NHS
Cheshire and Merseyside

Frequently Asked Questions - Medicines Optimisation of Direct-Acting Oral Anticoagulants (DOACs) for Atrial Fibrillation (AF) Programme

Rationale for Programme

- Cheshire and Mersey Integrated Care Board (ICB) advocate ongoing routine Direct Oral Anticoagulant (DOAC) or non-vitamin K antagonist oral anticoagulant (NOAC) medicine optimisation reviews for stroke prevention in AF. This position is supported by the Northwest Cardiac Strategic Clinical Network and Joint Cardiovascular Board.
- All patients on a DOAC for AF should have a medicine optimisation review to ensure their existing DOAC is appropriate according to recent bloods, age and weight. All patients prescribed any oral anticoagulant (OAC) should discuss the options with a healthcare professional at least once a year (NICE QS93 2015) . Adherence should be assessed regularly to support patients to take medication appropriately and safely. Stroke and bleeding risk will change over time and must be recalculated at least annually. Blood monitoring including Haemoglobin (Hb), liver and renal function should be monitored at least annually, and more regularly in people with renal dysfunction, over the age of 75 years or those who are frail (see separate document - SOP, appendix 1, table 1).
- NICE Guidance (NG196 2021) states that “For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation (taking into account MHRA advice on direct-acting oral anticoagulants about bleeding risk and the need to monitor renal function in patients with renal impairment) at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk”.
- Currently, all DOACs (apixaban, edoxaban, dabigatran and rivaroxaban) are recommended as options for anticoagulation in the NICE AF Guidelines (National Institute for Health and Care Excellence, 2021) considering individual patient bleeding risks and co-morbidities.
- There are no head-to-head comparative trials that demonstrates that one DOAC is significantly better than another and treatment should be based on individual patient factors and bleeding risk.
- NHSE commissioning recommendations for national procurement for DOACs (NHSE 2024) are that those patients commencing treatment for AF: subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should use the best value DOAC that is clinically appropriate for the patient. All patients prescribed a DOAC should have a review of treatment and dose within the past 12 months.
- Generic apixaban is the first line DOAC for new initiation across Cheshire and Mersey unless there is a contraindication or it is not clinically appropriate.
- Where once daily dosing is required, rivaroxaban is the best value DOAC unless there is a high risk of bleeding (see DOACs in AF Decision Aid), where edoxaban may be used.
- NHS Cheshire and Mersey ICB encourage routine DOAC medicines optimisation reviews to be undertaken in accordance with NICE recommendations It is recognised that the DOAC medicines optimisation may not currently be in funded planned work within PCNs.

What is non-valvular atrial fibrillation (AF)?

- The most recent European Society Cardiology guidance on AF (ESC 2020) suggests replacing the historic term ‘non-valvular’ AF with reference to the specific underlying conditions.

- The term “valvular AF" refers to patients with mitral stenosis (moderate or severe) or mechanical heart valves and such patients should be considered only for warfarin therapy for stroke prevention.
- The term “non-valvular AF” therefore encompasses cases of AF in the absence of the above. For the purposes of this review, all patients with AF will be reviewed.
- Biological valve replacements, or other valvular heart conditions, such as mitral regurgitation, aortic stenosis and aortic regurgitation, do not tend to result in conditions of low flow in the left atrium, and therefore are not thought to further increase the risk of thromboembolism brought by AF. This group of patients, when it comes to choice of oral anticoagulation, can also be included under the term non-valvular AF and the choice of oral anticoagulant (OAC) could include either warfarin or a DOAC.
- Edoxaban can be used 3 months after implantation of a bioprosthetic heart valve within the license. Apixaban, rivaroxaban and dabigatran do not recommend their use with any prosthetic valve in the SPC.

Individual patient considerations - *Which patients should not be prescribed a DOAC?*

- Creatinine Clearance (CrCl) <15ml/min in patients for apixaban, edoxaban and rivaroxaban are contraindicated and not appropriate – refer to the GP to review if anticoagulation appropriate and warfarin should be used if required.
- Patients with CrCl <30mls/min are contraindicated with dabigatran. It is advisable that if CrCl falls below 50mls/min then an alternative DOAC be considered other than dabigatran.
- Metallic heart valves – warfarin is recommended for these patients. DO NOT use a DOAC in a patient with a metallic heart valve as this is contraindicated.
- DOACs are contraindicated for those who are pregnant or breast feeding.
- A non-significant trend towards decreasing efficacy with increasing creatinine clearance >80mls/min was observed for edoxaban compared to well-managed warfarin and the SPC advises that it should be used with caution. However, all DOACs have some degree of renal clearance and all three Factor Xa inhibitors show the same trend to decreasing efficacy with increasing creatinine clearance. DOAC use is not contraindicated and therefore could be used in this population.
- See the SPC for each DOAC for a full list of contraindications.

Can DOACs be used in patients with extremes of weight?

- Patients with a BMI > 40 kg/m^2 or weight >120kg have traditionally been considered for warfarin as first line due to limited evidence for efficacy in this patient population.
- Newer evidence indicates that in patients with nonvalvular AF, DOACs compared to warfarin were associated with better safety and effectiveness across all BMI categories, including underweight and morbidly obese patients (Barakat et al., 2021) (Lee et al., 2021) (Jamieson et al., 2022) (Salah et al., 2023).

Consideration of patients with a higher risk of bleeding.

- Decision aid flow charts have been developed with advice from regional experts to ensure the appropriate DOAC is prescribed considering individual patient characteristics when initiating a de novo DOAC and when reviewing existing DOAC therapy.
- There are no head-to-head comparative trials between the four DOACs, however apixaban and dabigatran 110mg BD have not shown a significant increase in gastrointestinal (GI) bleeds unlike other DOACs (Lip et al., 2018).

- Proton pump inhibitors (PPIs) may be considered to reduce the risk of GI bleeding, especially those with a history of GI bleeding or ulcer and patients requiring concomitant use of antiplatelet therapy (Steffel et al., 2021).
- Rivaroxaban is associated with a higher overall risk of GI bleeding compared to other DOACs. If once daily dosing is required in patients with a high risk of bleed, then edoxaban is preferred (Suwa et al., 2023).
- Patients who have mild reflux or indigestion or who are on other medication that may increase the risk of GI bleed (e.g. aspirin, SSRI, bisphosphonate) can be initiated on a DOAC with a proton pump inhibitor (PPI) (Lee et al., 2024).

Will we need to change again if the price of other DOACs reduces?

- The proposed DOAC medicine optimisation review has been developed to ensure a consistent approach is taken to support the regular review of DOAC prescribing. The required frequency of the DOAC monitoring should be based on guidance and individual patient circumstances (see separate document - SOP appendix I, table 1).
- NHS Cheshire and Mersey ICB recommend that the routine DOAC medicines optimisation reviews should continue to be undertaken.
- Apixaban and rivaroxaban are now generically available which makes them the best value DOACs. Dabigatran is also available as a generic.
- NHSE recommends that clinicians should use the best value DOAC that is clinically appropriate for the patient.

Is the preferred/recommended DOAC for specific patient cohorts evidence based?

- Real-world evidence in AF patients have found that DOACs were more effective than warfarin at reducing stroke risk and lowered the risk of all-cause mortality, cerebral haemorrhage, and severe bleeding in AF patients compared to warfarin.
- This guidance is based on NHSE (2024) recommendations.

Should HAS-BLED or ORBIT be used to assess bleeding risk in AF patients?

- The appropriate use of bleeding risk assessment is to focus on modifiable bleeding risk factors for mitigation, and to flag up high bleeding risk patients for early review and follow up. NICE AF Guidelines (National Institute for Health and Care Excellence, 2021) recommends using the ORBIT tool to assess bleeding risk for patients with AF. This is currently not available in EMIS.
- The bleeding risk tools are not intended to aid decision making on whether to anticoagulate or not but a means to reduce bleeding risk.
- HAS-BLED was the tool previously used to assess bleeding risk in AF patients and is still available on EMIS and a score will be pulled into the EMIS template for DOAC reviews. NICE states other bleeding risk tools can be used if embedded in EMIS until ORBIT is established. Solely using ORBIT to assess the bleeding risk may categorise a great proportion of patients into the very low risk category and it does not take into consideration modifiable risk factors (Proietti et al., 2021). Also, HAS-BLED is supported by prospective trial evidence, with appropriate use associated with less major bleeding and an increase in oral anticoagulation uptake (Guo et al., 2020). Therefore, the following should be assessed and support offered if appropriate:

    - Uncontrolled hypertension (see NICE's guideline on hypertension in adults)

- Concurrent medication, including antiplatelets, selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs)
- Harmful alcohol consumption (see NICE's guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence)
- Reversible causes of anaemia

Undertaking individual patient reviews ***- Do I need to use the Cockcroft-Gault equation to estimate renal function or can I use eGFR?***

- All DOACs may require a dose adjustment based on renal impairment.
- Renal function should be calculated using the Cockcroft and Gault equation using **actual body weight** as per the trials and licensed information.
- **Creatinine clearance must be used for calculating renal function** using the Cockcroft and Gault equation (see below). eGFR is **not** a suitable alternative:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 1.04 \text{ (female) or } 1.23 \text{ (male)}}{\text{serum creatinine (micromol/l)}}$$

- The actual body weight must be used to calculate CrCl.

NB The clinical system mainly used in primary care (EMIS) has an inbuilt Cockcroft-Gault based renal function calculator which can be used to dose DOACs by selecting to use actual body weight. The pharmaceutical industry was contacted, and they confirmed that it was actual body weight used in the clinical trials for AF with all DOACs. Please check your local clinical system.

- Another option is to use the MD+ CALC Creatinine Clearance calculator (it can be downloaded as an app to an apple or android device). Always use the most up to date values and check the default units are correct when entering weight, serum creatinine and height. It would be good practice for the clinician reviewing the patient to document what method was used.

Undertaking individual patient reviews – Considerations with concurrent antiplatelet therapy (National Institute for Health and Care Excellence, 2020) (Steffel et al., 2021a)

- Before initiating a DOAC, or when reviewing patients on existing DOAC treatment, concurrent antiplatelet should be reviewed.
- In general, triple therapy (dual antiplatelet therapy plus anticoagulation) is not recommended for most patients due to an increased risk of bleeding. If triple therapy is needed, a short duration (e.g., no more than 30 days) is recommended.
- Following cardiac intervention, OAC plus a single antiplatelet (usually clopidogrel 75mg) for up to 12 months may be recommended, then continue OAC monotherapy. Triple therapy should only be given on the advice of a Cardiologist.
- For percutaneous coronary intervention (PCI) with stable ischaemic heart disease or acute coronary syndrome, use of OAC plus a $P2Y_{12}$ inhibitor for no more than 12 months is recommended, followed by oral anticoagulation alone.
- Patients with cerebrovascular disease and AF, who don't need carotid surgery, oral anticoagulation monotherapy is recommended.

- For patients who undergo a carotid endarterectomy, a short course of anticoagulation plus aspirin may be recommended in the post operative period, duration to be specified by vascular consultant, followed by oral anticoagulation alone.
- For patients undergoing endovascular procedures in interventional radiology who are already on a DOAC, should have a DOAC plus aspirin for 6 months post procedure followed by oral anticoagulation alone.
- Patients undergoing vascular surgical procedures may be recommended a short course, duration to be specified by the vascular consultant, of DOAC plus aspirin. Upon completion of the course the oral anticoagulation can be continued alone.
- A proton pump inhibitor (PPI) is recommended for patients on concurrent OAC and antiplatelet treatment.

Undertaking individual patient reviews – Considerations when CrCl >95mls/min

- The Cheshire and Mersey regional viewpoint is that DOACs can be used if CrCl>95mls/min
- There was a trend towards decreasing efficacy with increasing CrCl observed for edoxaban compared to well-managed warfarin. The data from the trials was non-significant and in small patient numbers. There were no statistically significant differences for any of the endpoints in the study (Giugliano et al., 2013).The EHRA (Steffel et al., 2021a) states that decreased efficacy of edoxaban 60 mg OD compared with warfarin was observed in patients with a CrCl of >95 mL/min. Interestingly, as a result of these findings, further post hoc analyses revealed a similar effect also for Rivaroxaban and Apixaban." The references for this are no longer available on the FDA site but a similar table for apixaban was presented in a conference abstract earlier last year (Hijazi et al., 2015). Although there was an apparent decrease in relative efficacy to prevent arterial thromboembolism in the upper range of CrCl, the safety and net clinical benefit of edoxaban compared with warfarin are consistent across the range of renal function (Bohula et al., 2016)

Undertaking individual patient reviews - *What happens if a patient has more than one indication to be on a DOAC?*

- There are several reasons why a patient might be taking a DOAC either for a fixed period of time or for the long-term.
- All DOACs are licenced and approved by NICE for stroke prevention in AF and treatment of a DVT/PE. Some DOACs are also used for thromboprophylaxis following joint replacement. This medicine optimisation review project is focussing on patients receiving a DOAC for stroke prevention in AF. If a patient is on a long-term DOAC for another indication it is advisable to confirm the dose and treatment length is appropriate.
- Rivaroxaban and apixaban remains the first choice agent depending on local formulary for the treatment of DVT and PE. The use of edoxaban and dabigatran to treat DVT/PE requires initial treatment with heparin for 5 days and is not necessarily a suitable first choice for this indication.
- Patients on a DOAC for a DVT/PE more than 6 months prior should be reviewed to ensure the DOAC and dose is still appropriate and adjust accordingly.
- Patients on a DOAC for an off-license indication as recommended by a specialist should not be changed to another DOAC without discussing with the specialist.

Undertaking individual patient reviews - *If clinically appropriate how do I change a patient to an alternative DOAC?*

- If patients require a change in DOAC due to clinical need, discuss the change in prescription with the patient and issue/arrange a prescription for the new DOAC with verbal and written explanation of how to change from one to another.
- Advise to use up the supply of existing DOAC before changing to the new DOAC.
- Advise to change to the new DOAC when the next dose of the existing DOAC would be due then continue as per the new dosage regime (see SOP for DOAC reviews in AF patients).

Undertaking individual patient reviews - *What drugs interact with DOACs and what should I do about them?*

- As with other anticoagulants, the risk of bleeding is increased if DOACs are used in combination with one or more antiplatelet drugs. This combination may be clinically appropriate in certain circumstances, but this should only be prescribed on the advice of a specialist and a clear treatment plan describing the intended duration of treatment.
- As with all anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets.
- Chronic use of NSAIDs with DOACs is not recommended due an increased clinically relevant risk of bleeding.
- All DOACs should be checked for clinically relevant interactions and adjusted accordingly – see SPC of individual DOACs and appendix 4, table 7 from the SOP.

Undertaking individual patient reviews - *Can DOACs go into a patient compliance device or be crushed?*

- There are no known issues with using apixaban, edoxaban and rivaroxaban in a compliance device.
- Dabigatran capsules must be stored within the manufacturer's original packaging (aluminum foil strips/bottles) to prevent physical instability. It is therefore not suitable for dispensing in compliance aids.

Undertaking individual patient reviews - *Is there an antidote to DOACs?*

- There are reversal agents available for both thrombin inhibitors and Xa inhibitors which could be considered if rapid reversal is required.
- Andexanet alpha is a reversal agent for factor Xa inhibitors and is licensed for apixaban and rivaroxaban.
- Andexanet alpha may be used off-license for patients on edoxaban as it is also a factor Xa inhibitor although this must be documented in the notes and the patient informed.
- Off-license use with edoxaban has been agreed across the region and is recommended by the Northwest Cardiology Strategic Clinical Network.
- Andexanet alpha is only approved for certain clinical situations e.g. life-threatening gastrointestinal bleeds.
- Idarucizumab is an available reversal agent for dabigatran, a thrombin inhibitor. This should be reserved for serious bleeds and recommended according to local guidelines.

Ongoing review of patients prescribed DOACs - *What happens if renal function changes?*

- If renal function decreases significantly then the DOAC dose may need to be reviewed.
- DOACs are not recommended if the CrCl is <15ml/min for apixaban, edoxaban and rivaroxaban or CrCl <30mls/min for dabigatran. These patients should receive warfarin if there is a clinical indication for long-term anticoagulation.
- If CrCl <50mls/min avoid dabigatran unless specifically indicated.
- Alternatively, if a reduced dose of a DOAC has been started during an acute impairment of renal function, then the dose will need to be reviewed if renal function subsequently improves.
- These optimisation reviews should facilitate a regular review to ensure patients who have a change in renal function are managed appropriately.

Ongoing review of patients prescribed DOACs (Steffel et al., 2021b) ***- How often do I need to check weight, renal function, haemoglobin (Hb) and liver function tests (LFTs)?***

- At initiation of treatment or when changing to an alternative DOAC, the renal function should have been confirmed within the last 3 months.
- Thereafter, renal function, Hb and LFTs should be monitored as per the table below:

Monitoring for DOACs	
Interval	**Patient Cohort**
Yearly	Patients other than those specified below
4 - monthly	≥75 years (especially if on dabigatran) or frail
X - monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10 (giving the X monthly value)
If needed	Any intercurrent condition that may impact renal or hepatic function (e.g. infection, NSAID use, dehydration etc.)

- At initiation of treatment or when changing to an alternative DOAC, the weight should have been recorded within the previous 3 months. If there has been recent acute illness or there is evidence of a suspicion of weight loss/gain, a more recent weight should be obtained.
- Once a patient has been reviewed and confirmed to be on the appropriate dose of DOAC, weight should be checked and reviewed annually or more frequently if intercurrent illness is causing weight fluctuations.

Reference list

Barakat, A.F., Jain, S., Masri, A., Alkukhun, L., Senussi, M., Sezer, A., Wang, Y., Thoma, F., Bhonsale, A., Saba, S. and Mulukutla, S. (2021). Outcomes of Direct Oral Anticoagulants in Atrial Fibrillation Patients Across Different Body Mass Index Categories. *JACC: Clinical Electrophysiology*, 7(5), pp.649–658. doi:https://doi.org/10.1016/j.jacep.2021.02.002.

Bohula, E.A., Giugliano, R.P., Ruff, C.T., Kuder, J.F., Murphy, S.A., Antman, E.M. and Braunwald, E. (2016). Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation*, [online] 134(1), pp.24–36. doi:https://doi.org/10.1161/circulationaha.116.022361.

Giugliano, R.P., Ruff, C.T., Braunwald, E., Murphy, S.A., Wiviott, S.D., Halperin, J.L., Waldo, A.L., Ezekowitz, M.D., Weitz, J.I., Špinar, J., Ruzyllo, W., Ruda, M., Koretsune, Y., Betcher, J., Shi, M., Grip, L.T., Patel, S.P., Patel, I., Hanyok, J.J. and Mercuri, M. (2013). Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*, [online] 369(22), pp.2093–2104. doi:https://doi.org/10.1056/nejmoa1310907.

Guo, Y., Lane, D.A., Chen, Y., Lip, G.Y.H. and mAF-App II Trial investigators (2020). Regular Bleeding Risk Assessment Associated with Reduction in Bleeding Outcomes: The mAFA-II Randomized Trial. *The American Journal of Medicine*, [online] 133(10), pp.1195-1202.e2. doi:https://doi.org/10.1016/j.amjmed.2020.03.019.

Hijazi, Z., Hohnloser, S.H.H., Andersson, U., Alexander, J.H., Granger, C.B., Hanna, M., Keltai, M., Parkhomenko, A., Lopez-Sendon, J.L., Lopes, R.D., Siegbahn, A. and Wallentin, L. (2015). Abstract 12404: Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation and Normal Renal Function over Time: Insights From the ARISTOTLE Trial. *Circulation*, 132(suppl_3). doi:https://doi.org/10.1161/circ.132.suppl_3.12404.

Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J.J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G.-A., Dilaveris, P.E., Fauchier, L., Filippatos, G., Kalman, J.M., La Meir, M., Lane, D.A., Lebeau, J.-P., Lettino, M., Lip, G.Y.H., Pinto, F.J. and Thomas, G.N. (2020). 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, 42(5). doi:https://doi.org/10.1093/eurheartj/ehaa612.

Jamieson, M.J., Byon, W., Dettloff, R.W., Crawford, M., Gargalovic, P.S., Merali, S.J., Onorato, J., Quintero, A.J. and Russ, C. (2022). Apixaban Use in Obese Patients: A Review of the Pharmacokinetic, Interventional, and Observational Study Data. *American Journal of Cardiovascular Drugs*, 22(6), pp.615–631. doi:https://doi.org/10.1007/s40256-022-00524-x.

Lee, S.-R., Ahn, H.-J., Choi, E.-K., Park, S.-H., Han, K.-D., Oh, S. and Lip, G.Y.H. (2024). Reduction of Upper Gastrointestinal Bleeding Risk With Proton Pump Inhibitor Therapy in Asian Patients With Atrial Fibrillation Receiving Direct Oral Anticoagulant: A Nationwide Population-based Cohort Study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, [online] 22(5), pp.981-993.e11. doi:https://doi.org/10.1016/j.cgh.2023.12.022.

Lee, S.-R., Choi, E.-K., Jung, J.-H., Park, S.-H., Han, K.-D., Oh, S. and Lip, G.Y.H. (2021). Body Mass Index and Clinical Outcomes in Asian Patients With Atrial Fibrillation Receiving Oral Anticoagulation. *Stroke*, 52(2), pp.521–530. doi:https://doi.org/10.1161/strokeaha.120.030356.

Lip, G.Y.H., Banerjee, A., Boriani, G., Chiang, C.E., Fargo, R., Freedman, B., Lane, D.A., Ruff, C.T., Turakhia, M., Werring, D., Patel, S. and Moores, L. (2018). Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*, [online] 154(5), pp.1121–1201. doi:https://doi.org/10.1016/j.chest.2018.07.040.

National Institute for Health and Care Excellence (2020). *Overview | Acute coronary syndromes | Guidance | NICE*. [online] www.nice.org.uk. Available at: https://www.nice.org.uk/Guidance/NG185.

National Institute for Health and Care Excellence (2021). *Overview | Atrial fibrillation: diagnosis and management | Guidance | NICE*. [online] www.nice.org.uk. Available at: https://www.nice.org.uk/guidance/ng196.

NHS England (2024). *NHS England» Operational note: Commissioning recommendations for national procurement for direct-acting oral anticoagulant(s) (DOACs)*. [online] www.england.nhs.uk. Available at: https://www.england.nhs.uk/long-read/commissioning-recommendations-for-national-procurement-for-doacs/.

NICE (2015). *Overview | Atrial fibrillation | Quality standards | NICE*. [online] www.nice.org.uk. Available at: https://www.nice.org.uk/guidance/qs93.

Proietti, M., Romiti, G.F., Vitolo, M., Potpara, T., Boriani, G. and Lip, G.Y.H. (2021). Comparison of HAS-BLED and ORBIT bleeding risk scores in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants: a report from the ESC-EHRA EORP-AF General Long-Term Registry. *European Heart Journal - Quality of Care and Clinical Outcomes*, 8(7). doi:https://doi.org/10.1093/ehjqcco/qcab069.

Salah, Q.M., Bhandari, S., Chand, A., Khan, S., Tirmzi, A., Sheikh, M., Khaldoun Khreis and Palleti, S.K. (2023). The Effectiveness and Safety of Direct Oral Anticoagulants in Obese Patients With Atrial Fibrillation: A Network Meta-Analysis. *Curēus*. doi:https://doi.org/10.7759/cureus.41619.

Steffel, J., Collins, R., Antz, M., Cornu, P., Desteghe, L., Haeusler, K.G., Oldgren, J., Reinecke, H., Roldan-Schilling, V., Rowell, N., Sinnaeve, P., Vanassche, T., Potpara, T., Camm, A.J. and Heidbüchel, H. (2021a). Corrigendum to: 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *EP Europace*, 23(10), pp.1676–1676. doi:https://doi.org/10.1093/europace/euab157.

Steffel, J., Collins, R., Antz, M., Cornu, P., Desteghe, L., Haeusler, K.G., Oldgren, J., Reinecke, H., Roldan-Schilling, V., Rowell, N., Sinnaeve, P., Vanassche, T., Potpara, T., Camm, A.J., Heidbüchel, H., Lip, G.Y.H., Deneke, T., Dagres, N., Boriani, G. and Chao, T.-F. (2021b). 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *EP Europace*, 23(10). doi:https://doi.org/10.1093/europace/euab065.

Suwa, M., Nohara, Y., Isao Morii and Kino, M. (2023). Safety and Efficacy Re-Evaluation of Edoxaban and Rivaroxaban Dosing With Plasma Concentration Monitoring in Non-Valvular Atrial Fibrillation: With Observations of On-Label and Off-Label Dosing. *Circulation reports*, [online] 5(3), pp.80–89. doi:https://doi.org/10.1253/circrep.cr-22-0076.

Written on behalf of the Cheshire and Merseyside healthcare partnerships (HCP), Cheshire and Merseyside Medicines Optimisation Steering Group, Cheshire and Merseyside Cardiac Strategic Clinical Network and Cheshire and Merseyside Cardiovascular Board. With thanks to:

Jo Bateman (Consultant)	Heart Failure Service Lead/Lead Cardiology Pharmacist, Countess of Chester Hospital NHS Foundation Trust. Lead Pharmacist, Cheshire and Mersey Cardiac Network. North-West Coast clinical networks
Prof Gregory Lip	Price-Evans Chair of Cardiovascular Medicine, at the University of Liverpool, UK – and Director of the Liverpool Centre for Cardiovascular Science at the University of Liverpool and Liverpool Heart & Chest Hospital.
Dr Joe Mills	Consultant Cardiologist, Liverpool Heart and Chest NHS Trust. UK National CVD Prevention Co-Ordinator (affiliated role between the British Cardiovascular Society and the European Society of cardiology). Cardiac Lead for the North-West Coast clinical networks
Susanne Lynch	Chief Pharmacist, Cheshire and Mersey Integrated Care System
Dr Tina Dutt	Consultant Haematologist, Roald Dahl Haemostasis and Thrombosis Centre, Associate Medical Director – Patient Experience, Liverpool University Hospitals NHS Foundation Trust, NIHR CRN NWC SRG Lead for Haematology, NHSE Blood Disorders CRG
Dr Nikhil Sharma	Clinical Lead for Stroke – Cheshire and Mersey Integrated Stroke Delivery Network
Prof Deirdre Lane	Professor of Cardiovascular Health, Liverpool Centre for Cardiovascular Sciences, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK
Dr John Paul Bishop	GP Partner Lawton House Surgery, Clinical Director Congleton and Holmes Chapel PCN. Clinical Lead Thriving, Surviving & Prevention Programme Cheshire CCG. Primary Care Clinical Lead Cheshire & Mersey Cardiac Network
Dr Sue Kemsley	GP partner Swanlow Medical Centre, Winsford, Cheshire. Primary care clinical lead for Cheshire and Mersey Strategic Cardiac Network. Primary Care Clinical Lipid Lead for Innovation Agency
Dr Stephen McGoldrick	Consultant Gastroenterologist, Countess of Chester Hospital NHS Foundation Trust
Mr Gareth Harrison	Vascular Lead Consultant, Countess of Chester Hospital NHS Foundation Trust

Acknowledgement to Tayside NHS Trust
Version 1 December 2021
Version 2 Sept 2022
Version 25th February 2025
Review date February 2027 or sooner if new information becomes available