

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of:

TA327 Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism;

TA341 Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism;

TA354 Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism;

TA261 Rivaroxaban for the treatment and secondary prevention of venous thromboembolism; and

TA287 Rivaroxaban for the treatment of acute symptomatic pulmonary embolism with or without symptomatic DVT and the prevention of recurrent VTE

Original publication date:	TA327: December 2014 TA341: June 2015 TA354: August 2015 TA261: July 2012 TA287: June 2013
Review date	TA327: December 2017 TA341: June 2018 TA354: August 2018 TA261: June 2015 moved to static list TA287: June 2015 moved to static list
Existing recommendations:	Recommended To see the complete existing recommendations and the original remits for TA327/341/354, see Appendix A.

1. Proposal

All of the guidance should be transferred to the 'static guidance list'.

2. Rationale

No new evidence has emerged that is expected to substantially change the recommendations in TA261, TA287, TA327, TA341 and TA354. The clinical guideline for venous thromboembolic diseases is being updated, with an expected publication date of March 2020, including an update of anticoagulation treatment for deep vein thrombosis or pulmonary embolism. The current clinical guideline (CG144, last updated in 2015) does not include recommendations on dabigatran etexilate, apixaban, edoxaban or rivaroxaban. The scope for the [guideline update](#) states that it will cross-refer to and contextualise to relevant NICE technology appraisal guidance on pharmacological treatment for confirmed deep vein thrombosis (DVT) and pulmonary embolism (PE). The clinical guideline will also be able to place these treatments into the appropriate clinical context.

3. Summary of new evidence and implications for review

Technology appraisals 261 and 287 for rivaroxaban were moved to the 'static list' in 2015. This means that they are only considered for review if new evidence becomes available that is likely to lead to a change in the existing recommendations. No such evidence has triggered a review of these topics.

New evidence is not expected to lead to a change in the recommendations in the original guidance for TA341; apixaban, TA327; dabigatran etexilate or TA354; edoxaban. The main uncertainties in the appraisals related to the comparative clinical effectiveness of the treatments, and adverse events specifically bleeding events. Most of the new studies on apixaban, dabigatran etexilate and edoxaban focused on observational evidence to assess implementation including; managing adverse events, clinicians' preferences, and evaluations of real-world evidence. A systematic review and cost-effectiveness analysis of oral anticoagulants was published in March 2017ⁱ. The review found that there is a lack of head-to-head trials comparing oral anticoagulants, existing trials are relatively short, and further research on comparative effectiveness is needed.

A concern raised by clinical experts and patients during the appraisals was the lack of antidotes to reverse bleeding for novel anticoagulants and they noted that research into reversal agents for apixaban, edoxaban and dabigatran etexilate was underway. Since the publication of the appraisals, idarucizumab, a reversal agent of dabigatran etexilate has been licensed. NICE has published an evidence summary of its effectiveness in reversing bleeding with dabigatran etexilate. Other reversal agents are in development that work for multiple novel anticoagulants including ciraparantag and andexanet alfa. These products do not yet have a marketing authorisation. Andexanet alfa was referred to the TA work programme as part of Batch 61 in October 2018.

There are new trial data available for the efficacy of edoxaban in people who have cancer and venous thromboembolism. The clinical trial informing the regulatory submission for and the appraisal of edoxaban included few people with cancer. Similarly the trials informing the appraisals of dabigatran etexilate and apixaban had few people with active cancer. The committee made no specific recommendations about people with cancer in these appraisals. The needs of people with cancer were discussed in detail in TA261 (the first appraisal of a direct factor Xa inhibitor in this

indication). The committee recognised the disadvantages of regular injections (the usual treatment for people with cancer is low molecular weight heparin), which some people might choose to decline. The Committee concluded that rivaroxaban should not be excluded as a treatment option for preventing venous thromboembolism in people with cancer.

<p>Has there been any change to the price of the technologies since the guidance was published?</p>
<p>The price of apixaban has decreased from £10.98 per 10-tab pack, 2.5mg, to £9.50. The price of dabigatran etexilate (TA327) has decreased from £65.90 per 60-capsule pack of 150 or 110mg dose, to £51.00. The price of edoxaban has decreased from £2.10 per tablet to £1.75 per tablet (15mg, 30mg and 60mg). The price of rivaroxaban has reduced from £2.10 per tablet to £1.80 per tablet (15mg or 20mg)</p>
<p>Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?</p>
<p>No.</p>
<p>Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?</p>
<p>The main uncertainty identified across technology appraisals (TA327, 341 and 351), was that the relative effectiveness of the intervention compared with other newer oral anticoagulants (rivaroxaban, dabigatran etexilate, apixaban or edoxaban) because there were no head-to-head trials evaluating the relative effectiveness of these anticoagulants. No new evidence was identified to address this uncertainty.</p> <p>The relative risk of bleeding had a big impact on the ICER across all three technology appraisals, and the relative risk of bleeding for dabigatran etexilate, apixaban and edoxaban tosylate compared with other oral anticoagulants (rivaroxaban, dabigatran, low molecular weight heparin or fondaparinux with or without vitamin K antagonist, e.g. warfarin) was unknown. New analysis using pooled data from two studies (RE-COVER and RE-COVER II) shows that bleeding events with dabigatran are significantly lower than with warfarin (HR 0.70; 95% CI 0.61, 0.79)ⁱⁱ. No other evidence that could address this uncertainty was identified.</p> <p>The Committee considered the use of dabigatran etexilate, apixaban and edoxaban for people with cancer and were unable to make specific recommendations for their use in this population due to insufficient evidence. A clinical trial has compared edoxaban with low molecular weight heparin in people with cancer who had acute symptomatic or incidental venous thromboembolism. Edoxaban was statistically non-inferior to low molecular weight heparin (dalteparin) with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparinⁱⁱⁱ</p>

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

See Appendix C for a list of related NICE guidance.

The search strategies from the original ERG reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from Jan 2012 (TA327), Jan2014 (TA341) and Jan 2015 (TA354) onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

No equalities issues were raised in the original guidance.

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Appendix A – Information from existing guidance

5. Original remit

TA327: To appraise the clinical and cost effectiveness of dabigatran etexilate within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

TA341: To appraise the clinical and cost effectiveness of apixaban within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

TA354: To appraise the clinical and cost effectiveness of edoxaban tosylate within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

TA287: To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of acute symptomatic deep vein thrombosis and the prevention of recurrent venous thromboembolism

TA261: To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment and secondary prevention of venous thromboembolism

6. Current guidance

TA327: Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

TA341: Apixaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

TA354: Edoxaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

TA287: Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

TA261: Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

TA327: Dabigatran etexilate costs £65.90 for a 60-capsule pack of the 150mg or 110mg doses (excluding VAT; BNF 67) and costs £2.20 per day of treatment

TA341 The cost of apixaban is £1.10 per tablet for either the 2.5 mg or 5 mg dose (excluding VAT; British national formulary [BNF] accessed January 2015). The daily cost of apixaban is £4.40 for the first 7 days followed by £2.20 thereafter.

TA354: Edoxaban costs £2.10 per 15-mg, 30-mg or 60-mg tablet (excluding VAT) and the daily cost of treatment is £2.10.

TA287: Rivaroxaban costs £2.10 per 15-mg or 20-mg tablet ('British national formulary' edition 65)

TA261: Rivaroxaban costs £2.10 per 15 mg or 20 mg tablet.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No

Options	Consequence	Selected – ‘Yes/No’
<p>The guidance should be updated in an on-going clinical guideline¹.</p>	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	<p>No</p>
<p>The guidance should be transferred to the ‘static guidance list’.</p>	<p>The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.</p>	<p>Yes</p>
<p>The guidance should be withdrawn</p>	<p>The guidance is no longer relevant, and an update of the existing recommendations would not add value to the NHS.</p> <p>The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.</p>	<p>No</p>

¹ Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the [guide to the processes of technology appraisal](#).

Appendix C – other relevant information

1. Relevant Institute work

Published

Venous thromboembolism (2016) NICE pathway

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

Venous thromboembolism: reducing the risk for patients in hospital. (2010) NICE guideline CG92

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. NICE technology appraisal guidance TA275. Published date: 27 February 2013. Review decision - the recommendations from TA275 will be incorporated into the ongoing update of CG36. (April 2013)

Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance TA245. Published date: 25 January 2012. Review decision - move to "static list" (March 2015)

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance TA249. Published date: 15 March 2012. Review decision - the recommendations from TA275 will be incorporated into the ongoing update of CG36. (April 2013)

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance TA157. Published date: 24 September 2008. Review decision - move to "static list" (August 2011)

Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. NICE technology appraisal guidance TA355. Published date: 23 September 2015. Review decision - the recommendations from TA275 will be incorporated into the ongoing update of CG36. (April 2013). Review date: September 2018

Reversal of the anticoagulant effect of dabigatran: idarucizumab. NICE Evidence summary ESNM73. Published date: May 2016

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal guidance TA256. Published date: 23 May 2012. Review decision - the recommendations from TA275 will be incorporated into the ongoing update of CG36. (April 2013)

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance TA170. Published date: 22 April 2009. Review decision - move to "static list" (May 2012)

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance TA261. Published date: 25 July 2012. Review decision - move to "static list" (June 2015)

Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. NICE technology appraisal guidance TA287. Published date: 26 June 2013. Review decision - move to "static list" (June 2015)

Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline 89. Published date March 2018

In progress

Betrixaban for preventing venous thromboembolism in people hospitalised for acute medical conditions. NICE technology appraisal guidance [ID913]. Publication expected September 2018

Suspended/terminated

Venous thromboembolism (recurrent) - idraparinux sodium. NICE technology appraisal guidance [ID395]. Publication suspended: July 2007 (The manufacturer of idraparinux sodium advised NICE that the regulatory strategy in relation to this product is not finalised. The Institute has therefore decided to remove this appraisal from its work programme).

Venous thromboembolism (prevention) - rivaroxaban. NICE technology appraisal guidance [ID463]. Publication suspended: June 2012 (the manufacturer of rivaroxaban advised NICE that it is not currently pursuing a licensing application for rivaroxaban in this indication, therefore, NICE has decided to suspend this appraisal on its current work programme for the time being)

Venous thromboembolism - apixaban (acute medical illness). NICE technology appraisal guidance [ID310]. Publication suspended: March 2014 (the manufacturer of apixaban advised NICE that it will no longer be pursuing a licensing application for apixaban in this indication, therefore NICE has decided to suspend this appraisal on its current work programme)

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Rivaroxaban (for the prevention of stroke and systemic embolism in patients who have experienced a recent embolic stroke of undetermined source; Prevention of recurrence of strokes following a recent (7 days to 6 months))	Anticipated date of MA: 02 2019 Scoping period> May 2018	

3. Registered and unpublished trials

Trial name and registration number	Details
Safety and Efficacy of Low Molecular Weight Heparin for 72 Hours Followed by Dabigatran for the Treatment of Acute Intermediate-Risk Pulmonary Embolism (NCT02596555)	Estimated Enrolment: 700 Estimated Study Completion Date: August 2019 This study is currently recruiting participants
A Prospective Randomised Controlled Study to Evaluate Outcomes of the Treatment With Pradaxa or Warfarin for Prevention of Recurrent VTE in Patients With Angiographically Confirmed Acute Massive Pulmonary Embolism Undergoing Endovascular Mechanical Fragmentation and Thrombolytic Therapy (NCT02979561)	Estimated Enrolment: 200 Estimated Study Completion Date: June 2018 This study is currently recruiting participants
The Prevalence of Post-Thrombotic Syndrome in Deep-Vein Thrombosis (DVT) Patients Treated With Dabigatran- a Cross-Sectional Assessment of RE-COVER Study Patients (NCT03050138)	Estimated Enrolment: 300 Estimated Study Completion Date: February 2019 This study is currently recruiting participants

Trial name and registration number	Details
<p>Characterization of Patients Following Acute Venous Thromboembolism (VTE) and Safety and Effectiveness of Dabigatran Etexilate (DE) in the Treatment and Secondary Prevention of Acute Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Comparison to Vitamin K Antagonist (VKA) in Routine Clinical Practice - RE-COVERY DVT/PE (NCT02596230)</p>	<p>Estimated Enrolment: 14000</p> <p>Estimated Study Completion Date: February 2019</p> <p>This study is active but not recruiting participants</p>
<p>The Efficacy and Safety of Dabigatran Etexilate and Different Intensity Warfarin for the Prevention of Stroke and Systemic Embolism in Patients With Non-valvular Atrial Fibrillation (NCT02646267)</p>	<p>Estimated Enrolment: 210</p> <p>Estimated Study Completion Date: August 2018</p> <p>This study is enrolling participants by invitation only.</p>
<p>Treatment of Intracerebral Hemorrhage in Patients on Non-vitamin K Antagonist Oral Anticoagulants (NOAC) With Tranexamic Acid (NCT02866838)</p>	<p>Estimated Enrolment: 109</p> <p>Estimated Study Completion Date: December 2019</p> <p>This study is currently recruiting participants</p>
<p>Apixaban for Routine Management of Upper Extremity Deep Venous Thrombosis (NCT02945280)</p>	<p>Estimated Enrolment: 375</p> <p>Estimated Study Completion Date: October 2019</p> <p>This study is currently recruiting participants</p>
<p>A Phase III, Randomized, Controlled, Double-Blind Study Evaluating the Safety of Two Doses of Apixaban For Secondary Prevention of Cancer Related Venous Thrombosis in Subjects Who Have Completed at Least Six Months of Anticoagulation Therapy (NCT03080883)</p>	<p>Estimated Enrolment: 370</p> <p>Estimated Study Completion Date: May 2020</p> <p>This study is not yet open for participant recruitment</p>

Trial name and registration number	Details
A Phase III, Randomized, Open Label Study Evaluating the Safety of Apixaban in Subjects With Cancer Related Venous Thromboembolism (NCT02585713)	<p>Estimated Enrolment: 315</p> <p>Estimated Study Completion Date: November 2018</p> <p>This study is currently recruiting participants</p>

4. Relevant services covered by NHS England specialised commissioning

NHS Commissioning Board (2013) [2013/14 NHS STANDARD CONTRACT FOR SPECIALISED VASCULAR SERVICES \(ADULTS\) PARTICULARS, SCHEDULE 2-THE SERVICES, A- SERVICE SPECIFICATIONS](#)

Appendix D – References

ⁱ Sterne, J. et al. (2017) Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. *Health technology assessment* 21 (9) 1-385.

ⁱⁱ Majeed, A. et al. (2016) Bleeding events with dabigatran or warfarin in patients with venous thromboembolism. *Thrombosis and haemostasis* 115 (2): 291-298.

ⁱⁱⁱ Raskob, GE et al (2018) Edoxaban for the treatment of Cancer-Associated Venous Thrombolism. *New England Journal of Medicine* 15;378(7): 615-624