9/240	9/240		23.3 %	1.00 [0.39, 2.56]
Massicotte 2003	1/36	4/40		6.3 %	0.31 [0.05, 1.91]
Total (95% CI)	**788**	**792**		**100.0 %**	**0.93 [0.59, 1.46]**

Total events: 38 (LMWH), 41 (VKA)

Heterogeneity: $Chi^2 = 3.12$, df = 4 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 7.1. Comparison 7 LMWH versus VKA during additional follow-up (category I and II trials), Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

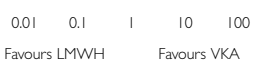
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	0/50	2/52		1.9 %	0.14 [0.01, 2.24]
Gonzalez 1999	3/93	3/92		5.5 %	0.99 [0.20, 5.01]
Hamann 1998	0/100	0/100			Not estimable
Hull 2007	15/369	15/368		27.1 %	1.00 [0.48, 2.07]
Hull 2009	17/240	12/240		25.7 %	1.44 [0.68, 3.05]
Lopaciuk 1999	5/101	2/101		6.4 %	2.42 [0.54, 10.89]
Lopez 2001	2/81	4/77		5.5 %	0.48 [0.09, 2.42]
Pini 1994	10/93	4/94		12.3 %	2.54 [0.86, 7.53]
Romera 2009	1/119	6/122		6.4 %	0.24 [0.05, 1.06]
Veiga 2000	6/50	5/50		9.3 %	1.22 [0.35, 4.26]
Total (95% CI)	**1296**	**1296**		**100.0 %**	**1.12 [0.77, 1.64]**

Total events: 59 (LMWH), 53 (VKA)

Heterogeneity: Chi^2 = 11.12, df = 8 (P = 0.20); I^2 =28%

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable



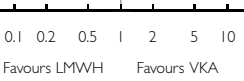
Analysis 7.2. Comparison 7 LMWH versus VKA during additional follow-up (category I and II trials), Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	0/50	0/52			Not estimable
Gonzalez 1999	0/93	0/92			Not estimable
Hamann 1998	0/100	0/100			Not estimable
Hull 2007	0/369	0/368			Not estimable
Lopaciuk 1999	0/101	0/101			Not estimable
Lopez 2001	0/81	0/77			Not estimable
Pini 1994	0/93	0/94			Not estimable
Romera 2009	0/119	0/122			Not estimable
Veiga 2000	0/50	0/50			Not estimable
Total (95% CI)	**1056**	**1056**			**Not estimable**
Total events: 0 (LMWH), 0 (VKA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 7.3. Comparison 7 LMWH versus VKA during additional follow-up (category I and II trials), Outcome 3 Mortality.

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

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

Outcome: 3 Mortality

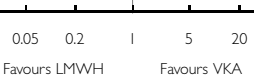
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	5/52		4.9 %	0.42 [0.09, 1.93]
Gonzalez 1999	4/93	3/92		5.1 %	1.33 [0.29, 5.99]
Hamann 1998	0/100	0/100			Not estimable
Hull 2007	35/369	35/368		47.6 %	1.00 [0.61, 1.63]
Hull 2009	13/240	12/240		17.8 %	1.09 [0.49, 2.43]
Lopaciuk 1999	1/101	2/101		2.2 %	0.51 [0.05, 4.96]
Lopez 2001	2/81	3/77		3.7 %	0.63 [0.11, 3.72]
Pini 1994	6/93	4/94		7.1 %	1.54 [0.43, 5.49]
Romera 2009	2/119	2/122		3.0 %	1.03 [0.14, 7.37]
Veiga 2000	7/50	6/50		8.6 %	1.19 [0.37, 3.80]
Total (95% CI)	**1296**	**1296**		**100.0 %**	**1.00 [0.71, 1.40]**

Total events: 72 (LMWH), 72 (VKA)

Heterogeneity: $Chi^2 = 2.55$, df = 8 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 0.00 (P = 1.0)

Test for subgroup differences: Not applicable



Analysis 8.1. Comparison 8 LMWH versus VKA during additional nine months of follow-up (category I trials), Outcome 1 Incidence of recurrent VTE.

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

Comparison: 8 LMWH versus VKA during additional nine months of follow-up (category I trials)

Outcome: 1 Incidence of recurrent VTE

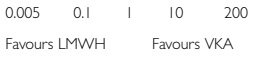
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	0/50	2/52		2.6 %	0.14 [0.01, 2.24]
Gonzalez 1999	3/93	3/92		7.6 %	0.99 [0.20, 5.01]
Hull 2007	15/369	15/368		37.4 %	1.00 [0.48, 2.07]
Hull 2009	17/240	12/240		35.5 %	1.44 [0.68, 3.05]
Pini 1994	10/93	4/94		16.9 %	2.54 [0.86, 7.53]
Total (95% CI)	**845**	**846**		**100.0 %**	**1.26 [0.81, 1.98]**

Total events: 45 (LMWH), 36 (VKA)

Heterogeneity: $Chi^2 = 4.63$, df = 4 (P = 0.33); $I^2 = 14\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable



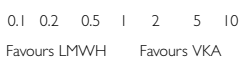
Analysis 8.2. Comparison 8 LMWH versus VKA during additional nine months of follow-up (category I trials), Outcome 2 Incidence of major bleeding.

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

Comparison: 8 LMWH versus VKA during additional nine months of follow-up (category I trials)

Outcome: 2 Incidence of major bleeding

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	0/50	0/52			Not estimable
Gonzalez 1999	0/93	0/92			Not estimable
Hull 2007	0/369	0/368			Not estimable
Pini 1994	0/93	0/94			Not estimable
Total (95% CI)	**605**	**606**			**Not estimable**
Total events: 0 (LMWH), 0 (VKA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 8.3. Comparison 8 LMWH versus VKA during additional nine months of follow-up (category I trials), Outcome 3 Mortality.

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

Comparison: 8 LMWH versus VKA during additional nine months of follow-up (category I trials)

Outcome: 3 Mortality

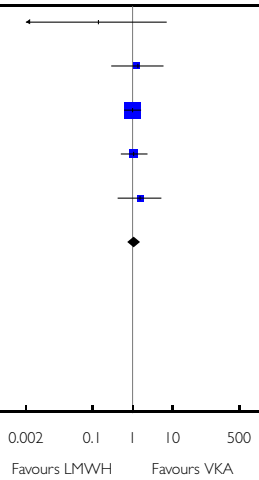
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	0/50	1/52		1.0 %	0.14 [0.00, 7.09]
Gonzalez 1999	4/93	3/92		6.5 %	1.33 [0.29, 5.99]
Hull 2007	35/369	35/368		60.7 %	1.00 [0.61, 1.63]
Hull 2009	13/240	12/240		22.7 %	1.09 [0.49, 2.43]
Pini 1994	6/93	4/94		9.1 %	1.54 [0.43, 5.49]
Total (95% CI)	**845**	**846**		**100.0 %**	**1.06 [0.72, 1.55]**

Total events: 58 (LMWH), 55 (VKA)

Heterogeneity: $Chi^2 = 1.50$, df = 4 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable



Analysis 9.1. Comparison 9 LMWH versus VKA for total period of 12 months of follow-up (category I and II trials), Outcome 1 Incidence of recurrent VTE.

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

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

Outcome: 1 Incidence of recurrent VTE

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	5/52		3.0 %	0.42 [0.09, 1.93]
Gonzalez 1999	11/93	22/92		12.6 %	0.44 [0.21, 0.93]
Hamann 1998	3/100	2/100		2.3 %	1.50 [0.26, 8.84]
Hull 2007	33/369	36/368		28.8 %	0.91 [0.55, 1.49]
Hull 2009	25/240	20/240		18.8 %	1.28 [0.69, 2.36]
Lopaciuk 1999	8/101	9/101		7.2 %	0.88 [0.33, 2.37]
Lopez 2001	2/81	7/77		3.9 %	0.29 [0.08, 1.12]
Pini 1994	16/93	8/94		9.7 %	2.17 [0.92, 5.09]
Romera 2009	6/119	13/122		8.1 %	0.46 [0.18, 1.18]
Veiga 2000	8/50	6/50		5.6 %	1.39 [0.45, 4.28]
Total (95% CI)	**1296**	**1296**		**100.0 %**	**0.88 [0.67, 1.15]**

Total events: 114 (LMWH), 128 (VKA)

Heterogeneity: Chi^2 = 15.23, df = 9 (P = 0.08); I^2 =41%

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable

Analysis 9.2. Comparison 9 LMWH versus VKA for total period of 12 months of follow-up (category I and II trials), Outcome 2 Incidence of major bleeding.

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

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

Outcome: 2 Incidence of major bleeding

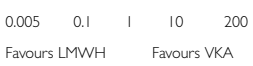
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	2/52		7.1 %	1.04 [0.14, 7.62]
Gonzalez 1999	1/93	2/92		5.5 %	0.50 [0.05, 4.91]
Hamann 1998	0/100	2/100		3.7 %	0.13 [0.01, 2.16]
Hull 2007	12/369	17/368		51.3 %	0.70 [0.33, 1.46]
Lopaciuk 1999	1/101	1/101		3.7 %	1.00 [0.06, 16.10]
Lopez 2001	0/81	4/77		7.2 %	0.12 [0.02, 0.89]
Pini 1994	3/93	3/94		10.7 %	1.01 [0.20, 5.12]
Romera 2009	1/119	3/122		7.3 %	0.37 [0.05, 2.68]
Veiga 2000	0/50	2/50		3.6 %	0.13 [0.01, 2.15]
Total (95% CI)	**1056**	**1056**		**100.0 %**	**0.56 [0.33, 0.95]**

Total events: 20 (LMWH), 36 (VKA)

Heterogeneity: $Chi^2 = 5.84$, df = 8 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 2.17 (P = 0.030)

Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9 LMWH versus VKA for total period of 12 months of follow-up (category I and II trials), Outcome 3 Mortality.

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

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

Outcome: 3 Mortality

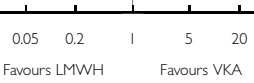
Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	5/52		3.1 %	0.42 [0.09, 1.93]
Gonzalez 1999	5/93	3/92		3.6 %	1.66 [0.40, 6.83]
Hamann 1998	1/100	1/100		0.9 %	1.00 [0.06, 16.10]
Hull 2007	60/369	59/368		46.3 %	1.02 [0.69, 1.51]
Hull 2009	22/240	21/240		18.2 %	1.05 [0.56, 1.97]
Lopaciuk 1999	6/101	6/101		5.3 %	1.00 [0.31, 3.20]
Lopez 2001	9/81	6/77		6.3 %	1.47 [0.51, 4.24]
Pini 1994	11/93	8/94		8.0 %	1.44 [0.56, 3.70]
Romera 2009	2/119	2/122		1.8 %	1.03 [0.14, 7.37]
Veiga 2000	10/50	7/50		6.6 %	1.52 [0.54, 4.30]
Total (95% CI)	**1296**	**1296**		**100.0 %**	**1.09 [0.84, 1.43]**

Total events: 128 (LMWH), 118 (VKA)

Heterogeneity: $Chi^2 = 3.03$, df = 9 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable



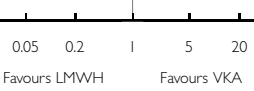
Analysis 10.1. Comparison 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials), Outcome 1 Incidence of recurrent VTE.

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

Comparison: 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials)

Outcome: 1 Incidence of recurrent VTE

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	5/52		4.2 %	0.42 [0.09, 1.93]
Gonzalez 1999	11/93	22/92		17.2 %	0.44 [0.21, 0.93]
Hull 2007	33/369	36/368		39.5 %	0.91 [0.55, 1.49]
Hull 2009	25/240	20/240		25.8 %	1.28 [0.69, 2.36]
Pini 1994	16/93	8/94		13.3 %	2.17 [0.92, 5.09]
Total (95% CI)	**845**	**846**		**100.0 %**	**0.95 [0.70, 1.30]**
Total events: 87 (LMWH), 91 (VKA)					
Heterogeneity: Chi^2 = 9.63, df = 4 (P = 0.05); I^2 =58%					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Not applicable					



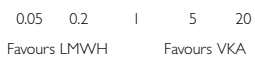
Analysis 10.2. Comparison 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials), Outcome 2 Incidence of major bleeding.

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

Comparison: 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials)

Outcome: 2 Incidence of major bleeding

Study or subgroup	LMWH n/N	VKA n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daskalopoulos 2005	2/50	4/52		13.8 %	0.52 [0.10, 2.67]
Gonzalez 1999	1/93	1/92		4.8 %	0.99 [0.06, 15.94]
Hull 2007	12/369	17/368		67.3 %	0.70 [0.33, 1.46]
Pini 1994	3/93	3/94		14.1 %	1.01 [0.20, 5.12]
Total (95% CI)	**605**	**606**		**100.0 %**	**0.72 [0.39, 1.32]**
Total events: 18 (LMWH), 25 (VKA)					
Heterogeneity: Chi^2 = 0.38, df = 3 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.07 (P = 0.28)					
Test for subgroup differences: Not applicable					

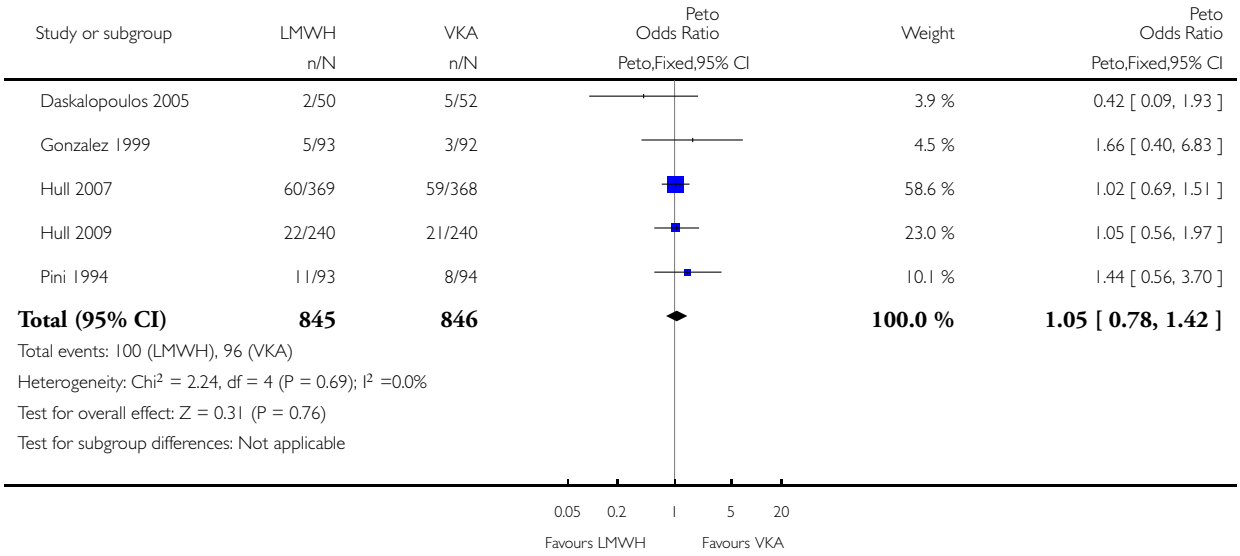


Analysis 10.3. Comparison 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials), Outcome 3 Mortality.

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

Comparison: 10 LMWH versus VKA for total period of 12 months of follow-up (category 1 trials)

Outcome: 3 Mortality



APPENDICES

Appendix 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

(*Continued*)

#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

(*Continued*)

#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

Appendix 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)

Appendix 3. Glossary

anticoagulant: medicine that helps 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

FEEDBACK

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.

WHAT'S NEW

Last assessed as up-to-date: 11 November 2016.

Date	Event	Description
11 November 2016	New citation required but conclusions have not changed	Reran searches, identified 1 new included study. Updated review text and added 'Summary of findings' table. New author joined review team. No changes to conclusions
11 November 2016	New search has been performed	Reran searches. Identified 1 new included study.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2000

Date	Event	Description
29 March 2012	New citation required but conclusions have not changed	New review authors have taken over this review; updated review and made no changes to conclusions
29 March 2012	New search has been performed	New review authors have taken over this review: reran searches, added 8 new included studies and long-term follow-up data from 1 study. Assessed risk of bias for all included studies
14 February 2011	Amended	Added link to anticoagulant feedback
28 August 2008	Amended	Converted to new review format
14 May 2003	New search has been performed	Added 2 new studies to included studies and 3 to ongoing studies

CONTRIBUTIONS OF AUTHORS

A Andras (AA) assessed trials for inclusion, extracted data, assessed risk of bias, analysed data, and drafted the manuscript.

A Sala Tenna (AST) drafted the manuscript.

M Stewart (MS) assessed trials for inclusion, extracted data, assessed risk of bias, analysed data, and drafted the manuscript.

DECLARATIONS OF INTEREST

AA: none known.

AST: none known.

MS: none known. MS is a member of the Cochrane Vascular editorial staff. To prevent conflict of interest issues, editorial decisions and activities related to this review were carried out by other editorial staff members when appropriate.

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Internal sources

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- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the original protocol as follows for the update published in 2012.

- We excluded trials that randomised only participants with cancer, as patients with malignancy are the topic of a different review (Akl 2014).

- We added secondary outcomes that were the same as primary outcomes but were measured over a different time frame. Primary outcomes now are measured during initial treatment covering three months, and secondary outcomes are considered for an additional nine months, or longer if data are available.

- We changed assessment of the methodological quality of included trials to include the updated and recommended Cochrane 'Risk of bias' tool (Higgins 2011).

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

NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects; *therapeutic use]; Hemorrhage [chemically induced; epidemiology]; Heparin, Low-Molecular-Weight [adverse effects; *therapeutic use]; Incidence; Odds Ratio; Randomized Controlled Trials as Topic; Recurrence; Venous Thromboembolism [*drug therapy; mortality]; Venous Thrombosis [drug therapy]; Vitamin K [*antagonists & inhibitors]

MeSH check words

Humans