

Venous thromboembolic diseases

Evidence Update April 2014

A summary of selected new evidence relevant to NICE clinical guideline 144 'Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing' (2012)

Evidence Update 55



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Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the [NICE Evidence Services](#) topic page for [venous thromboembolism](#).

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

¹  [Venous thromboembolic diseases](#). NICE clinical guideline 144 (2012)

A search was conducted for new evidence from 1 August 2011 to 11 November 2013. A total of 4724 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 40 references underwent a rapid critical appraisal process and then were reviewed by an [Evidence Update Advisory Group](#), which advised on the final list of 10 items selected for the Evidence Update. See [Appendix A](#) for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base, and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 144 ([NICE CG144](#)). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the [NICE clinical guideline development methods](#) for further information about updating clinical guidelines.

Other relevant NICE products

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE products has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following:

Technology appraisals

¹  [Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism](#). NICE technology appraisal 287 (2013)

 [Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism](#). NICE technology appraisal 261 (2012)

¹ [NICE-accredited guidance](#)

Medicines evidence commentaries

- [VTE: Aspirin for prolonged prophylaxis after anticoagulation ceases](#). Medicines evidence commentary January 2013

NICE Pathways

NICE Pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathway covers advice and recommendations related to this Evidence Update:

- [Venous thromboembolism](#). NICE Pathway

Quality standards

- [Diagnosis and management of venous thromboembolic diseases](#). NICE quality standard 29

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on [NICE CG144](#). Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from [NICE CG144](#).

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	No
<p>Treatment</p> <p>Pharmacological interventions</p> <ul style="list-style-type: none"> Several new oral anticoagulants have been approved for the management of venous thromboembolism (VTE) since the publication of NICE CG144 and have been or are currently being reviewed as part of the NICE technology appraisal programme. <p>Thrombolytic therapy</p> <ul style="list-style-type: none"> Thrombolytic therapy plus anticoagulation may improve venous patency and reduce the risk of post-thrombotic syndrome compared with anticoagulation in patients with deep vein thrombosis (DVT), but increase the likelihood of bleeding complications. Low-dose systemic pharmacological thrombolysis may be a treatment option for a subgroup of patients with pulmonary embolism (PE) who have a high thrombus burden but are not haemodynamically unstable. <p>Mechanical interventions</p> <ul style="list-style-type: none"> Routine long-term use of graduated elastic compression stockings does not appear to prevent post-thrombotic syndrome in patients with a first proximal DVT. 	<p>✓*</p>	<p>✓</p> <p>✓</p>
<p>Areas not currently covered by NICE CG144</p> <p>Aspirin for prevention of VTE recurrence</p> <ul style="list-style-type: none"> In people who have experienced a first unprovoked DVT or PE and completed initial anticoagulation therapy, low-dose aspirin compared with placebo may reduce the risk of VTE and vascular events without increasing the risk of bleeding. Although long-term anticoagulation is the most effective therapy for prevention of VTE recurrence, aspirin may be a potential alternative option in patients who have had an unprovoked VTE and are unable or unwilling to go on long-term anticoagulation therapy. 	<p>✓*</p>	

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact the guidance will be made when the need to update the guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

Key point	Potential impact on guidance	
	Yes	No
<p>Areas not currently covered by NICE CG144</p> <p>Management of calf DVT</p> <ul style="list-style-type: none"> Limited evidence does not appear to support routine use of anticoagulants over observation and re-imaging in patients with calf DVT. However, given the risks of propagation and of PE and DVT recurrence, management of patients with calf DVT with either anticoagulation therapy or serial imaging of the proximal veins is advised. <p>Risk stratification and outpatient treatment of patients with PE</p> <ul style="list-style-type: none"> Selected patients with PE who are at low risk of adverse events could safely receive anticoagulation treatment on an outpatient basis or be discharged within 3 days. The Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) could be used to select those patients with PE who are at low risk of mortality or serious adverse events and could be managed as outpatients. 		<p>✓</p> <p>✓</p>

1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Section headings are taken from [NICE CG144](#).

1.1 [Diagnosis](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 [Treatment](#)

Pharmacological interventions

Oral anticoagulants

Of the oral anticoagulants currently licensed for use in the UK, the 4 most commonly used are:

- warfarin: a vitamin K antagonist (VKA)
- 3 new oral anticoagulants: rivaroxaban, apixaban and dabigatran etexilate.

Rivaroxaban and apixaban are direct inhibitors of activated factor X (factor Xa), whereas dabigatran is a direct thrombin inhibitor. Another new oral anticoagulant, the direct factor Xa inhibitor edoxaban tosylate, is also in development.

[NICE CG144](#) recommends that patients with confirmed proximal deep vein thrombosis (DVT) – that is, DVT in the popliteal vein or above, sometimes referred to as 'above-knee DVT' – or pulmonary embolism (PE) should be offered a VKA within 24 hours of diagnosis. The VKA should be continued for 3 months, or beyond 3 months in patients with an unprovoked PE, taking into account the patient's risk of recurrence of venous thromboembolism (VTE) and whether they are at increased risk of bleeding. Extending the VKA beyond 3 months should be considered for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Healthcare professionals should discuss with the patient the benefits and risks of extending their VKA treatment.

[NICE CG144](#) does not include any specific recommendations on the use of the new oral anticoagulants rivaroxaban, apixaban, dabigatran and edoxaban. However, several related NICE technology appraisals have been published or are in development. New oral anticoagulants are also discussed in the [NICE clinical knowledge summary on oral anticoagulation](#).

[NICE technology appraisal 261](#) recommends **rivaroxaban** as an option for treating DVT and preventing recurrent DVT and PE after a diagnosis of acute DVT in adults. Additionally, [NICE technology appraisal 287](#) recommends rivaroxaban as an option for treating PE and preventing recurrent DVT and PE in adults.

A proposed NICE technology appraisal ([ID726](#)) of **apixaban** for the treatment and secondary prevention of DVT and/or PE is currently being considered through the topic selection process. Apixaban did not have UK marketing authorisation for the treatment and secondary prevention of VTE at the time of publication of this Evidence Update.

A NICE technology appraisal ([ID483](#)) of **dabigatran** for the treatment and secondary prevention of DVT and/or PE is currently underway. Dabigatran did not have UK marketing authorisation for the treatment and secondary prevention of VTE at the time of publication of this Evidence Update.

The Medicines and Healthcare Products Agency has issued a [drug safety update](#) on rivaroxaban, apixaban and dabigatran to clarify contraindications associated with the risk of serious haemorrhage with all 3 of these drugs. The agency has also issued a [drug safety update](#) on the need for renal function testing with dabigatran.

A proposed NICE technology appraisal ([ID662](#)) of **edoxaban** for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism is currently being considered through the topic selection process. At the time of publication of this Evidence Update, edoxaban did not have UK marketing authorisation for any indication and was not available in the UK.

Several new oral anticoagulants have been approved for the management of VTE since the publication of [NICE CG144](#). NICE has issued or is considering technology appraisals on these new oral anticoagulants. These recommendations are not incorporated within [NICE CG144](#). The emergence of these drugs may therefore have a potential impact on [NICE CG144](#), although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact the guidance will be made when the need to update the guidance is reviewed by NICE.

The NICE Pathway on [venous thromboembolism](#) brings together all related NICE guidance and associated products for the condition, including all relevant technology appraisals, in a set of interactive topic-based diagrams.

Thrombolytic therapy

Deep vein thrombosis

[NICE CG144](#) recommends that catheter-directed thrombolytic therapy should be considered for patients with symptomatic iliofemoral DVT who have:

- symptoms of less than 14 days' duration **and**
- good functional status **and**
- a life expectancy of 1 year or more **and**
- a low risk of bleeding.

The guideline does not make any recommendations on systemic thrombolytic therapy for DVT.

[Enden et al. \(2012\)](#) assessed outcomes after catheter-directed thrombolytic therapy plus standard anticoagulation therapy compared with standard anticoagulation therapy alone in patients with DVT. In the open-label, randomised controlled CaVenT study, 20 hospitals in Norway enrolled adults (n=209) with objectively verified DVT above mid-thigh level who had experienced symptoms for up to 21 days. All patients received initial anticoagulation therapy with subcutaneous low molecular weight heparin (LMWH; dalteparin or enoxaparin), then either long-term warfarin (standard treatment) or catheter-directed thrombolytic therapy with alteplase² followed by long-term warfarin. Patients in both groups were advised to use knee-high compression stockings daily for 24 months. The primary outcomes were post-thrombotic syndrome at 24 months (score on Villalta's scale of 5 points or higher) and iliofemoral patency at 6 months.

More patients in the catheter-directed thrombolytic therapy than in the standard treatment group had iliofemoral patency at 6 months (65.9%, 95% confidence interval [CI] 55.5 to 75.0% versus 47.4%, 95% CI 37.6 to 57.3%, p=0.012). In addition, fewer patients in the catheter-directed thrombolytic therapy group had post-thrombotic syndrome after 24 months (41.1%, 95% CI 31.5 to 51.4% versus 55.6%, 95% CI 45.7 to 65.0%, p=0.047). Catheter-directed

² At the time of publication of this Evidence Update, alteplase did not have UK marketing authorisation for treatment of DVT.

thrombolytic therapy was associated with 20 bleeding complications, 3 of which were major and 5 were clinically relevant.

Limitations of the evidence included the possibility of bias given that patients were not blinded to treatment allocation (although the clinicians who assessed patients at 6-month and 24-month follow-up were blinded). Additionally, despite recruiting the target number of patients, the final study population was close to the critical limit for detection of clinical effect because of loss of patients to follow-up.

[Watson et al. \(2014\)](#) conducted a Cochrane systematic review of randomised controlled trials that compared any type of thrombolytic therapy (systemic, loco-regional or catheter-directed) plus anticoagulation therapy with anticoagulation therapy alone in patients with acute DVT of the lower limb. Primary outcomes were: any improvement in venous patency; complete clot lysis; bleeding complications; stroke; post-thrombotic syndrome; venous ulceration; and mortality. A total of 17 studies (n=1103) were included in the review. Outcomes were classed as early (36 hours to 1 month) or intermediate (6 months or more), with post-thrombotic syndrome assessed at between 1 year and 6 years.

People who underwent any form of thrombolytic therapy were more likely than controls to have:

- Improvement in venous patency (risk ratio [RR]=2.48, 95% CI 1.35 to 4.57, p=0.0035; 9 studies, n=421)
- Complete clot lysis:
 - Early (RR=4.91, 95% CI 1.66 to 14.53, p=0.0041; 8 studies, n=592)
 - Intermediate (RR=2.37, 95% CI 1.48 to 3.80, p=0.00036; 8 studies, n=655)
- Bleeding complications (RR=2.23, 95% CI 1.41 to 3.52, p=0.00064; 17 studies, n=1103).

In addition, the incidence of post-thrombotic syndrome was lower in the thrombolytic therapy group (RR=0.64, 95% CI 0.52 to 0.79, p=0.000026; 4 studies, n=341). Similar results were reported when systemic, loco-regional and catheter-directed thrombolytic therapy were assessed individually.

Limitations of the review included the lack of data on long-term follow-up (that is, longer than 1 year), the differences in inclusion criteria of the studies analysed, and the age of some of the studies (10 were published in 1990 or earlier). The authors cautioned that not enough data were available to make any definitive comparison between the different drugs or routes of administration for thrombolytic therapy.

Together the evidence suggests that thrombolytic therapy plus anticoagulation may improve venous patency and reduce the risk of post-thrombotic syndrome compared with anticoagulation in patients with DVT, but increase the likelihood of bleeding complications. The evidence is consistent with recommendations in [NICE CG144](#) that catheter-directed thrombolytic therapy should be considered for patients with symptomatic iliofemoral DVT.

Key references

Enden T, Haig Y, Kløw NE et al. (2012) [Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis \(the CaVenT study\): a randomised controlled trial](#). *Lancet* 379: 31–8

Watson L, Broderick C, Armon MP (2014) [Thrombolysis for acute deep vein thrombosis](#). *Cochrane Database of Systematic Reviews* issue 1: CD002783

Pulmonary embolism

[NICE CG144](#) recommends that systemic pharmacological thrombolytic therapy should be considered for patients with PE and haemodynamic instability. These individuals should also be offered unfractionated heparin (UFH). Patients with PE and haemodynamic stability should not be offered systemic pharmacological thrombolytic therapy.

An open-label, randomised controlled trial by [Sharifi et al. \(2013\)](#) tested the efficacy and safety of low-dose systemic pharmacological thrombolysis for reduction of pulmonary artery pressure in patients with PE. Patients with symptomatic 'moderate' PE (that is, more than 70% thrombus involvement in 2 or more lobar arteries or left or right main pulmonary arteries on CT pulmonary angiography, or ventilation–perfusion mismatch in 2 or more lobes) were recruited from a single centre in the USA. Participants (n=121) were randomly assigned to receive a low dose of tissue plasminogen activator (50 mg for patients weighing 50 kg or more and 0.5 mg/kg for patients weighing less than 50 kg; standard dose 100 mg) plus anticoagulation therapy with UFH or LMWH (enoxaparin) or a control of anticoagulation therapy alone. The method of randomisation and whether allocation was concealed was unclear. The primary end points were development of pulmonary hypertension (pulmonary artery systolic pressure of 40 mmHg or more, as measured by echocardiography) and the composite of pulmonary hypertension and recurrent PE.

At enrolment, a similar proportion of patients had right ventricular enlargement (a right ventricular–left ventricular ratio of more than 0.9) in the thrombolysis group (20%) and the control group (23%). After a mean follow-up of 28±5 months, fewer patients in the thrombolysis group than in the control group had pulmonary hypertension (16% versus 57%, p<0.001) or pulmonary hypertension and recurrent PE (16% versus 63%, p<0.001). Mortality and PE recurrence did not differ significantly between the two groups, and no patient in either group experienced major or minor bleeding.

Limitations of the evidence included that the study was small and conducted at a single centre, and patients were not blinded to treatment allocation. In addition, pulmonary hypertension was estimated by echocardiography but not confirmed by a right heart catheter study.

The evidence potentially suggests that low-dose systemic pharmacological thrombolysis may be a treatment option for a subgroup of patients with PE who have a high thrombus burden but are not haemodynamically unstable. The evidence is unlikely to have an impact on [NICE CG144](#) owing to the small size of the study. Results from further larger studies – such as the [PEITHO Pulmonary Embolism Thrombolysis Study](#) – are needed to confirm whether there are subgroups of intermediate risk patients with normotensive PE and right ventricular function who would benefit from systemic pharmacological thrombolysis (in line with [NICE research recommendation 4.5](#)).

Key reference

[Sharifi M, Bay C, Skrocki L et al. \(2013\) Moderate pulmonary embolism treated with thrombolysis \(from the "MOPEIT" Trial\). American Journal of Cardiology 111: 273–7](#)

Mechanical interventions

Compression stockings

[NICE CG144](#) recommends offering below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications. Healthcare professionals should also:

- advise patients to continue wearing the stockings for at least 2 years
- ensure that the stockings are replaced 2 or 3 times per year or according to the manufacturer's instructions
- advise patients that the stockings need to be worn only on the affected leg or legs.

The NICE quality standard 'Diagnosis and management of venous thromboembolic diseases' ([NICE QS29](#)) recommends that people with proximal DVT are offered below-knee graduated compression stockings within 3 weeks of diagnosis.

[Kahn et al. \(2013\)](#) conducted a randomised controlled trial of elastic compression stockings to prevent post-thrombotic syndrome in patients with DVT. The SOX trial enrolled 806 patients with a first symptomatic proximal DVT from 24 centres in the USA and Canada. Participants (n=806) were randomly assigned within 14 days of diagnosis to 30–40 mmHg graduated elastic compression stockings, or placebo stockings that appeared identical but had less than 5 mmHg compression at the ankle. Patients were instructed to wear their stockings every day for 2 years. Most patients also received anticoagulation therapy with heparin for 5–10 days and warfarin for 3–6 months or longer. The primary outcome was the cumulative incidence of post-thrombotic syndrome during months 6 to 24 of follow-up, defined as Ginsberg's criteria of leg pain and swelling for at least 1 month.

No significant differences were seen between the elastic compression stockings group and the placebo stockings group for:

- Cumulative incidence of post-thrombotic syndrome, assessed by Ginsberg's criteria (14.2% versus 12.7%, hazard ratio [HR] adjusted for centre=1.13, 95% CI 0.73 to 1.76, p=0.58). Similar results were seen when the analysis was restricted to patients who reported use of stockings on 3 or more days a week (adjusted HR=0.96, 95% CI 0.53 to 1.74. p value not stated).
- Cumulative incidence of post-thrombotic syndrome events, judged by Villalta's scale (52.6% versus 52.3%, HR adjusted for centre=1.00, 95% CI 0.81 to 1.24, p value not stated).

Additionally, similar proportions of patients in the elastic compression stockings group and the placebo stockings groups had VTE recurrence (8.1% versus 9.6%) or died (8.8% versus 9.1%; no statistical analysis reported).

Limitations of the evidence included that more than 1 in 10 (14%) of patients withdrew or were lost to follow-up, and compliance decreased to around half of patients (55.6%) wearing their stockings for 3 or more days a week by the end of the 2-year study. In addition, the cumulative incidence of post-thrombotic syndrome was lower than reported in some previous studies, which could be because the present study used Ginsberg's criteria to assess post-thrombotic syndrome.

The evidence suggests that the routine long-term use of graduated elastic compression stockings does not appear to prevent post-thrombotic syndrome in patients with a first proximal DVT. However, graduated elastic compression stockings are still likely to be useful for symptom relief in patients who have had a DVT. These data appear contrary to current recommendations; therefore, the evidence may have a potential impact on [NICE CG144](#), although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact the guidance will be made when the need to update the guidance is reviewed by NICE.

Further research is needed to confirm the findings of this study and the subgroups of patients in whom graduated elastic compression stockings would be most effective. A Dutch multicentre randomised controlled trial comparing individually tailored duration of elastic compression stocking therapy with a standard 2-year duration of elastic compression therapy is currently in progress (the [IDEAL DVT study](#)).

Key reference

[Kahn SR, Shapiro S, Wells PS et al. \(2013\) *Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial*. Lancet pii: S0140–6736\(13\)61902-9](#)

1.3 [Patient information](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

[1.4 Self-management and self-monitoring for patients treated with a vitamin K antagonist](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

[1.5 Investigations for cancer](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

[1.6 Thrombophilia testing](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

Areas not currently covered by NICE CG144

Aspirin for prevention of VTE recurrence

[NICE CG144](#) recommends offering patients with confirmed proximal DVT or PE a choice of LMWH, fondaparinux or UFH, and a VKA, as pharmacological treatment. The guideline does not make any recommendations on the use of aspirin in DVT and PE.

Two randomised controlled trials compared low-dose aspirin with placebo for prevention of VTE recurrence in patients who had completed initial anticoagulant therapy after a first unprovoked VTE. A meta-analysis combining results of the 2 trials was prospectively planned; therefore, trial protocols were harmonised to ensure that treatments were identical and eligibility criteria and outcome definitions were similar.

[Brighton et al. \(2012\)](#) and [Becattini et al. \(2012\)](#) both enrolled patients aged 18 years or older who had experienced a first unprovoked episode (that is, an episode in the absence of underlying risk factors) of objectively diagnosed symptomatic DVT involving the popliteal vein or more proximal leg veins, or an acute PE. In Brighton et al. (the ASPIRE study), participants (n=822) had completed initial anticoagulation therapy with heparin followed by warfarin (or an effective alternative anticoagulant) for between 6 weeks and 24 months. In Becattini et al. (the WARFASA study), patients (n=403) had been treated with a VKA for 6 to 18 months. Participants in both studies were randomly assigned to aspirin 100 mg a day or placebo for at least 2 years. The primary efficacy outcome in both trials was recurrence of VTE (a composite of symptomatic, objectively confirmed DVT, non-fatal PE or fatal PE). The primary safety outcome in both trials was major bleeding (clinically-relevant non-major bleeding was also assessed in the trials as either a primary or secondary outcome).

In Brighton et al. (2012), a similar proportion of patients in the aspirin group and in the placebo group had recurrence of VTE during a median follow-up of 37.2 months (a rate of 6.5% a year versus 4.8% a year, HR=0.74 for aspirin, 95% CI 0.52 to 1.05, p=0.09). In Becattini et al. (2012; median follow-up ~24 months), fewer patients in the aspirin group than in the placebo group had recurrence of VTE (a rate of 6.6% a year versus 11.2% a year, HR=0.58, 95% CI 0.36 to 0.93, p=0.02). The difference in outcomes between the 2 trials may have been influenced by the difference in VTE event rates per year in the placebo groups (6.5% in Brighton et al. versus 11.2% in Becattini et al. [2012]). However, when results of the 2 trials were combined in the pre-specified meta-analysis, aspirin was found to significantly reduce the risk of recurrent VTE (pooled HR=0.68, 95% CI 0.51 to 0.90, p=0.007).

For safety outcomes, no significant difference was observed between groups in Brighton et al. (2012) in the rate of major or clinically-relevant non-major bleeding (1.1% a year with aspirin versus 0.6% a year with placebo, HR=1.72, 95% CI 0.72 to 4.11, p=0.22). In Becattini et al. (2012), 4 patients in each group experienced major or clinically relevant non-major bleeding

(HR=0.98, 95% CI 0.24 to 3.96, p=0.97). The pre-specified meta-analysis of both trials showed a significant reduction with aspirin versus placebo in the risk of major vascular events (a composite of VTE, myocardial infarction, stroke or cardiovascular death; pooled HR=0.66, 95% CI 0.51 to 0.86, p=0.002), and no significantly increased risk of clinically relevant bleeding (pooled HR=1.47, 95% 0.70 to 3.08, p=0.31).

Limitations of the evidence included that both studies had difficulties recruiting patients. Brighton et al. (2012) initially aimed to recruit 3000 patients, but because of slow recruitment the target sample size was reduced to 1500 patients. Becattini et al. (2012) spent 6 years recruiting participants, and their study was underpowered to show an effect of aspirin on the incidence of ischemic heart disease or cerebrovascular disease. A high proportion of patients in Brighton et al. (2012) discontinued the study drug during follow-up (28.5% of the aspirin group and 32.1% of the placebo group).

Together these 2 studies suggest that in people who have experienced a first unprovoked DVT or PE and completed initial anticoagulation therapy, low-dose aspirin compared with placebo may reduce the risk of VTE and vascular events without increasing the risk of bleeding. Although long-term anticoagulation is the most effective therapy for prevention of VTE recurrence, aspirin may be a potential alternative option in patients who have had an unprovoked VTE and are unable or unwilling to go on long-term anticoagulation therapy. The evidence may have a potential impact on [NICE CG144](#), although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact the guidance will be made when the need to update the guidance is reviewed by NICE.

A NICE medicines evidence commentary on '[VTE: Aspirin for prolonged prophylaxis after anticoagulation ceases](#)' also discusses these 2 papers.

Key references

Becattini C, Agnelli G, Schenone A et al. (2012) [Aspirin for preventing the recurrence of venous thromboembolism](#). *New England Journal of Medicine* 366: 1959–67

Brighton TA, Eikelboom JW, Mann K et al. (2012) [Low-dose aspirin for preventing recurrent venous thromboembolism](#). *New England Journal of Medicine* 367: 1979–87

Management of calf DVT

[NICE CG144](#) does not provide recommendations on identification and management of isolated calf vein DVT because an alternative diagnostic strategy of investigating with proximal scanning and repeat imaging as necessary has the same clinical utility and requires less patients being treated.

Two systematic reviews considered the management of patients with calf DVT.

[De Martino et al. \(2012\)](#) conducted a systematic review and meta-analysis of studies that compared anticoagulation treatment (VKA, fractionated heparin, UFH or fondaparinux) for a minimum of 1 month with control in patients with objectively proven isolated calf DVT. The primary outcome was development of PE during a minimum 30 days of follow-up.

The analysis included 8 studies (n=505): 2 randomised controlled trials; 3 retrospective cohort studies; 2 prospective cohort studies; and 1 combined retrospective and prospective cohort study. In a meta-analysis of studies reporting rates of PE, patients treated with anticoagulants had lower rates of PE than did controls (odds ratio [OR]=0.12, 95% CI 0.02 to 0.77, p=0.03; 5 studies, n=209). Patients who received anticoagulation therapy also had lower rates of thrombus propagation to the popliteal vein (OR=0.29, 95% CI 0.14 to 0.62, p=0.001; 6 studies, n=419). No difference was seen between the treatment groups in mortality (OR=0.57, 95% CI 0.06 to 5.66; 4 studies, n=208) or bleeding requiring cessation or reversal of therapy (OR=1.60, 95% CI 0.21 to 12.36, p=0.65; 3 studies, n=118).

The authors stated that the included studies were of poor to moderate methodological quality, and publication bias was detected for studies that assessed thrombus progression (the only outcome with enough studies to create a funnel plot). Few of the studies included were designed specifically to assess the effect of anticoagulation on PE in calf DVT, and only 5 incidents of PE were reported. The authors cautioned that the data available are not sufficiently robust to draw any conclusions on the potential benefits and harms of anticoagulation in patients with calf DVT.

[Masuda et al. \(2012\)](#) analysed studies of calf DVT that assessed at least 1 of the following 4 outcomes: propagation of calf DVT; PE; DVT recurrence; and post-thrombotic syndrome. A total of 31 studies were included in the systematic review – 6 randomised controlled trials and 25 observational studies or case series – that assessed anticoagulation versus surveillance (with or without compression treatment), anticoagulation alone, or surveillance alone in patients with objectively diagnosed calf DVT.

The rate of thrombus propagation to the popliteal vein or higher was 2.9% to 17.9% in the 18 studies that looked at propagation of calf vein thrombi. A pooled analysis of 6 high-to-moderate quality observational studies of surveillance alone found that around 15% of patients with calf DVT experienced propagation of the thrombus, with 8% of cases of propagation to the popliteal vein or higher. The 3 moderate-to-high-quality studies among the 13 that assessed PE reported PE rates of 0% to 6.2%. No high-quality studies reported DVT recurrence in patients with calf DVT. Among the 10 lower quality studies that did report this outcome, rates varied between 0% and 32%. Likewise no high-quality studies reported incidence of post-thrombotic syndrome; the 8 studies of lower quality that were included suggested the incidence could be up to 52%.

Limitations of Masuda et al. (2012) included that meta-analysis of the data was not possible because of the lack of well-designed trials comparing anticoagulation with surveillance in patients with calf DVT. In addition, many of the studies included in the review were judged by the authors to be of poor quality and had small sample sizes. The review included more studies reporting results of anticoagulation in patients with calf DVT than studies reporting surveillance of these patients, which may have led to sampling errors.

Limited evidence does not appear to support routine use of anticoagulants over observation and re-imaging in patients with calf DVT. However, given the risks of propagation and of PE and DVT recurrence, management of patients with calf DVT with either anticoagulation therapy or serial imaging of the proximal veins is advised. The uncertainty over the optimum management approach for calf DVT raised by these 2 papers means that the evidence is unlikely to have an impact on [NICE CG144](#).

These systematic reviews highlight that the evidence base for treating calf DVT is weak. Prospective randomised controlled trials are needed that compare anticoagulation treatment with standard therapy for management of isolated calf DVT. Such studies should consider PE, clot propagation, bleeding events and death, and have a follow-up long enough to adequately assess the development of post-thrombotic syndrome.

Key references

[De Martino RR, Wallaert JB, Rossi AP et al. \(2012\) A meta-analysis of anticoagulation for calf deep venous thrombosis. *Journal of Vascular Surgery* 56: 228–37](#)

[Masuda EM, Kistner RL, Musikasinthorn C et al. \(2012\) The controversy of managing calf vein thrombosis. *Journal of Vascular Surgery* 55: 550–61](#)

Risk stratification and outpatient treatment of patients with PE

The [full version of NICE CG144](#) states that PE risk stratification and outpatient management of PE were not considered during development of the guidance because these areas were beyond the scope of the guideline. It also states that the ideal combination of prognostic tools for PE risk stratification with the appropriate management strategy remains to be determined.

A systematic review and meta-analysis by [Zondag et al. \(2013\)](#) looked at the safety of outpatient treatment compared with inpatient treatment in low-risk patients with acute PE. The authors identified randomised controlled trials and cohort studies of patients with acute, symptomatic, objectively proven PE who were at low risk for adverse clinical outcomes and were receiving anticoagulation treatment. At least some of the study population had to have been treated as outpatients (discharged within 24 hours) or discharged early (discharged between 24 and 72 hours of admission). The 15 studies eligible for the review included 1657 patients who were treated as outpatients, 256 who were discharged early and 383 patients treated as inpatients. The factors for identifying patients suitable for outpatient treatment were largely based on exclusion of unsuitable patients for the following reasons: haemodynamic or respiratory instability, severe pain and need for parenteral narcotics, high risk of bleeding, comorbidities, or social problems needing hospital admission.

In pooled analyses, the absolute risk of VTE recurrence was similar in patients treated as outpatients (1.70%, 95% CI 0.92 to 3.1%; 13 studies, n=1657), patients discharged early (1.12%, 95% CI 0.22 to 5.43%; 3 studies, n=256) and patients treated as inpatients (1.18%, 95% CI 0.16 to 8.14%; 4 studies, n=383). In addition, the pooled risk of major bleeding did not differ significantly between outpatients (0.97%, 95% CI 0.58 to 1.59%), patients discharged early (0.78%, 95% CI 0.16 to 3.73%) and patients treated as inpatients (1.04%, 95% CI 0.39 to 2.75%). Although the point estimates of pooled risk of mortality were lower among patients treated as inpatients (0.74%, 95% CI 0.04 to 11.14%) than among those treated as outpatients (1.94%, 95% CI 0.79 to 4.84%) or those who were discharged early (2.34%, 95% CI 1.06 to 5.12%), the overlapping confidence intervals do not suggest any significant difference in mortality between groups.

Limitations of Zondag et al. (2013) included that the studies used different methods to identify patients at low risk of adverse clinical outcomes. In addition, few of the studies included were randomised controlled trials, several retrospective cohort studies were included, and only 3 studies assessed patients who were discharged early.

[Zhou et al. \(2012\)](#) conducted a systematic review and meta-analysis to assess the accuracy of 2 prognostic tools – the Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) – in predicting outcomes in patients with acute PE. The [PESI](#) uses 11 clinical variables derived from demographics, comorbid conditions and clinical findings to stratify patients with PE into 1 of 5 classes. Patients in classes I and II are categorised as at low risk of mortality and other adverse medical outcomes, whereas those in classes III to V are categorised as at high risk. The [sPESI](#) uses 6 of the 11 variables in the original PESI to assign points to patients. Patients with none of the variables (0 points) are categorised as low risk and those with 1 or more of the variables (1–6 points) are categorised as high risk. The present review included 21 observational studies that used the PESI or sPESI in patients with objectively diagnosed acute PE and that reported short-term prognostic outcomes.

In a pooled analysis, all-cause mortality was lower in patients classed as low risk by either version of PESI than in those classed as high risk (2.0% versus 16.7%, OR=0.13, 95% CI 0.12 to 0.15, p<0.00001; 19 studies, n=50,021). In subgroup analyses, mortality was likewise lower in patients classed as low risk by PESI (2.1% versus 13.2%, OR=0.14, 95% CI 0.13 to 0.16, p<0.00001; 14 studies, n=31,930) and in those categorised as low risk by sPESI (1.8% versus 25.2%, OR=0.10, 95% CI 0.08 to 0.14, p<0.00001; 9 studies, n=18,091).

PE-related mortality was lower in patients classed as low risk with PESI than in those at high risk (0.5% versus 6.0%, OR=0.09, 95% CI 0.05 to 0.17, $p<0.00001$; 7 studies, $n=4794$). The risk of serious adverse events was also lower in patients classed as low risk with PESI (1.2% versus 3.5%, OR=0.34, 95% CI 0.29 to 0.41, $p<0.00001$; 8 studies, $n=34,976$).

Limitations of Zhou et al. (2012) included that some patients were involved in several of the studies analysed and the haemodynamic status of the patients included in the analysis differed.

The evidence suggests that selected patients with PE who are at low risk of adverse events could safely receive anticoagulation treatment on an outpatient basis or be discharged within 3 days. The PESI and sPESI could be used to select those patients with PE who are at low risk of mortality or serious adverse events and could be managed as outpatients. Given that risk stratification and outpatient treatment of patients with PE were not included in the scope of [NICE CG144](#), this evidence is unlikely to have an impact on the guidance.

Key references

Zhou XY, Ben SQ, Chen HL et al. (2012) [The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis](#). *Respiratory Research* 13: 111

Zondag W, Kooiman J, Klok FA et al. (2013) [Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis](#). *European Respiratory Journal* 42: 134–44

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Areas not covered by NICE CG144

- [Optimal treatment pathway for isolated calf deep vein thrombosis \(DVT\)](#)

Further evidence uncertainties for VTE can be found in the [UK DUETs database](#) and in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Venous thromboembolic diseases](#). NICE clinical guideline 144 (2012)

In addition to the guideline inclusion and exclusion criteria, a definition of studies on accuracy of diagnostic tests and a minimum sample size were used as sifting criteria to identify the highest quality evidence from the large volume of material retrieved.

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 01 August 2011 (the end of the search period of [NICE CG144](#)) to 11 November 2013:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO (patient education only)

The Evidence Update search strategy replicated the strategy used by [NICE CG144](#) (for key words, index terms and combining concepts) as far as possible. Where this was not practical, then the search replicated the basic PICO (population, intervention, comparison, outcome) structure of the original searches. Where necessary, the strategy was adapted to take account of changes in search platforms and updated indexing language.

For [NICE CG144](#), separate searches for thromboembolism/VTE and pulmonary embolism were conducted. These two searches were run together as one search for this Evidence Update. The search term Thromboembolism/ was exploded to include more specific terms, and the term Postthrombotic Syndrome/ was added to the search strategy. No population search strategy was developed for the PsycInfo patient education search; instead, the Medline population search strategy was translated and relevant PsycInfo subject headings were added.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs and systematic reviews](#) and the following filters from [NICE CG144](#): diagnostic accuracy search terms (Appendix D, p.59); and patient education search terms (Appendix D, p.60).

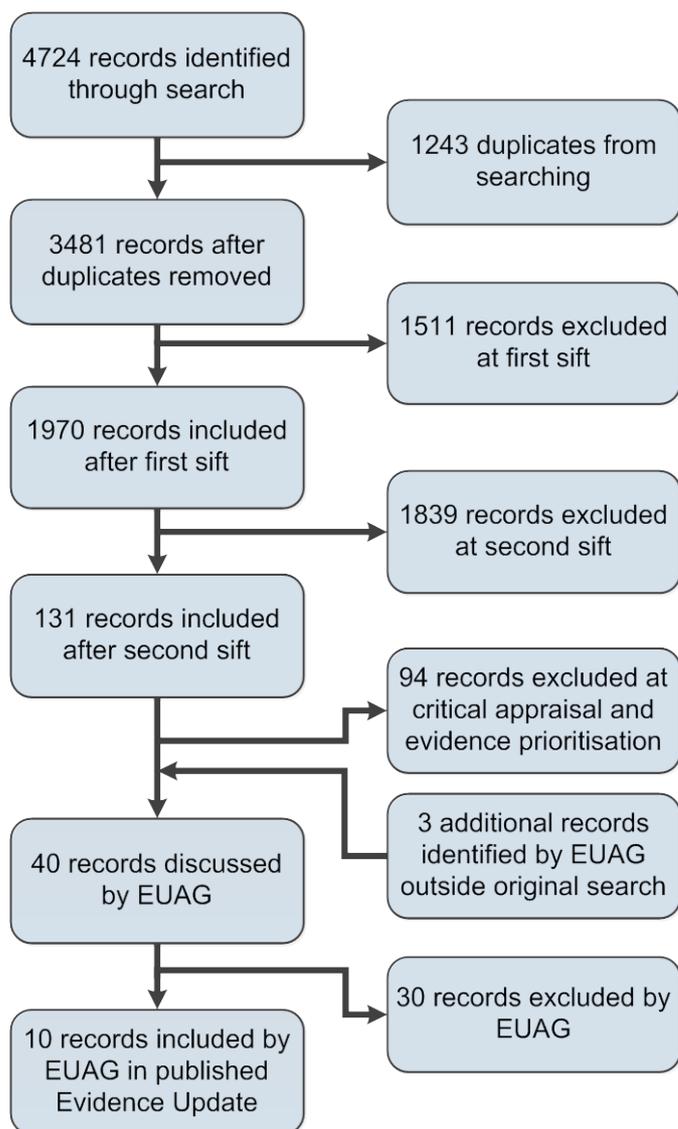
Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the [NICE Evidence Services](#) website for more information about [how NICE Evidence Updates are developed](#).

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Exp Thromboembolism/ or Thrombophlebitis/ or Venous Thrombosis/ or Postthrombotic Syndrome/	3	or/1-2
2	((venous or vein) adj (thrombosis or thrombus or thromboembolism or embol\$) or (dvt or vte) or thrombophlebitis or thrombophilia or ((post-thrombotic or postthrombotic) adj3 (syndrome or hypertension))).ti,ab.	4	Pulmonary Embolism/
		5	((pulmonary or lung) adj6 (embol\$ or post-thrombotic or postthrombotic)).ti,ab.
		6	or/4-5
		7	3 or 6

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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