Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (2012) NICE guideline CG144

Appendix A: Summary of new evidence from surveillance

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Diagnosis – Diagnostic investigations for deep vein thrombosis (DVT)			
144 – 01 In people with suspected DVT, what is the effectiveness of clinical probability scores in ruling out DVT? (1.1.1 – 1.1.6)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
144 – 02 In people with suspected DVT, what is the effectiveness of D-dimer in ruling out DVT? (1.1.1 – 1.1.6)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	Topic experts highlighted the diagnosis of venous thromboembolism (VTE) using D-dimer tests with reference to the use of age adjusted D-dimers to reduce the need for further imaging tests and prevent the continuation of treatment.	No new evidence was identified that would affect recommendations. Intelligence from topic experts highlighted studies on the effectiveness of D-dimer tests to rule out DVT, however, these studies had been considered during the 2-year Evidence Update and excluded at the time.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			No further evidence has been identified from the surveillance review to impact on recommendations.
144 – 03 In people with suspected DVT, what is the effectiveness of ultrasound in ruling out DVT? (1.1.1 – 1.1.6)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Diagnosis – Diagnostic investigations for pulmonary embolism (PE)			
144 – 04 In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay? (1.1.7 – 1.1.13)			
Surveillance decision This review question should be updated to include evidence on adjusting the D-dimer threshold.			
Evidence Update (2014) No relevant evidence identified.	A post-hoc analysis[1] of 2213 patients with suspected PE found that doubling the D-dimer threshold to <1.0 μ(-1) reduced the need for computed tomography pulmonary angiography (CTPA) but increased the incidence of VTE at 3 months. A prospective diagnostic study[2] enrolled 357 consecutive patients with suspected PE and with a Wells score >4 or a positive D-dimer result. Multiorgan (lung, heart and vein) ultrasonography was	Topic experts highlighted the diagnosis of VTE using ultrasonography, VQ SPECT, computed tomography and D-dimer tests with reference to the use of age adjusted D-dimers to reduce the need for further imaging tests and prevent the continuation of treatment. Topic experts highlighted the increase in false positive rates of D-dimer with age when using unadjusted thresholds. An age adjusted D-dimer may increase the proportion of patients, primarily over the	New evidence identified that may change current recommendations. One post-hoc analysis[1] found a reduced need for CTPA following an increase in the D-dimer threshold. However, this also increased the incidence of VTE at 3 months. A prospective diagnostic study found the addition of multiorgan ultrasonography to Wells score or D-dimer results as a diagnostic strategy to reduce the need for

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	performed before the standard multidetector CT pulmonary angiography (MCTPA) diagnostic test. Results for multiorgan ultrasonography found sensitivity of 90% and specificity of 86.2%.	age of 50, in whom further imaging can be safely withheld. In turn, this has the potential to reduce impact on resources and reduce the risks of imaging with less radiation exposure and complications from contrast injections. However, some topic experts believe this topic to be relatively low priority or that use of age adjusted thresholds would not make much clinical impact. A further consideration of age adjusted D-dimer concerns the use of different D-dimer assays with varying cut-off thresholds across services and laboratories. Topic experts also highlighted the following studies: A prospective diagnostic management outcome study[3] of 3346 patients aged 50 years or older with suspected PE found a significant increase in the number of patients in whom PE could be ruled out without further imaging tests following adjustment of the D-dimer threshold according to the patient's age. A systematic review and meta-analysis[4] of 12 studies combining 14844 patients assessed the accuracy of the pulmonary embolism rule-out criteria (PERC). The	further imaging with MCTPA for PE. Intelligence from topic experts highlighted the effectiveness and reduced risks of adjusting the D-dimer threshold according to the patient's age in safely ruling out the need for further diagnostic imaging tests. Topic experts also highlighted the accuracy of the PERC diagnostic test to rule out PE. Consideration of the use of different D-dimer assays with varying cut-off thresholds across services and laboratories should be made. New evidence suggests the current recommendation (1.1.10) to offer a D-dimer test may need to be updated to include consideration of the patient's age when setting the threshold to rule out further imaging tests for PE. However, some consideration should be given to the wording of any such new recommendation to suggest that each service validate its own D-dimer assay and this could be influenced by the patient's age.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
		diagnostic performance of PERC indicated high sensitivity and low negative likelihood ratio in ruling out PE. A meta-analysis[5] of 6 studies combining 7268 patients found age-adjusted D-dimer thresholds increased the number of patients in whom PE could be ruled out without further imaging tests compared to a fixed threshold.	
144 – 05 In people with suspected PE, what is the effectiveness of ventilation perfusion scans in ruling out PE? (1.1.7 – 1.1.13)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
144 – 06 In people with suspected PE, what it is the effectiveness of CT scans in ruling out PE? (1.1.7 – 1.1.13)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	The following study was highlighted by topic experts: A cross-sectional chart review[6] of 2216 patients with suspected VTE undergoing computed tomography pulmonary angiography (CTPA) found sub-segmental pulmonary embolism (SSPE)	New evidence is unlikely to impact on guideline recommendations. Intelligence from topic experts highlights the prevalence of sub-segmental PE amongst patients diagnosed using CTPA. However, currently there is a lack of new

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
		accounted for 15% of the 550 patients identified with PE. Anticoagulation treatment was found in 52.4% of patients with SSPE and included two incidences of major bleeding.	evidence on the effectiveness of CT scans in the SSPE population to suggest a change to recommendations.
Diagnosis – Patients with signs or symptoms of both deep vein thrombosis and pulmonary embolism (No clinical question in guideline (1.1.14))			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Treatment – Pharmacological interventions – Deep vein thrombosis or pulmonary embolism			
144 – 07 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT? (1.2.1 – 1.2.5) **144 – 08 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed PE? (1.2.1 – 1.2.5)**			
Surveillance decision Review questions 144-07 and 144-08 should be updated to include the new oral anticoagulants in the recommendations.			
Evidence Update (2014) The Evidence Update identified NICE Technology Appraisals that were in progress and relevant to CG144 at the time the Evidence Update was developed. NICE CG144 does not currently include recommendations on the use of the new oral anticoagulants as reviewed by the following Technology	**Pharmacological interventions for DVT** Two relevant studies[7,8] were identified evaluating the use of non-vitamin K antagonist oral anticoagulants (NOACs) in people with DVT. However, guidance on NOACs can be found in the Technology Appraisals TA354, TA341, TA327 and TA261 which are not mentioned in the guideline but are	Topic expert feedback indicated that it is common practice amongst GPs and hospitals to use NOACs instead of LMWH for the treatment of suspected DVT prior to confirmation by D-dimer. Topic experts suggest that D-dimer and ultrasound scans are not reliable after administration of an anticoagulant.	New evidence identified that may change current recommendations. The 4-year surveillance review identified new evidence for the efficacy and safety of NOACs which have not been previously considered in CG144. The evidence suggests similar rates of efficacy for NOACs compared with current standard treatments for VTE and

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Appraisals. These Technology Appraisals were all published after CG144 was developed and have been included in the CG144 pathway: TA354 Edoxaban is recommended as an option for treating and for preventing recurrent DVT and PE. TA341 Apixaban is recommended as an option for treating and for preventing recurrent DVT and PE. TA327 Dabigatran etexilate is recommended as an option for treating and for preventing recurrent DVT and PE. TA287 Rivaroxaban is recommended as an option for treating PE and for preventing recurrent VTE. TA261 Rivaroxaban is recommended as an option for treating and for preventing recurrent DVT and PE. The Evidence Update concluded that the approval of new oral anticoagulants for the management of DVT or PE by the NICE Technology Appraisals programme may impact on recommendations in CG144.	included in the VTE pathway. **Pharmacological interventions for PE** One relevant study[9] was identified evaluating the use of NOACs in people with PE. However, guidance on NOACs can be found in the Technology Appraisals TA354, TA341, TA327, TA287 and TA261 which are not mentioned in the guideline but are included in the VTE pathway. A Cochrane systematic review[10] aimed to assess the effectiveness and safety of anticoagulation in people with sub-segmental pulmonary embolism but found no RCTs that met the inclusion criteria. **Pharmacological interventions for VTE** Ten relevant studies[11-20] were identified evaluating the use of NOACs in people with VTE. However, guidance on NOACs can be found in the Technology Appraisals TA354, TA341, TA327, TA287 and TA261 which are not mentioned in the guideline but are included in the VTE pathway. **Patients with cancer and VTE** Four relevant studies[21-24] were identified evaluating the use of NOACs in people with VTE and cancer. However, guidance	Topic experts highlighted the recent use of direct oral anticoagulants in patients with VTE and suggest integration into the guideline following efficacy and safety studies and noted the NICE Technology Appraisals covering them. One topic expert highlighted the reduction of intracranial bleeding with direct oral anticoagulants for patients with VTE. One topic expert suggested that anticoagulant treatment should be for 3 months in patients with an isolated unprovoked distal DVT. Four topic experts highlighted the impact on costs of the increased uptake of direct oral anticoagulants including drug costs and follow up services costs. One topic expert identified a trial on idarucizumab for the reversal of anticoagulant effects of dabigatran however the trial does not meet the RCT or systematic review study design criteria for inclusion in this review. Topic experts identified studies investigating the effectiveness of anticoagulation for treatment of VTE in patients with cancer:	a trend towards reduced risks of bleeding. NICE Technology Appraisals have, since the publication of CG144, approved the use of NOACs for the treatment and prevention of venous thromboembolism. Intelligence from topic experts highlights the current use of NOACs in practice and their effectiveness in subgroups of people with cancer. Topic experts also highlighted the use of NOACs to treat DVT prior to confirmation by D-dimer. Recommendation 1.1.3 is to offer a parenteral anticoagulant. However, NOACs are not licensed for this use and other topic experts indicated that D-dimer is not reliable following use of an anticoagulant. Intelligence from topic experts identified evidence for idarucizumab to reverse the anticoagulant effects of pharmacological interventions. NICE is currently producing an evidence summary for this medicine which, when published, will be linked to the treatment pathway for VTE. An ongoing NIHR HTA study may provide some insight into the optimal NOAC treatment for VTE when it is published.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	on NOACs can be found in the Technology Appraisals TA354, TA341, TA327, TA287 and TA261 which are not mentioned in the guideline but are included in the VTE pathway. A meta-analysis[25] of 11 studies in people with cancer and VTE found a significant reduction in mortality for LMWH compared with unfractionated heparin (UFH) at 3-month follow-up. Analysis of 3 studies found no significant reduction in VTE recurrence between LMWH and UFH. Analysis of 2 studies found no significant differences in mortality, recurrent VTE, major bleeding or minor bleeding between heparin and fondaparinux. Analysis of one study found no significant difference in mortality between dalteparin and tinzaparin. A Cochrane systematic review and meta-analysis[26] of 7 RCTs of people with cancer and VTE found no significant difference in survival benefit from long-term treatment with LMWH or VKA. LMWH was associated with a significant reduction in VTE compared with VKA. An RCT[27] of 900 people with active cancer and VTE found no significant	A systematic review[28] of 5 RCTs combining 24,455 people with acute VTE found no significant differences for rates of recurrent VTE, fatal PE and overall mortality between NOACs compared with VKAs. A significant reduction in risk of bleeding complications was associated with NOACs compared with VKAs. A subgroup analysis[29] of people with cancer from the AMPLIFY trial found no significant differences in risks of recurrent VTE or major bleeding between apixaban and enoxaparin plus warfarin. An NIHR HTA study comparing oral anticoagulants for the prevention and treatment of VTE is currently ongoing. The results of this study may provide data on the effectiveness of pharmacological treatment and the optimal medication for management of VTE.	There are currently no recommendations in CG144 for the use of NOACs. The new evidence suggests that new recommendations on the use of NOACs for the treatment of VTE are justified. The proposed update to pharmacological interventions is limited to anticoagulant treatments and does not include pharmacological thrombolysis or analgesia.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	differences in rates of recurrent VTE, mortality or major bleeding between tinzaparin and warfarin treatments. A significant reduction in clinically-relevant non-major bleeding was found for tinzaparin compared with warfarin.		
144 – 09 What is the optimal treatment duration for pharmacological interventions? a) 6 months vs 3 months b) longer vs shorter duration of treatment (1.2.1 – 1.2.5)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	An RCT[30] of 347 people with cancer and a first episode of DVT treated with LMWH for 6 months investigated the role of residual vein thrombosis on optimal duration of treatment. Treatment for a further 6 months with LMWH was not associated with a significant difference for the primary end point of recurrent VTE or the secondary end point of major bleeding between patients with and without residual vein thrombosis. A systematic review[31] of 11 RCTs including 3716 people with VTE found a significant reduction in the risk of recurrent VTE during prolonged treatment with VKA. No significant increase in recurrent VTE was found following	One topic expert highlighted the long-term use of anticoagulants specifically in 80-90 year old patients who had a VTE 20 years prior and questioned whether the treatment is for life or if there is support to stop anticoagulants at any time.	New evidence is unlikely to impact on guideline recommendations. The 4-year surveillance review identified new evidence to suggest prolonged treatment with either LMWHs or VKAs reduced the risk of recurrent VTE, however bleeding complications remained. This evidence compliments the current recommendations (1.2.1 – 1.2.5) to offer these medications for an initial period of 3-6 months before assessing the risks and benefits of continued treatment.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	cessation of prolonged VKA treatment. A significant increase in bleeding complications was found with prolonged VKA treatment. However, the abstract does not define the length of time referred to as prolonged.		
Treatment – Thrombolytic therapy – Deep vein thrombosis			
144 – 10 What is the effectiveness of thrombolytic therapy and mechanical thrombectomy to manage acute DVT? (1.2.6)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) The CaVenT study, an RCT[32] comparing catheter-directed thrombolytic therapy (CDT) plus standard anticoagulation therapy with standard anticoagulation therapy alone in people (n=209) with DVT was included. At 6 months, significantly more people had iliofemoral patency in the CDT group. At 24 months, significantly fewer people had post-thrombotic syndrome in the CDT group. However, CDT was also associated with bleeding complications. A Cochrane systematic review[33] of 17 RCTs (n=1103) compared any type of thrombolytic therapy (systemic, loco-	An RCT[34] of people with iliofemoral DVT found a significant reduction in risk of deep venous reflux and an increased venous patency with the addition of CDT to anticoagulation and compression stockings. A meta-analysis[35] of 6 studies in people with proximal DVT found significant improvements in complete clot lysis and venous patency together with lower rates of post-thrombotic syndrome and venous obstruction with the addition of CDT compared with anticoagulation alone. A significant increase in major bleeding episodes was found for the CDT group.	A topic expert identified the following study investigating post-thrombotic syndrome following catheter-directed thrombolysis: A 5-year follow-up of the CaVenT study[36] compared standard treatment with compression stockings and anticoagulants (control group) to standard treatment plus CDT with alteplase in people (n=176) with DVT. At 5-year follow-up, a significant reduction in risk of post-thrombotic syndrome was found for the CDT group. However, quality of life scores did not differ between the groups.	New evidence is consistent with guideline recommendations. 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 DVT, but increase the likelihood of bleeding complications. The 4-year surveillance review identified new evidence suggesting efficacy of catheter-directed thrombolysis for the treatment of patients with iliofemoral or proximal DVT. Overall, this evidence is consistent with

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
regional or catheter-directed) in addition to anticoagulation therapy with anticoagulation therapy alone in people with DVT of the lower limb. Thrombolytic therapy was associated with a significantly increased likelihood of improvement in venous patency and complete clot lysis. However, thrombolytic therapy also significantly increased incidences of bleeding complications compared to anticoagulation therapy alone. 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 people with DVT, but increase the likelihood of bleeding complications. The evidence was considered to be consistent with recommendations in NICE CG144 that CDT should be considered for people with symptomatic iliofemoral DVT.			recommendations in NICE CG144 that catheter-directed thrombolytic therapy should be considered for patients with symptomatic iliofemoral DVT. However, there is currently a lack of evidence for the effectiveness of CDT for proximal DVT to impact recommendations.
Treatment – Thrombolytic therapy – Pulmonary embolism			
144 – 11 What is the effectiveness of open surgical thrombectomy, combination of mechanical and pharmacological thrombolysis, pharmacological thrombolytic therapy and heparin to manage acute PE? (1.2.7, 1.2.8)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
This review question should not be updated.			
Evidence Update (2014) One open-label, RCT[37] tested the efficacy and safety of low-dose systemic pharmacological thrombolysis for reduction of pulmonary artery pressure in people (n=121) with PE. The Evidence Update concluded that low-dose systemic pharmacological thrombolysis may be a treatment option for a subgroup of people with PE who have a high thrombus burden but are not haemodynamically unstable. However, it was considered that this evidence was unlikely to have an impact on the guideline recommendations due to the small size of the study. The Evidence Update noted that the results from the ongoing PEITHO Pulmonary Embolism Thrombolysis Study would be 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.	A meta-analysis[38] of 15 RCTs combining 1247 people with moderate PE compared thrombolytic therapy with heparin. The analysis found a significant reduction in recurrent PE or death, a non-significant increase in major bleeding, and a significant increase in non-major bleeding for thrombolytic therapy. A meta-analysis[39] of 11 RCTs combining 1833 people with haemodynamically stable PE found a significantly increased risk of major bleeding and a significant reduction of recurrent PE for thrombolysis compared with heparin. Non-significant increased risks of intracranial haemorrhage and fatal bleeding were associated with thrombolysis. A non-significant reduction for all-cause death was associated with thrombolysis compared with heparin. A meta-analysis[40] of RCTs comparing adjunctive thrombolytic therapy with heparin found 1510 people with acute submassive PE for inclusion. No significant differences in the composite endpoint of all-cause death or recurrent PE or for the outcome of major bleeding	Topic experts highlighted the following study: A meta-analysis[45] of 16 RCTs combining 2115 people with PE including those who were haemodynamically stable with right ventricular dysfunction compared thrombolytic therapy with anticoagulant therapy. The analysis found thrombolytics were associated with lower all-cause mortality and increased risks of major bleeding compared with anticoagulants.	New evidence is consistent with guideline recommendations. The 2-year Evidence Update concluded that low-dose systemic pharmacological thrombolysis may be a treatment option for a subgroup of patients with pulmonary embolism who have a high thrombus burden but are not haemodynamically unstable. This evidence was used to inform the 2015 Addendum to the CG144 guideline with a new recommendation developed (1.2.8). The 4-year surveillance review identified new evidence to suggest improved efficacy for thrombolytic therapy with reduced rates of recurrent PE, mortality, and clinical deterioration for patients with PE. However, the risk of bleeding complications was found to be higher with thrombolysis compared to treatment with anticoagulation. Intelligence from topic experts identified evidence to suggest thrombolytic therapy was associated with lower all-cause mortality and increased major bleeding compared to anticoagulant treatment for

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	were found between treatments. A significant reduction in the incidence of the composite endpoint of all-cause death or clinical deterioration was found with thrombolytic therapy compared to heparin. An RCT[41] of 50 haemodynamically stable people with submassive PE found significant increases in the incidence of in-hospital death or clinical deterioration for treatment with an anticoagulant alone (enoxaparin) compared with anticoagulant plus a thrombolytic (alteplase or streptokinase). A systematic review[42] of 7 studies combining 594 people with submassive PE found no significant differences in mortality or recurrent PE between thrombolysis treatment and intravenous heparin. A meta-analysis[43] of 7 RCTs combining 1631 people with intermediate-risk PE found no significant differences in rates of all-cause mortality or major bleeding between thrombolysis and anticoagulation. The thrombolysis group was associated with significantly lower rates of clinical deterioration and		people with haemodynamic stability and right ventricular dysfunction. Overall, this evidence is consistent with current recommendations (1.2.7 – 1.2.8) to offer thrombolytic therapy to people with PE depending on their haemodynamic stability.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	recurrent PE compared with anticoagulation. A meta-analysis[44] of 8 RCTs combining 1755 people with intermediate-risk PE found thrombolytic therapy was associated with reduced all-cause mortality and recurrent PE compared with anticoagulation. Major and minor bleeding rates were higher with thrombolytic therapy compared with anticoagulation.		
Treatment – Mechanical interventions – Proximal deep vein thrombosis or pulmonary embolism			
144 – 12 What is the clinical effectiveness of vena caval filters to manage venous thromboembolic diseases in people that are unable to have pharmacological treatment? (1.2.10 – 1.2.12)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	An RCT[46] of 399 people with acute PE found no significant differences in rates of recurrent PE, DVT, major bleeding or mortality with the addition of a retrievable vena caval filter compared with anticoagulation alone.	*Comments from topic experts:* One topic expert suggests inferior vena cava filters in trauma patients should not be recommended.	New evidence is consistent with guideline recommendations. The 4-year surveillance review identified new evidence to suggest similar rates of efficacy and safety for retrievable vena caval filter compared with anticoagulation. This evidence is consistent with current recommendations to offer a vena caval filter to people who cannot have

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			anticoagulation treatment.
144 – 13 What is the effectiveness of graduated compression stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases? (1.2.9)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) One RCT, the SOX trial[47], of elastic compression stockings to prevent post-thrombotic syndrome in people with DVT (n=806) 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 people with a first proximal DVT. However, graduated elastic compression stockings are still likely to be useful for symptom relief in people who have had a DVT. The data from the SOX trial was used to inform the 2015 Addendum to the CG144 guideline with the addition of a new recommendation (1.2.9).	No relevant evidence identified.	Topic experts highlight the SOX trial investigating the efficacy of compression stockings to prevent post-thrombotic syndrome. This trial was included in the Evidence Update (2014) and subsequently used to inform the 2015 Addendum to CG144. Following triage, topic experts highlighted the OCTAVIA[48] study which found an increased incidence of post-thrombotic syndrome when elastic compression stockings were stopped after 12 months compared to continuing their use for a further 12 months in patients (n=518) with proximal DVT. However, the absolute difference in incidence rates was found to be not non-inferior as the upper limit of the 95% confidence interval exceeded the non-inferiority limit.	No new evidence was identified that would affect recommendations. 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. Intelligence from topic experts supports the Evidence Update conclusion that compression stockings have limited effect on incidence of post-thrombotic syndrome. The data from the SOX trial was used to inform the 2015 Addendum to the CG144 guideline with the addition of a new recommendation (1.2.9). The new recommendation is not to offer graduated compression stockings to prevent post-thrombotic syndrome or recurrent VTE.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Patient information			
144 – 14 Does the provision of information and support about the management of VTE improve patient outcomes? (1.3.1 – 1.3.4)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Self-management and self-monitoring for patients treated with a vitamin K antagonist			
144 – 15 What is the effectiveness of self-monitoring or self-management compared to hospital/GP testing for long-term pharmacological treatments? (1.4.1)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	One topic expert commented on 'self-monitoring updates' however no further details provided. One topic expert suggested a review of clinic/day-case management of VTE however no rationale provided.	No new evidence was identified that would affect recommendations. Topic experts commented on self-monitoring and day-case management of VTE however no further details or supporting references were provided. No evidence was found by the 4-year review to support topic expert comments or impact recommendations.
Investigations for cancer			
144 – 16 Do investigations for cancer in patients with spontaneous VTE (DVT or PE) improve patient outcomes (morbidity and mortality)? (1.5.1, 1.5.2)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
This review question should be updated.			
Evidence Update (2014) No relevant evidence identified.	An RCT[49] of 854 people with unprovoked VTE found no significant differences in rates of cancer diagnosis, mean time to a cancer diagnosis or rates of cancer-related mortality with the addition of abdomen and pelvis computed tomography to limited occult-cancer screening. A Cochrane systematic review[50] of 2 studies combining 396 people with unprovoked VTE found that there was no difference in the number of cancer-related deaths or number of people identified with cancer between patients tested for cancer and those not tested. Diagnosis of cancer was found to be earlier with testing compared to no tests however no statistical information was provided for this outcome and no other outcomes were reported.	Topic experts highlighted the reduced need for cancer screening tests in patients with VTE due to the low rate of identified cancer and increased costs. Topic experts also highlighted the safety risks of increased radiation from CT scans for cancer in patients with VTE. One topic expert suggested that the NICE recommendation to consider CT scans for cancer in patients with unprovoked DVT or PE has a significant impact on radiology workloads. Topic experts suggest that further screening with CT should be considered if guided by clinical assessment or if other risk factors are present. Following triage, topic experts highlighted an RCT[51] (n=394) that found no difference in rates of cancer diagnosis between a limited screening strategy plus an F-FDG PET/CT scan and a limited screening strategy alone in patients with unprovoked VTE.	New evidence identified that may change current recommendations. The 4-year surveillance review identified new evidence to suggest that routine screening with CT of the abdomen and pelvis does not provide a clinically significant benefit in diagnosis or mortality rates for cancer in patients with VTE. Intelligence from topic experts also highlights the lack of benefit in routine additional cancer screening and the increased risk of radiation from CT scans. This new evidence is inconsistent with the current recommendation to offer investigations for cancer to all patients with unprovoked DVT or PE. Some consideration should be given to the wording of any new recommendation to suggest that further screening with CT should be considered if guided by clinical assessment or if other risk factors are present.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Thrombophilia testing			
144 – 17 What is the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event? (1.6.1 – 1.6.4)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
144 – 18 Does thrombophilia testing improve the outcomes of first degree relatives of people who have had thromboembolic disease and thrombophilia? (1.6.5)			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Areas not currently covered in the guideline			
NQ – 01 Aspirin for prevention of VTE recurrence			
Surveillance decision This review question should not be updated.			
Evidence Update (2014) Two RCTs (ASPIRE[52] study, n=822; WARFASA[53] study, n=403) compared low-dose aspirin with placebo for prevention of VTE recurrence in people who had completed initial anticoagulant	No relevant evidence identified.	One topic expert suggested the need to consider the role of long-term low dose aspirin.	New evidence is unlikely to impact on the guideline. The 2-year Evidence Update identified evidence to suggest a low dose of aspirin following initial anticoagulation therapy

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
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 - 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 on long-term anticoagulation therapy. The evidence was considered to have a potential impact on CG144 however a decision to defer the update of this question was made to allow the publication of the EINSTEIN CHOICE trial.			may reduce the risk of recurrent VTE without increasing the risk of bleeding. The evidence was considered to have a potential impact on CG144 however a decision at the 2-year review to defer the update of this question was made to allow the publication of the EINSTEIN CHOICE trial. The EINSTEIN CHOICE trial is currently recruiting participants. Also, NICE has produced a Medicines Evidence Commentary on the ASPIRE study. Considering that no further evidence has been found by the 4-year surveillance review, it is unlikely the recommendations will be impacted at this time. The progress of the EINSTEIN CHOICE trial will be assessed at the next surveillance review of the guideline.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
NQ – 02 Management of calf DVT			
Surveillance decision This review question should not be updated.			
<u>Evidence Update (2014)</u> Two systematic reviews (De Martino 2012[54], included 8 studies, n=505; Masuda 2012[55], included 31 studies) considered the management of people with calf DVT. The Evidence Update concluded that the evidence does not appear to support routine use of anticoagulants over observation and re-imaging in people with calf DVT. However, given the risks of propagation and of PE and DVT recurrence, management of people with calf DVT with either anticoagulation therapy or serial imaging of the proximal veins is advised. The Evidence Update highlighted several limitations with each review including few RCTs, poor methodological quality and publication bias of included studies. The uncertainty over the optimum management approach for calf DVT raised by these 2 papers and their limitations meant that the evidence was	No relevant evidence identified.	None identified relevant to this question.	New evidence is unlikely to impact on the guideline. The 2-year Evidence Update identified evidence considering the management of people with calf DVT. The Evidence Update concluded that the evidence does not appear to support routine use of anticoagulants over observation and re-imaging in people with calf DVT and was therefore considered unlikely to impact on the guideline No new evidence was identified through the 4-year surveillance to change this conclusion.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
considered to be unlikely to have an impact on NICE CG144.			
NQ – 03 Risk stratification and outpatient treatment of patients with PE			
Surveillance decision This review question should be considered for inclusion in the guideline.			
Evidence Update (2014) A systematic review and meta-analysis[56] (included 15 studies, n=1657) looked at the safety of outpatient treatment compared with inpatient treatment in low-risk patients with acute PE. A second systematic review and meta-analysis[57] assessed the accuracy of 2 prognostic tools – the Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) – in predicting outcomes in people with acute PE. 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	No relevant evidence identified.	Topic experts suggested there is an increasing drive to manage low risk PE patients in the community as soon as possible. Topic experts highlighted the increased use of ambulatory care units as an alternative to hospital care for the treatment of PE. Topic experts highlighted that some outpatient services for DVT have also added PE to their service. A saving of reduced bed days and reduced inpatient treatment were identified as benefits of outpatient treatment Further benefits of having an ambulatory pathway for PE were identified as allowing quicker diagnosis and avoiding hospital admissions. Topic experts identified the use of mortality risk and Pulmonary Embolism Severity Index (PESI) scores to identify	New evidence identified that may change current recommendations. CG144 does not currently include recommendations regarding outpatient treatment of PE. The 2-year Evidence Update identified evidence suggesting 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. Intelligence from topic experts highlighted evidence for the potential to treat people with low risk PE as outpatients. Topic experts also generally agreed on the use of the PESI score and clinical judgement to define low risk PE. Intelligence from topic experts also identified the availability of ambulatory

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
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 was considered unlikely to have an impact on the guidance.		patients with a low risk of adverse events who could be safely discharged or treated as outpatients. Topic experts highlighted that the PESI score is evidence-based and is the most widely used measure of PE severity. Topic experts also identified the use of the Hestia criteria and the simplified PESI as measures of PE severity. Topic experts noted that there is some evidence that additional investigations of BNP, NT, ProBNP and high-sensitivity troponin may help further risk stratify PE patients. Topic experts also noted the use of clinical judgement when identifying low risk PE patients. Topic experts highlighted the following studies: An RCT[58] compared incidence of adverse outcomes in 550 people with PE either directly discharged from hospital or managed as inpatients following use of the Hestia criteria. The trial found no significant difference in adverse event incidents between those treated as inpatients and those treated as	services for PE. Although outpatient treatment of PE was not included in the scope of CG144, there is an option at this 4-year review for potential inclusion in the guideline. Topic experts agreed that there is a need to establish a new area in the guideline to incorporate recommendations on outpatient treatment for PE.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
		outpatients. A systematic review and meta-analysis[59] combining 1258 people with acute symptomatic PE compared the incidence of adverse events for patients treated as outpatients. The analysis found low rates of adverse events in this population, however a comparator was not included.	
Research recommendations			
Diagnostic investigations for deep vein thrombosis			
RR – 01 What is the clinical and cost effectiveness of a whole-leg ultrasound scan compared with a proximal leg vein ultrasound scan in the diagnosis of acute DVT?			
Surveillance decision This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	Topic experts suggest that there may be an indication for a whole-leg ultrasound scan in circumstances where a serial ultrasound is not available, when a repeat scan would be very difficult to arrange or in patients receiving an anticoagulant prior to a D-dimer test.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			research recommendation from the NICE research recommendations database and NICE version of the guideline.
Pharmacological interventions			
RR – 02 What is the clinical and cost effectiveness of long-term oral anticoagulation treatment in specific subgroups of patients with a first unprovoked VTE?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) No relevant evidence identified.	See 144-09	See 144-09	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New relevant evidence found but update not planned. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
RR – 03 In patients with VTE and active cancer who have had 6 months of anticoagulation treatment with LMWH, what is the clinical benefit (in terms of VTE recurrence rates, all-cause mortality and major bleeding) and cost effectiveness of continued anticoagulation treatment with LMWH versus a VKA?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Evidence Update (2014) No relevant evidence identified.	See 144-09	See 144-09	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New relevant evidence found but update not planned. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
Thrombolytic therapy			
RR – 04 What is the clinical and cost effectiveness of clot removal using catheter-directed thrombolytic therapy or pharmacomechanical thrombolysis compared with standard anticoagulation therapy for the treatment of acute proximal DVT?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) See 144-10	See 144-10	See 144-10	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			or stand it down. New relevant evidence found but update not planned. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
RR – 05 What is 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?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) See 144-11 .	See 144-11	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New relevant evidence found but update not planned. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
RR – 06 Does thrombolysis in patients with acute PE and right ventricular dysfunction improve long-term quality of life and/or reduce the incidence of chronic thromboembolic pulmonary hypertension (CTEPH)?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) See 144-11	See 144-11	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New relevant evidence found but update not planned. This research recommendation was added as part of the 2015 addendum update. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
RR – 07 Does lower-dose thrombolysis reduce the risk of major bleeding and improve outcomes in patients with acute PE and right ventricular dysfunction?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014)	See 144-11	None identified relevant to this question.	**Proposal on retaining the research**

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
See 144-11			**recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New relevant evidence found but update not planned. This research recommendation was added as part of the 2015 addendum update. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
Mechanical interventions			
RR – 08 What is the effectiveness of stockings, when adherence is adequate, for preventing post-thrombotic syndrome in people with confirmed DVT?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.			
Evidence Update (2014) See 144-13	See 144-13	See 144-13	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			on whether to retain the recommendation or stand it down. No new relevant evidence found. This research recommendation was added as part of the 2015 addendum update. Therefore it is proposed to keep this research recommendation ongoing as not enough yet done to trigger an update.
Investigations for cancer			
RR – 09 A confirmatory trial to assess the impact of additional investigations for cancer in patients with VTE (CT abdo/pelvis, sputum cytology, and mammography) in patients with a first episode of apparently unprovoked VTE, on treatment for VTE, on morbidity due to VTE recurrence and overall survival, with patients diagnosed with a cancer associated VTEs receiving LMWH for at least 6 months instead of a VKA for 3 months			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
Evidence Update (2014) No relevant evidence identified.	See 144-16	See 144-16	New evidence identified and an update to the guideline is proposed.
RR – 10 Identification of novel non-invasive alternative strategies for the diagnosis of underlying cancers without the radiation risk associated with CT scanning and mammography			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			recommendation.
RR – 11 Assessment of patient views on the threshold risk for occult cancer, at which they would prefer to be investigated with a 1-2 per 10,000 lifetime risk of cancer, irrespective of the impact of diagnosis on survival			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
Thrombophilia testing			
RR – 12 Do antithrombin, protein C or protein S deficiencies increase the risk of recurrence to a clinically significant degree when anticoagulation is stopped as compared to those patients with venous thrombosis who do not have thrombophilia?			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
Evidence Update (2014) No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.

References

1. van der Hulle T, den Exter PL, Erkens PG et al. (2013) Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism. Journal of Thrombosis & Haemostasis 11:1986-1992.

2. Nazerian P, Vanni S, Volpicelli G et al. (2014) Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism. Chest 145:950-957.

3. Righini M, van EJ, den Exter PL et al. (2014) Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. JAMA - Journal of the American Medical Association.311 (11) (pp 1117-1124), 2014.Date of Publication: 2014. 1117-1124.

4. Singh B, Mommer SK, Erwin PJ et al. (2013) Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism--revisited: a systematic review and meta-analysis. [Review]. Emergency Medicine Journal 30:701-706.

5. van EN, van der Hulle T, van EJ et al. (17-5-2016) Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med .

6. Goy J, Lee J, Levine O et al. (2015) Sub-segmental pulmonary embolism in three academic teaching hospitals: a review of management and outcomes. J Thromb Haemost 13:214-218.

7. Piazza G, Mani V, Grosso M et al. (2014) A randomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy versus low-molecular weight heparin/warfarin in patients with symptomatic deep vein thrombosis-edoxaban thrombus reduction imaging study (etris). Circulation .

8. Robertson L, Kesteven P, and McCaslin JE. (2015) Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. [Review]. Cochrane Database of Systematic Reviews 6:CD010956.

9. Robertson L, Kesteven P, and McCaslin JE. (2015) Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. [Review]. Cochrane Database of Systematic Reviews 12:CD010957.

10. Yoo Hugo HB, Queluz Thais HAT, and El DR. (2016) Anticoagulant treatment for subsegmental pulmonary embolism. Cochrane Database of Systematic Reviews .

11. Alotaibi GS, Almodaimegh H, McMurtry MS et al. (2013) Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis. [Review]. Thrombosis Research 132:185-189.

12. Sardar P, Chatterjee S, and Mukherjee D. (2013) Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials. [Review]. Drugs 73:1171-1182.

13. Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R et al. (2014) Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. [Review]. Thrombosis Research 134:774-782.

14. Alotaibi G, Alsaleh K, Wu C et al. (2014) Dabigatran, rivaroxaban and apixaban for extended venous thromboembolism treatment: network meta-analysis. [Review]. International Angiology 33:301-308.

15. Kakkos SK, Kirkilesis GI, and Tsolakis IA. (2014) Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. [Review]. European Journal of Vascular & Endovascular Surgery 48:565-575.

16. Chai-Adisaksopha C, Crowther M, Isayama T et al. (9-10-2014) The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. [Review]. Blood 124:2450-2458.

17. Castellucci LA, Cameron C, Le GG et al. (17-9-2014) Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. [Review]. JAMA 312:1122-1135.

18. Wu C, Alotaibi GS, Alsaleh K et al. (2015) Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention. Thrombosis Research 135:243-248.

19. Bloom BJ, Filion KB, Atallah R et al. (15-3-2014) Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. [Review]. American Journal of Cardiology 113:1066-1074.

20. Schulman S, Kakkar AK, Goldhaber SZ et al. (18-2-2014) Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 129:764-772.

21. Prins MH, Lensing, Brighton TA et al. (2014) Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): A pooled subgroup analysis of two randomised controlled trials. The Lancet Haematology.1 (1) (pp e37-e46), 2014.Date of Publication: 2014. e37-e46.

22. Larsen TB, Nielsen PB, Skjoth F et al. (2014) Non-vitamin K antagonist oral anticoagulants and the treatment of venous thromboembolism in cancer patients: a semi systematic review and meta-analysis of safety and efficacy outcomes. [Review]. PLoS ONE [Electronic Resource] 9:e114445.

23. Carrier M, Cameron C, Delluc A et al. (2014) Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. [Review]. Thrombosis Research 134:1214-1219.

24. Vedovati MC, Germini F, Agnelli G et al. (2015) Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. [Review]. Chest 147:475-483.

25. Akl EA, Kahale L, Neumann I et al. (2014) Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. [Review][Update of Cochrane Database Syst Rev. 2011;(6):CD006649; PMID: 21678360]. Cochrane Database of Systematic Reviews 6:CD006649.

26. Akl EA, Kahale LA, Barba M et al. (2014) Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database of Systematic Reviews .

27. Lee AY, Kamphuisen PW, Meyer G et al. (18-8-2015) Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. JAMA 314:677-686.

28. van der Hulle T, Kooiman J, den Exter PL et al. (2014) Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 12:320-328.

29. Agnelli G, Buller HR, Cohen A et al. (2015) Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thromb Haemost 13:2187-2191.

30. Napolitano M, Saccullo G, Malato A et al. (10-11-2014) Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. Journal of Clinical Oncology 32:3607-3612.

31. Middeldorp S, Prins MH, and Hutten BA. (2014) Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. [Review][Update of Cochrane Database Syst Rev. 2006;(1):CD001367; PMID: 16437432]. Cochrane Database of Systematic Reviews 8:CD001367.

32. Enden T, Haig Y, Klow NE et al. (7-1-2012) 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 379:31-38.

33. Watson L, Broderick C, and Armon MP. (2014) Thrombolysis for acute deep vein thrombosis. Cochrane Database of Systematic Reviews .

34. Haig Y, Enden T, Slagsvold C-E et al. (2014) Residual rates of reflux and obstruction and their correlation to post-thrombotic syndrome in a randomized study on catheter-directed thrombolysis for deep vein thrombosis. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2:123-130.

35. Du GC, Zhang MC, and Zhao JC. (2015) Catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone in the treatment of proximal deep vein thrombosis - a meta-analysis. [Review]. Vasa 44:195-202.

36. Haig Y, Enden T, Grotta O et al. (2016) Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol. 3:e64-e71.

37. Sharifi M, Bay C, Skrocki L et al. (15-1-2013) Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 111:273-277.

38. Chen H, Ren C, and Chen H. (2014) Thrombolysis versus anticoagulation for the initial treatment of moderate pulmonary embolism: a meta-analysis of randomized controlled trials. [Review]. Respiratory Care 59:1880-1887.

39. Riera-Mestre A, Becattini C, Giustozzi M et al. (2014) Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. [Review]. Thrombosis Research 134:1265-1271.

40. Nakamura S, Takano H, Kubota Y et al. (2014) Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. Journal of Thrombosis & Haemostasis 12:1086-1095.

41. Taherkhani M, Taherkhani A, Hashemi SR et al. (2014) Thrombolytic-plus-Anticoagulant Therapy versus Anticoagulant-Alone Therapy in Submassive Pulmonary Thromboembolism (TVASPE Study): A Randomized Clinical Trial. The Journal of Tehran Heart Center 9:104-108.

42. Cao Y, Zhao H, Gao W et al. (2014) Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism. Patient preference & adherence 8:275-282.

43. Xu Q, Huang K, Zhai Z et al. (2015) Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: a meta-analysis. Journal of Thoracic Disease 7:810-821.

44. Gao GY, Yang P, Liu M et al. (2015) Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis. Thrombosis Research 136:932-937.

45. Chatterjee S, Chakraborty A, Weinberg I et al. (18-6-2014) Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 311:2414-2421.

46. Mismetti P, Laporte S, Pellerin O et al. (28-4-2015) Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA 313:1627-1635.

47. Kahn SR, Shapiro S, Ducruet T et al. (2014) Graduated compression stockings to treat acute leg pain associated with proximal DVT. A randomised controlled trial. Thrombosis & Haemostasis 112:1137-1141.

48. Mol GC, van de Ree MA, Klok FA et al. (2016) One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. BMJ 353:i2691.

49. Carrier M, Lazo-Langner A, Shivakumar S et al. (20-8-2015) Screening for Occult Cancer in Unprovoked Venous Thromboembolism. New England Journal of Medicine 373:697-704.

50. Robertson L, Yeoh SE, Stansby G et al. (2015) Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE. [Review]. Cochrane Database of Systematic Reviews 3:CD010837.

51. Robin P, Le Roux PY, Planquette B et al. (2016) Limited screening with versus without (18)F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial. Lancet Oncol 17:193-199.

52. Brighton TA, Eikelboom JW, Mann K et al. (22-11-2012) Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 367:1979-1987.

53. Becattini C, Agnelli G, Schenone A et al. (24-5-2012) Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 366:1959-1967.

54. De Martino RR, Wallaert JB, Rossi AP et al. (2012) A meta-analysis of anticoagulation for calf deep venous thrombosis. J Vasc Surg 56:228-237.

55. Masuda EM, Kistner RL, Musikasinthorn C et al. (2012) The controversy of managing calf vein thrombosis. J Vasc Surg 55:550-561.

56. Zondag W, Kooiman J, Klok FA et al. (2013) Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. European Respiratory Journal 42:134-144.

57. Zhou XY, Ben SQ, Chen HL et al. (2012) The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res 13:111.

58. den Exter PL, Zondag W, Klok FA et al. (31-3-2016) Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule With or Without NT-proBNP Testing in Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. Am J Respir Crit Care Med .

59. Piran S, Le GG, Wells PS et al. (2013) Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. [Review]. Thrombosis Research 132:515-519.