

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA355; Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Original publication date:	23 September 2015
Review date	September 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA355, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list' and can be incorporated into the forthcoming update of CG180.

2. Rationale

No new evidence has emerged that is expected to substantially change the recommendations in TA355. The clinical guideline for management of atrial fibrillation is being updated, with an expected publication date of September 2020. The current clinical guideline does not include edoxaban as an option for managing atrial fibrillation and it would be appropriate to incorporate this in the clinical guideline to reflect current treatment options.

3. Summary of new evidence and implications for review

The clinical evidence in the original appraisal came from 1 randomised controlled trial (ENGAGE AF-TIMI 48) which directly compared edoxaban, a direct oral anticoagulant (DOAC) with warfarin, a vitamin K antagonist. No new published trials were identified that investigated the indication appraised in TA355. The additions to the evidence base since TA355 support the committee's conclusions that edoxaban has similar efficacy to other DOACs in clinical practice and therefore there is no new evidence that is likely to change the recommendations of the original guidance. The net price of edoxaban has decreased since the original appraisal. The original guidance was positive therefore this price change is unlikely to change the recommendations of the original guidance.

Has there been any change to the price of the technology since the guidance was published?

The price of edoxaban has decreased from £58.80 for a 28-tablet pack (60mg or 30mg) to £49.00 and the daily cost has decreased from £2.10 to £1.75 (excluding VAT). (BNF, accessed July 2018)

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no changes or proposed changes to the marketing authorisation.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The original guidance considered edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. The main source of information came from 1 randomised controlled trial (ENGAGE AF-TIMI 48) comparing edoxaban to warfarin, which the committee concluded was well designed and generalisable to clinical practice.

The committee concluded that edoxaban was as clinically effective as warfarin but there was uncertainty about the effectiveness of edoxaban compared to other DOACs, analysed through a network meta-analysis. New evidence in the form of a meta-analysis (Bruins Slot and Berge, 2018) confirms that factor Xa inhibitors as a class of drug (of which edoxaban is one), significantly reduce the risk of stroke and system embolism compared with warfarin, supporting the committee's conclusions. New evidence in the form of an indirect treatment comparison (Skjoth et al, 2014) shows some differential effects by DOAC choice. However, this indirect treatment comparison was based on the same major randomised controlled trials of other DOACs that were used in the original submission, therefore the uncertainty surrounding the results is similar.

The committee considered the impact of poor renal function on edoxaban efficacy and concluded that this was not a clinically relevant subgroup. New evidence in the form of subgroup analyses (Bohula et al, 2016; Kimachi et al, 2017; Lip et al, 2017) supported the committee's conclusions.

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.

A surveillance review of CG180 was carried out in September 2017 and the decision was made to update the guideline. The update will focus on

- diagnosis and assessment
- assessment of stroke and bleeding risks
- interventions to prevent stroke
- rate and rhythm control
- prevention and management of postoperative atrial fibrillation

Additional comments

A new randomised controlled trial (NCT03129490) will complete in 2021 which directly compares the DOACs with each other. This may reduce uncertainty surrounding DOAC choice which is particularly relevant because the committee recognised warfarin use is declining in clinical practice with the introduction of DOACs.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May, 2014 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 above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues relevant to the committee's recommendations were raised in the original guidance.

GE paper sign off: Janet Robertson, 29 August 2018

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of edoxaban tosylate within its licensed indication for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation.

6. Current guidance

1.1 Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, including:

- congestive heart failure
- hypertension
- diabetes
- prior stroke or transient ischaemic attack
- age 75 years or older.

1.2 The decision about whether to start treatment with edoxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of edoxaban compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people considering switching from warfarin, edoxaban's potential benefits should be considered against its potential risks, taking into account the person's level of international normalised ratio (INR) control.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Edoxaban costs £58.80 for a 28-tablet pack (60 mg or 30 mg) and the daily cost of treatment is £2.10 (excluding VAT).

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

Appendix B

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline ¹ .	<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>	No
The guidance should be transferred to the ‘static guidance list’.	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.	Yes
The guidance should be withdrawn	<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>	No

¹ Information on the criteria for NICE allowing a technology appraisal in an ongoing 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

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation (2013) NICE technology appraisal 275

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (2012) NICE technology appraisal 249. Reviewed April 2013 - the recommendations from TA249 will be incorporated, verbatim, into the ongoing update of clinical guideline 36 'Atrial fibrillation' (now CG180). The appraisal will be moved to the static list of technology appraisals and will remain extant once the guideline is published, preserving the funding direction.

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (2012) NICE technology appraisal 256. Reviewed April 2013 - the recommendations from TA256 will be incorporated, verbatim, into the ongoing update of clinical guideline 36 'Atrial fibrillation' (now CG180). The appraisal will be moved to the static list of technology appraisals and will remain extant once the guideline is published, preserving the funding direction.

Atrial fibrillation: management. (2014) NICE clinical guideline 180. A NICE surveillance report in 2017 recommended an update of CG180 and stated "Topic experts advised that the recommendations from the technology appraisal (TA355) should be incorporated into the guideline."

Atrial fibrillation (2015) NICE quality standard 93. NICE checked this quality standard in 2017. The source guidance on atrial fibrillation is being updated and NICE are assessing what changes will need to be made to the quality standard. Expected publication date: 17 September 2020

Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system) (2014) NICE diagnostics guidance 14

AliveCor Heart Monitor and AliveECG app (Kardia Mobile) for detecting atrial fibrillation (2015) NICE medtech innovation briefing 35

In progress

[Lead-I electrocardiogram \(ECG\) devices for detecting atrial fibrillation using single-time point testing in primary care](#) NICE diagnostics guidance. Expected publication date: 20 February 2019

Suspended/terminated

Atrial fibrillation - idraparinux sodium. NICE technology appraisal. Status: suspended (the manufacturer of idraparinux sodium has advised us 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).

Atrial fibrillation - vernakalant. NICE technology appraisal. Status: suspended - following on from information received from the manufacturer, regarding the timings of the launch of the product in the UK, 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
Nothing relevant		Nothing relevant

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
<p>Edoxaban has a marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).'</p> <p>£58.80 for a 28-tablet pack (60 mg or 30 mg)</p>	<p>No proposed change to indication.</p> <p>£49.00 for a 28-tablet pack (60 mg or 30 mg)</p>

4. Registered and unpublished trials

Appendix C

Trial name and registration number	Details
Evaluation of the Safety and Efficacy of an Edoxaban-based Compared to a Vitamin K Antagonist-based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention (PCI) With Stent Placement (NCT02866175)	1500 participants Study Completion Date: March 2019 Recruiting
A Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation (PROBE) Parallel Group Study Comparing Edoxaban vs. VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation (ELIMINATE-AF) (NCT02942576)	560 participants Study Completion Date: November 2018 Recruiting
The Danish Non-vitamin K Antagonist Oral Anticoagulation Study. A Cluster Randomized Study Comparing Safety and Efficacy of Edoxaban, Apixaban, Rivaroxaban and Dabigatran for Oral Anticoagulation in Atrial Fibrillation (DANNOAC-AF) (NCT03129490)	11000 participants Study Completion Date: September 2021 Recruiting
A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study of DU-176b in Patients With NVAf Aged 80 Years or Older Who Are Ineligible for Available Oral Anticoagulation Therapy (NCT02801669)	500 participants Study Completion Date: December 2019 Recruiting
Efficacy and Safety of Non-vitamin K Oral Anticoagulants and Vitamin K Oral Anticoagulants on Some Metabolic and Coagulation Parameters in Diabetic and Nondiabetic Patients With First Diagnosis of Non-valvular Atrial Fibrillation (NCT02935855)	320 participants Study Completion Date: March 2018 Recruiting
Optimal Antithrombotic Therapy in Ischemic Stroke Patients With Non-Valvular Atrial Fibrillation and Atherothrombosis (NCT03062319)	400 participants Study Completion Date: January 2021 Recruiting

Appendix C

Trial name and registration number	Details
Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes - An Investigator-driven, Prospective, Randomised, Double-blind, Multi-centre Trial Initiated by the European Society of Cardiology and AFNET (NCT02618577)	3400 participants Study Completion Date: September 2019 Recruiting

Appendix D – References

Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, Braunwald E (2016) Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation*. 134: 24-36.

Bruins Slot KMH, Berge E (2018) Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Cochrane Database of Systematic Reviews* 3 Art. No.: CD008980.

Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S (2017) Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database of Systematic Reviews* 11 Art. No.: CD011373.

Lip GYH, Al-Saady N, Ezekowitz MD, Banach M, Goette A (2017) The relationship of renal function to outcome: A post hoc analysis from the Edoxaban versus warfarin in subjects Undergoing cardioversion of Atrial Fibrillation (ENSURE-AF) study. *American Heart Journal* 193: 16-22.

Skjoth F, Larsen TB, Rasmussen L, Lip GYH (2014) Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: An indirect comparison analysis. *Thrombosis and Haemostasis*. 111 (5): 981-988.