Atrial fibrillation 1

Stroke prevention in atrial fibrillation

Ben Freedman, Tatjana S Potpara, Gregory Y H Lip

Atrial fibrillation is found in a third of all ischaemic strokes, even more after post-stroke atrial fibrillation monitoring. Data from stroke registries show that both unknown and untreated or under treated atrial fibrillation is responsible for most of these strokes, which are often fatal or debilitating. Most could be prevented if efforts were directed towards detection of atrial fibrillation before stroke occurs, through screening or case finding, and treatment of all patients with atrial fibrillation at increased risk of stroke with well-controlled vitamin K antagonists or non-vitamin K antagonist anticoagulants. The default strategy should be to offer anticoagulant thromboprophylaxis to all patients with atrial fibrillation unless defined as truly low risk by simple validated risk scores, such as CHA₂DS₂-VASc. Assessment of bleeding risk using the HAS-BLED score should focus attention on reversible bleeding risk factors. Finally, patients need support from physicians and various other sources to start anticoagulant treatment and to ensure adherence to and persistence with treatment in the long term.

Introduction

Ischaemic strokes related to atrial fibrillation usually result from cardioembolism of a large cerebral artery, and therefore tend to be larger (figure 1) and more frequently fatal or associated with greater disability than strokes from other causes. However, strokes related to atrial fibrillation are largely preventable, because oral anticoagulants (OACs) are so effective. In meta-analyses, vitamin K antagonists (VKAs; eg, warfarin) reduced stroke or systemic thromboembolism by 64% and all-cause mortality by 26% compared with placebo (five studies) or untreated controls (one study); the use of non-VKA OACs (NOACs) offers additional significant reductions of 19% and 10%, respectively, relative to warfarin. Several steps are needed to reduce the stroke burden associated with atrial fibrillation. The first is recognition of the risk of stroke in patients with atrial fibrillation, followed by risk assessment using simple risk scores such as CHA₂DS₂-VASc, and prescription of appropriate stroke prevention to all who are not at low risk of stroke. Second, a system is needed to recognise the pre-symptomatic phase of atrial fibrillation rather than wait for stroke to be the first clinical manifestation. Finally, measures are needed to achieve optimum treatment, including excellent international normalised ratio (INR) control if VKAs are used, excellent adherence to thromboprophylactic drugs (ie, VKAs or NOACs) as prescribed, and long-term persistence with treatment. In this paper, we provide an overview of all three aspects of stroke prevention in atrial fibrillation, in the hope that greater awareness will result in reduction of the overall ischaemic stroke burden associated with atrial fibrillation.

Atrial fibrillation as a cause of ischaemic stroke

Of all strokes with an established cause, over 85% are ischaemic strokes, and the association of atrial fibrillation with ischaemic stroke of cardioembolic origin is well recognised. Indeed, findings from recent population-based studies or stroke registries consistently showed a substantial atrial-fibrillation-attributable risk of stroke, especially in the elderly; at least one in three to four patients with atrial fibrillation been detected before the stroke (appendix p 5), suggesting an even stronger association of atrial fibrillation with stroke than previously thought. In over 25% of strokes related to atrial fibrillation, the stroke was the first manifestation of previously unknown atrial fibrillation, which in most cases could have been prevented by OAC treatment, had atrial fibrillation been detected before the stroke (appendix p 5).

Sometimes, even extensive post-stroke diagnostic testing does not elucidate the cause of the stroke (ie, large-vessel disease, cardioembolism, or small-vessel disease); such cryptogenic strokes comprise around 25% of all strokes. In two randomised trials assessing various post-stroke cardiac rhythm monitoring strategies in patients with cryptogenic stroke, previously unknown atrial fibrillation was eventually detected by prolonged monitoring in 30% of patients in the CRYSTAL-AF trial and in 16% of patients with 30-day monitoring in the EMBRACE trial, identification of atrial fibrillation after stroke would qualify patients for...
secondary prevention using OACs instead of the standard non-atrial fibrillation post-stroke treatment, aspirin. In a meta-analysis of 50 studies, atrial fibrillation was detected in 24% of patients after stroke by combined short-term and long-term monitoring. The optimum, cost-effective technique and duration of post-stroke monitoring beyond the first 24 h remains uncertain. At present, prolonged post-stroke monitoring is optional.

Replacement of the term cryptogenic stroke with the more explicitly defined embolic stroke of undetermined source (ESUS), a non-lacunar brain infarct without evident proximal arterial stenosis or cardioembolic sources, has been increasingly advocated. A substantial proportion of patients with ESUS have paroxysmal atrial fibrillation. The risk of stroke recurrence is high after incident ESUS. Electrocardiographic documentation of atrial fibrillation is mandatory for OAC use in the context of stroke prevention. The CRYSTAL-AF and EMBRACE post-stroke monitoring trials, at least 75% of atrial fibrillation episodes were asymptomatic, which emphasises the unreliability of symptoms for detection of atrial fibrillation. Two ongoing randomised trials will compare the efficacy and safety of the NOACs dabigatran (RE-SPECT ESUS) and rivaroxaban (NAVIGATE ESUS; NCT02313909) versus aspirin in unselected patients after ESUS, which might obviate the need for post-stroke monitoring.

**Previous management of atrial fibrillation in patients presenting with stroke**

Although most strokes related to atrial fibrillation can be prevented using OACs, findings from contemporary registry-based and observational real-world reports from various geographical regions have consistently shown that OAC treatment is underused in patients with atrial fibrillation who are at risk of stroke. No OAC is used in around a third of eligible patients with atrial fibrillation, and in over 50% of patients who receive warfarin the quality of anticoagulation control remains suboptimum.

In the Canadian Stroke Registry, only 10% of patients with known atrial fibrillation and acute ischaemic stroke were previously well managed on warfarin (an additional 29% were on subtherapeutic warfarin), whereas in secondary prevention (ie, those with a history of stroke) the percentages increased to 18% and 39%, respectively (appendix p 6). In the Adelaide Stroke Incidence Study, warfarin had been prescribed before stroke in 27% of patients with previous atrial fibrillation (15% therapeutic and 12% subtherapeutic; appendix pp 3, 4). Findings from a registry of over 94000 ischaemic strokes from Sweden suggested that of all patients with ischaemic stroke, 20% had known but untreated or inadequately treated atrial fibrillation and 9% had previously unknown atrial fibrillation; in these patients stroke could have been prevented by either treatment with an OAC according to current guidelines or by screening for atrial fibrillation (appendix pp 3, 4). In the UK, according to the Sentinel Stroke National Audit Programme (SSNAP), there has been some improvement over previous anticoagulant treatment rates in patients with stroke with known atrial fibrillation over the past 3 years, but antiplatelet drugs, largely aspirin, were still the sole antithrombotic prescribed in 26% of patients in the 12 months ending March, 2016.

Aspirin is still widely misused for primary or even secondary stroke prevention in a quarter to a third of patients with atrial fibrillation who are eligible for OACs, presumably because of misperception of efficacy and safety for stroke prevention in atrial fibrillation, which is likely to contribute to continuing underuse of anticoagulants. Aspirin is neither effective nor safe as thromboprophylaxis for atrial fibrillation, even possibly increasing stroke risk in elderly patients, and has largely been removed from guidelines. The consequence of aspirin misuse is evident in stroke registries (appendix pp 3, 4, 6), with a high proportion of atrial-fibrillation-related strokes occurring in patients treated only with aspirin, despite a CHADS, or CHADS-VASc score of at least 2 (appendix pp 3, 4). Replacing aspirin with OACs, and prescribing OACs for the 20% of high-risk patients with known atrial fibrillation who receive no OAC treatment (appendix p 6) constitutes a simple solution to reduce the atrial fibrillation stroke burden, provided effective measures to close this evidence–treatment gap are implemented.

**Finding unknown atrial fibrillation to prevent stroke**

Almost 10% of all ischaemic strokes (representing >25% of strokes related to atrial fibrillation) occur simultaneously with first-detected atrial fibrillation. Measures to screen or case-find unknown asymptomatic atrial fibrillation, and then treat with OACs, should logically have a major effect on reducing stroke burden. The inbuilt assumptions are that unknown asymptomatic
Atrial fibrillation is common, and that prognosis of unknown asymptomatic atrial fibrillation is similar to that in the pivotal trials, which included a small but unknown proportion of patients with incidentally detected atrial fibrillation (eg, during a routine clinic visit). Such pre-symptomatic atrial fibrillation has sometimes been assumed to have a benign prognosis.

In a study of asymptomatic incidentally detected atrial fibrillation in general practice, prognosis was far from benign, with a doubling of stroke and all-cause mortality compared with age-matched and sex-matched patients without atrial fibrillation. Moreover, anticoagulant treatment reduced the stroke rate from 4% to 1% after only 1.5 years compared with no treatment; this rate is almost identical to that in matched controls without atrial fibrillation seen contemporaneously (figure 2).

A similar adverse prognosis of atrial fibrillation first discovered in the absence of symptoms was noted in Olmsted county (MN, USA). In the EORP-AF registry, patients who had never experienced symptoms actually had a worse prognosis than those with symptoms.

Patients with pacemakers or similar implanted devices frequently have brief or even prolonged episodes of asymptomatic atrial fibrillation, and these have been associated with a more than doubling of the stroke risk, and a 3-5 times increase in the risk of subsequent atrial fibrillation. Longer (>18 h) episodes of atrial fibrillation have the highest adverse prognosis. Ongoing randomised trials of anticoagulant treatment of device-detected asymptomatic atrial fibrillation (eg, ARTESIA [NCT01938248] and NOAH [NCT02618577]) are investigating the role of two NOACs, apixaban or edoxaban, versus aspirin for the treatment of device-detected subclinical atrial fibrillation. Even excessive atrial ectopics or runs (defined as ≥20 beats) of atrial tachycardia without definitive atrial fibrillation carry a similar prognosis. This finding, coupled with the only partial temporal association of stroke with device-detected atrial fibrillation episodes, suggests that as well as being a risk factor for stroke, atrial fibrillation is also a powerful risk marker for an abnormal atrial or systemic substrate, which can lead to stroke.

Screening or case finding in either the clinic or community will detect atrial fibrillation in 1.4% of patients on a single screen in those aged at least 65 years. Using stepped screening with patient-activated handheld electrocardiograph (ECG) devices for 2 weeks in 75-76-year-olds detects atrial fibrillation in 3% of patients. Opportunistic case finding using pulse palpation and ECG if irregular is as effective as systematic 12-lead electrocardiography, and is more cost-effective. Hence, opportunistic clinic pulse screening forms the basis of guideline recommendations on screening.

Cheaper, faster, yet accurate devices providing automated atrial fibrillation diagnosis, including handheld single-lead ECGs, blood pressure oscillometry, and smartphone photoplethysmography, are likely to improve the cost-effectiveness. Indeed, screening for unknown atrial fibrillation is likely to be cost-effective for stroke prevention and might lead to revisions of recommendations about screening for atrial fibrillation to prevent stroke.

**Stroke risk factors and risk stratification**

Atrial fibrillation increases the risk of stroke and systemic thromboembolism, but the excess risk also depends on the presence of various additional risk factors, which

![Figure 2: Effect of treatment on incidentally detected atrial fibrillation](image-url)

**Figure 2:** Effect of treatment on incidentally detected atrial fibrillation  
AF=axial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.
were defined from findings from the non-warfarin placebo or control arms of historical randomised trials done two decades ago or from large observational epidemiological studies. There is good evidence of increased risk in patients with previous stroke or systemic embolism, age at least 65 years, recent decompensated heart failure (irrespective of ejection fraction; hence, heart failure with reduced or preserved ejection fraction, eg, hypertrophic cardiomyopathy), moderate-to-severe left ventricular dysfunction on cardiac imaging, diabetes mellitus, hypertension, or vascular disease (ie, peripheral artery disease or previous myocardial infarction). Female sex is probably a stroke risk modifier, with accentuation of risk in those older than 65 years or with at least one additional stroke risk factor. The age threshold conferring excess stroke risk seems to be even lower (age ≥50 years) in east Asians.

More recent attention has been directed towards defining the stroke risk associated with a single stroke risk factor, since not all risk factors carry equal weight, and risk in atrial fibrillation varies depending on clinical setting (eg, community based vs hospitalised) and according to ethnic origin and availability of appropriate methods to establish event rates. The evidence is compelling that even a single stroke risk factor confers an excess risk of thromboembolism and mortality (figure 3), with a positive net clinical benefit for OAC treatment compared with aspirin or no antithrombotic treatment for such patients.

The more common stroke risk factors have been incorporated into stroke risk stratification scores (appendix pp 7, 8), designed to help practical decision making in everyday practice. The most comprehensive review and comparison of stroke and bleeding risk scores is provided in the 2014 National Institute for Health and Care Excellence (NICE) guidelines, which are based on systematic reviews, evidence appraisal, and cost-effectiveness. Risk scores based on clinical factors have modest predictive value for identifying high-risk patients, and additional refinement of clinical-factor-based scores to improve identification of high-risk patients can be made by the addition of biomarkers (eg, von Willebrand factor, natriuretic peptides, or troponin) and imaging (eg, cerebral or cardiac imaging). Even then, c statistics (ie, how well a score predicts an event) suggest only modest discrimination despite addition of several biomarkers, but with additional costs and a major loss of simplicity and practicality for everyday clinical use.

Stroke risk is a continuum, and the artificial categorisation into low or high risk still leads to many patients with high-risk atrial fibrillation being undertreated. The default should be to use OACs to treat all patients with atrial fibrillation unless clearly defined as truly low risk. Hence, clinicians should be most concerned with identifying the very-low-risk patients who do not need thromboprophylaxis. The CHA2DS2-VASc score is useful as a simple clinical score for easy initial identification of low-risk patients (CHA2DS2-VASc score 0 in males and 1 in females) who have stroke rates of 1% or lower per year, who do not need antithrombotic treatment.

One common misperception is that paroxysmal atrial fibrillation carries a low risk of stroke, whereas in many studies the risk is almost identical to that of persistent or permanent atrial fibrillation, notwithstanding considerations of variable arrhythmia burden and associated risk factors, especially since patients with paroxysmal atrial fibrillation tend to be younger and have fewer risk factors. Guidelines recommend treating paroxysmal atrial fibrillation with OACs using identical rules as apply to persistent or permanent atrial fibrillation.

---

**Figure 3:** Risk of stroke with a single additional risk factor
Data from Fauchier and colleagues.

**Figure 4:** Recommended decision pathway for treatment of newly diagnosed non-valvular atrial fibrillation
VKA=warfarin. KA=ketanserin. *Also calculate the HAS-BLED score. If HAS-BLED ≥3, address the modifiable bleeding risk factors and plan a closer clinical follow-up.
fibrillation; unfortunately, in practice, this is often not done.60

Thromboprophylaxis in patients with atrial fibrillation

Guidelines recommend different approaches to thromboprophylaxis in atrial fibrillation. Some use CHA2DS-VASc score in a categorical approach; for example, the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines48 define patients with atrial fibrillation as low, moderate, or high risk, and recommend antithrombotic treatment on that basis. Patients at high risk are those with a CHA2DS-VASc score of at least 2, for whom OACs are recommended; low risk are those with a CHA2DS-VASc score of 0, for whom no antithrombotic treatment should be considered. For those with a CHA2DS-VASc score of 1, OACs, aspirin, or no antithrombotic treatment can be chosen, depending on risk factors and patient values and preferences.

The 2014 NICE guidelines28 and European Society of Cardiology guidelines37 recommend that the initial step should be to identify low-risk patients (CHA2DS-VASc score 0 in males, 1 in females) who do not need antithrombotic treatment. The next step is to offer effective stroke prevention with OACs (either VKAs with good quality anticoagulation control or NOACs) to those with at least one additional stroke risk factor. Since the default should be to give anticoagulants to all patients with atrial fibrillation unless defined as truly low risk, we recommend this simplified approach (figure 4), because the decision to provide anticoagulation is already made with at least one additional stroke risk factor irrespective of score value or the addition of biomarkers or imaging. Since patients with atrial fibrillation have high rates of hospital admission and risk stratification is not a static one-off process, low-risk patients should be regularly reviewed to establish whether risk has increased. Aspirin alone should not be offered for stroke prevention in atrial fibrillation.61–63

Bleeding risk assessment should also be part of the clinical decision-making process. In most cases, an elevated bleeding risk score should not be used as a reason to withhold anticoagulation, because stroke risk almost invariably outweighs serious bleeding risk, but patients at high risk of bleeding should be flagged up for more careful review and follow-up, especially in the era of electronic health record alerts, with prompt attention given to common reversible bleeding risk factors within the score.70 These include uncontrolled hypertension; control of a known previous bleeding site, especially gastrointestinal; labile INRs if on a VKA; and excess alcohol or concomitant non-steroidal anti-inflammatory drug use.71 The simplest and best validated score is HAS-BLED27 (appendix pp 9, 10), which reliably predicts bleeding in patients on OACs (whether VKAs or other anticoagulants37), aspirin, or no antithrombotic treatment. HAS-BLED has also been validated in

![Table: Choosing the oral anticoagulant drug to fit the patient profile](image-url)

- Recurrent stroke, systemic embolic event, or transient ischaemic attack despite good anticoagulation control (TTR >70%)
  - Dabigatran 150 mg BID
- Moderate-to-severe renal impairment (CrCl 15–49 mL/min)
  - Apixaban 5 mg BID*, rivaroxaban 15 mg once daily, dabigatran (if CrCl 30–49 mL/min‡), or edoxaban 30 mg once daily†
- High risk of gastrointestinal bleeding
  - Apixaban 5 mg BID* or dabigatran 110 mg BID
- Gastrointestinal symptoms or dyspepsia
  - Apixaban 5 mg BID* or dabigatran 110 mg BID
- High risk of bleeding (HAS-BLED ≥2)
  - Dabigatran 110 mg BID, apixaban 5 mg BID*, or edoxaban 60 mg once daily||
- Once daily dosing or preference to have a lower pill burden
  - VKA, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily¶|
- Asian patients (consider drugs with reduced risk of intracranial haemorrhage and major bleeding in Asian subgroups)
  - Apixaban 5 mg BID*, dabigatran†, or edoxaban 60 mg once daily||
- Less likely to do well on VKA with good TTR (SAmE-TT2R2 score ≥2)
  - VKA with additional education and more regular follow-up, dabigatran†, rivaroxaban 20 mg once daily¶, apixaban 5 mg BID*, or edoxaban 60 mg once daily||

Figure 5: Choice of oral anticoagulant drug to fit the patient profile

A simplified schema to assist physician choice of anticoagulant (VKA or individual NOAC) according to patient characteristic. BID=twice daily. CrCl=creatinine clearance. NOAC=non-vitamin K antagonist oral anticoagulant. TTR=time in therapeutic range. VKA=vitamin K antagonist. *Reduced to 2 5 mg BID with two of three criteria from age ≥80 years, bodyweight ≤60 kg, or serum creatinine concentration ≥133 μmol/L. ‡110 mg BID for patients with a CrCl 30–49 mL/min (most countries, but not in the USA); in the USA only, 75 mg BID (available in the USA only) for patients with CrCl 15–29 mL/min (and only 150 mg BID dose available in the USA for CrCl 30–49 mL/min). †30 mg with CrCl 15–49 mL/min, P-glycoprotein inhibitors, or weight <60 kg. §110 mg BID dose not available in the USA for atrial fibrillation. ¶Reduced to 15 mg if CrCl 15–49 mL/min. ||Dose to be halved if the patient has any of the following: CrCl 15–49 mL/min, bodyweight ≤60 kg, or concomitant use of P-glycoprotein inhibitors.
non-atrial fibrillation populations, including venous thromboembolism and patients undergoing bridging therapy. Simpler scores that aim to provide information valid for both VKAs and NOACs are likely to inappropriately categorise many patients who subsequently bleed as low risk or substantially underestimate bleeding risks in VKA-treated patients by ignoring labile INR as a risk criterion.25,26 More complex scores using biomarkers offer statistically improved prediction of high-risk patients, but are less simple for everyday clinical use and do not focus on the reversible bleeding risk factors.27

VKAs are effective and safe if well managed with good quality anticoagulation control, as shown by the time in therapeutic range (TTR) of over 70%.28 However, a good TTR can be difficult to obtain in clinical practice, or in some populations such as Asians.29 The control of VKAs is affected by several clinical features, and some common factors have been incorporated into the SAMe-TT$_R$ score (appendix pp 9, 10).30 Although prediction of the actual TTR is modest, the score is best used pragmatically to flag patients unlikely to do well on a VKA (score >2), because of labile INRs or poor TTR and the consequent risk of thromboembolism, death, or bleeding.29,30 Such patients should be targeted for more regular review and follow-up; educational interventions and counselling, which improve TTR,41 or use of NOACs.62

With availability of four NOACs in addition to VKAs, we can fit a particular drug to a patient’s clinical profile,1,44 by use of available evidence from large randomised trials and observational cohorts (figure 5 and discussed later). Various clinical considerations when choosing a particular type or dose of NOAC can be summarised by the mnemonic ABCDE: abnormally low weight (dose reduction might be needed); bleeding risk, especially previous or recent gastrointestinal bleeding; creatinine clearance (ie, renal function); drug interactions (eg, P-glycoprotein inhibitors); and elderly age (dose reduction might be needed).

### From clinical trials to real-world practice

The efficacy of warfarin compared with placebo or aspirin for stroke prevention in patients with non-valvular atrial fibrillation was established almost 30 years ago (table).4 In a meta-analysis66 of eight more recent stroke prevention trials (2005–11), the pooled rate of residual stroke or systemic embolism in the warfarin arms was significantly lower than in earlier trials (1·66% vs 2·09%), probably because of improved management of warfarin treatment (mean TTR 63·6% vs 42–81%), and four of six earlier trials with a TTR <60%, whereas the rates of major bleeding (1·4–3·4%) and intracranial haemorrhage (ICH; 0·61%) were similar.66

Owing to many limitations (panel 1),67 VKA treatment outside the trial setting is often suboptimal, and NOACs are increasingly used as a viable alternative. A meta-analysis6 of four landmark NOAC trials in non-valvular atrial fibrillation revealed a significant 19% stroke risk reduction vs warfarin (table).

<table>
<thead>
<tr>
<th>Included trials</th>
<th>Number of patients</th>
<th>Comparison</th>
<th>Stroke or SE RR or HR (95% CI)</th>
<th>Major bleeding RR or HR (95% CI)</th>
<th>Gastrointestinal bleeding RR or HR (95% CI)</th>
<th>ICH RR or HR (95% CI)</th>
<th>All-cause mortality RR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart et al (2007)4</td>
<td>5 primary, 1 secondary prevention trial</td>
<td>2900</td>
<td>Adjusted-dose warfarin vs placebo or no treatment</td>
<td>64% (49 to 74) RR reduction with warfarin</td>
<td>Not calculated</td>
<td>-66% (-23 to 18)</td>
<td>6 vs 3 events</td>
</tr>
<tr>
<td>Hart et al (2007)4</td>
<td>12 trials</td>
<td>3647</td>
<td>Adjusted-dose warfarin vs antiplatelet treatment</td>
<td>39% (22 to 52) RR reduction with warfarin</td>
<td>Not calculated</td>
<td>-70% (-23 to 14)</td>
<td>20 vs 7 events</td>
</tr>
<tr>
<td>Hart et al (2007)4</td>
<td>7 trials</td>
<td>3990</td>
<td>Aspirin vs placebo or no treatment</td>
<td>19% (-1 to 35) RR reduction with aspirin</td>
<td>Not calculated</td>
<td>2% (-9 to 52)</td>
<td>8 vs 4 events</td>
</tr>
<tr>
<td>Ruff et al (2014)4</td>
<td>4 trials</td>
<td>42 411 on a NOAC, 29 272 on warfarin</td>
<td>NOACs vs adjusted-dose warfarin</td>
<td>Overall RR 0·81 (0·73 to 0·91); ischaemic stroke RR 0·92 (0·83 to 1·02); haemorrhagic stroke RR 0·49 (0·38 to 0·64)</td>
<td>Not calculated</td>
<td>RR 0·86 (0·71 to 1·00)</td>
<td>RR 1·25 (1·01 to 1·55)</td>
</tr>
</tbody>
</table>

### Table: Meta-analyses of randomised, controlled trials or observational studies on the efficacy and safety of antithrombotic treatments for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation

### Notes

HR=hazard ratio. ICH=intracranial haemorrhage. NOAC=non-vitamin K antagonist oral anticoagulant. RR=relative risk. SE=systemic embolism. *Major extracranial bleeding.
Panel 1: Essential features of vitamin K antagonists and non-vitamin K antagonist oral anticoagulants

Vitamin K antagonists
- Slow onset and offset of action, with some thrombophilia during onset and offset
- Narrow therapeutic window (target INR 2.0–3.0)
- Several interactions with food and other drugs, which affect the anticoagulation intensity
- Variable dose response depending on the individual’s genetic background
- INR-guided dosing necessitates regular INR monitoring and frequent dose adjustments
- TTR of >65–70% is vital for optimum stroke prevention
- Used in clinical practice for a long time; not expensive

Non-vitamin K antagonist oral anticoagulants
- Fast onset and offset of action; onset faster than offset
- Fixed once or twice daily dosing
- A few clinically relevant interactions with other drugs; no food interaction
- Stable, dose-related anticoagulant effect; no need for regular laboratory monitoring of anticoagulation intensity, but renal function assessment is mandatory at baseline and during follow-up, depending on baseline renal function
- Strict adherence to non-vitamin K antagonist oral anticoagulant treatment crucial for optimum efficacy
- Relatively new drugs, expensive, but cost-effective, in comparison with vitamin K antagonists

See appendix pp 11–17 for more details. INR=international normalised ratio. TTR=time in therapeutic range.

Non-vitamin K antagonist oral anticoagulants

- Used in clinical practice for a long time; not expensive
- TTR of >65–70% is vital for optimum stroke prevention
- Variable dose response depending on the individual’s genetic background
- Several interactions with food and other drugs, which affect the anticoagulation intensity
- Narrow therapeutic window (target INR 2·0–3·0)
- Slow onset and offset of action, with some thrombophilia during onset and offset
- Need for regular laboratory monitoring of anticoagulation intensity
- Requires individualised titration based on renal function
- Requires close monitoring of renal function
- No food interactions

Vitamin K antagonists

- Slow onset and offset of action, with some thrombophilia during onset and offset
- Narrow therapeutic window (target INR 2.0–3.0)
- Several interactions with food and other drugs, which affect the anticoagulation intensity
- Variable dose response depending on the individual’s genetic background
- INR-guided dosing necessitates regular INR monitoring and frequent dose adjustments
- TTR of >65–70% is vital for optimum stroke prevention
- Used in clinical practice for a long time; not expensive

Non-vitamin K antagonist oral anticoagulants

- Fast onset and offset of action; onset faster than offset
- Fixed once or twice daily dosing
- A few clinically relevant interactions with other drugs; no food interaction
- Stable, dose-related anticoagulant effect; no need for regular laboratory monitoring of anticoagulation intensity, but renal function assessment is mandatory at baseline and during follow-up, depending on baseline renal function
- Strict adherence to non-vitamin K antagonist oral anticoagulant treatment crucial for optimum efficacy
- Relatively new drugs, expensive, but cost-effective, in comparison with vitamin K antagonists

See appendix pp 11–17 for more details. INR=international normalised ratio. TTR=time in therapeutic range.

reduction versus VKAs, which was driven by the reduction in haemorrhagic stroke and no real change in ischaemic stroke; comparable safety in terms of major bleeding, with impressive reductions in ICH, at the cost of increased gastrointestinal bleeding; and a 10% reduction in all-cause mortality relative to warfarin (table and appendix pp 11–13). The efficacy and safety of NOACs over warfarin seems to be even greater in east Asians compared with non-Asians.

Randomised trials provide the most objective evidence on a drug treatment, but the results might not be fully applicable to a range of real-world settings, because of the trial-specific inclusion and exclusion criteria. Notwithstanding some limitations, post-marketing observational studies, including prospective international registries and large administrative datasets, provide valuable complementary information on treatment performance in daily clinical practice. A meta-analysis of real-world observational studies on dabigatran versus warfarin for stroke prevention in non-valvular atrial fibrillation (table) yielded results broadly consistent with the main RE-LY trial. Key findings from those studies are shown in panel 2 and the appendix (pp 14–17). In real-world studies of rivaroxaban with lower risk patients, compared with the pivotal ROCKET-AF trial, the rates of stroke, major bleeding, and death seemed to be lower, but findings from more recent propensity-score-matched real-world studies with rivaroxaban consistently showed similar thromboembolism and bleeding risks to warfarin (appendix pp 14–17). In a large propensity-weighted analysis from a Danish nationwide cohort study, no significant differences were found between NOACs and warfarin for ischaemic stroke, but the risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran than for warfarin. Warfarin and rivaroxaban had comparable annual bleeding rates.

Findings from large prospective international observational registries show that many patients with atrial fibrillation who are eligible for OACs because of high risk of stroke are still not treated with OACs, particularly the elderly or those at high risk of bleeding. Findings from registry studies highlight the gaps in daily clinical practice alluded to earlier, and identify the unmet needs regarding evidence-based guidance on optimum strategies for stroke prevention in some subsets of patients with atrial fibrillation. Key findings and a detailed summary are shown in panel 2 and the appendix (pp 18–25).

Specific management considerations

Because of the overlap in stroke and bleeding risk factors, high-risk patients with atrial fibrillation are often denied OACs without an absolute contraindication. Elderly people and most patients with a history of bleeding (eg, previous gastrointestinal bleeding with a healed culprit lesion) clearly benefit from OAC resumption. Patients with atrial fibrillation after intracerebral haemorrhage or those with severe renal disease represent other high-risk groups that were excluded from randomised trials, but findings from observational studies suggest some benefit from OACs.

Patients with atrial fibrillation undergoing percutaneous coronary intervention and stenting need a complex management strategy including OACs with single or dual antiplatelet treatment, to balance risk of stroke, recurrent ischaemia, or stent thrombosis against the risk of serious bleeding with combined treatment. Dependent on the patient risk profile and clinical setting (ie, acute coronary syndrome vs stable disease), triple treatment with OACs plus dual antiplatelet treatment, followed by OACs plus a single antiplatelet drug such as clopidogrel, should be used for the shortest period advisable. Thereafter, OAC monotherapy (a NOAC or well-managed VKA) should continue.

Catheter atrial fibrillation ablation is superior to medical treatment at eliminating clinical atrial fibrillation recurrences, but should not be used to avoid OAC treatment; the decision regarding long-term OAC use after ablation should be based on individual stroke risk and not the estimated procedural success. Reports on the association of left atrial appendage isolation with appendage thrombus and stroke are conflicting, with results showing either improvement or a neutral effect, and there might even be a downside depending on the procedural details. Two ongoing trials are investigating...
early rhythm control (EAST; NCT01288352) or atrial fibrillation ablation versus antiarrhythmic drug treatment (CABANA; NCT00911508) on long-term risk of stroke and death.

Percutaneous left atrial appendage occlusion using the WATCHMAN, Amplatzer Cardiac Plug, or WaveCrest device or the Lariat endocardial and epicardial ligation technique might be an alternative for patients with atrial fibrillation who are at high risk of both stroke and bleeding or with contraindications to OACs; however, interventional cardiologists need to be trained in the procedure, and patients must receive dual antiplatelet treatment for at least 6 weeks after the procedure.19

Modifiable cardiovascular risk factors (eg, hypertension, obesity, dyslipidaemia, obstructive sleep apnoea, physical inactivity, and smoking) are important contributors to atrial fibrillation substrate progression and increased atrial fibrillation burden. Emerging evidence shows that aggressive risk factor management is likely to improve symptoms and reduce atrial fibrillation recurrence, thus facilitating rhythm control in patients with or without atrial fibrillation catheter ablation.20,105 Lifestyle interventions are likely to favourably affect cardiovascular outcomes, but whether these will reduce stroke remains to be established.

**Population-centred or patient-centred interventions**

Nurse-led clinics are an attractive possibility to improve uptake of stroke prevention strategies. In a randomised trial of 712 patients,106 appropriate OAC prescription increased from a high base of 83% in the usual care...
group to 99% in the nurse-led clinic. Although cardiovascular death and hospital admissions were both significantly reduced by the intervention, stroke was infrequent, with only 1% of patients having stroke in 22 months of follow-up, and was not significantly different between groups in this well-managed patient cohort. Another approach is to link population screening for unknown atrial fibrillation with screening for known but untreated atrial fibrillation, referring such individuals to a cardiology team to prescribe OACs.46

Marketing of NOACs has probably resulted in a rise in the proportion of eligible patients receiving anticoagulation; after introduction of NOACs in the UK, the proportion of patients with a CHA2DS2-VASc score of at least 2 starting anticoagulants for atrial fibrillation increased from 41% to 65%.35 Patient support groups (e.g., Atrial Fibrillation Association and StopAfib.org) also have a part to play in increasing patient awareness of atrial fibrillation and its attendant stroke risk, and reducing reluctance to start OACs.

A neglected aspect of stroke prevention is ensuring that patients who start OACs continue to take the treatment indefinitely. Unfortunately, persistence with OACs, or rather non-persistence, is a major issue; 21–50% of patients discontinue VKAs by 1 year after inception.101 Findings from many studies have shown lower persistence with warfarin than a single NOAC. In one study,102 persistence with warfarin was significantly lower than with NOACs at 1 year (65% vs 83%; appendix p 2). This difference in persistence of drug treatment is likely to be a major factor in strokes related to atrial fibrillation, because cessation of VKAs more than doubles the stroke risk, with a peak in the first year after cessation, and a high absolute increase for at least 3 years after cessation.103 In view of the shorter half-life with NOACs, poor patient adherence also translates to a higher risk of stroke and mortality despite overall good adherence to these drugs.103,105 Therefore, greater efforts are needed to support the patient to increase adherence and continue OACs long term, whether with decision aids, educational measures, or patient counselling.105,107

Future directions

Increasing awareness of the role of unrecognised atrial fibrillation should accelerate efforts to detect atrial fibrillation before stroke has occurred and institute effective thromboprophylaxis with OACs. Widespread recognition of the role of undertreatment of atrial fibrillation in causation of ischaemic stroke will be of crucial importance to focus efforts to close the evidence–treatment gap for OACs, and replace aspirin with OACs in the therapeutic armamentarium. Basic and clinical research is needed to better understand the pathological atrial substrate leading to cardioembolism for which atrial fibrillation is likely to be a marker. In the longer term, efforts should be directed at primary prevention of atrial fibrillation, which might need similar lifestyle modifications as advocated for prevention of coronary heart disease.

Contributors

BF drafted, collated, and revised the manuscript. TSP did the literature searches. TSP and GYH drafted and revised the manuscript.

Declaration of interests

BF has received research grants to undertake investigator-initiated studies from Bristol-Myers Squibb/Pfizer, Bayer, and Boehringer Ingelheim; has been a consultant for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Servier, AstraZeneca, and Gilead; and has been a speaker for Bayer, Bristol-Myers Squibb/Pfizer, and AstraZeneca. TSP has been a consultant for Bayer, AstraZeneca, and Pfizer; and a speaker for Bayer, Pfizer, and AstraZeneca. GYH has been a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daichi Sankyo; and a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daichi Sankyo.

Acknowledgments

We thank Alistair Corbett for providing the stroke images in figure 1, and James Leyden and Leif Fröhing for providing additional information on antiplatelet treatment for appendix figure 2 (pp 3, 4) from the studies they led.

References


61 Lip GY, Skjøth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHADS-VASc score. J Am Coll Cardiol 2015; 65: 1385–94.


63 Lip GY, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. Thromb Haemost 2015; 114: 826–34.


79 Proietti M, Lane DA, Lip GYH. Relation of the SAMe-TT2R2 score to quality of anticoagulation control and thromboembolic events in atrial fibrillation patients: observations from the SPORTIF trials. Int J Cardiol 2016; 216: 168–72.

80 Clarksden SM, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomized trial. Platelet 2011; B: 17407.


95 Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014; 35: 1355–79.


