Venous thromboembolism: reducing the risk
Evidence Update February 2012

A summary of selected new evidence relevant to NICE clinical guideline 92 ‘Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital’ (2010)
Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/venous-thromboembolism). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

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

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Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:


Over 2000 pieces of evidence were identified and assessed, of which 22 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group (EUAG), comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Other relevant NICE guidance

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


Quality standards


Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

¹ NICE-accredited guidance is denoted by the accreditation symbol
**Key messages**

The following table summarises what the EUAG decided were the key messages from the Evidence Update. It also indicates the EUAG’s opinion on whether new evidence identified by the Evidence Update reinforces or has the potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

<table>
<thead>
<tr>
<th>Key message</th>
<th>Effect on guidance</th>
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<tbody>
<tr>
<td>Assessing the risks of VTE and bleeding</td>
<td></td>
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<tr>
<td>• Evidence appears to confirm that thalidomide in patients with multiple myeloma (MM) may increase the risk of venous thromboembolism (VTE), and evidence now also suggests an elevated risk with lenalidomide in this population.</td>
<td>✓</td>
</tr>
<tr>
<td>• The most effective thromboprophylaxis in patients receiving thalidomide or lenalidomide for MM does not yet appear to have been established by current evidence and further research is needed.</td>
<td>✓</td>
</tr>
<tr>
<td>• Protein Z deficiency may be a potential thrombophilia to consider, however current evidence does not provide a robust basis for screening and further research is needed.</td>
<td>✓</td>
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<tr>
<td>• Increased risk of VTE associated with immobilisation appears to be confirmed by current evidence, however more research is needed to investigate factors contributing to this risk.</td>
<td>✓</td>
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|   | Potential change | No change |

<table>
<thead>
<tr>
<th>Using VTE prophylaxis</th>
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<tbody>
<tr>
<td>• Mechanical thromboprophylaxis may be of similar efficacy to heparin with a reduced risk of bleeding.</td>
<td>✓</td>
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<tr>
<td>• Graduated compression stockings (GCS) appear to be an effective means of VTE prevention in surgical patients with or without other methods of thromboprophylaxis. There is insufficient evidence to recommend GCS alone in high-risk surgical patients. The efficacy of thigh-length versus knee-length GCS does not yet appear to have been established.</td>
<td>✓</td>
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<tr>
<td>• Rosuvastatin may potentially prevent VTE however more research is needed.</td>
<td>✓</td>
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<table>
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<tr>
<th>Medical patients</th>
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<tr>
<td>• Heparin-based thromboprophylaxis appears to be more effective than controls (mechanical prophylaxis, placebo or no intervention) in high-risk general medical patients. Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) appear to be of equal efficacy.</td>
<td>✓</td>
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<tr>
<td>• The safe time to re-initiate anticoagulation (AC) following a stroke in patients already receiving AC at the time of the stroke, and appropriate level of AC upon resumption, does not appear to have been established by current evidence.</td>
<td>✓</td>
</tr>
<tr>
<td>• Using GCS to reduce deep vein thrombosis (DVT) after stroke does not appear to be supported by current evidence. More evidence may be needed to evaluate intermittent pneumatic compression after stroke.</td>
<td>✓</td>
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</tbody>
</table>
### Key message

<table>
<thead>
<tr>
<th>Effect on guidance</th>
<th>Medical patients (continued)</th>
<th>Surgical patients</th>
<th>Other patient groups</th>
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<tbody>
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<tr>
<td>No change</td>
<td>Routine thromboprophylaxis in patients with cancer and a central venous catheter (CVC) does not appear to be supported by current evidence, in line with current guidance that only patients with a CVC at increased risk of VTE should receive anticoagulation. Evidence does not appear to indicate a preferred type of anticoagulation in these patients.</td>
<td>Prolonged use of LMWH after major abdominal or pelvic surgery (particularly cancer surgery) appears to reduce VTE risk without an increased risk of bleeding.</td>
<td>Spinal trauma involving the spinal cord may place patients at greater risk of VTE, and patients may benefit from early postsurgical thromboprophylaxis.</td>
</tr>
<tr>
<td>✓</td>
<td>Limited evidence suggests that heparin may potentially be associated with reduced mortality in patients with cancer, however more evidence is needed.</td>
<td>Limited evidence suggests that patients undergoing surgery for spinal trauma or deformation may be at elevated risk of VTE, and those undergoing elective spinal surgery may be at lower risk. The appropriate timing of postoperative anticoagulation is currently unclear.</td>
<td>The most effective thromboprophylaxis strategy in pregnancy and up to 6 weeks postpartum has not been established by current evidence.</td>
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<tr>
<td>✓</td>
<td>Pharmacological thromboprophylaxis may be more effective than mechanical methods for VTE prevention after elective spine surgery, however the potential for increased bleeding events may need to be considered. More evidence is needed to determine the most effective thromboprophylaxis strategy in these patients.</td>
<td>Regional anaesthesia for total hip replacement (THR) or total knee replacement (TKR) appears to be associated with a lower risk of VTE than general anaesthesia, in line with current guidance.</td>
<td>Current evidence for the most effective thromboprophylaxis strategy in patients in critical care appears to be limited.</td>
</tr>
<tr>
<td>✓</td>
<td>Pharmacological thromboprophylaxis may be more effective than mechanical methods for VTE prevention after elective spine surgery, however the potential for increased bleeding events may need to be considered. More evidence is needed to determine the most effective thromboprophylaxis strategy in these patients.</td>
<td>There is a lack of robust evidence to indicate the efficacy of rivaroxaban versus dabigatran etexilate and LMWHs in VTE prevention following elective THR or TKR. More evidence is needed to compare directly the clinical effectiveness and cost effectiveness of these agents.</td>
<td></td>
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<tr>
<td>✓</td>
<td>A NICE technology appraisal has recently recommended apixaban as an option for the prevention of VTE following elective THR and TKR.</td>
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<td></td>
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<tr>
<td>✓</td>
<td>The most suitable method of thromboprophylaxis in pelvic and acetabular fractures is not clear from current evidence.</td>
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</tr>
<tr>
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1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

1.1 Assessing the risks of VTE and bleeding

Multiple myeloma treated with thalidomide or lenalidomide

A systematic review by Carrier et al. (2011) included 71 studies of over 5000 patients (15 randomised controlled trials [RCT] and 56 prospective cohort studies) examining the risk of venous thromboembolism (VTE), and the effect of thromboprophylaxis, in patients with multiple myeloma (MM) treated with either thalidomide or lenalidomide in combination with dexamethasone. From meta-analysis (individual studies included in the meta-analyses not identified), newly diagnosed patients treated with thalidomide plus dexamethasone had a VTE rate of 4.1 per 100 patient-cycles (95% confidence interval [CI] 2.8 to 5.9; n = 628), and in previously treated patients the VTE rate was 0.8 per 100 patient-months (95% CI 0.1 to 2.1; n = 321). In those treated with lenalidomide plus dexamethasone, VTE rate per 100 patient-cycles in newly diagnosed patients was 0.8 (95% CI 0.07 to 2.00; n = 278) and in previously treated patients was 0.7 per 100 patient-months (95% CI 0.4 to 0.9; n = 361).

Formal comparisons could not be made of the different thromboprophylaxis strategies, most of the included studies were not designed to look at VTE as an outcome, and there was some heterogeneity between studies used for the pooled estimates. The authors concluded that potential benefits of individual regimens could not be established. It should also be noted that this evidence was not specific to patients admitted to hospital, whereas NICE clinical guideline (CG) 92 covers only patients who are hospitalised.

Within its limitations, the evidence appears to reinforce the potential VTE risk factors of active cancer or cancer treatment already listed in NICE CG92, with the full guideline more specifically noting that thalidomide potentially increases deep vein thrombosis (DVT) in patients with MM. The new evidence now also suggests a potentially elevated VTE risk with lenalidomide, which may be a consideration for future reviews of NICE CG92. Further information is available from the Medicines and Healthcare products Regulatory Agency on the thrombosis and thromboembolism risks associated with thalidomide and lenalidomide.

Although the study highlighted a potentially high VTE risk in this group of patients, it was unable to establish the most effective approach to thromboprophylaxis. Large, well-conducted RCTs are needed to address this.

Key reference

Protein Z

Sofi et al. (2010) conducted a meta-analysis of 28 case-control studies (8996 patients) to investigate the relationship between protein Z (a vitamin-K dependent plasma glycoprotein) and vascular thrombotic disease. The study highlighted a potential association between low protein Z levels and increased thrombosis risk (odds ratio [OR] = 2.90; 95% CI 2.05 to 4.12; p < 0.00001; 28 studies). Subgroup analyses also revealed an association between low levels of protein Z and both arterial vascular disease (p = 0.0002; 18 studies of 5087 patients) and venous thromboembolic disease (p = 0.01; 8 studies of 2696 patients). The evidence
indicates that protein Z deficiency may be another potential thrombophilia to consider, however current evidence does not provide a robust basis for screening and further research including cost-effectiveness analysis of testing is needed. This evidence is currently unlikely to affect NICE CG92.

Key reference
Abstract: www.schattauer.de/de/magazine/uebersicht/zeitschriften-a-z/thrombosis-and-haemostasis/contents/archive/issue/1059/manuscript/12547.html

Immobilisation in medical in-patients
A meta-analysis by Pottier et al. (2009) of 43 studies (36 cohort studies and 7 case-control studies; 24,181 patients) investigated the effect of immobilisation on VTE risk in medical in-patients. The risk of VTE was approximately doubled by immobilisation. From the 36 cohort studies, the overall relative risk (RR) with immobilisation was 1.86 (95% CI 1.61 to 2.14; p < 0.001; data from 5420 immobilised patients out of 21,447) and from the seven case-control studies, the overall odds ratio (OR) was 2.52 (95% CI 1.70 to 3.74; p < 0.001; data from 406 immobilised patients out of 2734).

The authors acknowledged some limitations of the review, including the heterogeneous definition of immobilisation across the included studies, and the potential confounding effects of both age and the underlying condition that led to the immobility. Furthermore, the authors were unable to pool results according to underlying thromboprophylaxis as this information was not available in most of the studies.

Within the limitations of the review, immobilisation appears to be a marker of increased risk in medical in-patients. This is acknowledged in NICE CG92 by current recommendations that recognise immobility as a risk factor and encourage patient mobilisation as soon as possible. As the authors suggest, a prospective cohort study clearly defining immobility and listing all VTE risk factors and underlying diseases may provide more robust evidence.

Key reference

1.2 Reducing the risk of VTE
No new key evidence was found in this section.

1.3 Using VTE prophylaxis

Mechanical VTE prophylaxis
Eppsteiner et al. (2010) conducted a meta-analysis of 16 RCTs (3887 patients) to compare the effect of mechanical compression versus heparin on VTE and bleeding following surgery or trauma. Mechanical compression appeared to be of similar benefit to heparin in terms of both VTE (RR = 1.07; 95% CI 0.72 to 1.61; 16 RCTs) and pulmonary embolism (PE; RR = 1.03; 95% CI 0.48 to 2.22; 15 RCTs). However for postoperative bleeding, compression was associated with a significantly reduced risk versus heparin (risk ratio = 0.46; 95% CI 0.31 to 0.70; ten RCTs). A subgroup analysis suggested that low molecular weight heparin (LMWH) may reduce DVT risk versus compression (RR = 1.80; 95% CI 1.16 to 2.79).
There was considerable heterogeneity between the included studies (which comprised a number of different types of surgery and a wide variety of compression devices) therefore potential uncertainty remains over which patient groups should be given mechanical methods in preference to heparin, and which particular methods should be used. Only four of the studies looked at compression stockings, and this evidence may be insufficient to justify compression stockings alone in high risk patients who could have heparin. However, the analysis does appear to support mechanical methods for patients with high bleeding and VTE risk, such as those with major trauma. This is in line with NICE CG92, and underscores the importance of a combined assessment of VTE and bleeding risk for all hospital patients.

A Cochrane review by Sachdeva et al. (2010) investigated graduated compression stockings (GCS) for DVT prevention. Eight RCTs of 887 patients comprising 1279 ‘analytic units’ (AU; in most trials the analytic unit was patients, but in some trials a single limb was randomised) looked at GCS alone. Within these eight RCTs, 13% of AUs treated with GCS developed DVT versus 26% of controls (Peto odds ratio [POR] = 0.35; 95% CI 0.26 to 0.47; p < 0.00001). In ten RCTs (576 patients; 1248 AUs) looking at GCS combined with other prophylaxis, 4% of AUs treated with GCS plus another method developed DVT versus 16% of controls (OR = 0.25; 95% CI 0.17 to 0.36; p < 0.00001). Only one study of medical patients was included therefore evidence in this group of patients is potentially limited. The remaining studies were all of surgical patients with the exception of one study in obstetrics and gynaecology.

The evidence appears to offer support for GCS in surgical patients with or without other methods of thromboprophylaxis, in line with current recommendations in NICE CG92. The authors acknowledge that complications associated with GCS were not specifically addressed in any of the RCTs, which may require further investigation as there may be groups of patients for whom complications may outweigh benefits.

The review was not able to answer the question of the efficacy of thigh-length versus knee-length GCS. NICE CG92 currently recommends either thigh or knee length. The CLOTS-2 trial (CLOTS Trial Collaboration 2010) appeared to demonstrate superiority of thigh-length versus knee-length GCS, and a Cochrane review ‘Knee length versus thigh length graduated compression stockings for prevention of deep vein thrombosis’ (Sajid et al.) is currently in progress which may help to address this question.

Key references
Abstract: www.springerlink.com/content/nn43u7516xx12h68/


Supporting references
Full text: www.annals.org/content/early/2010/09/20/0003-4819-153-9-201011020-00280.full

Sajid M, Desai M, Morris RW et al. Knee length versus thigh length graduated compression stockings for prevention of deep vein thrombosis (Cochrane protocol)
Pharmacological VTE prophylaxis

A Cochrane review by Li et al. (2011) identified one RCT of 17,802 participants, which as one of its secondary endpoints assessed the effect of the statin rosuvastatin for preventing VTE. This study showed a significant reduction in the incidence of VTE (OR = 0.57; 95% CI 0.37 to 0.86). Statins are known to have many pleiotropic effects other than simple reduction of cholesterol and since statins are widely available and already prescribed for many other conditions, this finding is of potential importance. However, caution needs to be applied as the conclusions about VTE were based on secondary endpoints of a single study using one statin. It should also be noted that this evidence was not specific to patients admitted to hospital, whereas NICE CG92 covers only patients who are hospitalised.

This evidence is unlikely to affect current recommendations in NICE CG92, and further data are needed before statins could be considered for VTE prevention or as a substitute for other forms of VTE prophylaxis.

Key reference

1.4 Medical patients

General medical patients

Bump et al. (2009) performed a meta-analysis of 14 RCTs (24,515 patients) to examine the evidence for thromboprophylaxis in general medical patients. From the eight studies comparing either unfractionated heparin (UFH) or LMWH to controls (mechanical prophylaxis, placebo, or no intervention) it was found that heparin-based prophylaxis reduced DVT (RR = 0.55; 95% CI 0.36 to 0.83; seven RCTs) and PE (RR = 0.70; 95% CI 0.53 to 0.93; seven RCTs – although analysis of only the higher quality trials did not show significance), but had no significant effect on death (RR = 0.92; 95% CI 0.57 to 1.43; seven RCTs), and was not significantly associated with major bleeding (RR = 1.20; 95% CI 0.55 to 2.58; seven RCTs). From studies that directly compared UFH with LMWH, no significant differences were observed for DVT (RR = 0.90; 95% CI 0.57 to 1.43; six RCTs), PE (RR = 0.82; 95% CI 0.26 to 2.63; five RCTs) or thrombocytopenia (RR = 0.52; 95% CI 0.06 to 4.18; three RCTs).

The authors stated that all included trials were conducted in patients with elevated VTE risk (although this was not clearly defined) and felt that the evidence could not therefore confidently be extrapolated to all general medical patients. However, the evidence does appear to broadly concur with current recommendations in NICE CG92 that heparin-based prophylaxis may be appropriate in higher risk general medical patients. The data also suggested equal efficacy of both UFH and LMWH.

Key reference

Patients with stroke

In a meta-analysis of 63 publications (all case series or case reports; 492 patients) Hawryluk et al. (2010) looked at the management of re-initiating anticoagulation (AC) following haemorrhagic stroke in patients already on AC at the time of the stroke. Haemorrhagic complications were experienced by 7.7% of patients (most of which occurred within 72 hours of the index stroke, peaking at 0–24 hours) and thromboembolic complications were seen.
in 6.1% of patients (most of which occurred 72 hours after the index stroke, peaking at 73–120 hours).

Any conclusions are limited by potential reporting bias within the evidence as the meta-analysis is based entirely on case series and case reports, including 36 case reports of single patients. Uncertainties therefore remain as to the safe time to re-initiate AC following haemorrhagic stroke in patients who were already on AC at presentation, and the appropriate level of AC upon resumption. Further guidance on the management of AC following haemorrhagic stroke can be found in ‘Stroke’ (NICE CG68).

Naccarato et al. (2010) performed a Cochrane review of four RCTs (two trials of GCS including 2615 patients; and two trials of intermittent pneumatic compression [IPC] including 177 patients) to examine physical methods of DVT prevention in stroke. Use of GCS did not significantly reduce risk of DVT (OR = 0.88; 95% CI 0.72 to 1.08) or death (OR = 1.13; 95% CI 0.87 to 1.47). There was a non-significant trend towards lower DVT risk with IPC (OR = 0.45; 95% CI 0.19 to 1.10) but no effect on death (OR = 1.04; 95% CI 0.37 to 2.89).

The majority of the GCS data came from one trial of 2518 patients, which also showed that patients treated with GCS were at greater risk of skin problems such as breaks, ulcers, blisters and necrosis (OR = 3.47; 95% CI 2.22 to 5.41; p < 0.001). The IPC data were based on smaller numbers of patients.

The evidence does not appear to support GCS in reducing DVT after stroke, confirming the approach recommended in NICE CG92. The use of IPC after stroke also appears not to be supported, although evidence is more limited. NICE CG92 states that IPC (or a foot impulse device) may be considered in patients following a stroke; more evidence would be needed before routine IPC could be potentially recommended in patients with stroke. The ongoing CLOTS-3 trial may help to address this question.

**Key references**


**Supporting reference**

CLOTS-3 trial - A randomised trial to establish the effectiveness of intermittent pneumatic compression to prevent post stroke deep vein thrombosis. [www.controlled-trials.com/ISRCTN93529999](www.controlled-trials.com/ISRCTN93529999)

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**Patients with cancer**

**Central venous catheters**

A Cochrane review of 12 RCTs (3611 patients) by Akl et al. (2011) investigated anticoagulation for patients with cancer and central venous catheters (CVC). Seven RCTs assessed heparin, five assessed vitamin K antagonists (VKA) and two compared heparin with warfarin. Both heparin and VKA had no significant effect on death, symptomatic DVT, or major bleeding.

This evidence appears to support the recommendation in NICE CG92 that prophylaxis should not routinely be offered to patients with a CVC unless at increased risk of VTE. No preferred type of anticoagulation was evident from this review, and the currently recommended treatment in NICE CG92 (LMWH, or UFH in renal failure) for this patient group is unlikely to be affected.
**Parenteral anticoagulation**

*Akl et al. (2011)* performed a Cochrane review of nine RCTs (2857 patients) to examine parenteral anticoagulation with heparin in patients with any form of cancer who have no therapeutic or prophylactic indication for anticoagulation. Heparin had no significant effect on mortality at 12 months (RR = 0.93; 95% CI 0.85 to 1.02; eight RCTs of 2531 patients), however in post-hoc analysis it did appear to show an effect on mortality at 24 months (RR = 0.92; 95% CI 0.88 to 0.97; five RCTs of 1175 patients). A subgroup analysis of patients with small cell lung cancer (SCLC) from two RCTs showed an effect on mortality at 12 months versus other cancers (SCLC: RR = 0.86, 95% CI 0.75 to 0.98; other cancers: RR = 0.96; 95% CI 0.86 to 1.07; p = 0.03) although this effect was not apparent at 24 months. No significant effect on mortality was seen at 12 or 24 months for advanced cancers versus non-advanced cancers (p = 0.51 at 12 months). Heparin was associated with a reduced VTE risk (RR = 0.55; 95% CI 0.37 to 0.82; seven RCTs of 2264 patients) but had no effect on major or minor bleeding.

Apart from SCLC, there was no indication of which particular cancers respond best to this type of therapy, and firm conclusions are potentially limited by the heterogeneity of studies in terms of type and stage of cancer, and also treatment length which ranged from 5 weeks to 12 months. The evidence is unlikely to affect NICE CG92 but further research may be warranted.

**Key reference**

*Akl EA, Gunukula S, Barba M et al. (2011)* Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database of Systematic Reviews issue 1: CD006652


### 1.5 Surgical patients

**Gastrointestinal**

*Rasmussen et al. (2009)* conducted a Cochrane review of four RCTs (901 patients) to examine prolonged thromboprophylaxis with LMWH for at least one month after abdominal or pelvic surgery. Two RCTs involved abdominal or pelvic cancer surgery, and two involved major abdominal surgery (one of which also included non-cardiac thoracic surgery) for either malignant or benign diseases. Incidence of overall VTE was 14.3% (95% CI 11.2 to 17.8%) in controls versus 6.1% (95% CI 4.0 to 8.7%) with prolonged LMWH (a statistically significant difference: POR = 0.41; 95% CI 0.26 to 0.63; p < 0.0005). The incidence of symptomatic VTE was also significantly different: 1.7% (95% CI 0.8 to 3.4%) in controls versus 0.2% (95% CI 0.0 to 1.2%) with prolonged LMWH (POR = 0.22; 95% CI 0.06 to 0.80; p = 0.02). Bleeding incidence did not differ significantly between groups: 3.7% (95% CI 2.4 to 5.5%) in controls versus 4.1% (95% CI 2.7 to 6.0%) with LMWH (POR = 1.11; 95% CI 0.62 to 1.97; p = 0.73). There was no significant heterogeneity in the included trials.

VTE risk appeared to be significantly reduced with prolonged LMWH use, without an increased risk of bleeding. As most patients were undergoing cancer surgery, this evidence appears to support the current recommendation in NICE CG92 that pharmacological VTE prophylaxis should be extended to 28 days postoperatively for patients undergoing major cancer surgery of the abdomen or pelvis. Introducing this into practice may be organisationally challenging for some units as it requires coordination with primary care but
the potential benefits of prolonged therapy, which appear to be confirmed by this review, may warrant consideration of these arrangements.

**Key reference**

**Neurological (cranial or spinal)**

A meta-analysis of 29 studies (patient numbers not stated) by Cheng et al. (2010) investigated anticoagulation risk in spinal surgery. The included studies were grouped according to the spine condition treated: degenerative conditions; deformity; fracture or trauma; infection; and multiple spine conditions. Among 15 cohort studies (ten prospective, four retrospective, one both pro- and retrospective) investigating incidence of thromboembolic events without pharmacological prophylaxis, a higher risk of DVT was observed after surgery for non-spinal cord injury trauma (6%; range 0–19%; two studies) and deformity (5.3%; range 2–14%; three studies), with a lower risk seen following surgery for degenerative conditions (2.3%; range 0–9%; seven studies). The risk of DVT in elective surgery without pharmacological prophylaxis was 1–2%. From six cohort studies (five prospective, one retrospective) evaluating adverse events with anticoagulation, the risk of major bleeding ranged from 0–4.3% across a variety of anticoagulants. Conclusions about the safe timing of anticoagulation in the perioperative period could not be made as no studies were identified that attempted to define this.

It should be noted that some of these conclusions are drawn from a small number of studies (only two studies looked at thromboembolic risk with spinal trauma surgery and three with deformity, for example), and that the search period dated back to 1979. Including older studies meant that DVT was in some cases confirmed by a fibrinogen uptake test (now no longer used), and potential relevance of the evidence may be diminished due to changes in surgical procedures and accompanying risk in the last 30 years. It was also not clear from the review whether there may have been selection bias within individual studies, particularly related to bleeding risk of patients. Finally, the authors deemed the strength of the evidence to be low or very low across all spinal conditions. Interpretation of the risks of DVT associated with the different types of surgery, particularly the seemingly low risk of elective surgery without pharmacological prophylaxis, may need to consider this context.

Within the potential limitations of the review, the evidence suggests that patients undergoing surgery for spinal trauma and deformity may be at elevated risk of thromboembolism and pharmacological prophylaxis may be appropriate, whereas elective surgery appeared to be associated with a lower risk. This appears to agree with current recommendations in NICE CG92 that patients should be assessed on an individual basis to weigh up risk of bleeding versus VTE, particularly for trauma patients who may tend to exhibit a greater degree of heterogeneity at presentation. Evidence for the most appropriate time to begin postoperative anticoagulation is still unclear.

Sansone et al. (2010) performed a meta-analysis of 14 observational studies (4383 patients) to examine the risk of thromboembolism and the efficacy of prophylaxis following elective spinal surgery. Pooled analysis of all patients (receiving either no prophylaxis, or mechanical or pharmacological prophylaxis) indicated a prevalence of DVT of 1.09% (95% CI 0.54 to 1.64%). Pharmacological prophylaxis appeared to reduce DVT prevalence versus both mechanical (p = 0.047) and no prophylaxis (p < 0.01). Among three studies of 2071 patients receiving pharmacological prophylaxis (aspirin, LMWH or warfarin), there were eight reports of an epidural haematoma requiring surgery (all in patients receiving postoperative LMWH), with three patients left with permanent neurological deficit.
Although this evidence appears to show benefit of pharmacological over mechanical prophylaxis, the consideration of potential risks such as haematoma means that recommendations in NICE CG92 (commencing mechanical prophylaxis followed by addition of pharmacological prophylaxis in patients at low risk of major bleeding) are unlikely to be affected. More evidence is still needed to determine the most effective protocols for thromboprophylaxis in patients undergoing spinal surgery.

Key references


Orthopaedic surgery
Total hip and knee replacement – regional anaesthesia
Hu et al. (2009) conducted a meta-analysis of 21 RCTs and found that compared with general anaesthesia, local anaesthesia for total knee replacement (TKR) or total hip replacement (THR) was associated with a reduced incidence of both DVT (OR = 0.45; 95% CI 0.24 to 0.84; ten RCTs of 910 patients) and PE (OR = 0.46; 95% CI 0.29 to 0.80; eight RCTs of 747 patients). The search encompassed a wide date range and some included studies were performed in the 1980s when differences in surgical techniques may limit relevance to modern practice. However, the data appear to be in agreement with current recommendations in NICE CG92 that regional anaesthesia should be considered in order to lower potential risk of VTE.

Key reference
Abstract: www.web.jbjs.org.uk/cgi/content/abstract/91-B/7/935

Total hip and knee replacement – dabigatran etexilate and rivaroxaban
NICE technology appraisals (TA) have recommended both dabigatran etexilate (NICE TA157) and rivaroxaban (NICE TA170) as options for the prevention of VTE following elective THR and TKR.

Melillo et al. (2010) performed a systematic review of four RCTs (12,383 patients) to examine thromboprophylaxis with rivaroxaban versus the LMWH enoxaparin in patients undergoing THR or TKR. No meta-analyses were conducted, but in all RCTs rivaroxaban appeared to be significantly more effective than LMWH for a composite endpoint of DVT, non-fatal PE and all-cause mortality (level of significance ranged from p < 0.0001 to p = 0.0118 for this comparison in each of the four RCTs). No significant differences in major bleeding (between start of treatment and 2 days after the last dose) between the two treatments were seen in the individual trials, although the authors concede that all bleeding events may not have been recorded due to the way bleeding was defined. The data appear to support the use of rivaroxaban, however the authors state that the doses of enoxaparin used may not have been optimal in all studies, and the very specific research question meant only four studies were included in the review. More studies are still needed to define the optimal balance between VTE prevention and bleeding risk, and which pharmacological prophylaxis is optimal.
A further systematic review of nine RCTs (19,218 patients) by Loke and Kwok (2011) investigated thromboprophylaxis with rivaroxaban versus dabigatran etexilate in elective orthopaedic surgery. When compared with enoxaparin, dabigatran etexilate did not significantly reduce VTE risk (RR = 1.12; 95% CI 0.97 to 1.29; p = 0.12; three RCTs of 8209 patients) whereas rivaroxaban did appear to reduce the risk of VTE (RR = 0.56; 95% CI 0.43 to 0.73; p < 0.0001; six RCTs of 11,009 patients). In an indirect comparison (with enoxaparin as the common control), rivaroxaban appeared to be superior to dabigatran etexilate in preventing VTE (RR = 0.50; 95% CI 0.37 to 0.68) but with a slight trend to a greater haemorrhage risk (RR = 1.14; 95% CI 0.80 to 1.64). All studies included in the review looked at elective orthopaedic surgery only (TKR or THR) and not trauma.

No trials directly compared rivaroxaban and dabigatran etexilate, and the authors stated that all data came from studies sponsored by pharmaceutical companies as there are currently no independently conducted trials. Any conclusions about their comparative efficacy for prevention of VTE following elective orthopaedic surgery are therefore limited.

In general, these agents may be more convenient than LMWH, especially for extended use after hospital discharge, and have the advantage of oral administration with no requirement for monitoring. However, they are currently more expensive. The absence of large trials directly comparing rivaroxaban, dabigatran etexilate and LMWHs means evidence to indicate any preference for these therapies remains limited. Their comparative clinical effectiveness and cost effectiveness will need to be investigated in future studies. NICE CG92 and NICE TAs of dabigatran etexilate (NICE TA157) and rivaroxaban (NICE TA170) do not discuss any preference for either of these treatments.

Further NICE TAs are currently in progress for dabigatran etexilate for the treatment of acute VTE events (issue date to be confirmed), rivaroxaban for prevention of VTE in people hospitalised for acute medical conditions (issue date to be confirmed) and rivaroxaban for treatment and secondary prevention of VTE (expected July 2012).

Key references
Abstract: www.theannals.com/content/44/6/1061.short

**Total hip and knee replacement – apixaban**

NICE TA245 has recently recommended apixaban as an option for the prevention of VTE following elective THR and TKR, which should be referred to as the latest guidance.

A further NICE TA is currently in progress for apixaban for the prevention of VTE in acute medical illness (issue date to be confirmed).

**Pelvic and acetabular fractures**

In a systematic review of 11 studies (1760 patients), Slobogean et al. (2009) examined thromboprophylaxis for pelvic and acetabular fractures. The included studies were mostly observational with minimal control data, and there was significant heterogeneity between studies (five different types of intervention were used across the 11 studies). The nature of the evidence base prevented a meta-analysis, and the authors stated that there was limited evidence to guide decisions around prophylaxis in these patients, and were unable to draw
any firm conclusions. Further research is therefore needed and current evidence is unlikely to affect NICE CG92.

**Key reference**

**Upper extremity DVT**

**Smith et al. (2011)** performed a systematic review of 20 publications to assess cases of upper extremity DVT following trauma or elective orthopaedic surgery to determine epidemiology and outcome. The included literature described 38 cases of upper extremity DVT and 19 cases of PE. The most common index injury leading to DVT and PE was to the glenohumeral joint and humerus (accounting for 27 cases), and 17 of the PE cases followed shoulder surgery. The authors were unable to perform a meta-analysis due to the heterogeneity of the reports and could therefore only provide a narrative review of the evidence. The study highlights a number of cases of upper extremity DVT and PE, and suggests that it may need to be considered, particularly following orthopaedic surgery and trauma in the upper extremities. The evidence is unlikely to affect current recommendations in NICE CG92, with other risk factors already noted by the guidance, such as length of surgery, continuing to be the main focus.

**Key reference**
Abstract: [www.springerlink.com/content/f474214tt22q3514/](www.springerlink.com/content/f474214tt22q3514/)

### 1.6 Other patient groups

**Spinal injury**

In a meta-analysis of 21 studies (no further details available), **Ploumis et al. (2009)** investigated thromboprophylaxis in acute spinal injury. Prevalence of DVT was found to be lower in patients without spinal cord injury versus those with spinal cord injury (OR = 6.0; 95% CI 2.9 to 12.7; p < 0.00001; five studies). Starting thromboprophylaxis within 2 weeks of injury appeared to result in less DVT compared with delayed prophylaxis (OR = 0.2; 95% CI 0.1 to 0.4; p < 0.00001; two studies). When compared with UFH, LMWH appeared to reduce significantly the incidence of both DVT and bleeding (OR = 2.6; 95% CI 1.2 to 5.6; p < 0.01 and OR = 7.5; 95% CI 1.0 to 58.4; p < 0.05 respectively; five studies).

This evidence suggests that patients with spinal trauma involving the spinal cord may be at increased risk of VTE, and that commencing thromboprophylaxis as early as possible in the context of bleeding risks may lead to better clinical outcomes. The data may also suggest a potentially greater efficacy of LMWH versus UFH in this patient group.

The meta-analyses are based on limited numbers of studies and recommendations in NICE CG92 are unlikely to be affected.

**Key reference**
Pregnancy and up to 6 weeks post partum

Tooher et al. (2010) conducted a Cochrane review of 13 RCTs (1774 women who were pregnant or had delivered in the previous 6 weeks and were at increased risk of VTE) to investigate prophylaxis of VTE in pregnancy and the early postnatal period. Four of the included trials looked at antenatal thromboprophylaxis (LMWH versus UFH in two trials; heparin versus no treatment in two trials), eight examined postnatal prophylaxis after Caesarean section (hydroxyethyl starch versus UFH in one trial; heparin versus placebo in four trials; UFH versus LMWH in three trials), and one looked at postnatal prophylaxis (UFH versus no treatment). The review looked at four primary outcomes: maternal death; symptomatic thromboembolic events; symptomatic PE; and symptomatic DVT. No statistically significant differences were detected between treatments for any of these primary outcomes. For the few significant differences that were detected for other outcomes, the authors stated that due to the small number of studies included, the number of different comparisons and the generally small size of trials, the data were potentially insufficient to make firm conclusions. This evidence is unlikely to affect NICE CG92 and large RCTs to examine interventions for VTE in this patient group are needed.

Key reference

Critical care

Ribic et al. (2009) performed a systematic review of nine studies (eight prospective cohort studies and one RCT; 629 patients) to examine thromboprophylaxis with LMWH in medical-surgical critically ill patients. The heterogeneity of the studies precluded any meta-analysis, and the authors were only able to state the range of incidence rates observed across the studies for VTE (5.1–15.5% with LMWH; 28.2% with placebo in the RCT), bleeding complications (7.2–23.1% with LMWH; 15.9% with placebo in the RCT) and mortality (1.4–7.4% with LMWH; 7.4% with placebo in the RCT).

Some of the methodology and search strategy reporting was unclear (for example the abstract stated that MEDLINE and EMBASE were searched, however the full article only mentioned MEDLINE). There appears to be insufficient evidence to make firm conclusions and more studies in this group of patients are required. In critically ill patients, it is important to strike a balance between VTE reduction and complications such as bleeding, particularly as these patients may tend to exhibit a high degree of heterogeneity. This evidence is unlikely to affect NICE CG92, which currently states that each patient should be assessed initially for VTE and bleeding risk, and pharmacological prophylaxis used when appropriate in patients with a low bleeding risk. In other patients, mechanical methods of VTE prophylaxis may be preferred.

Key reference
Abstract: www.sciencedirect.com/science/article/pii/S08839444108002414

1.7 Patient information and planning for discharge

No new key evidence was found for this section.
2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Assessing the risks of VTE and bleeding

- Thromboprophylaxis strategies for multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide
- Is protein Z influenced by the acute phase response?
- Optimal cut-off value for protein Z in the estimation of thrombotic risk
- The best method for protein Z measurement

Using VTE prophylaxis

- Low molecular weight heparin (LMWH) versus compression therapy for deep vein thrombosis (DVT) prophylaxis
- Unfractionated heparin versus compression therapy for deep vein thrombosis (DVT) prophylaxis
- Elastic compression stockings for prevention of deep vein thrombosis
- Statins for primary prevention of venous thromboembolism

Medical patients

- Predictors for the timing and intensity of anticoagulation therapy following central nervous system haemorrhage in patients with high thromboembolic risk
- Physical methods for preventing deep vein thrombosis in stroke
- Anticoagulation for patients with cancer and central venous catheters

Surgical patients

- Safe perioperative window for anticoagulation after spine surgery
• Risk stratification for venous thromboembolic disease following elective spine surgery
  www.library.nhs.uk/duets/viewResource.aspx?resid=411731

• Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Other patient groups

• Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

• Low-molecular-weight heparin (LMWH) for thromboprophylaxis in critically ill medical-surgical patients

Further evidence uncertainties for VTE can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment which 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:


### Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 10 December 2008 (the end of the search period of NICE clinical guideline 92) to 08 August 2011:

- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. Several search strategies were used in the original guideline to answer specific clinical questions (see Appendix C of the full guideline). This Evidence Update aims to identify the most recent evidence for any intervention for VTE, therefore only the population/condition search strategy from the original guideline was included (see ‘VTE terms’, Appendix C, p.37 of the full guideline).

The Evidence Update includes reliable systematic reviews only due to a high volume of evidence (NHS Evidence defines reliable systematic reviews as those published by a journal which conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] standards [www.prisma-statement.org/endorsers.htm](http://www.prisma-statement.org/endorsers.htm). If not published by one of these journals, a systematic review is deemed reliable if the abstract reports the inclusion/exclusion criteria, confirms two or more sources have been searched, and incorporates a synthesis of included studies). Scottish Intercollegiate Guidelines Network filters were used to retrieve systematic reviews ([www.sign.ac.uk/methodology/filters.html](http://www.sign.ac.uk/methodology/filters.html)).

One other study (Li et al. 2011) was also identified outside of the literature search.

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

### Table 1 MEDLINE search strategy (adapted for individual databases)

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<td>2</td>
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Figure 1 Flow chart of the evidence selection process

EUAG – Evidence Update Advisory group
Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group
The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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