Executive summary

CRG seek comments from Greater Manchester on this position statement regarding the prescribing of best value direct oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation.

When developing the statement CRG carefully considered, amongst other things:

- The financial savings associated with increased edoxaban use,
- A clinician's freedom to prescribe the treatment they think is most appropriate for their patient
- The available evidence base to support (or not) the use of one medicine over another.
- The Investment and Impact Fund indicators
- The high court ruling that has invalidated the patent for apixaban, and may yet be subject to appeal.

CRG want edoxaban to be the first choice DOAC for use in non-valvular AF, and an alternative used where edoxaban would not be safe or appropriate. This position is still current at the time of publication of the draft statement, despite the legal issues surrounding apixaban.

GMMMG therefore seek feedback from a wide range of stakeholders regarding this statement. This can be done using the webform found at: https://gmmmg.nhs.uk/consultations/

June 2022

Edoxaban For The Treatment Of Non Valvular Atrial Fibrillation (NVAF)

The Clinical Reference Group discussed the above at its meeting on 14th June 2022. The recommendation of this subgroup is as follows:

Recommendation	**CRG recommend edoxaban as the first line direct oral anticoagulant (DOAC) for preventing stroke for patients with NVAF in the following groups:** • **Patients commencing anticoagulation for stroke prevention in NVAF.** • **Patients for whom it is appropriate to convert from a vitamin K antagonist to a DOAC.** **Clinicians should only initiate an alternative DOAC (dabigatran, rivaroxaban, or apixaban) when edoxaban is contra-indicated or is not appropriate.** **For patients already prescribed a DOAC for the treatment of AF: subject to the criteria specified in the relevant NICE technology appraisal guidance, local policy may be developed to review patients currently prescribed apixaban, rivaroxaban or dabigatran, where clinically appropriate.**
Background	In January 2022, NHS England published an operational note on commissioning recommendations for national procurement for DOACs. This document advised clinicians to prescribe edoxaban as first line DOAC therapy. For patients with NVAF there is no one DOAC suitable for all patients. Choice should be based on a range of factors including co-morbidities and patient preference. Where there is no strong clinical reason to use a specific DOAC, clinicians should use the DOAC with the lowest net acquisition cost, which is currently edoxaban. Clinicians may use an alternative DOAC (dabigatran, rivaroxaban, or apixaban) when the alternative has a proven clinical advantage. Converting patients between DOAC therapy may be done on a case-by-case basis and after an informed, shared decision has been reached between the healthcare professional and the patient and/or their carer. An announcement at the end of May 2022 concerned a legal challenge to the patent of apixaban which was upheld by the High Court. The ruling effectively means generic apixaban is available in the UK, but not currently in sufficient quantity nor at a price to replace edoxaban as the best value DOAC.
Efficacy and Safety	All DOACS are licensed 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 (NYHA Class ≥ II stated for apixaban and dabigatran), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. All four DOACS are licensed and have trial evidence of efficacy and safety in use for patients undergoing direct current cardioversions. (Rivaroxaban – X-VERT/ARC;

	ENSURE-AF-Edoxaban; NCT01593150-Dabigatran; EMANATE-Apixaban). There are currently no head-to-head Randomised Controlled Trials (RCTs) that directly compare DOACs against each other. Network meta-analyses (NMAs) have been published, incorporating RCTs and observational studies with various methodologies. These have limitations given the heterogeneity of the different trials, and should be interpreted with caution. All DOACs are shown to be non-inferior (or superior in the case of apixaban and dabigatran 150mg) to warfarin for stroke prevention in AF. A meta-analysis showed all high dose DOACs have comparable efficacy for the composite primary and bleeding outcomes (NICE TA355). Major bleeding rates are significantly lower for edoxaban and apixaban compared to warfarin than those seen with dabigatran and rivaroxaban (Lopez-Lopez et al 2017). All DOACS are contraindicated in the following groups of patients: • Hypersensitivity to the active substance or any of its excipients. • Clinically significant active bleeding • A lesion or condition, if considered a significant factor for major bleeding • Co-administration with other anticoagulants, except under specific circumstances (e.g. switching to warfarin). • Antiphospholipid syndrome; there is a risk of recurrent thrombotic events. See MHRA DSU. • Prosthetic heart valves Specific cautions and contraindications exist for each DOAC, the list below is specific to edoxaban, see SPCs for more information: • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Uncontrolled severe hypertension. • Pregnancy and breastfeeding. • Interactions between edoxaban and other medicines are common, see SPC. • Edoxaban is not recommended if CrCl <15ml/min. There is a trend towards lower efficacy with increasing CrCl (vs.warfarin). Edoxaban should only be used in high CrCl after careful evaluation of the individual thromboembolic and bleeding risk. SPS suggest consider using another anticoagulant if CrCL >95ml/min. • Edoxaban is the only DOAC not to have a licensed reversal agent (clinical trials of andexanet alfa for this indication are ongoing). For information on switching between a vitamin K antagonist and edoxaban, see SPC The RDTC have published a DOAC comparison document which provides further information on some of the clinical differences between the DOACs.

Cost-effectiveness/ affordability	The NHS expects to spend more on DOACs in the future than today as more patients with atrial fibrillation (AF) are diagnosed and treated. The intent of the recent NHSE procurement exercise (concluded in October 2021) was that any savings released would allow more patients with AF and other cardiovascular disease (CVD) to be diagnosed and treated. The NHSE commissioning recommendations outline the best value treatment choices and if followed, will make it more affordable to treat these additional patients. The framework prices are commercial in confidence.
Monitoring	Where applicable, uptake of edoxaban will be monitored as part of the Primary Care Investment and Impact Fund (IIF) and can be monitored via the GM BI tool: http://nww.bigmcsu.salford.nhs.uk/sites/mm/Pages/Home.aspx
Patient perspective	Direct oral anticoagulants are an effective treatment to reduce the risk of stroke for patients who have atrial fibrillation. The recent procurement exercise undertaken by NHS England enables more patients to be treated for the same cost to the NHS. To maximise these benefits, prescribers in Greater Manchester are advised to use the lowest cost DOAC as the first line treatment, this is currently edoxaban.
References and further information	• https://www.england.nhs.uk/wp-content/uploads/2022/01/B1279-national-procurement-for-DOACs-commissioning-recommendations-v1.pdf • https://www.sps.nhs.uk/wp-content/uploads/2019/07/DOACs-in-Renal-Impairment-Practice-Guide-to-Dosing-Issues-v3-Feb-2020-AW.pdf • https://rdtc.nhs.uk/prescribing-support-document/comparison-of-doacs-for-atrial-fibrillation/ • Lopez-Lopez et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359:j5058.