EDUCATION in HEART

Anticoagulation in atrial fibrillation

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LEARNING OBJECTIVES

- To understand the (high) prevalence of atrial fibrillation in the overall population and identify sub-groups at higher risk

- To understand the diagnostic procedures available to diagnose atrial fibrillation in patients deemed to be at higher risk, such as post-stroke

- To recognise and overcome barriers to anticoagulation

- To identify patients at higher risk of thromboembolic and haemorrhagic complications

- To understand indications for antithrombotic therapy in specific groups of AF patients

One in 3 of us will be diagnosed with Atrial Fibrillation (AF) at some point in our lives.(1) Over 1.2M individuals in the UK have been diagnosed with AF, and thousands still remain undiagnosed.(2,3) Due to the ageing population, the number of individuals with AF in Europe will double in the next 50 years(3), contrasting with a fall in the incidence of myocardial infarction and stroke over recent decades.(4,5) This shift in cardiovascular epidemiology is important as AF associates with a myriad of cardiovascular and non-cardiovascular complications (**FIGURE 1**), and contributes to a 1.5 to 2-fold increase in all-cause mortality.(6)

(7) The risk of ischaemic stroke in AF patients is 3 to 5 times higher.(7),(8) AF is found in 30% of patients admitted with ischaemic stroke and associates with a higher risk of fatal outcome.(9) The risk of AF-related stroke can be mitigated through anticoagulation, with a 66% risk reduction with vitamin-K antagonists (VKA)(10) and at least similar effectiveness with non-VKA.(11) For every 1% increase in anticoagulant use, there is a 0.8% decrease in the weekly rate of stroke.(12) Stroke rates in adequately anticoagulated AF patients are similar to those of patients without documented AF,(13) with only 1 out of 10 anticoagulated AF patients dying from stroke or bleeding.(14) This manuscript will expand on the topic of anticoagulation in AF patients.

Comprehensive AF screening is key to prevent AF-related morbidity and mortality

Despite the bulk of evidence supporting anticoagulation use for stroke prevention, many AF patients are not on this therapy. The two main reasons for this are: (i) asymptomatic arrhythmia events occur more frequently than symptomatic ones in paroxysmal AF.(15) However, silent AF episodes still matter as far as stroke risk is concerned.(16) **Secondly**, screening for AF in patients at risk is often not effective.

Detection of subclinical AF is possible through a variety of strategies and tools, including manual pulse palpation in those with suspicious symptoms,(17) external surface monitoring with intermittent 12-lead ECG, Holter monitors, portable ECG recorders or handheld single-ECG devices with automated algorithms, adhesive patch electrocardiographic monitors and smartwatches.

Intermittent short electrocardiographic recordings repeated over a longer-term period with mobile phones and smartwatches (using photoplethysmography technology) has higher sensitivity for AF detection compared with single-time point measurement.(18) Implantable cardiac monitors are a reasonable option in patients at very high risk of AF but in whom all other options failed to provide conclusive results. Cardiac electronic devices (CIED) (i.e. pacemakers and defibrillators) can facilitate AF detection, but AF overdiagnosis can also occur, as CIED-detected atrial high-rate episodes can sometimes be caused by oversensing or other atrial arrhythmias. Close inspection of the stored electrogram is mandatory, particularly if anticoagulation prescription is expected.

AF has been recognised in 20-30% of patients with a cryptogenic stroke when monitoring is long enough.(19) In this case, AF is probably causal, but often there is no temporal relationship between the detection of AF and the occurrence of stroke. Still, even the unrelated detection of AF post-stroke predicts recurrent thromboembolism. Increased AF yield from monitoring is seen not only in patients with history of ischaemic stroke of unidentified cause but also elderly patients with additional risk factors for AF, such as hypertension, diabetes mellitus or heart failure, and in those with markers of atrial myopathy, such as frequent atrial ectopy, high natriuretic peptides, dilated left atrium or significant atrial scar. Presently it is uncertain whether AF screening in the general population is cost-effective or improves health outcomes. Resources could be better invested in high-risk populations and patients with stroke of undetermined source could be a potential candidate-group. However, absence of definite data on the duration of AF requiring anticoagulation, the lack of proximate temporal relationship between AF and stroke and the unclear benefit of anticoagulation in that scenario(20,21) leads to questions about that strategy. American guidelines state that prolonged rhythm monitoring of approximately 30 days is reasonable within 6 months of a cryptogenic stroke,(22) whereas ESC guidelines recommend continuous ECG monitoring for ≥72 hours, and possibly noninvasive monitors or implantable loop recorders for longer periods of time.(23)

In summary, although the optimal AF monitoring device should ideally be non-invasive, inexpensive and simple to use, the ability to offer long-term monitoring and immediate feedback are

of paramount importance. Particularly in patients with cryptogenic stroke, screening should be performed for as long as possible. In resource-limited regions where prolonged ECG monitoring may not be possible, repeat single time point ECG is probably feasible and should be recommended. **FIGURE 2** suggests a protocol for AF screening for patients with ischaemic stroke of unidentified cause.

Overcoming barriers to anticoagulation in AF patients

Up to the early 2000s, less than 70% of high-risk AF patients were receiving adequate oral anticoagulation with VKA in most parts of the world.(24) The introduction of DOACs associated with improved rates of anticoagulation use, but up to 40-50% of AF patients may still not be on this medication (**FIGURE 3**).(25) There is a significant variability in DOAC prescription across different parts of the world, even when limiting this assessment to resource-rich countries,(25,26) and the rate of anticoagulation prescription remains far from optimal, particularly for those at highest risk. An increase in the use of DOACs in younger AF patients at lower risk of stroke has not been paralleled by a similar increase in more elderly patients at higher risk. Almost a third of AF patients presenting with stroke were naïve to any antithrombotic therapy prior to the event.(27)

Persisting barriers to appropriate antithrombotic therapy include the difficulty in diagnosing AF, inadequate risk stratification, the advanced age of the patient and a high perceived risk of falls and haemorrhage. The requirement for regular monitoring, frequent dose adjustments and dietary restrictions with VKA is less of an issue nowadays as DOACs become preferred agents. When it comes to initiating anticoagulation in elderly patients, or those at presumably high risk of falls, many physicians still hesitate. While this is understandable to some extent, as falls may lead to subdural haematomas, intracerebral haemorrhage and hip fracture bleeding, which can be life-threatening, withholding anticoagulation in elderly patients leads to increased morbidity and mortality. Warfarin is superior to Aspirin in reducing the risk of a composite endpoint of fatal or disabling stroke, intracranial haemorrhage or arterial embolism in elderly or very elderly patients,(28) with antiplatelet treatment becoming progressively less effective in reducing stroke risk with advanced age.(29)

Apixaban reduces the risk of stroke by >50% compared with aspirin among AF patients unsuitable for VKAs, while bleeding complications occur at similar rate. The superiority of Apixaban is prominent among patients ≥75.(30) For every 1000 patients aged ≥75 treated with Apixaban rather than Aspirin, 41 strokes or systemic embolisms are prevented at the expense of 4 extra major bleeds. Aspirin is no longer recommended for cardioembolic stroke prevention.

The perceived risk of falls and bleeding and concerns about impaired cognition, limited compliance (such as in those with dementia) or advanced multisystem atrophy explain why anticoagulation is often withheld in the elderly population. While elderly patients with multiple risk factors for falling, such as sedative use, cognitive impairment and gait disturbance should have closer follow-up in clinic, there is evidence that **a)** they are still at (very) low risk of anticoagulant-related major bleeding(31) and **b)** the benefits of anticoagulation outweigh its risks even in those who eventually fall.(32) Furthermore, bleeding risk perceptions often do not correlate with the actual risk of bleeding, and accurately estimating bleeding risk is difficult as most risk factors overlap with those for stroke. Although at least 2% of anticoagulated patients with AF experience bleeding events every year, ischaemic strokes are far more likely.(29)

To summarise, elderly patients in general should not be denied anticoagulation, or prescribed antiplatelet agents instead, on the assumption that they are at increased risk of falls and bleeding. Except for patients with active bleeding or severely impaired cognition and drug compliance, strong consideration should be given to a DOAC.

Anticoagulants for which AF patients?

Even among non-valvular AF patients at the highest risk category of the CHA_2DS_2-VASc score, nearly 80% will not sustain a stroke within a year in the absence of anticoagulation.(33) In the four largest AF anticoagulation trials, the annual risk of bleeding-related mortality was 2 to 3%.(34) This suggests that some patients may not need anticoagulation and could be unnecessarily exposed to a low risk of bleeding-related fatality if put on this therapy. Major bleeding represents 6% of the causes of death

in AF patients on anticoagulation.(14) This is a strong argument against the *"one size fits all"* strategy of universal anticoagulation. The CHA_2DS_2VASc score performs well at identifying patients who should not receive anticoagulants, with a high negative predictive value for the lower risk stratum. Conversely, the number of embolic events in non-anticoagulated patients outweighs that of severe bleeding episodes, and data confirm the unequivocal benefit of anticoagulation in stroke prevention. It is therefore essential that all patients are stratified for their thromboembolic and bleeding risks, as the combination of both will help the clinician and patient weight the potential benefits and risk of anticoagulation, and target correctable risk factors.

The 2014 NICE guidelines on AF recommend the use of the CHA_2DS_2-VASc score for assessing thromboembolic risk.(17) This score was derived from data from the *Euro Heart Survey on Atrial Fibrillation*(35) and its simplicity and capability of providing a broad estimate of annual stroke risk has led to its wide usage. However, it has modest discriminative performance and may be overinclusive, leading to unnecessary anticoagulation of a few patients who may not require it at that time in their lives. NICE guidelines discourage using anticoagulants in men with a CHA_2DS_2-VASc score of zero and women with a score of 1. Anticoagulation can be considered in men with a score of 1, and should be offered to individuals with a score of 2 or above. To avoid the cumbersome practice of selecting different CHA_2DS_2-VASc thresholds for males and females when recommending anticoagulation prescription, Australian clinical guidelines suggested the use of the sexless CHA_2DS_2-VA score.(36) Patients with moderate to severe mitral stenosis, hypertrophic cardiomyopathy or mechanical heart valves represent subsets of high risk patients requiring mandatory anticoagulation regardless of the CHA_2DS_2-VASc score.

Over the years, other risk scores like ATRIA,(37) R-CHA_2D_S2VASc,(38) ABC,(39) QStroke(40) and GARFIELD-AF(41) (**FIGURE 4**) were tested against CHA_2DS_2VASc but have yet failed to replace it. The potential improvement in discrimination is counterbalanced by the complexity of these tools, sometimes requiring calculators, and the need for education and training as well as validation studies.

Estimation of the risk of bleeding should also constitute a routine part of the management of AF patients. NICE recommends using the HAS-BLED score for this purpose (42). This score allows not only an estimation of the bleeding risk but also raised awareness for correctable risk factors (e.g. uncontrolled hypertension, labile INR, concomitant utilization of antiplatelet agents and non-steroidal anti-inflammatory drugs, and harmful alcohol consumption). As stroke events exceed bleeding episodes even in patients at high bleeding risk, anticoagulation should not be withheld in patients with high HAS-BLED score; rather, these patients should be reviewed regularly and modifiable bleeding risk factors addressed. As for thromboembolic risk stratification, multiple schemes have been developed (e.g. HEMORR2HAGES,(43) ATRIA,(44) ABC,(45) ORBIT,(46) GARFIELD-AF(41)) (**FIGURE 4**), and a NICE appraisal on this matter and the role of Patient Involvement in Shared-Decision Making should be made available soon.

Available anticoagulants: which one to choose?

While anti-platelet treatment is no longer recommended for this purpose, VKA have been shown to prevent 2/3 of embolic strokes and reduce all-cause mortality. However, their use is limited by its slow onset of action, multiple drug- and food-interactions, unpredictable pharmacokinetic properties and need for regular and sometimes intensive monitoring. The DOACs have more rapid onset of action, do not usually require bridging with parenteral anticoagulants, have fewer drug- or food-interactions and do not require routine monitoring. Two classes of DOACs have been developed for stroke prevention in nonvalvular AF: direct factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) and direct thrombin inhibitors (Dabigatran). A meta-analysis of all four agents showed reduced risk of stroke, intracranial bleeding and all-cause mortality, but increased risk of gastrointestinal bleeding compared with warfarin.(11) There is no evidence to suggest that any of the DOACs is superior to others, although small differences in outcomes between different agents have been suggested by large observational studies.(47)

DOACs are not recommended for patients with prosthetic heart valves or valvular AF (e.g. rheumatic mitral stenosis), in which cases VKAs are recommended. The difficulty in achieving a time in therapeutic range (TTR) >70% with VKAs associates with increased stroke and bleeding risk and these patients should be changed to a DOAC (provided there is no contraindication). For patients well controlled on a VKA, as defined by TTR >70% and lack of thromboembolic or bleeding events, it is reasonable to continue VKA treatment. However, changing to a DOAC should be considered in case of complications or patient preference. For patients naïve to any antithrombotic therapy, the decision on which anticoagulant to choose must take several aspects into consideration, including patient weight (significantly underweight or overweight patients were less represented in DOAC studies), likelihood of adherence (crucial, particularly for DOAC patients given the shorter half-life), history of renal or hepatic impairment, limitations in gut absorption (e.g. with previous gastric bypass), previous haemorrhagic events or recurrent stroke despite good drug adherence, intended pregnancy or breastfeeding (no data for DOACs), concerns with compliance and medication cost. Physicians should take an individualized approach taking the patient's preferences into consideration, as well as underlying comorbidities and estimated risks of stroke and bleeding. Importantly, inappropriate underdosing of DOACs is common and physicians should be aware of the importance of correct dosing of these drugs to guarantee its safety and effectiveness. The off-label underdosing of DOACs associates with increased risk of stroke with no significant difference in major bleeding.(48) An algorithm for helping physicians select the most appropriate anticoagulant according to the patient's characteristics is suggested in **FIGURE 5**.

Anticoagulation in specific groups of AF patients

This chapter focus briefly on the management of anticoagulation in a few specific contexts, but for more detailed recommendations interested readers should look elsewhere.(49)

<u>Cardiovascular interventions</u>

The majority of cardiovascular interventions can be performed safely on continued anticoagulation, and heparin bridging is generally not recommended as it may result in increased risk of bleeding. For those undergoing endovascular procedures or catheter ablation, consideration should be given to uninterrupted anticoagulation,(50) although temporary, short-term, discontinuation of a DOAC in patients at low stroke risk is also a reasonable strategy. AF ablation can be performed safely on uninterrupted or minimally-interrupted DOAC,(51) and heparin bridging is not recommended for these patients as it leads to increased haemorrhagic risk.(52) Continued warfarin treatment at the time of device implantation markedly reduces the incidence of clinically significant device-pocket haematoma compared with bridging therapy with heparin,(53) while continued DOAC therapy is as safe as interrupted therapy with regard to clinically significant pocket haematoma.(54) AF patients undergoing percutaneous coronary interventions should continue their anticoagulation during and after stenting, and a short period of triple therapy (anticoagulation, aspirin and clopidogrel) is recommended, followed by a period of dual therapy (preferably with anticoagulation and clopidogrel). The use of prasugrel or ticagrelor as part of triple therapy should be avoided whenever possible.

Surgical patients

The decision to withhold anticoagulation should take into consideration not only the prior assessment of thromboembolic and bleeding risk, but also the potential consequences for the patient in case of bleeding (e.g. intracranial, cardiac or neuraxial surgical interventions are of particular concern). If a decision is made to discontinue the anticoagulant due to high bleeding risk, bridging should be limited to those at high or very high thromboembolic risk. Patients with mechanical heart valves, particularly those with a mitral prosthesis, should not have their anticoagulation withheld for procedures which are not considered high-risk for bleeding events. However, when withholding anticoagulation is absolutely essential, heparin bridging is necessary. Patients undergoing low bleeding risk interventions should continue their anticoagulation (this is the case of most dental and cutaneous interventions).

Elective surgery should be delayed if possible in patients who had ischaemic stroke the preceding month, and also AF patients who were not adequately anticoagulated.

Asymptomatic AF detected by cardiac electronic devices

Approximately one-third of patients with CIED, CHA_2DS_2-VASc ≥2 and no known history of AF is shown to develop sub-clinical AF episodes lasting >6 hours.(55) This increases to almost 50% when considering episodes >6 minutes.(55) Although these patients are at increased risk of stroke,(16) the risk associated with sub-clinical, short atrial high-rate episodes is less than what might be expected for clinically diagnosed paroxysmal AF,(56) and a temporal relationship between these episodes and stroke is seen in only a minority of cases. There is currently no evidence from randomized studies that implanting a CIED to detect AF and initiating oral anticoagulation in those in whom AF is detected is beneficial. In the *Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing* (ASSERT) Trial, device-detected asymptomatic AF episodes >24 hours associated with stroke risk comparable to clinical AF,(57) and from the TRENDS study, in which an atrial arrhythmia burden of ≥5.5 hours, but not less, appeared to double thromboembolic risk.(56) At the present time, it is reasonable to consider oral anticoagulation, preferably in the form of a DOAC, in patients with subclinical AF lasting longer than a few minutes and who would otherwise be considered for this therapy in the presence of clinical AF, provided the patient is not at high risk of bleeding. As half of all patients with sub-clinical AF transition to higher AF burden thresholds during follow-up,(58) prompt detection of atrial high-rate episodes or subclinical AF by device diagnostics may allow closer follow-up and faster detection of progression to a longer AF burden, particularly if remote monitoring is used, in which case the benefit of anticoagulation should be less controversial.

Anticoagulation in patients with renal dysfunction or on dialysis

Renal dysfunction increases the risk of stroke and bleeding. While the benefit of oral anticoagulation in patients with mild to moderate renal dysfunction is clear,(59) patients with end-stage renal disease

on dialysis were systematically excluded from large cardiovascular-focused randomized trials. The superior bleeding risk profile of DOAC may seem attractive for the dialysis population, but anticoagulation may not be beneficial for these patients.(60) Both Dabigatran and Rivaroxaban may associate with higher risk of bleeding than Apixaban,(60) although only Dabigatran is mostly excreted via the renal route. Both agents are however safe and effective in patients with mild or moderate renal impairment. Apixaban is mainly excreted via the biliary route and has shown a favourable risk profile across all levels of renal function, including end-stage dysfunction on dialysis,(60) with patients with impaired renal function experiencing the greatest reduction in major bleeding compared with warfarin.(61) The recently presented *RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation* (RENAL-AF) trial suggested that Apixaban is as safe as warfarin in dialysis patients, although the trial was interrupted prematurely due to loss of funding.(62) In a very large cohort with end-stage renal disease and AF, Apixaban use associated with lower risk of major bleeding compared with warfarin, with a standard 5 mg twice-daily dose also associating with reductions in thromboembolic and mortality risk.(63) These findings suggest that Apixaban may be a more favourable option in patients with renal impairment, including its severe stage. Still, the evidence for this is limited given the lack of randomized data involving patients on dialysis. A left atrial appendage occlusion device is a reasonable option to reduce stroke risk in AF patients who have a contraindication to long-term anticoagulation, but these devices have not been tested in patients on dialysis. **TABLE** provides useful data on how to adjust DOAC dosage in patients with renal impairment.

Anticoagulation in pregnancy

Anticoagulation can cause miscarriage and haemorrhagic complications, including post-partum bleeding and retroplacental haemorrhage, but it is recommended for pregnant women with AF and a CHA_2DS_2-VASc score of ≥2 to prevent cardioembolic stroke.(23) DOACs are not recommended during pregnancy as their safety has not been tested. Conversely, although VKAs can be used in the second and third trimesters, they can cross the placenta and increase the risk of foetal loss, as well as result

in embryopathy in the first trimester in a dose-dependent manner. While low-dose VKA (e.g. warfarin at less than 5 mg/day) associates with low risk of teratogenicity, higher dosages can result in limb defects or nasal hypoplasia in up to 10% of cases. Thus, VKAs should ideally be replaced by continuous dose-adjusted unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) in the first trimester, and in the 2-4 weeks prior to delivery to avoid foetal bleeding and maternal haemorrhage during labour. Heparin compounds are usually safe during pregnancy, although long-term use of UFH may associate with maternal osteoporosis and thrombocytopenia. More frequent administration of UFH or LMWH is typically required due to the increase in plasma volume and glomerular filtration rate and placenta degradation heparinase. To reduce the risk of bleeding during labour, heparin compounds should be discontinued 12 hours before planned induction.

Managing bleeding in anticoagulated patients

Anticoagulation associates with increased haemorrhagic risk. Although DOACs in general seem less likely to cause bleeding compared with warfarin, particularly intracranial, high-dose DOACs have been shown to associate with increased risk of gastrointestinal bleeding.(11) Fortunately, the majority of bleeding events are not life-threatening and can be managed conservatively. **FIGURE 6** provides general advice on how to deal with bleeding in AF anticoagulated patients. This implies a prompt assessment of bleed severity and haemodynamic instability. Knowing the time of ingestion of last dose of anticoagulant and measuring anticoagulant activity are also crucial. Local measures such as manual compression whenever possible, fluid replacement and transfusion of blood products, direct procedural treatment (e.g. endoscopy for gastrointestinal bleeding) and anticoagulation reversal are all possibly indicated depending on the severity of the bleed.

CONCLUSION

Anticoagulation is an effective treatment for stroke prevention in AF patients. However, the rate of anticoagulation prescription is still sub-optimal even in the DOAC era, leading to increased morbidity

and mortality. Reasons for this include the advanced age of the patient, an inaccurate perception of the risk of falls and bleeding and the failure to diagnose AF when it is occurring in a paroxysmal fashion. AF screening for as long as possible is crucial in patients who sustained an ischaemic stroke of unidentified cause, as AF is eventually diagnosed in a significant percentage of these patients.

KEY POINTS

- In patients with a history of ischaemic stroke of unidentified cause, AF screening should be performed for as long as possible. Twenty-four hour ECG monitoring is insufficient for this purpose.

- In elderly patients with AF, anticoagulation (preferably in the form of a DOAC) should not be withheld or replaced by an antiplatelet agent on the presumption of a high risk of falls and bleeding. Even in patients who fall, anticoagulation reduces stroke-related morbidity and mortality and the overall risk of death.

- The risk of ischaemic stroke in AF patients who are not on anticoagulation far exceeds the risk of severe haemorrhagic complications caused by this treatment.

- Anticoagulation can be considered in men with a CHA_2DS_2VASc score of 1, and should be offered to individuals with a score ≥2, regardless of the HAS-BLED score.

- Decisions on periprocedural management of antithrombotic therapy should be based on the patient's clinical status and inherent risk of thromboembolism and bleeding, but also the procedure-related haemorrhagic risk. Uninterrupted oral anticoagulation for low risk procedures appears to be safe and is gaining strong evidence support.

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Standard dose	5 mg twice daily	20 mg once daily	60 mg once daily	150 mg twice daily
Dose adjustment	▪ Decrease dose to 2.5 mg twice daily if patient has a serum creatinine ≥1.5 mg/dL, plus one of the following: age ≥80 years or weight ≤60 kg ▪ End-stage renal disease on dialysis: 5 mg twice daily; decrease dose to 2.5 mg twice daily if one additional characteristic of age ≥80 years or weight ≤60 kg is present	▪ CrCl >50 mL/min: no dosage adjustment required ▪ 15 mg once daily in patients with CrCl 15–50 ml/min ▪ End-stage renal disease on dialysis: 15 mg/day (but avoid if possible)	▪ CrCl >95 mL/min: avoid; increased risk of ischaemic stroke compared with warfarin ▪ CrCl >50 to 95 mL/min: no dosage adjustment required ▪ CrCl 15-50 mL/min: 30 mg/day ▪ 30 mg once daily in patients with one or more of the following: CrCl 15–50 ml/min; body weight ≤60 kg; concomitant use of the P-gp inhibitors cyclosporine, dronedarone, erythromycin or ketoconazole	▪ Decrease dose to 110 mg twice daily in patients 80 years or receiving concomitant verapamil; consider also for patients aged 75–80 years, patients with CrCl 30–50 ml/min, patients with gastritis or peptic ulcer (but avoid if possible), or patients at increased bleeding risk ▪ CrCl 30-50 mL/min and coadministration with dronedarone or ketoconazole: consider reducing dose to 75 mg twice daily ▪ CrCl 15-30 mL/min: consider 75 mg twice daily (but avoid if possible) ▪ CrCl <15 mL/min or dialysis: No data available; avoid

Legends: CrCl – Creatinine clearance; P-gp – P-glycoprotein

FIGURE LEGENDS

Figure 1 - Clinical events in the AF population

Cerebrovascular complications in red, other cardiovascular events in blue, and other non-cardiovascular risks in green. Relative risk and 95% confidence intervals are illustrated based on *Odutayo et al.* [10]

Figure 2 – Suggested protocol for the screening of AF in patients with ischaemic stroke of unidentified cause

Legend: AF – Atrial fibrillation; AFL – Atrial flutter; CI – Contraindication; ILR – Implantable loop recorder; LAA – Left atrial appendage.

Figure 3 – Trends in anticoagulation used

Modified from Rose AJ et al, Anticoagulant Prescribing for Non-Valvular Atrial Fibrillation in the Veterans Health Administration. J Am Heart Assoc. 2019 Sep 3;8(17):e012646. doi: 10.1161/JAHA.119.012646.

Figure 4 – Parameters included in risk scores developed to predict stroke or bleeding

Figure 5 – Different antithrombotic drugs for different scenarios

Additional points to consider: avoid Dabigatran in patients at high risk of myocardial infarction; avoid low-dose Edoxaban in Asian patients with supranormal renal function. NOTE: The suggestions in this figure and based on the drugs' pharmacokinetics and observational data rather than solid evidence from randomized data.

Legend: AF – Atrial fibrillation; DOAC – Direct oral anticoagulant; GI – Gastrointestinal; PPI – Proton pump inhibitor; VKA – Vitamin K antagonist.

* Only for Child-Pugh class A or B

Figure 6 – Management of active bleeding in patients on anticoagulation

Legend: AF – Atrial fibrillation; DOAC – Direct oral anticoagulant; GI – Gastrointestinal; LAAO – Left atrial appendage occlusion; OAC – Oral anticoagulation; (a)PCC – (activated) Prothrombin complex concentrate; PPI – Proton pump inhibitor; VKA – Vitamin K antagonist.

NOTE: Andexanet Alfa is currently not available in the UK.

REFERENCES

1. Weng L-C, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. Circulation. 2018 Mar 6;137(10):1027–38.

2. Heart statistics.B HF Statistics Factsheet - UK. [Internet]. [cited 2020 Jan 31]. Available from: file:///C:/Users/Sergio/Downloads/bhf-cvd-statistics-uk-factsheet.pdf

3. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013 Sep 14;34(35):2746–51.

4. Pearson-Stuttard J, Bajekal M, Scholes S, O'Flaherty M, Hawkins NM, Raine R, et al. Recent UK trends in the unequal burden of coronary heart disease. Heart. 2012 Nov;98(21):1573–82.

5. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014 Jan 18;383(9913):245–54.

6. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016 Sep 6;354:i4482.

7. Lin HJ, Wolf PA, Benjamin EJ, Belanger AJ, D'Agostino RB. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. Stroke. 1995 Sep;26(9):1527–30.

8. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978 Oct;28(10):973–7.

9. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996 Oct;27(10):1760–4.

10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857–67.

11. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014 Mar 15;383(9921):955–62.

12. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. Eur Heart J. 2018 21;39(32):2975–83.

13. Freedman B, Martinez C, Katholing A, Rietbrock S. Residual Risk of Stroke and Death in Anticoagulant-Treated Patients With Atrial Fibrillation. JAMA Cardiol. 2016 01;1(3):366–8.

14. Marijon E, Le Heuzey J-Y, Connolly S, Yang S, Pogue J, Brueckmann M, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the

randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013 Nov 12;128(20):2192–201.

15. Israel CW, Grönefeld G, Ehrlich JR, Li Y-G, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol. 2004 Jan 7;43(1):47–52.

16. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012 Jan 12;366(2):120–9.

17. NICE National Institute of Clinical Excellence (2014) Atrial fibrillation: Management (NICE Clinical Guideline 180). [Internet]. [cited 2020 Jan 31]. Available from: https://www.nice.org.uk/guidance/cg18

18. Wasserlauf J, You C, Patel R, Valys A, Albert D, Passman R. Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2019;12(6):e006834.

19. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener H-C, Bernstein RA, et al. Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. Circ Arrhythm Electrophysiol. 2016 Jan;9(1):e003333.

20. Diener H-C, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. New England Journal of Medicine. 2019 May 16;380(20):1906–17.

21. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. New England Journal of Medicine. 2018 Jun 7;378(23):2191–201.

22. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Jul;45(7):2160–236.

23. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 07;37(38):2893–962.

24. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010 Jul;123(7):638-645.e4.

25. Rose AJ, Goldberg R, McManus DD, Kapoor A, Wang V, Liu W, et al. Anticoagulant Prescribing for Non-Valvular Atrial Fibrillation in the Veterans Health Administration. J Am Heart Assoc. 2019 03;8(17):e012646.

26. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. Eur Heart J. 2018 Aug 21;39(32):2975–83.

27. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. JAMA. 2017 14;317(10):1057–67.

28. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493–503.

29. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FDR, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009 Apr;40(4):1410–6.

30. Ng KH, Shestakovska O, Connolly SJ, Eikelboom JW, Avezum A, Diaz R, et al. Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. Age Ageing. 2016 Jan;45(1):77–83.

31. Donzé J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. Am J Med. 2012 Aug;125(8):773–8.

32. Garwood CL, Corbett TL. Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. Ann Pharmacother. 2008 Apr;42(4):523–32.

33. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011 Jan 31;342:d124.

34. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández A-I, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Causes of Death in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2016 Dec 13;68(23):2508–21.

35. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263–72.

36. NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ. 2018 Oct;27(10):1209–66.

37. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc. 2013 Jun 21;2(3):e000250.

38. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation. 2013 Jan 15;127(2):224–32.

39. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016 May 21;37(20):1582–90.

40. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. BMJ. 2013 May 2;346:f2573.

41. Dalgaard F, Pieper K, Verheugt F, Camm AJ, Fox KA, Kakkar AK, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. BMJ Open. 2019 11;9(11):e033283.

42. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093–100.

43. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006 Mar;151(3):713–9.

44. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011 Jul 19;58(4):395–401.

45. Hijazi Z, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016 Jun 4;387(10035):2302–11.

46. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J. 2015 Dec 7;36(46):3258–64.

47. Lip Gregory Y.H., Keshishian Allison, Li Xiaoyan, Hamilton Melissa, Masseria Cristina, Gupta Kiran, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. Stroke. 2018 Dec 1;49(12):2933–44.

48. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. Journal of the American College of Cardiology. 2017 Jun 13;69(23):2779–90.

49. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. Europace. 2018 01;20(8):1231–42.

50. Shahi V, Brinjikji W, Murad MH, Asirvatham SJ, Kallmes DF. Safety of Uninterrupted Warfarin Therapy in Patients Undergoing Cardiovascular Endovascular Procedures: A Systematic Review and Meta-Analysis. Radiology. 2016 Feb;278(2):383–94.

51. Ha FJ, Barra S, Brown AJ, Begley DA, Grace AA, Agarwal S. Continuous and minimally-interrupted direct oral anticoagulant are both safe compared with vitamin K antagonist for atrial fibrillation ablation: An updated meta-analysis. Int J Cardiol. 2018 01;262:51–6.

52. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Aug 27;373(9):823–33.

53. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med. 2013 May 30;368(22):2084–93.

54. Birnie DH, Healey JS, Wells GA, Ayala-Paredes F, Coutu B, Sumner GL, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). Eur Heart J. 2018 21;39(44):3973–9.

55. Perino AC, Fan J, Askari M, Heidenreich PA, Keung E, Raitt MH, et al. Practice Variation in Anticoagulation Prescription and Outcomes After Device-Detected Atrial Fibrillation. Circulation. 2019 28;139(22):2502–12.

56. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009 Oct;2(5):474–80.

57. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017 May 1;38(17):1339–44.

58. Boriani G, Glotzer TV, Ziegler PD, De Melis M, Mangoni di S Stefano L, Sepsi M, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. Heart Rhythm. 2018;15(3):376–83.

59. Ha JT, Neuen BL, Cheng LP, Jun M, Toyama T, Gallagher MP, et al. Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann Intern Med. 2019 06;171(3):181–9.

60. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Hemodialysis. J Am Coll Cardiol. 2020 Jan 28;75(3):273–85.

61. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012 Nov;33(22):2821–30.

62. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF). Presented by Sean D. Pokorney at the American Heart Association Annual Scientific Sessions (AHA 2019), Philadelphia, PA, November 16, 2019.) [Internet]. Available from: https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/29/renal-af

63. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation. 2018 09;138(15):1519–29.