NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Clinical guideline

CG144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

Publication date

June 2012

2-year surveillance report for GE

August 2014

Key findings

	Potential impact on guidance	
	Yes	**No**
Evidence from Evidence Update	✓	
Evidence identified from focused literature search	✓	
Feedback from the GDG Chair	✓	
Anti-discrimination and equalities considerations		✓
Feedback from Triage Panel meeting	✓	

No update	**CGUT update**	Standard update	Transfer to static list	Change review cycle
	✓			

Surveillance recommendation

GE is asked to consider the proposal to update the following clinical questions in the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team (CGUT):

- What is the effectiveness of stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?
- What is the effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?

GE is asked to note that this 'yes to update' proposal will not be consulted on.

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2-year surveillance review of CG144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

Background information

Guideline issue date: June 2012

2-year review: 2014

NCC: National Clinical Guideline Centre

Triage Panel recommendation

1. Through the 2-year Evidence Update of CG144 new evidence which may potentially impact guideline recommendations was identified in the following three clinical areas which were considered in turn by the Triage Panel:

    - *What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT and/or PE?*

      Several new oral anticoagulants have been approved for the management of VTE since the publication of CG144 and have been or are currently being reviewed as part of the NICE Technology Appraisal (TA) programme. As these recommendations are not incorporated within CG144, the emergence of these drugs may therefore have a potential impact on CG144. However, the Triage Panel felt that given the number of TAs currently in development that are relevant to this guideline and other new evidence likely to be available at the next review point (for example, the EINSTEIN CHOICE study data) it would be pertinent to wait until then before deciding on an update in this area.

      Decision - NICE to defer update of this clinical question.

- *What is the effectiveness of stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?*

  One RCT of elastic compression stockings (ECS) to prevent post-thrombotic syndrome in patients with DVT was included in the Evidence Update (SOX trial - Kahn 2014). The trial suggests that the routine long-term use of graduated ECS does not appear to prevent post-thrombotic syndrome (PTS) in patients with a first proximal DVT. Whilst the panel had some concerns about the SOX trial, it was generally agreed that the current statement in the guideline recommending stockings for *all* patients for two years is no longer supported by the evidence. Current practice has mostly moved as a result of new evidence and stockings are no longer given for the prevention of PTS, although there may still be a place for use of stockings in symptom relief.

  Decision - NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team.

- *Aspirin for prevention of VTE recurrence*

  Two RCTs (WARFASA study - Becattini 2012 and ASPIRE study - Brighton 2012) comparing low-dose aspirin with placebo for prevention of VTE recurrence in patients who had completed initial anticoagulant therapy after a first unprovoked VTE were identified in the EU. 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 recurrence of VTE and vascular events without increasing the risk of bleeding. However, the panel considered that as the EINSTEIN CHOICE study was focussed on the issue of secondary prevention of VTE, it would be appropriate to await the results of this ongoing, very large, multicentre trial.

  Decision - NICE to defer update of this clinical question.

2. In addition to the three areas above, it was also noted at the meeting that the PEITHO trial has now reported since the Evidence Update. The PEITHO trial addresses the issue of systemic pharmacological thrombolysis in pulmonary embolism with haemodynamic stability but right ventricular dysfunction (RVD) for whom the guideline does not make any recommendations. The topic experts felt that guidance on the use of systemic pharmacological thrombolysis in pulmonary embolism with haemodynamic stability but right ventricular dysfunction is needed; they felt that this area was a high priority for update and that deferral to the next surveillance point would be inappropriate.
3. A focussed literature search for systematic reviews and RCTs on the effectiveness of systemic pharmacological thrombolytic therapy in pulmonary embolism with haemodynamic stability but right ventricular dysfunction, was carried out.Searches were conducted for the period 01 August 2011 (the end of the search period for the guideline) to 30 June 2014 and relevant abstracts were assessed. Clinical feedback on the focussed search and its findings was obtained from the GDG Chair.
4. Through an assessment of abstracts from the focussed search, seven studies relating to systemic pharmacological thrombolysis in pulmonary embolism with haemodynamic stability but right ventricular dysfunction were identified:

Clinical area : Systemic pharmacological thrombolytic therapy in patients with moderate risk PE		
What is the effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?		
Evidence summary	**GDG chair/clinical perspective**	**Impact**
Four RCTs[1-4] and 3 meta-analyses[5-7] were identified. Overall, the identified studies indicate that treatment of patients with pulmonary embolism who are haemodynamically stable but who have evidence of right ventricular dysfunction, with systemic pharmacological thrombolytic drugs, is associated with increased probability of a favourable outcome.	Feedback indicated that new evidence has emerged relating to the use of systemic pharmacological thrombolytic drugs in pulmonary embolism with haemodynamic stability but right ventricular dysfunction, which may impact on the guideline.	The identified new evidence indicates that there is a group of patients with pulmonary embolism and haemodynamic stability but right ventricular dysfunction, who may benefit from systemic pharmacological thrombolysis. This differs from the the guideline which categorised patients with PE into two groups – haemodynamically unstable and haemodynamically stable. The new trials are in a subgroup of haemodynamically stable patients – those with evidence of right heart strain or myocardial injury. No recommendations on this group of patients are included in the guideline although the GDG provided a research recommendation on the clinical and cost effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction. There is now a body of evidence which indicates that there is a group of patients with pulmonary embolism and haemodynamic stability but right ventricular dysfunction, who may benefit from systemic pharmacological thrombolysis.

2-year Evidence Update

5. The 2-year Evidence Update on CG144: VTE diseases (published April 2014) was used as the primary source of evidence for the surveillance decision. The search dates of the Evidence Update were 01 August 2011 to 11 November 2013.

6. New evidence that was deemed to have potential impact on current recommendations was identified for three sections of the guideline, as mentioned previously.

Ongoing trials

7. Two relevant ongoing trials were identified. The IDEAL study is a Dutch multicentre RCT comparing individually tailored duration of elastic compression stocking therapy with a standard 2-year duration of elastic compression; estimated study completion date is July 2016. However, it was felt that updating this area should not wait until this trial has published given the new evidence identified.
8. The other is the EINSTEIN CHOICE study, a phase III clinical trial by Bayer HealthCare, Germany, aimed at evaluating two doses of once-daily rivaroxaban against aspirin for the secondary prevention of symptomatic VTE; completion date is not known.

Anti-discrimination and equalities considerations

9. None identified.

Implications for other NICE programmes

10. This guideline relates to a published quality standard for diagnosis and management of venous thromboembolic diseases (QS29, published March 2013)
11. An update of the clinical question on the effectiveness of stockings to prevent post thrombotic syndrome may need consideration of its impact on Quality statement 4: Mechanical interventions which states that “people with proximal deep vein thrombosis are offered below-knee graduated compression stockings within 3 weeks of diagnosis”.

Conclusion

12. Through the Evidence Update of CG144 new evidence which may potentially impact guideline recommendations was identified for three areas of the guideline and discussed at the Triage Panel meeting.
13. Only one of these three areas considered by the triage panel was assessed as requiring an update at this time. However, an additional area was identified and a focussed search revealed that this area of the guideline also needs to be updated.

Surveillance recommendation

14. GE is asked to consider the proposal to update the following clinical questions in the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team:
    - What is the effectiveness of stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?
    - What is the effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?
15. GE is asked to note that this 'yes to update' proposal will not be consulted on.

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Centre for Clinical Practice
August 2014

Appendix 1 - Decision matrix

Surveillance and identification of triggers for updating CG144. The table below provides summaries of the evidence/intelligence that were identified for the triage panel meeting on 13 June 2014.

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
144-01 In people with suspected DVT, what is the effectiveness of clinical scores in ruling out deep vein thrombosis?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-02 In people with suspected DVT, what is the effectiveness of D-dimer in ruling out deep vein thrombosis?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-03 In people with suspected DVT, what is the effectiveness of ultrasound in detecting deep vein thrombosis?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-04 In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-05 In people with suspected PE, what is the effectiveness of CT scan in ruling out PE?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-06 In people with suspected PE, what is the effectiveness of ventilation perfusion scans in ruling out PE?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-07 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT and/or PE?			
Since the publication of CG144, two NICE technology appraisals, one each on the use of rivaroxaban for the treatment of DVT and PE, respectively, have been published and a number of oral anticoagulants are currently being reviewed as part of the NICE technology appraisal programme.	Not applicable	Not applicable	Several new oral anticoagulants have been approved for the management of VTE since the publication of CG144 and NICE has issued or is considering technology appraisals on these new

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
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			oral anticoagulants. These recommendations are not incorporated within 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.
144-08 What is the optimal treatment duration for pharmacological interventions?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-9 What is the effectiveness of thrombolytic therapy and mechanical thrombectomy to manage acute DVT?			
Two studies comparing thrombolytic therapy plus standard anticoagulation therapy with standard anticoagulation therapy alone in patients with DVT were found. The Evidence Update concluded that 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.	Not applicable	Not applicable	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.

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
144-10 What is the effectiveness of open surgical thrombectomy, combination of mechanical and pharmacological thrombolysis, pharmacological thrombolytic therapy and heparin to manage acute PE?			
One open-label, randomised controlled trial tested the efficacy and safety of low-dose systemic pharmacological thrombolysis for reduction of pulmonary artery pressure in patients with PE. The Evidence Update concluded that 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.	Not applicable	Not applicable	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).
144-11 What is the effectiveness of vena caval filters to manage venous thromboembolic diseases in people that are unable to have pharmacological treatment?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
144-12 What is the effectiveness of stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?			
One RCT of elastic compression stockings to prevent post-thrombotic syndrome in patients with DVT was found. The Evidence Update concluded that routine long-term use of graduated elastic compression stockings does not appear to prevent post-thrombotic syndrome in patients with a first proximal DVT.	Not applicable	Not applicable	The RCT 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 CG144.
144-13 Does provision of information and support about management of VTE improve patient outcomes?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-14 What is the effectiveness of self-monitoring compared to hospital/GP testing for long-term pharmacological treatments?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-15 Does screening for cancer in patients with spontaneous venous thromboembolism (DVT or PE) improve patient outcomes (morbidity and mortality)?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
144-16 What is the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
144-17 Does thrombophilia testing improve the outcomes of 1st degree relatives of people who had thromboembolic disease and thrombophilia?			
No new key evidence was found for this section.	Not applicable	Not applicable	Not applicable
Areas not currently covered by the guideline – Aspirin for prevention of VTE recurrence			
Two RCTs compared low-dose aspirin with placebo for prevention of VTE recurrence in patients who had completed initial anticoagulant therapy after a first unprovoked VTE. The Evidence Update concluded 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.	Not applicable	Not applicable	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 - people who have experienced VTE are at risk of it recurring and CG144 recommends treatment with an anticoagulant drug for 3 months, or longer in some circumstances - aspirin may be a potential alternative option in patients who have had an unprovoked VTE and are unable or unwilling to go

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
			on long-term anticoagulation therapy. The evidence may therefore have a potential impact on CG144.
Areas not currently covered by the guideline – Management of calf DVT			
Two systematic reviews considered the management of patients with calf DVT. The Evidence Update concluded that 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.	Not applicable	Not applicable	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.
Areas not currently covered by the guideline - Risk stratification and outpatient treatment of patients with PE			
A systematic review and meta-analysis looked at the safety of outpatient treatment compared with inpatient treatment in low-risk patients with acute PE, while another systematic	Not applicable	Not applicable	The evidence suggests that selected patients with PE who are at low risk of adverse events could safely receive

Main findings and conclusion of the 2-year Evidence Update (April 2014)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
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, was found. The Evidence Update concluded 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 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.			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 CG144, this evidence is unlikely to have an impact on the guidance.

References

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