

Optimising stroke prevention in patients with atrial fibrillation in primary care

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Abstract

In clinical practice, atrial fibrillation (AF) is the most common cardiac arrhythmia seen, and with an ageing population its prevalence is expected to rise. Guidelines recommend anticoagulant therapy for AF-related stroke prevention, based on an individual's predicted risk of stroke; options include vitamin K antagonists (VKAs) and the non-VKA oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban. The NOACs fulfil most criteria associated with an ideal anticoagulant and have demonstrated improved benefit–risk profiles compared with warfarin in patients with non-valvular AF. Although patients with AF commonly have other chronic conditions that may complicate treatment, a recent meta-analysis showed a similar treatment effect of NOACs in almost all challenging-to-treat subgroups encountered in clinical practice compared with the general patient population. Encouragingly, data on the real-world efficacy and safety of NOACs are growing and lend support to the increased use of NOACs in this indication.

Keywords: Anticoagulation, atrial fibrillation, real-world, stroke prevention

Summary points

The non-vitamin K antagonist oral anticoagulants have demonstrated favourable benefit–risk profiles in large phase III trials, and these findings have been supported by real-world studies involving unselected patients representative of those encountered in routine clinical practice and including those deemed 'challenging-to-treat'

Accurate detection of atrial fibrillation and assessment of stroke and bleeding risk is crucial in identifying patients who should receive anticoagulation

Elderly populations represent a significant proportion of patients seen in general practice, and advanced age should not be regarded as a contraindication to treatment; acetylsalicylic acid is not considered an effective treatment option to reduce the risk of stroke in patients with non-valvular atrial fibrillation (except for those declining oral anticoagulation), particularly in fragile elderly patients, for whom this drug was historically prescribed

The frequency of follow-up visits, in particular to check compliance, should be tailored according to patients' clinical characteristics and needs, but there is no requirement for routine coagulation monitoring, unlike vitamin K antagonists

ischaemic and other structural heart disease². In addition to being associated with significantly increased rates of mortality³, AF is also associated with significantly increased rates of heart failure, which is both a common cause and consequence of AF and greatly worsens the prognosis⁴. However, it is stroke that is the most devastating consequence of AF, with an average fivefold increased risk⁵.

AF-related strokes are often more severe than other strokes^{6,7} because the clots that embolise from the left atrium or left atrial appendage are often much larger⁸ than from other sources of emboli. These clots usually lodge in large cerebral vessels, commonly the middle cerebral artery, resulting in huge neurological and functional deficits and increased mortality compared with other stroke types. Moreover, the strokes suffered by patients with AF are more likely to lead to extended hospital care than strokes in patients without AF, thus impacting on patients' quality of life⁷.

Current evidence suggests that, in the UK, AF has a causative role in almost 20% of all strokes⁹. This is likely to represent a significant underestimate given that long term electrocardiogram (ECG) monitoring in patients who would previously have been diagnosed as having cryptogenic stroke has demonstrated a significant AF burden in these patients¹⁰.

With improved AF detection and stroke prevention, it is estimated that approximately 8000 strokes could be avoided and 2100 lives saved every year in the UK, resulting in substantial healthcare savings of £96 million^{11,12}.

A key objective of this short review is to provide primary care clinicians with the confidence to manage patients with AF in

Atrial fibrillation: a clinical and economic burden to society

Atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of about 1.5–2% in the general population^{1,2}. Its incidence is predicted to rise sharply over the coming years as a consequence of the ageing population and increased life expectancy in those with

need of anticoagulation, including the safe and appropriate use of the non-vitamin K antagonist oral anticoagulants (NOACs) apixaban, dabigatran, rivaroxaban (approved in the EU, US and several other countries worldwide) and edoxaban (approved in the EU, US and Japan).¹³⁻²⁰ The focus will be on how to accurately identify, risk-stratify and counsel patients on the risks and benefits associated with the different treatment options.

Who to treat. Accurate detection and assessment of stroke and bleeding risk

Many patients with AF are asymptomatic, particularly the elderly, less active patients who may not notice the reduction in cardiac performance associated with AF. Unfortunately, it remains the case that AF is undetected in up to 45% of patients²¹, and stroke is very often the first presentation of AF.

Both the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) guidelines recommend opportunistic screening in patients aged ≥ 65 years by manual pulse palpation followed by ECG in patients found to have an irregular pulse^{1,22}. Opportunistic screening (manual pulse palpation) was shown to be as effective as systematic screening (ECG) in detecting new cases²³, and this simple strategy should be used to screen at-risk patient groups as often as possible. Hypertension and increasing age are the two leading risk factors for developing AF, but other high-risk groups include patients with obstructive sleep apnoea, morbid obesity or a history of ischaemic heart disease²⁴⁻²⁶. In the context of proactive AF detection, many initiatives have been launched worldwide to encourage primary care clinicians to integrate manual pulse checks into their routine practice. The Know Your Pulse campaign was launched by the AF Association and Arrhythmia Alliance during Heart Rhythm Week in 2009 and was quickly endorsed by the Department of Health in the UK and by many other countries. This initiative has assisted in diminishing some of the gaps in AF detection²¹.

The most frequently used tools to evaluate stroke risk in patients with non-valvular AF (AF that is not associated with rheumatic valvular disease or prosthetic heart valves) are the CHADS₂²⁷ and CHA₂DS₂-VASc²⁸ scores, with recent guidelines favouring the use of the latter and emphasising the need to effectively identify 'truly low-risk' patients¹. The CHA₂DS₂-VASc score is superior to CHADS₂ in identifying these truly low-risk patients, who should not be routinely offered anticoagulation¹. Patients with any form of AF (i.e. paroxysmal, persistent or permanent), and regardless of whether they are symptomatic, should be risk stratified in this way. The risk of stroke should also be assessed using CHA₂DS₂-VASc in patients with atrial flutter and probably for the majority of patients who have been successfully cardioverted in the past²². Unless the initial underlying cause has been removed (e.g. corrected hyperthyroidism) and there is no significant underlying structural heart disease, the risk of patients suffering from a recurrence of AF following 'successful' cardioversion remains

high²⁹. The ESC guidelines recommend that anticoagulation should be offered to patients with a CHA₂DS₂-VASc score ≥ 1 based on assessment of risk of bleeding complications and the patient's clinical features and preferences¹.

The new Quality and Outcomes Framework (QOF) for 2015–2016 now recommends the use of CHA₂DS₂-VASc for risk stratification and no longer recommends antiplatelet agents as a therapeutic option for stroke prevention in patients with non-valvular AF³⁰; this should result in significantly more patients receiving anticoagulation for this indication. The changes to QOF 2015–2016 compared with 2014–2015 are summarised in Table 1³⁰.

Table 1. Summary of changes to UK the Quality and Outcomes Framework (QOF) 2015–2016³⁰

NICE indicator ID	Changes	2014–2015 points	2015–2016 points
NM45: Patients with AF and CHADS ₂ =1 currently treated with anticoagulant therapy or antiplatelet therapy	Retired	6	–
NM46: Patients with AF and a latest record of a CHADS ₂ ≥ 1 currently treated with anticoagulant therapy	Replaced by NM82	6	–
NM82: Patients with AF and CHA ₂ DS ₂ -VASc ≥ 2 currently treated with anticoagulant therapy	Replacement	–	12
NM81: Patients with AF in whom stroke risk has been assessed using the CHA ₂ DS ₂ -VASc risk-stratification scoring system in the preceding 12 months (excluding those with a previous CHADS ₂ or CHA ₂ DS ₂ -VASc ≥ 2)	New indicator	–	12

Key: AF = atrial fibrillation; CHADS₂ = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke (doubled); CHA₂DS₂-VASc = Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74 years, Sex category (female); NICE = National Institute for Health and Care Excellence

The Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) clinical audit software detection tool is now very widely used in primary care to improve clinical outcomes in the AF population by identifying patients likely to benefit from anticoagulation. GRASP-AF systematically scans general practice software systems and calculates CHADS₂ and CHA₂DS₂-VASc scores in patients who are coded as having AF, thus enabling physicians to identify high-risk patients who are not adequately treated for stroke prevention³¹. Identification of AF patients who are poorly controlled on warfarin (defined as

having a time in therapeutic range <65% or a labile international normalised ratio [INR], e.g. one INR value >8 or two INR values <1.5 or >5 within the past 6 months)²² is crucial because these patients are more likely to experience major bleeding or stroke. These patients should be reviewed and, if possible, the cause for the poor warfarin control should be identified. The Warfarin Patient Safety Audit tool is another software tool that has been developed to help identify patients with poor warfarin control³².

Primary care clinicians are being urged to objectively assess the bleeding risk of AF patients who are receiving, or about to receive, anticoagulation^{1,22,32}. HAS-BLED is the bleeding assessment scheme advocated by both NICE and the ESC^{1,22}, this has been validated in several independent cohorts and was shown to correlate well with the risk of major bleeding, in particular intracranial bleeding¹. The key aspect of HAS-BLED is that, unlike CHADS₂ and CHA₂DS₂-VASc, it consists of risk factors that are modifiable. It should, therefore, not be a tool to influence the decision of whether to anticoagulate, but instead to identify ways to reduce the risk of bleeding in patients receiving an anticoagulant; for example, optimising blood pressure control, stopping unnecessary antiplatelet or anti-inflammatory agents and reducing alcohol consumption can all significantly reduce HAS-BLED scores and bleeding risk¹. In addition, it needs to be emphasised that the absolute number of patients with AF experiencing a serious bleeding event while receiving anticoagulant therapy is low (~2–3%/year in the XANTUS, PMSS and Dresden NOAC Registry real-world studies), with prospective real-world studies indicating that most bleeding events can be managed conservatively^{33–35}. Whilst concerns have been raised about not having a reversal agent to counter the anticoagulant action of NOACs in patients who experience serious bleeding, the low incidence of major bleeding in real-world and phase III studies and its conservative management in most cases demonstrate that such agents would not be required routinely. Despite these low rates of major bleeding, reversal agents have been developed and successfully completed phase III studies and undergone approval in some markets, including idarucizumab in the UK^{36,37}. Notably, high-risk patients with AF were shown to be more willing to endure bleeding events in order to avoid a stroke and its consequences³⁸, thus reinforcing the message that “we can replace blood but we cannot replace brain tissue”.

Adequate anticoagulation therapy should follow appropriate patient identification

Identifying the right treatment option for patients with AF is likely to improve clinical outcomes. Involving patients in the decision-making process and rationale, and ensuring they understand the net benefit–risk of treatment options, is likely to lead to better compliance and improved clinical outcomes. The ESC guidelines consider patients with valvular AF (patients with AF in the presence of either rheumatic mitral stenosis [very rare now in the UK] or prosthetic heart valves) to be at high

risk, and these patients should be anticoagulated with a VKA regardless of the presence of any other risk factors¹. Warfarin is very effective at reducing the risk of stroke compared with acetylsalicylic acid (ASA)^{39,40}, but an unpredictable dose–response relationship and multiple drug and food interactions can be problematic for some patients, and many patients remain sub-optimally treated⁴¹. ASA is also not considered an effective treatment option to reduce the risk of stroke in patients with non-valvular AF especially in frail, elderly patients in whom ASA was historically prescribed. The GARFIELD-AF registry (10,614 patients enrolled in the first cohort) revealed that real-world anticoagulant prescribing in AF populations deviates substantially from guideline recommendations: 40.7% of patients with a CHA₂DS₂-VASc score ≥2 did not receive anticoagulant therapy, and a further 38.7% with a score of 0 received anticoagulant therapy. At diagnosis, 55.8% of patients overall were given a VKA, just over one quarter (25.3%) received an antiplatelet drug alone, and ~4.5% received a NOAC²⁴. Inappropriate prescribing was further confirmed by data from UK general practices (n=1857, representing a practice population of 13.1 million registered patients) using the GRASP-AF tool. Only 55% of patients with high-risk AF (CHADS₂ ≥2) were receiving oral anticoagulation (OAC) therapy, whereas a further 34% of patients with no known contraindication did not receive OAC therapy⁴².

The NOACs have altered the landscape in terms of stroke prevention management by increasing the available options for patients. These agents exhibit some important practical advantages over traditional therapy (e.g. no requirement for routine anticoagulation monitoring, simple fixed dosing oral regimens, fast onset of action, fewer drug reactions and no food interactions), leading to their increased uptake in primary care.

Key patient groups who are likely to benefit from the NOACs include patients poorly controlled on VKAs, those predicted to require medications that interact with VKAs (e.g. patients who require frequent antibiotics), those without severe renal impairment or those with a prior ischaemic stroke while receiving a VKA with an adequate INR. These agents could also be a good choice for patients living a considerable distance from their local hospital or surgery and commuters. The NICE guidelines state that primary care clinicians should consider clinical features and patient preference before deciding on the most appropriate option for patients²². In addition, cost may be important in some settings. All of the NOACs have demonstrated cost-effectiveness versus warfarin, and although cost models vary by country, there is little doubt that these agents provide cost-effectiveness largely through the number of adverse events avoided and their associated costs⁴³.

Choice of anticoagulant: which to choose?

The demonstration of a favourable benefit–risk profile (stroke prevention vs bleeding events) in large phase III studies involving over 70,000 patients has resulted in the regulatory

approval of apixaban, dabigatran, edoxaban and rivaroxaban⁴⁴⁻⁴⁷ for the prevention of stroke and systemic embolism in patients with non-valvular AF and one or more risk factors.

Overall, NOACs have demonstrated an improved benefit compared with warfarin, with lower rates of intracranial haemorrhage (for all NOACs) and similar or superior efficacy for stroke prevention⁴⁴⁻⁴⁸. Statistically significant relative risk reductions (RRRs) in the incidence of fatal bleeding events were seen with low-dose dabigatran (110 mg twice daily [bd]; RRR=42%), both tested doses of edoxaban (30 mg once daily [od] and 60 mg od; RRR=65% and 45%, respectively) and rivaroxaban (20 mg od; RRR=50%)^{46,47,49}; rates of fatal bleeding were also lower in patients treated with apixaban compared with warfarin (34 patients vs 55 patients, respectively)⁴⁴. These data are promising, especially considering the current lack of a specific antidote for any of the NOACs, and it is likely that the very short half-life of these drugs play an important role in mitigating the bleeding risk.

Owing to a lack of head-to-head comparisons between the NOACs in phase III clinical trials, patient characteristics, drug compliance, tolerability issues and cost may be important considerations¹. In addition, subanalyses of phase III trial data for rivaroxaban, apixaban and dabigatran indicate that the challenging-to-treat patient groups often encountered by primary care clinicians can be treated effectively and safely with the NOACs (Table 2). A recent meta-analysis showed a similar treatment effect for almost all subgroups encountered in clinical practice; NOACs appeared to be at least as effective as VKAs in reducing the risk of stroke and systemic embolism and no more hazardous in relation to the risk of major bleeding events, irrespective of patient co-morbidities⁵⁰.

Table 2. Novel oral anticoagulants studied in key patient subgroups*

Subgroup analysis	Rivaroxaban	Dabigatran	Apixaban
Factors related to disease	ROCKET AF	RE-LY	ARISTOTLE
Heart failure	✓ ⁵⁹	✓ ⁶⁰	✓ ⁶¹
Renal impairment	✓ ⁶²	✓ ⁶³	✓ ⁶⁴
Prior stroke	✓ ⁶⁵	✓ ⁶⁶	✓ ⁶⁷
VKA-naïve	✓ ⁶⁸	✓ ⁶⁹	✓ ⁷⁰
Prior MI or CAD	✓(prior MI) ⁷¹	✓(CAD or prior MI) ⁷²	✓CAD ⁷³
PAD	✓ ⁷⁴	—	—
PK/PD	✓ ⁷⁵	✓ ⁷⁶	—
East Asian patients	✓ ⁷⁷	✓ ⁷⁸	⁷⁹
Elderly	✓ ⁸⁰	✓ ⁴⁹	✓ ⁸¹

Major bleeding predictors	✓ ⁸²	—	—
Obesity	—	—	—
Diabetes	✓ ⁸³	✓ ⁸⁴	✓ ⁸⁵
Valvular heart disease	✓ ⁸⁶	—	✓ ⁸⁷
Paroxysmal versus persistent AF	✓ ⁸⁸	✓ ⁸⁹	✓ ⁹⁰

*No subgroup analyses have been presented for edoxaban **Key:** AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation; CAD = coronary artery disease; CHADS₂= Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke (doubled); MI = myocardial infarction; PAD = peripheral artery disease; PK/PD = pharmacodynamics/pharmacokinetics; RE-LY = Randomized Evaluation of Long-term anticoagulation therapy; 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; VKA = vitamin K antagonist

Because patient selection in clinical trials is based on strict inclusion/exclusion criteria, patient populations in such studies are not always representative of patients routinely seen in real-world practice. In addition, bleeding events may be managed differently in clinical trials versus routine clinical practice. Real-world data are, therefore, needed to help validate drug safety and effectiveness in unselected patient populations. Following phase III clinical trials and the widespread approval of the NOACs in stroke prevention in patients with non-valvular AF, real-world experience has been steadily accumulating. The current real-world data for rivaroxaban, apixaban and dabigatran have been very reassuring and bridge the evidence gap between clinical studies and real-world experience^{33-35,51-57}.

The lack of routine coagulation monitoring with NOACs does not remove the necessity for regular follow-up. Instead, the frequency of visits can be tailored according to patients' clinical characteristics and needs. NOACs are all partially eliminated by the kidneys; therefore, regular monitoring of renal function is important either to use a lower recommended dose of these drugs or to avoid them. For example, renal function should be monitored every 6 months in patients who have stage III chronic kidney disease (creatinine clearance [CrCl] 30–60 ml/min)⁵⁸. Apixaban, rivaroxaban and edoxaban are not recommended in patients with CrCl <15 ml/min, and dabigatran is contraindicated in patients with CrCl <30 ml/min^{13,15,17,19}. Reduced-dose regimens of NOACs are recommended for patients at higher risk of bleeding events, including those with reduced renal function. For example, a reduced apixaban dose of 2.5 mg bd is indicated in patients with at least two of the following characteristics: age ≥80 years,

body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dl (133 $\mu\text{mol/l}$); a reduced rivaroxaban dose of 15 mg od is indicated in patients with CrCl 15–49 ml/min⁵⁸; edoxaban is recommended at a reduced dose of 30 mg od in patients with CrCl 15–50 ml/min and contraindicated in patients with CrCl >95 ml/min⁵⁸; and a reduced dose of 110 mg bd dabigatran should be considered in patients with CrCl 30–50 ml/min who are at a high risk of bleeding⁵⁸. Follow-up visits should also systematically document patient compliance, thromboembolic and bleeding events, side-effects, co-medications and blood test results⁵⁸.

Conclusions

The NOACs have demonstrated favourable benefit–risk profiles in large phase III trials, and these findings have been supported by real-world studies involving unselected patients, including those deemed challenging to treat. The NOACs also address many of the limitations associated with VKA use, thus assisting with their integration into clinical practice for stroke prevention in patients with non-valvular AF. In addition, the results from subgroup analyses should provide primary care clinicians with the confidence to manage stroke-prevention strategies in a wide variety of patients with AF.

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Competing Interests

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