Factfile: Stroke Prevention in Atrial Fibrillation (AF)

Summary
- AF is the commonest risk factor for embolic stroke.
- Most AF patients, whether paroxysmal or persistent, are at a high risk of stroke and so stand to benefit from oral anticoagulant therapy.
- Aspirin affords very little stroke protection in AF patients.
- Warfarin therapy should be monitored closely to maintain INR levels between 2 and 3 as far as possible.
- Newer oral anticoagulants are as effective as warfarin.

Introduction
Atrial fibrillation (AF) affects around a million people in the UK. It increases the risk of stroke five-fold and is directly responsible for a fifth of all strokes. Strokes related to AF are associated with a two-fold higher mortality and three-fold higher risk of severe disability than those from other causes. Consequently, AF and AF-related stroke are a major burden on the NHS. The past few years have seen exciting developments in risk stratification and therapeutic interventions to reduce stroke risk.

Risk Stratification
Stroke risk can vary up to twenty-fold between patients with AF depending upon the presence or absence of clinical risk factors. These risk factors are best collated in the CHA2DS2-VASc risk score which is superior to the older CHADS2 score. (Figure 1).

Until recently, the emphasis was on identifying 'high-risk' AF patients who might benefit from oral anticoagulation (OAC). It is now appreciated that most AF patients are at high risk of stroke, and so emphasis has shifted to identifying the minority of truly 'low-risk' patients who do not need OACs (1).

Current recommendations are to consider OAC for all AF patients with a CHA2DS2-VASc score of 1 or greater (1). This includes all patients other than those who suffer from Lone AF (AF with no coexisting structural heart disease, hypertension or diabetes) and who are less than 65 years of age.

It is important to note that patients with paroxysmal AF are at a similar risk of stroke as those with persistent AF.

Assessment of Bleeding Risk
The decision to initiate OAC involves a careful evaluation of the patient's risk of bleeding. The HAS-BLED score (Figure 2) allows physicians to make an informed assessment of bleeding risk, and makes them think of the correctable risk factors for bleeding. It is important to emphasize that a high HAS-BLED score alone should not be used to exclude patients from OAC.

Stroke Prevention
Prevention of strokes is usually achieved by pharmacological intervention, but it can also be achieved in a minority of patients by devices that occlude the atrial appendage, the commonest source of emboli in AF patients.

Role of Aspirin
The evidence for effective stroke prevention with aspirin in AF is very weak. On the contrary, aspirin is associated with a significantly increased risk of bleeding and intracranial hemorrhage, especially in the elderly. As such, the use of aspirin should be reserved for only those patients who are intolerant to all forms of OAC. This should constitute only a small minority of AF patients today. Furthermore, addition of aspirin to other anticoagulant drugs is associated with a significantly increased risk of bleeding. Patients with coexisting stable coronary artery disease who are on warfarin do not ordinarily require concomitant aspirin.

Role of Warfarin
Warfarin and other vitamin K antagonists (VKA) – which are rarely prescribed in the UK - act by inhibiting hepatic, vitamin K dependent clotting factors. Warfarin has been used for over 50 years, and has been shown to decrease the risk of AF-related stroke by around two-thirds. The advantages of warfarin include very low prescribing costs, decades of experience with its use, and the ability to reverse its action in an emergency with vitamin K. However, there are several issues with warfarin that limits its use. Warfarin interacts with several drugs and foods. This makes frequent INR testing mandatory, and maintaining safe and effective anticoagulation challenging. Secondly, warfarin has a relatively narrow safe therapeutic window (INR level between 2.0 and 3.0), and the inevitable, frequent under- and over-shoots across this range expose the patient to thrombotic and bleeding events respectively. A time in therapeutic range (TTR) of >65-70% has been shown to correlate strongly with better health outcomes, but this contrasts with real-life data where TTR levels in the community typically range between 50-60%. Emphasis should be on ensuring consistently high TTR levels. This may require frequent INR monitoring as well as a strict adherence to diet and drug regimens to avoid potential interactions. Near-patient testing with home-INR monitoring kits may be helpful in this regard, but this requires a high level of patient motivation and education and effective quality control of the kits used.

Partly because of these issues uptake of warfarin treatment in AF patients has been relatively poor. It is estimated that only around half of eligible AF patients in the UK are on warfarin and, of these, only around half have ideal TTR levels. This suboptimal practice has been estimated to result in an additional 8000 embolic strokes annually.

Newer Oral Anticoagulants
The newer oral anticoagulants (NOACs) for stroke prevention in AF fall into two classes: direct thrombin inhibitors (e.g. dabigatran) and direct factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban).

Dabigatran
The RE-LY (Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate) trial (2) was a prospective, randomized, open-label trial comparing two blinded doses of dabigatran etexilate [110 mg twice daily. (D110) or 150 mg twice daily (D150)] with open-label adjusted-dose warfarin, aiming for an INR of 2.0 – 3.0. The population had a mean CHADS2 score of 2.1.

BHF resources
The following resources may be useful for you or your patients:

Atrial Fibrillation
Heart Rhythms

You will find details of all our publications at bhf.org.uk/publications

Our research
Read more about the research we fund into finding treatments for cardiovascular disease.

You will find information about all of the research we fund at bhf.org.uk/research

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For the primary efficacy endpoint of stroke and systemic embolism, D150 was seen to be superior to warfarin, with no significant difference in the primary safety endpoint of major bleeding. D110 was non-inferior to warfarin, with 20% fewer major bleeds. Rates of haemorrhagic stroke and intracranial hemorrhage were lower with both doses of dabigatran, but gastrointestinal bleeding was significantly increased with D150.

Based on the results of RE-LY, dabigatran has been approved for prevention of stroke and systemic embolism in AF by the European Medical Agency (EMA), the United States Federal Drug Administration (FDA) and the National Institute for Health and Clinical Excellence (NICE) in the UK.

The RELY-ABLE study was an extension of the RE-LY trial and was designed to assess the long-term safety and efficacy of dabigatran (3). Over an additional follow up period of 2.3 years, patients on both D110 and D150 were seen to have annual risks of stroke and major bleed identical to those during the RE-LY study period. This study, along with the post-market release data available since 2010, suggests that dabigatran can be used safely over the longer-term.

Rivaroxaban
The double-blind ROCKET-AF trial randomized 14,264 high-risk patients with AF to either rivaroxaban 20 mg daily [15 mg daily for those with estimated creatinine clearance (CrCl) 30 – 49 mL/min] or warfarin (4). The population was at considerably higher risk for stroke than in other NOAC AF trials (mean CHADS score 3.5), and the mean TTR in the Warfarin group was 55% (median 58%), which was lower than in other randomized trials. Rivaroxaban was seen to be non-inferior to warfarin for the primary endpoint of stroke and systemic embolism. There was no reduction in rates of mortality or ischaemic stroke, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage. Rivaroxaban has been approved for stroke prevention in non-valvular AF by EMA, FDA and NICE.

Apixaban
The AVERROES (Apixaban Versus Acetylsalicylic acid to Prevent Strokes) study was a randomized, double-blind trial of 5,599 AF patients, who were not suitable candidates for or were unwilling to take warfarin, for treatment with either apixaban [5 mg twice daily] or aspirin (81 – 324 mg/day, with 91% taking≤162 mg/day) (5). After a mean follow-up of 1.1 years, the trial was stopped early due to a significant 55% reduction in the primary endpoint of stroke or systemic embolism with apixaban compared with aspirin, with no significant difference in rates of major bleeding or intracranial heamorrhage. The ARISTOTLE (Apixaban versus Warfarin in Patients with Atrial Fibrillation) trial was a randomized, double-blind, double-dummy trial comparing apixaban [5 mg twice daily] with dose-adjusted warfarin aiming for an INR of 2.0 – 3.0 in 18,201 patients with non-valvular AF (6). There was a significant reduction in the primary efficacy outcome of stroke or systemic embolism by 21% with apixaban compared with warfarin, with a 31% reduction in major bleeding and a significant 11% reduction in all-cause mortality. Rates of haemorrhagic stroke and intracranial haemorrhage were significantly lower in patients treated with apixaban than with warfarin. At the time of writing, apixaban has gained regulatory approval from the EMA and is being considered by the FDA and the NICE.

Summary of NOACs
The clinical trial data with all 3 NOACs are consistent in showing that they are at least as effective as warfarin in preventing stroke and are associated with a lower risk of intracranial hemorrhage. NOACs have a rapid onset of action with the peak anticoagulation effect typically seen within a few hours of administration. Unlike warfarin, NOACs do not require dose adjustment. But their duration of action is less than 24 hours which underscores the need for regular patient compliance for adequate anticoagulant effect, particularly since there is no available assay to measure the level of anticoagulation. NOACs are contraindicated in the presence of severe renal dysfunction, although rivaroxaban and apixaban in lower doses (15 mg daily, and 2.5 mg twice daily respectively) may be used in the presence of moderate renal dysfunction. NOACs do not have specific antidotes, and so the management of any bleeding complications relies on stopping the drug and supporting the patient until the anticoagulant effect has resolved. NOACs have not been studied in patients with valvular AF or those with prosthetic heart valves, and so should not be used in these patients.

Left atrial appendage occlusion devices
The left atrial appendage is the main site of thrombus formation in patients with AF. For patients in whom OAC therapy is contraindicated because of a history of severe bleeding, percutaneous closure of the appendage with an occlusion device can be considered (7). The device is deployed percutaneously, under local anaesthetic via a cardiac catheter under X-ray guidance. Device deployment can be technically challenging and the procedure can be associated with a serious complication rate of up to 7% (7). It is also important to note though these patients still require long-term aspirin therapy with its associated risks.

Figure 1
CHA2DS2-VASc score

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/thromboembolism	2
V	Vascular disease	1
A	Age 65-74 years	1
S	Sex category (i.e. female sex)	1
Maximum score		**9**
Patients at Low Risk for Stroke		0 or 1 (if female)

Figure 2
HAS-BLED bleeding risk score

Letter	Risk factor	Score
H	Hypertension (uncontrolled)	1
A	Abnormal renal and liver function - 1pt each	1 or 2
S	Stroke	1
B	Bleeding history	1
L	Labile INRs	1
E	Elderly (age>65 years)	1
D	Drugs (e.g. NSAIDS/ Aspirin) or alcohol (8 or more alcoholic drinks per week) - 1pt each	1 or 2
Maximum score		**9**
Patients at High Risk for Bleeding		≥3

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