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Review

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Update on anti-coagulation in atrial fibrillation

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Summary

Atrial fibrillation (AF), the most common clinically relevant arrhythmia, affects 2.2 million individuals in the USA and 4.5 million in Europe, resulting in significant morbidity and mortality. Pharmacotherapy aimed at controlling both heart rate and rhythm is employed to relieve AF symptoms, though debate continues about which approach is preferable. AF prevalence rises with age from 0.4% to 1% in the general population to 11% in those aged >70 years. AF is associated with a pro-thrombotic state and other comorbidities; age, hypertension, heart failure and diabetes mellitus all play a key role in AF pathogenesis. Anti-coagulation is essential for stroke prevention in patients with AF and is recommended for patients with one or more risk factors for stroke. Used within the recommended therapeutic range, warfarin and other vitamin K antagonists decrease the incidence of stroke and mortality in AF patients. Warfarin remains under-used, however, because of the perceived high risk of haemorrhage, narrow therapeutic window and need for regular monitoring. Several novel anti-coagulants show promise in AF-related stroke prevention. In particular, the novel, oral, direct thrombin inhibitor, dabigatran etexilate, recently licensed by the US Food and Drug Administration (FDA) and Health Canada has shown improved efficacy and safety compared with warfarin for stroke prevention in AF, and has the potential to replace warfarin in this indication. The increasing number of new therapeutic options, including improved anti-arrhythmic agents, novel anti-coagulants and more accessible ablation techniques, are likely to deliver better care for AF patients in the near future.

Introduction

Atrial fibrillation (AF) is the most common clinically relevant arrhythmia seen in the USA and Europe, found in 1–2% of the population and affecting an estimated 2.2 million individuals in the USA and 4.5 million in Europe.[1,2] It is responsible for one-third of hospitalizations for cardiac rhythm disturbances[2] and is associated with significant morbidity and mortality, including a 4- to 5-fold increased risk of stroke and a 3-fold increased risk of heart failure,[3] resulting in significant effects on quality of life (QoL) and a high socioeconomic burden.

The primary goals of pharmacotherapy in AF are to restore sinus rhythm, control heart rate and prevent stroke. Anti-coagulation therapy is an essential strategy in the prevention of stroke in AF patients. Although warfarin and other vitamin K antagonists (VKAs) decrease stroke incidence and mortality in AF patients, warfarin is perceived to be associated with a high risk of haemorrhage and is difficult to

use in an optimal manner resulting in under-use. This review explores currently available AF therapies and examines the evidence for newer treatment options.

Diagnosis, epidemiology and burden of AF

Diagnosis

Typical signs and symptoms of AF relate to irregular heart rate and include palpitations, chest pain, shortness of breath, fainting and fatigue.[2] AF can be asymptomatic, however, and is sometimes diagnosed only after a stroke or transient ischaemic attack (TIA). Diagnosis of AF involves investigation of the aetiology and nature of the arrhythmia via patient history, physical examination, electrocardiogram, transthoracic echocardiogram and routine blood tests; some patients also require coronary angiography or magnetic tomography. Early diagnosis of AF reduces mortality and morbidity,[4] and thus programmes to improve self-diagnosis, such as the 'Know Your Pulse' global campaign, are underway in several countries.[5]

The American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines recommend classification of AF into three primary types:[2] paroxysmal (recurrent episodes that self-terminate in <7 days); persistent (non–self-terminating recurrent episodes lasting >7 days that can be converted to sinus rhythm by electrical or pharmacological cardioversion); and permanent (ongoing long-term AF resistant to electrical or pharmacological cardioversion). Individuals may experience different types of AF at different times, and it is therefore practical to categorize patients by their most frequent presentation.

The recent (2010) ESC guidelines describe a continuum of AF, recognizing that the condition begins with short, infrequent episodes and often progresses to longer, more sustained and frequent attacks.[1] The guidelines also acknowledges the fact that AF can be asymptomatic. Five categories of AF are described: first diagnosed, paroxysmal (which usually resolves within 48 h but may continue for up to 7 days), persistent (lasting >7 days or requiring cardioversion), long-standing persistent (lasting $\geqslant$1 year) and permanent (accepted by the patient and physician, and not managed using rhythm control).[1]

Guidelines also categorize AF relating to patient characteristics.[2] Lone AF presents in the absence of clinical or cardiographic findings of other cardiovascular disease, usually in patients aged <60 years. Valvular AF has heart valve disease as its leading cause, while non-valvular AF presents in the absence of rheumatic mitral valve disease, mitral valve repair or artificial heart valve. Secondary AF occurs in the setting of other conditions such as acute myocardial infarction, cardiac surgery, hyperthyroidism or pneumonia.

Epidemiology

AF is associated with conditions such as hypertension, primary heart diseases, lung diseases, excessive alcohol consumption[6] and hyperthyroidism. Sufferers may also have a genetic susceptibility to the condition.[7] Current evidence suggests that hypertension and obesity play a key role in AF pathogenesis; inflammation may be a trigger to initiate AF.[8]

AF prevalence is highly age-dependent, increasing from 0.4–1% in the general population to 11% in those aged >70 years, and around 17% in individuals aged $\geqslant$85 years.[2,9–11] However, with a growing elderly population, AF prevalence is likely to more than double during the next 50 years.[12]

Stroke risk

The Framingham Study data indicate that AF is associated with a pro-thrombotic state that increases stroke risk 5-fold.[13] A thrombus, commonly formed in the left atrial appendage, embolizes, travels in the circulation and blocks a blood vessel in the brain.[2] Paroxysmal, persistent and permanent AF all appear to confer the same risk of stroke.[14] The likelihood of AF-related stroke varies among patients and is dependent on several factors; increasing age is one of the strongest risk factors.

Stroke risk is classified in several risk stratification schemes including $CHADS_2$, CHA_2DS_2-VASc, AF Investigators, Framingham, Birmingham/National Institute for Clinical Excellence [NICE] and ACC/AHA/ESC based on multivariate analyses of study cohorts or expert consensus.[15,16] These schemes most frequently include features such as prior stroke/TIA, patient age, hypertension and diabetes mellitus; absolute stroke rates and patients categorized as low risk or high risk can differ substantially across the various schemes.

The $CHADS_2$ score has been the most widely used to measure AF stroke risk and to guide anticoagulant therapy choice. $CHADS_2$ was developed by the National Registry of AF, based on point allocations for AF risk factors and has been validated in a clinical trial involving more than 11 000 subjects[17] (Table 1). For each 1-point increase in $CHADS_2$, stroke rate per 100 000 years without antithrombotic therapy increases by a factor of 1.5 (Table 2). A $CHADS_2$ validation study classified a

Table 1 $CHADS_2$ scoring classification[17]

	Condition	Points
C	Congestive heart failure	1
H	Hypertension: blood pressure consistently >140/90 mmHg (or treated hypertension on medication)	1
A	Age >75 years	1
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischaemic attack	2

Table 2 Annual stroke risk according to $CHADS_2$ score[17]

	$CHADS_2$ score	Stroke risk (%)	95% CI
Low risk	0	1.9	1.2–3.0
Moderate risk	1	2.8	2.0–3.8
	2	4.0	3.1–5.1
High risk	3	5.9	4.6–7.3
	4	8.5	6.3–11.1
	5	12.5	8.2–17.5
	6	18.2	10.5–27.4

score of 0–1 as low risk, 1–2 as moderate risk and 3–6 as high risk (Table 2). However, this system has several limitations that may lead to over- or under-estimation of stroke risk in AF. First, it does not account for every risk factor for stroke. Patients with a history of stroke or TIA as their only risk factor have a $CHADS_2$ score of 2 indicating moderate risk, despite having very high risk of recurrent stroke.[18] Age >75 years does not confer a uniform single risk, as shown by the AF Working Group study.[19] Finally, well controlled hypertension may be less of a risk than other $CHADS_2$-defining factors, as stroke risk only markedly rises with mean systolic blood pressure >140 mmHg in anti-coagulated patients.[20] $CHADS_2$ scoring has been found to classify the greatest proportion of patients as moderate risk compared with other schemes, which can cause confusion over appropriate treatments (aspirin vs. VKAs). Thus, the ACC/AHA/ESC guidelines recommend that the 'selection of anti-thrombotic agent should be based upon the absolute risks of stroke and bleeding, and the relative risk and benefit for a given patient'.

An improved stratification system (CHA_2DS_2-VASc) includes new risk factors such as female gender, vascular or heart disease, and age >65 years; it also considers both definitive and combination risk factors.[16] In this scheme, patients with no risk factors are designated low risk; one combination risk factor [heart failure/left ventricular ejection fraction (LVEF) $\leqslant$40, hypertension, diabetes, vascular disease, female gender, age 65–74 years] confers intermediate risk; and previous stroke, TIA or embolism, age $\geqslant$75 years or $\geqslant$2 combination risk factors (heart failure/LVEF $\leqslant$40, hypertension, diabetes, vascular disease, female gender, age 65–74 years) confers high risk. The recent ESC guidelines recommends that for individuals with a CHA_2DS_2-VASc score of 1, 2 or above, oral anti-coagulant therapy is desirable.[1] Aspirin therapy is now recommended for very few patients who are at very low risk of stroke.

The ESC 2010 guidelines specify that assessment of bleeding risk before administration of anti-coagulant therapy in AF should make use of the HAS-BLED scoring system, which assigns one point to the following risk factors. **H**ypertension, **A**bnormal liver or renal function (1 point each), **S**troke, **B**leeding history or disposition, **L**abile international normalized ratios, **E**lderly status (age $\geqslant$65 years) and **D**rug or alcohol use (1 point each); high risk is defined by the scheme as 3 points or higher.[1,21]

Burden

AF-associated strokes are generally more severe than strokes not associated with AF and are more likely to be fatal,[22] with ~50% of patients dying within 1 year in one population-based registry study.[23] The high morbidity associated with AF complications, especially stroke, has a significant impact on QoL and healthcare resource utilization.[24] In a retrospective analysis of three federally funded databases, estimated total annual medical costs for AF treatment in US inpatient, emergency room and outpatient hospital settings were $US6.65 billion (2005 expenditure).[25] Similarly, in 2000 the direct costs of treating AF in the UK were estimated at £459 million or 0.88% of total National Health Service expenditure, via analysis of epidemiological studies and government datasets.[26] As a whole, AF-related stroke carries a high socioeconomic burden.

Disease management

The goals of AF management are to prevent stroke with anti-thrombotic therapy (recommended for all AF patients, except for those with lone AF), symptom

relief and preservation of left ventricular function by either controlling heart rate or restoring normal sinus rhythm.[27] The choice between rate or rhythm control depends upon individual patient characteristics. The main treatment options for AF are shown in Figure 1. Anti-coagulation should be continued in patients at risk of stroke,[27] and is generally recommended even after restoration of normal sinus rhythm.

Rate and rhythm control

Correction of the underlying arrhythmia in AF may appear to be the best treatment option. However, rate control has been shown to be at least as effective in improving mortality, stroke rate, AF symptoms and QoL.[28,29] Rate control has also been shown to be a more cost-effective strategy than rhythm control, with reduced medical resource requirements.[30]

In the emergency setting, the priority is to maintain haemodynamic stability by urgently restoring sinus rhythm or controlling ventricular rate. Direct current cardioversion should be considered for AF patients who are haemodynamically unstable, or who show signs of myocardial ischaemia or heart failure.[2,31] If AF has presented recently (<7 days) and the patient is haemodynamically stable, cardioversion with anti-arrhythmic drugs can be effective. Class IC agents, such as flecainide or propafenone, are commonly used in stable AF.[31] If AF has been present for >48 hours, atrial thrombus must be excluded and adequate anti-coagulation initiated. Class IC anti-arrhythmics are not recommended for elderly AF patients due to the risk of co-morbidities, such as coronary artery disease or left ventricular dysfunction. In these patients, and where arrhythmia has persisted for >1 week, a class III agent, such as amiodarone may be preferred.[31]

Anti-arrhythmic agents vary in their mode of administration, efficacy in restoring and maintaining sinus rhythm, and are associated with pro-arrhythmogenic effects, serious side-effects (Table 3) and drug–drug interactions. Amiodarone has proven very effective for maintenance of sinus rhythm after cardioversion, but its use is limited by side-effects, including heart disturbances (Table 3).[31] In one trial in elderly AF patients, the newly introduced agent, dronedarone, reduced AF recurrence versus placebo, and also had beneficial effects on cardiovascular mortality/morbidity, although the difference for all-cause death was statistically non-significant. Dronedarone therapy also lacked many of the side-effects associated with amiodarone.[32] Dronedarone is, however, considered to be less effective than amiodarone.

Even with a variety of anti-arrhythmic drugs and repeated external cardioversions, only 39–63% of AF patients maintain sinus rhythm.[28,29] Rate control may therefore be a beneficial alternative strategy, especially in elderly patients. Rate control aims to achieve a resting heart rate of 60–80 beats/min (bpm) and avoid periods with an average heart rate over 1 h of >100 bpm. A recent study [RAte Control Versus Electrical Cardioversion Of Persistent Atrial Fibrillation (RACE)], however, suggests that resting heart rates <110 bpm may be equally efficient.[33] Rate control agents include beta-blockers, non-dihydropyridine calcium antagonists and digoxin, administered alone or in combination.

The merits of rate versus rhythm control have been much debated. Rhythm control does not reduce mortality; the two largest trials of rate

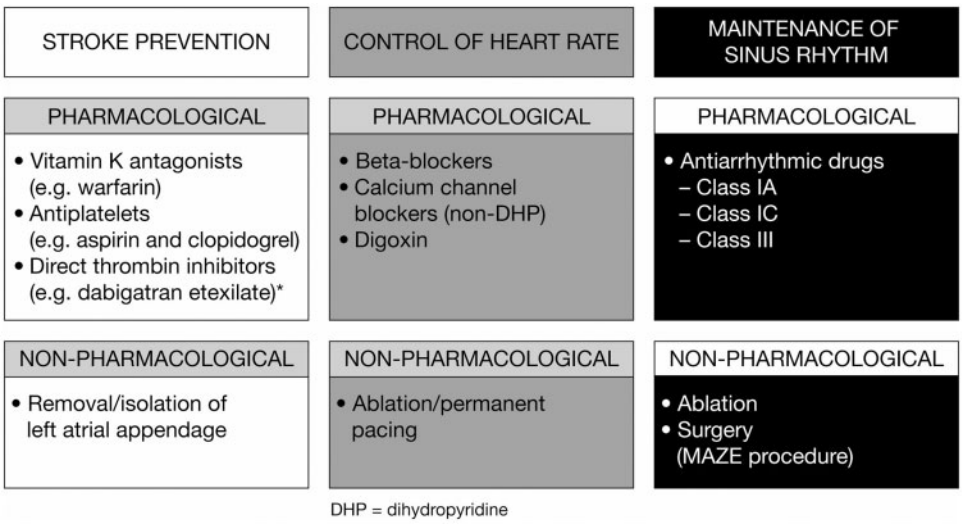

Figure 1. Treatment options in AF[27.] Figure adapted from Prystowsky.[27] *Recently licensed in the US, Canada and Japan.

Table 3 Anti-arrhythmic agents for the conversion of AF of up to or more than 7 days duration[2]

Agent	Class	Administration	Main adverse effects
Agents with proven efficacy: AF duration ⩽ 7 days only			
Flecainide	IC	Oral or IV	Hypotension, atrial flutter with high ventricular rate
Propafenone	IC	Oral or IV	Hypotension, atrial flutter with high ventricular rate
Agents with proven efficacy: AF duration ⩽ 7 days and >7 days			
Dofetilide	III	Oral	QT prolongation, torsades de pointes
Ibutilide	III	IV	QT prolongation, torsades de pointes
Amiodarone	III	Oral or IV	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)
Dronedarone	III	Oral	Diarrhoea, nausea, abdominal pain, vomiting, asthenia
Less effective or incompletely studied agents			
Disopyramide	IA	IV	Dry mouth, constipation, urinary retention, depression of left ventricular contractility
Procainamide	IA	IV	Hypotension
Quinidine	IA	Oral	QT prolongation, torsades de pointes, GI upset, hypotension
Should not be administered			
Digoxin	–	Oral or IV	AV block and increased ventricular ectopy
Sotalol	III	Oral or IV	QT prolongation, torsades de pointes

AV = atrioventricular; GI = gastrointestinal; IV = intravenous.
Adapted from Fuster V et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace.* 2006; 8 (9):651-745 by permission of the European Society of Cardiology and the European Heart Rhythm Association.

versus rhythm control suggested that rhythm control may show a trend towards increased mortality,[28,29] possibly due to anti-arrhythmic drug toxicity or inappropriate withdrawal of anti-coagulant therapy. Patient QoL is similar in rate and rhythm control groups.[34,35] Rate control is less costly than rhythm control, involving fewer hospitalizations.[30,36,37] Even using rhythm control strategies, it is common to prescribe additional rate control drugs,[38] which can have side-effects including deterioration of left ventricular function and left atrial enlargement, irrespective of rate control.[39]

Patients who maintain sinus rhythm have improved long-term prognosis.[40] Newer rhythm control drugs with advantages over current treatments may make rhythm control strategies more appealing. Vernakalant is an atrial-selective, sodium ion and potassium ion channel blocker approved by the US Food and Drug Administration (FDA) for intravenous conversion of recent-onset AF. Phase II and III clinical trials have shown efficacy for vernakalant in stopping AF in ~50% of cases vs. 0–10% for placebo, with very few side-effects. An oral formulation is currently under assessment in clinical trials; preliminary results suggest that high-dose oral vernakalant prevents AF recurrence without proarrhythmia.[41] Ranolazine, a sodium channel blocker approved for chronic angina, is also in development for AF; it has shown safe conversion of new-onset or paroxysmal AF, and promotion of sinus rhythm maintenance in two small trials. Other atrial-selective drugs in development for AF include several investigational compounds (e.g. AZD7009, AVE0118, AVE1231), which have had mixed results.[41]

Non-pharmacological ablation techniques for rhythm control in AF are becoming more popular and may offer benefits over pharmacotherapy for some patients. Ablation catheters are inserted transvenously into the left atrium and positioned to isolate or destroy pulmonary vein foci that may trigger or maintain AF. Ablation success rates vary depending on AF type. Curative rates of 80–90% can be achieved in patients with paroxysmal AF and normal heart structure; however, success rates are limited in other cases, such as persistent AF with remodelled atrial tissue, and success relies upon operator experience.[42] Furthermore, in rare instances the procedure may cause life-threatening complications, such as stroke, pericardial tamponade and atrial–oesophageal fistula. Ablation must therefore be performed by highly trained electrophysiologists at specialized centres. It is usually reserved for predominantly younger, symptomatic patients resistant or intolerant to drug therapies, or for those with

heart failure or critical ejection fraction. Newer, more specialized ablation catheters have recently become available in Europe, which should both speed up and simplify the ablation process, increasing the number of physicians capable of performing the procedure.[42] As the understanding of AF pathophysiology improves, and confidence in the technique spreads, ablation may become more widespread.

Less frequently used AF interventions include left atrial appendage (LAA) closure or removal, which may aid stroke prevention as >90% of thrombi form in the left atrial appendage in AF. The WATCHMAN® device is a self-expanding nitinol frame with a membrane on the proximal face that is constrained within a delivery catheter until deployment. It is designed to be permanently implanted at, or slightly distal to, the opening of the LAA to trap potential emboli. Another LAA occluder under investigation, the AMPLATZER® Cardiac Plug, has been derived from the AMPLATZER® septal device.[43] So far, outcome data are only available for the WATCHMAN® device. The Embolic Protection in Patients with Atrial Fibrillation (PROTECT–AF) trial indicated a reduced risk for thromboembolic events after LAA occlusion.[44]

There is a trend towards 'upstream' therapy in AF to target underlying conditions and risk factors. Statins and suppressors of the rennin–angiotensin system [e.g. angiotensin-converting enzyme inhibitors (ACEIs)], which prevent atrial remodelling, have a role to play in AF. Statin therapy prior to ablation surgery appears to improve post-operative freedom from paroxysmal and persistent AF in cardiac surgery patients.[45] ACEIs and angiotensin receptor blockers appear to prevent new AF, reduce potential recurrence in high-risk individuals and help prevent AF recurrence following direct current cardioversion.[46]

VKAs for stroke prevention in AF

Anti-coagulation therapy is recommended in addition to rate or rhythm control for the majority of patients, even for those converted into sinus rhythm. Current treatment guidelines recommend aspirin or no treatment for those at low risk of stroke; oral anti-coagulants, aspirin or VKAs such as warfarin for patients at moderate risk; and oral anti-coagulants or VKAs for those at high risk of stroke.[1,2,47] The 2010 ESC guidelines strongly recommend oral anti-coagulant therapy over aspirin; oral anti-coagulant therapy is the treatment of choice for those at high risk of AF, and is preferred over aspirin therapy for moderate-risk individuals.[1] Adjusted-dose warfarin is effective for stroke prevention in AF, reducing stroke by 64% [95% confidence interval (CI) 49–74] and all-cause mortality by 26% (95% CI 3–43) in a meta-analysis of published randomized trials.[48] However, VKAs carry a considerable bleeding risk, making the risk–benefit ratio inappropriate for patients at lower risk of stroke. Furthermore, VKAs have limitations including drug–drug and drug–food interactions, slow onset and offset of action, and a narrow therapeutic range, with regular monitoring and dose-adjustment required.[49] Patients not maintained within the therapeutic range are at increased risk of bleeding or stroke (Figure 2).[50] The greatest concern is increased risk of intracranial haemorrhage (ICH), which persists even if the optimal INR of 2.0–3.0 is maintained, and increases in the presence of other risk factors including advanced age and high blood pressure.[51]

Achieving good INR control can be challenging. In well-controlled clinical trials, patients remained within therapeutic range for ~66% of the time, whereas in clinical practice only ~44% of time was spent within the therapeutic range.[52–54] Such challenges have led to the under-use of VKAs, which has been associated with adverse outcomes.[55] An assessment of Medicare claims data for 1993–1996 showed that only 55% of eligible patients were prescribed anti-thrombotic therapy at hospital discharge, with 34% receiving warfarin.[55] A cross-sectional study of a large health maintenance organization (1996–1997) showed that warfarin was used in only ~55% of 11 082 eligible patients.[56] Thus, novel anti-coagulants that are more efficacious and have better safety profiles are needed.

Developments in stroke prevention in AF

Several novel anti-coagulants targeting different components of the coagulation cascade are being trialled for stroke prevention (Figure 3, Table 4).[57]

Dabigatran etexilate

Dabigatran etexilate is an oral pro-drug, metabolized to the potent direct thrombin inhibitor (DTI) dabigatran. It is licensed in over 70 countries for thromboprophylaxis following total elective hip and knee replacement,[58] and is the newest anti-coagulant licensed for stroke prevention in AF in Canada and for reduction of risk of stroke in the USA.[59,60] The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY®) trial, one of the largest AF outcomes trials completed to date,

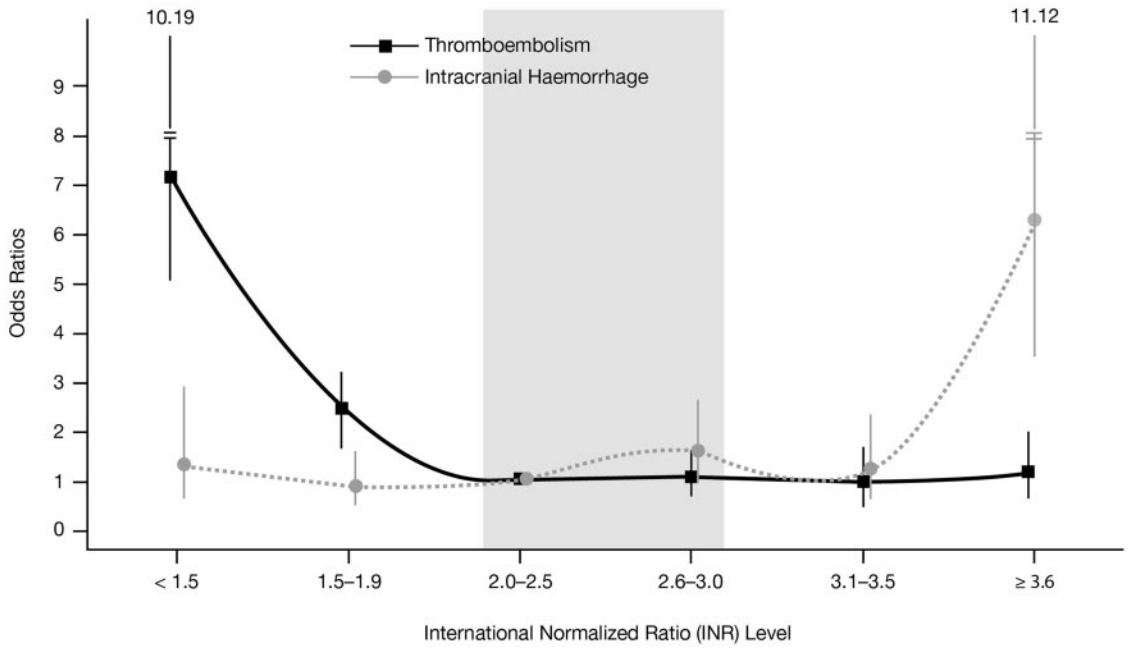

Figure 2. Narrow therapeutic range with VKA.[50] Reproduced with permission from Singer *et al.*[50]

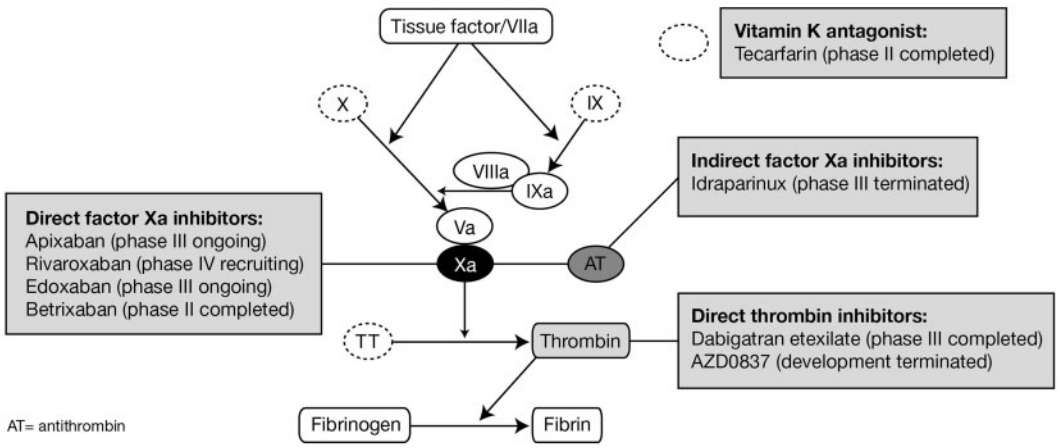

Figure 3. Coagulation cascade targets for novel anti-coagulants. Adapted from Bates and Weitz.[57] Copyright © 2006, John Wiley and Sons. Reproduced with permission of Blackwell Publishing Ltd.

compared two doses of dabigatran etexilate (150 mg twice daily [bid] and 110 mg bid) with warfarin (INR 2.0–3.0) in patients with AF and at least one additional risk factor for stroke.[61] The study included 18 113 patients randomized at 951 centres in 44 countries.[62] The primary endpoint was the composite of stroke (haemorrhagic and ischaemic) and non-CNS systemic emboli.

In AF patients at risk of stroke (50% warfarin-experienced and 50% warfarin-naive), 150 mg dabigatran etexilate bid was significantly more effective than well controlled warfarin for stroke prevention [1.11% per year vs. 1.71%, hazard ratio (HR) 0.65, 95% CI 0.52–0.81, $P < 0.001$] and vascular death (2.28% per year vs. 2.69%, HR 0.85, 95% CI 0.72–0.99, $P = 0.04$) with a similar risk of major bleeding. However, rates of total and life-threatening bleeding were both significantly lower with 150 mg bid dabigatran etexilate than with warfarin.[63] Importantly, VKAs are effective in preventing 64% of all strokes,[48] whereas in the RE-LY® study, dabigatran etexilate (150 mg bid) further reduced the risk of stroke or systemic emboli by an additional 35% (RRR) compared with well-controlled warfarin.[63] Compared with no anti-coagulant treatment in patients with AF, three out of four strokes may be prevented by dabigatran etexilate 150 mg bid.[64] Furthermore, dabigatran etexilate 110 mg bid

Table 4 Novel anti-coagulants for stroke prevention in AF

Compound name	Mechanism of action	Trial efficacy outcomes	Adverse outcomes
Dabigatran etexilate	Direct thrombin inhibitor	**RELY® trial**: 150 mg bid more effective and 110 mg bid similarly effective versus warfarin for stroke prevention in patients with AF and $\geqslant$1 additional risk factor[63]	150 mg bid similar major bleeding and 110 mg bid lower major bleeding versus warfarin. Both doses had lower haemorrhagic stroke and ICH versus warfarin
AZD0837 *Development discontinued July 2010*	Direct thrombin inhibitor (extended release formulation)	300 mg qd similar thrombogenesis (D-dimer) suppression to warfarin[69]	Lower clinically relevant bleeding rates[69]
Apixaban	Direct FXa inhibitor	**ARISTOTLE trial**: versus warfarin in patients with AF and $\geqslant$1 additional risk factor; ongoing (results expected in 2011)[71] **AVERROES trial**: more effective versus aspirin for stroke prevention in patients with AF and $\geqslant$1 additional risk factor considered unsuitable for warfarin[73]	Similar major bleeding rate to aspirin[73]
Rivaroxaban	Direct FXa inhibitor	**ROCKET-AF trial**: non-inferior versus warfarin in the ITT analysis for stroke/non-CNS embolism in non-valvular AF with prior stroke/TIA or two additional stroke risk factors[75] Lower ICH incidence versus warfarin[76,77]	Similar rates of major and non-major bleeding as warfarin[75]
Edoxaban (DU-176 b)	Direct FXa inhibitor	**ENGAGE-AF TIMI-48** trial ongoing (2008-2012) of 30/60 mg qd versus warfarin for AF with moderate stroke risk[79]	Phase II trial: 30/60 mg qd similar safety profile to warfarin in $CHADS_2$ $\geqslant$2; 30/60 mg bid more bleeding events[78]
Betrixaban	Direct FXa inhibitor	**EXPLORE-Xa trial**: 40 mg qd better coagulation activity (measured by D-dimer levels) versus warfarin[83]	40 mg qd fewer major and non-major bleeds versus warfarin. 60/80 mg more frequent nausea, vomiting and diarrhoea[83]
Tecarfarin	Vitamin K antagonist	Phase II trial versus warfarin showed improved time in therapeutic range[84] **EmbraceAC trial**: comparable with warfarin for time in therapeutic range[85]	

AF; atrial fibrillation; bid = twice daily; CNS = central nervous system; ICH = composite of haemorrhagic stroke, subarachnoid haemorrhage and subdural haematoma; qd = once daily; TIA = transient ischaemic attack.

showed similar efficacy for stroke prevention as warfarin, with significantly lower rates of major bleeding (2.87% vs. 3.57% per year, HR 0.80, 95% CI 0.70–0.93, $P = 0.003$) and other bleeding events.[63]

Rates of haemorrhagic stroke and ICH (composite of haemorrhagic stroke, subarachnoid haemorrhage and subdural haematoma) were significantly lower in patients taking either dose of dabigatran etexilate than in individuals taking warfarin. Rates of haemorrhagic stroke were 0.38% in the warfarin group, 0.10% (HR 0.26, 95% CI 0.14–0.49, $P < 0.001$) in the 150 mg dabigatran etexilate group and 0.12% (HR 0.31, 95% CI 0.17–0.56, $P < 0.001$) in the 110 mg dabigatran etexilate group. Respective rates of ICH were 0.76% for warfarin, 0.32%

(HR 0.41, 95% CI 0.28–0.60, $P<0.001$; 150 mg dabigatran etexilate) and 0.23% (HR 0.30, 95% CI 0.19–0.45, $P<0.001$; 110 mg dabigatran etexilate).[63]

Dabigatran etexilate was generally well tolerated, with reported adverse event rates similar to those reported with the use of warfarin. Dyspepsia occurred more frequently for both doses of dabigatran etexilate than with warfarin (150 mg dabigatran etexilate, 11.3% and 110 mg dabigatran etexilate, 11.8% versus warfarin, 5.8%; $P<0.001$ for both comparisons).[62] Dyspepsia may be manageable by taking dabigatran etexilate with food, with the use of antacids and/or administration of proton pump inhibitors. In addition, the higher dose of dabigatran etexilate was associated with a higher risk of gastrointestinal bleeding than with either the lower dose or warfarin (1.56% per year for 150 mg dabigatran etexilate vs. 1.15% per year for 110 mg dabigatran etexilate, and 1.07% per year for warfarin, $P=0.001$ for the comparison of 150 mg dabigatran and warfarin, $P=0.52$ for the comparison of 110 mg dabigatran and warfarin).[63] The incidence of myocardial infarction was numerically higher with dabigatran etexilate than with warfarin, but this imbalance did not reach statistical significance. Neither dose of dabigatran etexilate appeared to cause liver toxicity.[62]

Dabigatran etexilate possesses other benefits compared with warfarin therapy. It has a rapid onset and offset of action, and a predictable and consistent pharmacodynamic profile.[65,66] The elimination half-life of dabigatran etexilate is 12–17 h, which allows for twice-daily dosing.[62] Due to a more consistent and predictable anti-coagulant effect there is no requirement for routine anti-coagulation monitoring.[66] Finally, dabigatran etexilate has a low potential for drug–drug interactions; has no food–drug interactions; and does not interact with the cytochrome 450 (CYP450) enzyme system.[67,68] Based on these improvements including superior efficacy of the 150 mg dose relative to warfarin, the predictability and consistency of its pharmacokinetic and anticoagulant activity, dabigatran etexilate has the potential to replace much of the use of warfarin and other oral VKAs for stroke prevention in patients with AF. In addition, the availability of two doses (75 mg bid and 150 mg bid in the USA, and 110 mg and 150 mg bid in Canada) allows a lower dose to be used in vulnerable patient groups. For example, in the USA, 75 mg bid can be used in patients with a creatinine clearance of 15–30 ml/min, while in Canada, 110 mg bid may be suitable for use in patients $\geqslant 80$ years and/or at risk of bleeding.[59,60]

AZD0837

AZD0837 is another pro-drug, which is converted to a selective and reversible DTI. The safety of an extended-release formulation has been assessed in a phase II, randomized, controlled trial.[69] Nine hundred and fifty-five patients with AF were randomized to receive AZD0837 150 mg once daily (qd), 300 mg qd, 450 mg qd or 200 mg bid, or warfarin (INR 2.0–3.0), for 3–9 months. AZD0837 300 mg qd provided similar thrombogenic suppression to warfarin with lower bleeding rates (any bleeding: 5.3% vs. 14.5%; clinically relevant bleeding: 0% vs. 2.8% for AZD0837 and warfarin, respectively with no liver toxicity. A 10% increase in serum creatinine was observed, which returned to baseline after cessation of therapy.[69] As of July 2010, however, the development of AZD0837 had been discontinued by the manufacturer.[70]

Apixaban

Apixaban is a direct factor Xa inhibitor that prevents conversion of prothrombin to thrombin. Apixaban is under investigation for thrombolic and haemorrhagic events compared with warfarin (INR 2.0–3.0) in the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial, an international, double-blind, randomized, non-inferiority trial of 18 206 AF patients with at least one additional risk factor for stroke.[71] In this trial, 5.0 mg is the standard apixaban dose, however, 2.5 mg will be used in patients estimated to have higher apixaban exposure. A similar randomized, double-blind, superiority trial comparing 5 mg apixaban bid with aspirin (81–324 mg qd) for prevention of stroke or systemic embolism in $\geqslant 5600$ patients with AF and at least one risk factor for stroke has recently been completed [the Apixaban Versus Acetylsalicylic acid to Prevent Strokes (AVERROES) trial].[72,73] This study was terminated prematurely after the first interim efficacy analysis and the results showed an incidence of stroke of 1.6% per year with apixaban, vs. 3.7% per year with aspirin (apixaban HR 0.45, 95% CI 0.32–0.62, $P<0.001$); both treatments were associated with similar rates of major bleeding (1.4% per year with apixaban vs. 1.2% with aspirin; apixaban HR 1.13, 95% CI 0.74–1.75, $P=0.57$).[73]

Rivaroxaban

Rivaroxaban, another factor Xa inhibitor, is being tested in several indications and is currently licensed for thromboprophylaxis following elective total hip and knee replacement.[74] A Phase III, randomized, double-blind, non-inferiority study (ROCKET-AF

trial) investigating the efficacy of 20 mg qd rivaroxaban versus warfarin to prevent stroke in non-valvular AF patients with prior stroke/TIA or at least two additional stroke risk factors[75], has recently completed. In this trial, which included over 14 000 patients, rivaroxaban was non-inferior ($P < 0.001$) to dose-adjusted warfarin for the primary endpoint; a composite of stroke and non-central nervous system embolism. For this endpoint, rivaroxaban provided a relative risk reduction of 21% over warfarin ($P = 0.015$) in the on-treatment analysis; however, in the intention-to-treat analysis, rivaroxaban failed to demonstrate superiority ($P = 0.117$). Both rivaroxaban and warfarin were associated with similar rates of major and non-major bleeding ($P = 0.442$). The incidence of ICH was significantly lower in subjects taking rivaroxaban than in individuals receiving warfarin ($P = 0.019$).[76,77]

Edoxaban

A multicentre, Phase II study was conducted to investigate the safety of the factor Xa inhibitor edoxaban (DU-176 b) in AF patients with a $CHADS_2$ score $\geqslant 2$. In total, 1146 patients were randomized to blinded edoxaban (30 mg qd, 60 mg qd, 30 mg bid or 60 mg bid) or open-label warfarin (INR 2.0–3.0) for 3 months. Results indicate that 30 and 60 mg qd edoxaban had a similar safety profile to warfarin, whereas the 30 and 60 mg bid groups experienced more bleeding events than those receiving warfarin.[78] A phase III, randomized, double-blind trial [Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE-AF TIMI-48)] is now currently assessing the safety and efficacy of 30 and 60 mg qd edoxaban compared with warfarin in patients with AF and a moderate risk of stroke.[79]

Betrixaban

Another factor Xa inhibitor, betrixaban, was selected from a promising range of investigational compounds in early development.[80] The anticoagulant effects of betrixaban in humans was initially investigated in the US and Canadian trial, in which it was compared with enoxaparin for prevention of thromboembolism after knee replacement surgery [the Evaluation of betriXaban for the Prevention of vEnous thRomboembolism in daily practice (EXPERT) trial].[81] In this study, 215 patients were randomized to treatment with betrixaban 15 mg or 40 mg bid, or enoxaparin 30 mg subcutaneously every 12 h for 10–14 days. Betrixaban inhibited thrombin generation and anti-Xa levels in a dose- and concentration-dependent manner and was well tolerated, with no indication of increased bleeding events.

A Phase II trial of the safety, tolerability and pilot efficacy of daily oral 40, 60 or 80 mg doses of betrixaban versus warfarin for anti-coagulation in AF patients has recently been completed (EXPLORE-Xa).[82] Betrixaban 40 mg had fewer instances of major and clinically relevant non-major bleeding compared with patients taking warfarin (1 vs. 4 patients) and slightly better coagulation activity (as measured by D-dimer levels). Nausea, vomiting and diarrhoea were the only adverse events that occurred more frequently in the betrixaban than in warfarin patients, and occurred only in patients taking the 60 mg and 80 mg doses.[83]

Tecarfarin

Tecarfarin is an oral VKA similar to warfarin, but is reportedly metabolized by esterases rather than the CYP450 system, thereby potentially avoiding CYP450-mediated drug–drug or drug–food interactions. A 6- to 12-week, open-label, multicentre, Phase II trial of tecarfarin versus warfarin in 66 AF patients showed that tecarfarin improved patient time in the therapeutic range.[84] A recent phase II/III, randomized, double-blind, parallel-group, active-control study (EmbraceAC) involving 612 patients in the USA, treated with either tecarfarin or warfarin, showed that both achieved comparable patient times in therapeutic range (74.0% vs. 73.2%, respectively, $P = 0.506$); the primary endpoint of the trial (superiority of tecarfarin over warfarin) was therefore not attained.[85]

While many novel anti-coagulants are currently in development and undergoing clinical trials, dabigatran etexilate 150 mg bid has been proven to have superior efficacy to well-controlled warfarin for stroke prevention in AF in a phase III study. It was approved by the FDA and Health Canada in October 2010. We await results from recently completed or ongoing trials of other anti-thrombotic agents.

Conclusions

AF is associated with a pro-thrombotic state and several other comorbidities that increase the risk of stroke in an age-dependent fashion. Rate and rhythm control are employed to relieve the symptoms of AF; however, anti-arrhythmic drugs are fairly toxic and have variable efficacy. Rate control is easier to manage and has equivalent mortality and QoL outcomes to rhythm control; thus the debate continues as to which therapy is preferable. Rhythm control using non-pharmacological ablation

techniques has thus far been limited because of the need for specialist centres and highly trained operators. However, the advent of improved ablation catheters and increased understanding of AF pathophysiology should enhance confidence in performing this technique.

Anti-coagulation therapy is an essential strategy in AF patients with additional stroke risk factors and can decrease the incidence of stroke and mortality in AF patients. However, warfarin is under-used because of a high perceived risk of haemorrhage (especially ICH) and limitations that make the drug difficult to manage. Dabigatran etexilate is a novel DTI offering improvements in efficacy and safety compared with warfarin for stroke prevention in AF. In addition, several other novel anti-coagulants in development show promise, and their efficacy and safety are currently being evaluated in the prevention of stroke in AF patients. New therapeutic options, such as improved anti-arrhythmics, novel anti-coagulants and more accessible ablation techniques are likely to deliver better care for AF patients in the near future.

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