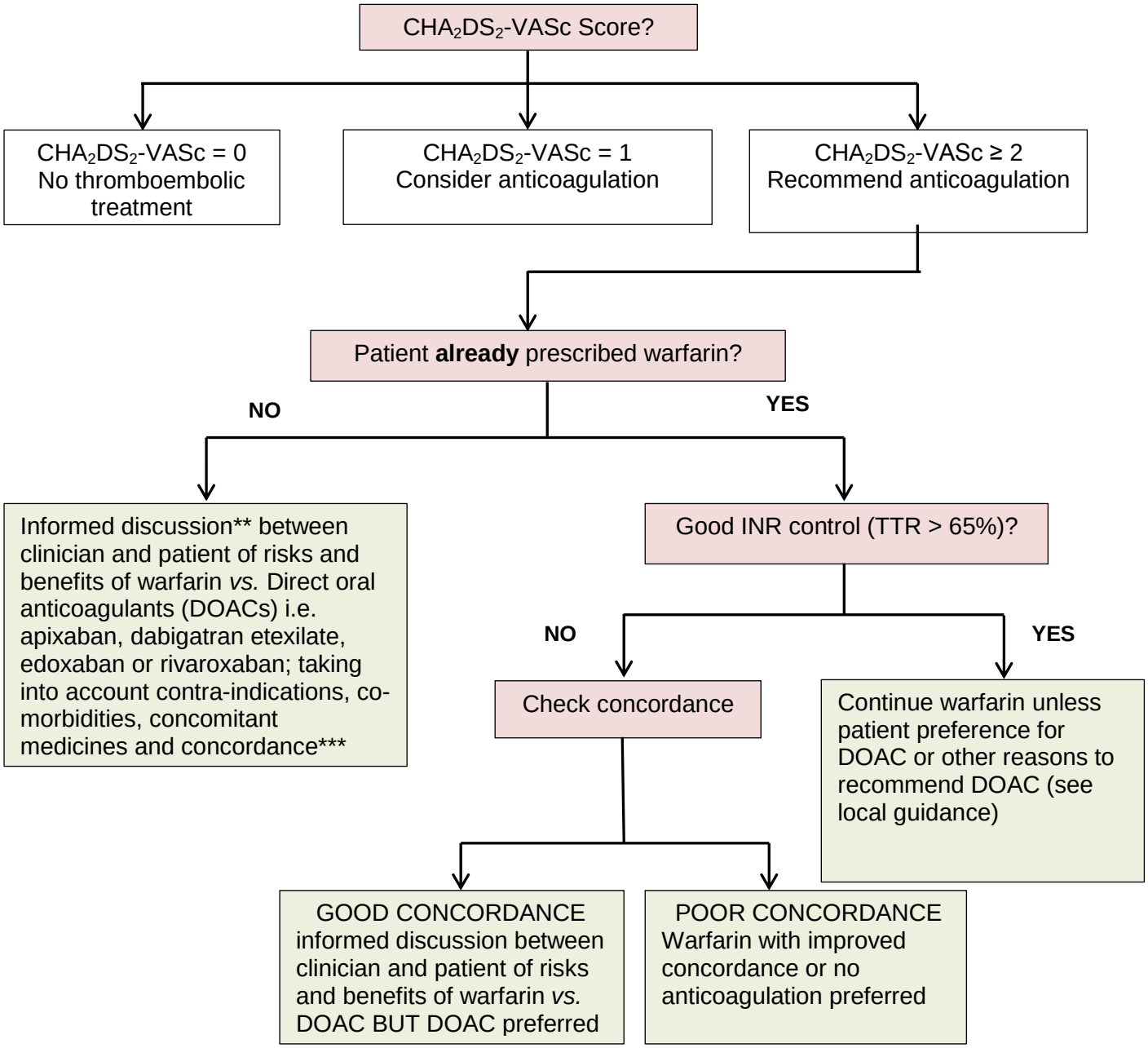
Treatment Pathway – Prevention of Stroke and Systemic Embolism in Adults with Non-Valvular Atrial Fibrillation

Use CHA_2DS_2-VASc to risk stratify thromboembolic risk in non-valvular atrial fibrillation (AF)
Use HAS-BLED* to stratify bleeding risk (ref: NICE Clinical Guideline 180)



*HAS-BLED ≥3, high bleeding risk, consider reversible causes for bleeding e.g. aspirin/NSAID use, uncontrolled hypertension, labile INR, and consider risk of bleeding *vs.* risk of stroke – usually the balance remains in favour of stroke prevention.
**Patient FAQs can be found at http://www.southworcsccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=36455
*** Caution with DOAC in patients with high bleeding risk including: very elderly e.g. age >80, previous bleeding event, HAS-BLED ≥3, low body weight < 60kg, renal impairment (Manufacturers advise to avoid apixaban if eGFR< 15ml/min; dabigatran contraindicated if eGFR<30ml/min; avoid edoxaban if eGFR< 15ml/min, rivaroxaban contraindicated if eGFR<15ml/min, caution if eGFR 15-30ml/min).

INR = International Normalised Ratio; TTR = Time to Therapeutic Range; eGFR: estimated Glomerular Filtration Rate

- **Aspirin is not recommended as an alternative to anticoagulation for stroke prevention in AF (NICE CG 180)**
- **For the purpose of this treatment pathway non-valvular AF may be defined as AF in the absence of mitral stenosis or a prosthetic mitral valve.**
- **Once a diagnosis of atrial fibrillation (AF) and decision to anticoagulate a patient has been made, National Institute for Health and Care Excellence (NICE) requires a prescriber to discuss the treatment options with the individual patient and the treat appropriately.**

Potential advantages of warfarin

- Warfarin has been prescribed for more than 50 years and remains an established and cost effective option for anticoagulation in patients.
- Anticoagulant effect is measured routinely, enabling concordance to be assessed.
- Easier to manage acute major bleeding with warfarin.
- Poor concordance with warfarin is not an indication for initiating a DOAC. Patients with poor concordance may be at greater risk of thromboembolic complications with DOACs as their shorter half-lives will potentially result in more time without any degree of anticoagulation.
- There is no long-term safety data for any of the DOACs and limited knowledge about their use in certain groups; e.g. high bleeding risk, severe renal impairment, liver dysfunction, mechanical heart valves.

Potential advantages of DOACs

- No need for routine anticoagulant monitoring
- DOAC dosing regimens are uncomplicated and a more stable level of anticoagulation is achieved with full concordance.
- DOACs provide immediate anticoagulant effect (time to peak effect ranges from 1-4 hours); warfarin time to peak effect ranges from 3-5 days.
- Fewer potential interactions with other medications, alcohol and diet.
- All three DOACS reduced the risk of intracranial bleeding compared to warfarin in clinical trials.

Efficacy

- Warfarin has been used for over 50 years and has proven long term efficacy. Dabigatran 150mg twice daily reduced the rate of stroke compared to warfarin with a similar rate of major bleeding in the RE-LY trial[1]. Dabigatran 110mg twice daily was associated with a rate of stroke comparable to warfarin, but a lower rate of major bleeding. These modest benefits appeared to decrease with improving INR control.
- Rivaroxaban was non-inferior to warfarin in reducing the rate of stroke, with comparable rate of major bleeding in the ROCKET-AF trial[2].
- Apixaban use resulted in modest reductions in the rates of stroke and major bleeding and reduced mortality compared to warfarin in the ARISTOTLE trial[3].
- Edoxaban was found to be non-inferior to warfarin in the ENGAG AF-TIMI 48 trial, although there was a trend towards less favourable outcomes in patients with normal renal function.[4]
- Differences between study populations, study designs, and times within target INR range limit the comparisons which can be drawn between apixaban, dabigatran, edoxaban and rivaroxaban.
- Limited long term safety and efficacy data available for DOACs; patients were followed up for 2 years in the RE-LY trial[1], 1.9 years in the ROCKET-AF trial[2], 1.8 years in the ARISTOTLE trial[3] and 2.8 years in the ENGAG AF-TIMI 48 trial[4].
- NICE concluded that there was not sufficient data to differentiate between apixaban, rivaroxaban and dabigatran clinically or in cost effectiveness. Edoxaban was not licensed when NICE Clinical Guideline 180 was published.

Safety

- Warfarin has long term safety data and a known profile.
- In RE-LY[1], dabigatran150mg and warfarin had comparable rates of major bleeding, reduced antidote
- Dabigatran 110mg had a lower rate of major bleeding than warfarin.
- In ROCKET-AF[2], the risk of major bleeding was comparable between rivaroxaban and warfarin. Rivaroxaban reduced the risk of intracranial bleeding, but increased the risk of major GI bleeding.

- Apixaban was shown in the ARISTOTLE[3] study to reduce the risks of all cause death, major bleeding, non major bleeding and any bleeding.
- Bleeding risk with dabigatran and rivaroxaban is increased in patients aged >75 years. Bleeding risk on dabigatran is also increased with impaired renal function or low body weight (<50 kg)
- In ENGAG AF-TIMI 48, bleeding rates appear to be lower than warfarin for edoxaban but other DOACs have a less complex relationship with renal function.[4] The SPC states: *trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with non-valvular AF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.*

Licences for DOACs

All the current DOACs are licensed as an option for the prevention of stroke and systemic embolism in people with **non-valvular** AF with one or more of the following risk factors:

Risk factors	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Previous stroke, TIA or systemic embolism	✓ **(but not systemic embolism)**	✓	✓ **(but not systemic embolism)**	✓**(but not systemic embolism)**
LV ejection fraction below 40%		✓		
Symptomatic heart failure NYHA class 2 or above	✓	✓	✓	✓
Age 75 years or older	✓	✓	✓	✓
Age 65 years or older with either diabetes mellitus, CAD or hypertension		✓		
Hypertension	✓		✓	✓
Diabetes Mellitus	✓		✓	✓

Please note: patients at the lower stroke risk age 65 with no other risk factors than gender would be recommended for anticoagulation, but would not be licensed for treatment with a DOAC.

NICE specifically recommend within CG182:CKD – early identification and management of chronic kidney disease in adults in primary and secondary care; that apixaban be considered in preference to warfarin in people with a confirmed eGFR of 30-50ml/min/1.73m^2 and non-valvular AF who have one or more of the follow-up risk factors:

- Prior stroke or transient ischaemic attack
- Age 75 years or older
- Hypertension
- Diabetes Mellitus
- Symptomatic heart failure

Summary of Product Characteristics (SPC)*

Please refer to the relevant SPC and patient information leaflet (PIL) provided by the manufacturers with regards to dosing, cautions, contra-indications, interactions and side-effect profile so as to ensure the most current information is referred to. SPC Links: **Apixaban, **Dabigatran**, **Edoxaban**, **Rivaroxaban**

Patient alert cards are available for all oral anticoagulants and should be made available to patients when they are initiated on treatment. The specific patient alert cards can be found at https://www.medicines.org.uk/emc/

NICE Clinical Guideline 180: Atrial Fibrillation (Update)

NICE has published single Technology Appraisals (TAs) for the prevention of stroke and systemic embolism in atrial fibrillation:
NICE TA275: Apixaban; **NICE TA249: Dabigatran etexilate**; **NICE TA354: Edoxaban**; **NICE TA256: Rivaroxaban**

All DOACS are available to Worcestershire patients as an option in accordance with these NICE TAs. **Worcestershire Acute Hospitals NHS Trust 'Warfarin & Other Oral Anticoagulant Drugs Guidelines & Procedures'**, based on British Committee for Standards in Haematology (BCSH) and National Patient Safety Agency (NPSA) guidance discusses the detailed management of oral anticoagulants both in the community and secondary care and are available on the Trust **intranet**.

1. Connolly SJ *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139-51. [*Erratum, N Engl J Med* 2010; 363:1877.]
2. Patel MR *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883-91
3. Granger CB *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981-92.
4. Giugliano RP *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; 369:2093-2104.