Atrial fibrillation

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The management of atrial fibrillation has evolved greatly in the past few years, and many areas have had substantial advances or developments. Recognition of the limitations of aspirin and the availability of new oral anticoagulant drugs that overcome the inherent drawbacks associated with warfarin will enable widespread application of effective thromboprophylaxis with oral anticoagulants. The emphasis on stroke risk stratification has shifted towards identification of so-called truly low-risk patients with atrial fibrillation who do not need antithrombotic therapy, whereas oral anticoagulation therapy should be considered in patients with one or more risk factors for stroke. New antiarrhythmic drugs, such as dronedarone and vernakalant, have provided some additional opportunities for rhythm control in atrial fibrillation. However, the management of the disorder is increasingly driven by symptoms. The availability of non-pharmacological approaches, such as ablation, has allowed additional options for the management of atrial fibrillation in patients who are unsuitable for or intolerant of drug approaches.

Introduction

Atrial fibrillation is the most common sustained cardiac rhythm disorder, and is increasing in prevalence and incidence.[1] It is recognised as an increasing health-care burden, because of an ageing population and improved survival from disorders such as acute myocardial infarction. The lifetime risk for development of atrial fibrillation is about one in four for men and women aged 40 years and older, whereas for those without previous or concurrent congestive heart failure or myocardial infarction the lifetime risk is still about 16%.[2,3] The presence of atrial fibrillation independently increases the risk of mortality and morbidity due to stroke and thromboembolism, congestive heart failure, and impaired quality of life, resulting in a high health-care cost and public health burden.[4,5]

In this Seminar, we review the epidemiology and pathophysiology of atrial fibrillation, and specifically address areas in which management of the disorder has advanced or developed since previous overviews on this topic.[5,6]

Epidemiology

In the UK, findings from the Screening for Atrial Fibrillation in the Elderly (SAFE) study[7] showed a baseline prevalence of atrial fibrillation of 7·2% in patients aged 65 years and older, with an increased prevalence in men (7·8%) and in those aged 75 years and older (10·3%), and a yearly incidence of new atrial fibrillation of about 1·6%. Investigators of one community survey reported a rise in incidence of atrial fibrillation of 12·6% during the past two decades, and projected that 15·9 million people in the USA will have the disorder by 2050.[1] There are known ethnic differences in prevalence, with the arrhythmia being less common in non-white populations than in white people, even after adjustment for comorbidities associated with atrial fibrillation.[8]

Atrial fibrillation is present in 3–6% of acute medical admissions,[4] for which the most common comorbidities are coronary artery disease and congestive heart failure; in the community setting, hypertension is the most common causal risk factor.[4,5] Atrial fibrillation is a common complication in the postoperative setting, especially after cardiothoracic surgery.[9] However, it can also exist in isolation (known as lone atrial fibrillation), which is essentially a diagnosis of exclusion—ie, when there is a normal clinical examination, a normal chest radiograph and electrocardiogram (ECG) (apart from atrial fibrillation, with no evidence of previous myocardial infarction or left ventricular hypertrophy), a structurally normal heart on echocardiography, and no history of cardiovascular disease.

Many patients are asymptomatic (silent atrial fibrillation) and a presentation with a complication associated with atrial fibrillation (eg, stroke) might be the first manifestation of the arrhythmia, when the disorder is first diagnosed. Even in patients with acute stroke, prolonged ECG monitoring would detect atrial fibrillation in one in 20 patients.[10] Opportunistic screening—eg, palpitation of the pulse (for an irregular rhythm) when patients visit their family doctor—was shown to be more cost effective than was a systematic screening strategy for atrial fibrillation.[7]

Search strategy and selection criteria

We searched Medline between January, 2000, and September, 2011, with the following terms individually or in combination: "atrial fibrillation", "rate control", "rhythm control", "antithrombotic therapy", "anticoagulation", "stroke risk", "bleeding risk", "antiplatelet therapy", "vernakalant", and "dronedarone". Additionally, we studied abstracts from national and international cardiovascular meetings to identify unpublished studies. The extensive detailed published work for the underlying pathophysiology of atrial fibrillation, including haemodynamic considerations and electrophysiology of atrial fibrillation, will not be addressed in this Seminar, which focuses on management aspects.

Risk factors

Atrial fibrillation commonly coexists with cardiovascular risk factors and disorders, which in turn increase the risk of complications associated with the arrhythmia. Common predisposing factors for atrial fibrillation

include both non-cardiovascular (eg, chest disease, infection) and cardiovascular (eg, hypertension, congestive heart failure, valvular heart disease, diabetes mellitus, and vascular disease) risk factors. Data from the Atherosclerosis Risk in Communities (ARIC) study[11] have shown that 56·5% of new-onset atrial fibrillation could be attributed to common cardiovascular risk factors, including hypertension, obesity, diabetes mellitus, and smoking. Although the precise mechanisms contributing to development of the disorder are unclear, several factors are likely, including activation of renin–angiotensin–aldosterone system, haemodynamic loading and structural changes in atria, focal triggers initiating paroxysmal atrial fibrillation, and atrial fibrosis promoting re-entry in persistent atrial fibrillation.[12] The disorder can also be triggered by rapid atrial activation associated with other supraventricular tachycardias, such as atrial tachycardia or flutter, atrioventricular nodal re-entry tachycardia, or Wolff-Parkinson-White syndrome.

The Framingham study published a risk score for development of atrial fibrillation that incorporated the presence of age, sex, body-mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, and congestive heart failure; additional incorporation of echocardiographic measurements only slightly improved the predictive ability of this risk schema.[13] In a biracial population, the ARIC study[14] showed that a score incorporating age, race, height, smoking status, systolic blood pressure, hypertension drug use, precordial murmur, left ventricular hypertrophy, left atrial enlargement, diabetes, coronary artery disease, and congestive heart failure was predictive of development of atrial fibrillation. Genetic factors have also attracted much attention as a possible heritable component for the disorder (webappendix p 1).[15–23]

Initial diagnostic considerations

For an assessment of a patient with atrial fibrillation, confirmation of the diagnosis and documentation of the arrhythmia are needed. Guidelines from the European Society of Cardiology (ESC) define atrial fibrillation as a cardiac arrhythmia with the following characteristics: the surface ECG shows absolutely irregular RR intervals; there are no distinct P waves on the surface ECG; and the atrial cycle length (ie, the interval between two atrial activations), when visible, is usually variable and less than 200 ms (>300 beats per min).[4]

In persistent atrial fibrillation, the presence of the disorder is usually evident on a standard 12-lead ECG. A 24-h Holter monitor can be used in patients with paroxysmal atrial fibrillation, but an automatic (asymptomatic) or patient-activated (symptomatic) event loop recorder might be needed in those with infrequent paroxysms. A 12-lead ECG can also indicate the presence of pre-excitation in Wolff-Parkinson-White syndrome (a short PR interval or delta wave) and other inherited cardiac arrhythmic syndromes, such as long QT (prolonged QT interval) and Brugada syndrome (right bundle branch block and ST segment elevation in right precordial leads), and inherited cardiomyopathic syndrome, such as lamin A/C mutation (atrioventricular block) and hypertropic cardiomyopathy.

Increasing interest has been directed towards quantification of arrhythmia burden with implantable devices, because of a possible association between atrial fibrillation burden and stroke risk.[24–26] A stand-alone implantable event recorder can be used to measure atrial fibrillation burden.[27] Measurement of such burden can be better than clinical risk factors in prediction of stroke risk.[28]

Because atrial fibrillation commonly coexists with many other cardiac and non-cardiac comorbidities, exclusion—when relevant and dependent on clinical history and examination—of associated diseases such as thyroid disease (eg, by biochemical testing), structural heart disease (eg, with echocardiography), and intrathoracic pathology (eg, by chest radiograph) is important. Most cardiologists would do a transthoracic echocardiogram in patients with newly diagnosed atrial fibrillation.[29]

Management

Management of atrial fibrillation needs early identification and treatment of predisposing factors and concomitant disorders, with the use of upstream therapy (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, statins, and omega-3 polyunsaturated fatty acids) when appropriate.[4] After assessment of thromboembolic risk and appropriate thromboprophylaxis, rate or rhythm control strategies should be considered (figure 1).[4]

Subdivision into clinical subtypes of atrial fibrillation can help to define the objectives of management.[4] See Online for webappendix

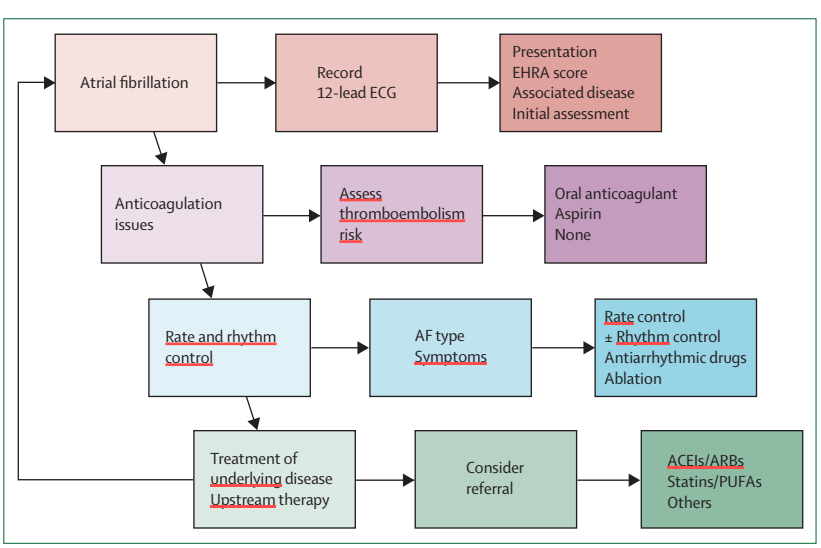

Figure 1: **Management cascade for patients with atrial fibrillation**
ECG=electrocardiogram. EHRA=European Heart Rhythm Associaton. ACEIs=angiotensin-converting enzyme inhibitors. ARBs=angiotensin-receptor blockers. PUFAs=polyunsaturated fatty acids. Adapted from European Society of Cardiology guidelines.[3]

Paroxysmal atrial fibrillation is defined as atrial fibrillation that is self-terminating, usually within 48 h. Persistent atrial fibrillation is present when an episode of atrial fibrillation either lasts longer than 7 days or needs cardioversion. Longstanding persistent atrial fibrillation has lasted for 1 year or more and is when a rhythm control strategy is used. Permanent atrial fibrillation exists when the presence of the arrhythmia is accepted by the patient (and physician), when cardioversion has failed or has been deemed inappropriate.[4] The management of patients with atrial fibrillation should broadly be guided by symptoms, the presence or absence of haemodynamic compromise, and associated comorbidities.

Stroke prevention

A prothrombotic state has been described in atrial fibrillation, and it contributes to the most common (and most important) complication of thromboembolism.[30] The presence of atrial fibrillation is an independent risk factor for stroke and thromboembolism, and stroke in association with atrial fibrillation increases mortality and morbidity, with greater disability, longer hospital stays, and lower rates of discharge to patients' own homes.[31] Although atrial fibrillation increases the risk of stroke five-fold, this risk is not homogeneous and changes cumulatively with the presence of stroke risk factors (webappendix pp 1–7).[32–34] These risk factors have been used to formulate various stroke risk stratification schema (webappendix p 9). The risk schemes have traditionally categorised patients into strata of low, moderate, and high risk, despite the risk continuum and the (artificial) three-strata categorisation being poorly predictive of events.[35–37] Generally, management guidelines have traditionally recommended that high-risk patients be given oral anticoagulation, whereas patients at moderate (or intermediate) risk can be treated with oral anticoagulation or aspirin, and low-risk patients with aspirin.[6]

Indeed, the high-risk group of patients were identified so that they could be targeted for oral anticoagulation therapy, given that warfarin has substantial variability of a narrow therapeutic international normalised ratio (INR) range (INR 2–3), both within and between patients. The INR is affected by many genetic factors, diet, drugs, and alcohol; regular INR monitoring and lifestyle modifications thus restrict the number of eligible patients who can take this therapy.[38,39] The time in therapeutic range is an important determinant of protection against ischaemic stroke and the risk of major haemorrhage, when good anticoagulation control (time in therapeutic range ≥70%) is associated with a low risk of stroke and bleeding events.[40]

In view of the availability of new oral anticoagulation drugs that can overcome the limitations of warfarin, and with new information about stroke risk factors, emphasis has shifted to identification of the so-called truly low-risk patient with atrial fibrillation, for whom antithrombotic therapy might not be appropriate, by consideration of other common stroke risk modifiers (that previous guidelines[41,42] referred to as weaker or less validated stroke risk factors), such as female sex, age 65–74 years, and vascular disease.[43–45] Webappendix pp 1–7 provides a discussion of various stroke risk stratification schemes, including the advantages and disadvantages of the commonly used and simple $CHADS_2$ score,[46–49] and newer schemes such as the CHA_2DS_2-VASc score, which was designed to complement the $CHADS_2$ score (table 1 and table 2).[50–52] A CHA_2DS_2-VASc score of 0 is truly low risk and no antithrombotic therapy would suffice, whereas patients with one or more stroke risk factors (CHA_2DS_2-VASc score of ≥1) could be treated with oral anticoagulation, either with well controlled warfarin (therapeutic INR values) or one of the new oral anticoagulation agents.[4]

Nonetheless, the approach to thromboprophylaxis in atrial fibrillation requires not only assessment of stroke risk, but also consideration of bleeding risk.[53,54] However, some of the risk factors for anticoagulation-related bleeding are also risk factors for stroke. Various models for prediction of bleeding have been proposed, although few have been derived and validated in populations with atrial fibrillation (webappendix p 10) and many were not user-friendly, requiring complex mathematical formulae or including risk factors that are not measured in routine clinical practice.[55] The HAS-BLED (uncontrolled Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly >65 years, Drugs/alcohol concomitantly) score has been proposed as a simple bleeding risk assessment in patients with atrial fibrillation (webappendix p 10).[56,57] The formal assessment of bleeding risk allows informed decision making and makes clinicians think about the correctable risk factors for bleeding—eg, concomitant aspirin use or poorly controlled hypertension—that can be modified to reduce bleeding risk.[4,58,59]

Thromboprophylaxis in atrial fibrillation

In one study,[49] adjusted dose warfarin reduced stroke risk by 64% (95% CI 49–74) and, importantly, all-cause mortality by 26% (3–43) compared with placebo. In a cohort of Medicare patients, the use of warfarin increased between 1992 and 2002, which greatly reduced the incidence of ischaemic stroke over that decade but not the rate of haemorrhagic strokes.[60] By contrast, the value of aspirin in atrial fibrillation has been debated. In Hart and colleagues' meta-analysis,[49] antiplatelet therapy reduced strokes by 22% (95% CI 6–35) compared with control. When the analysis was confined to aspirin-only trials, aspirin produced a non-significant 19% (–1 to 35) reduction in the incidence of stroke, with no significant effect on mortality (relative risk reduction 14%, –7 to 31). Although there was no statistical heterogeneity between the trials, the effect size of trials confined to aspirin monotherapy was driven by one positive trial, the SPAF-1

study,[61] which showed a 42% stroke risk reduction with aspirin 325 mg daily compared with placebo, with great heterogeneity between the anticoagulation-eligible and anticoagulation-ineligible groups of the trial (94% *vs* 8% stroke risk reduction). Aspirin was ineffective in patients older than 75 years and did not prevent severe strokes. Furthermore, the SPAF-1 trial was stopped at an interim stage and its result could be exaggerated.

Oral anticoagulation was associated with a 39% (95% CI 22–50) risk reduction compared with antiplatelet therapy,[49] which provides indirect evidence that antiplatelet therapy could be very modestly effective for stroke prevention; however, this finding could be attributable to the therapy's effect on vascular disease, rather than on atrial fibrillation per se. In low-risk patients with atrial fibrillation, one prospective randomised trial[62] showed no difference between aspirin and control for the primary endpoint of thromboembolism-related complications, with a non-significant increase in more major bleeding (and intracranial haemorrhage) among patients given aspirin.

Findings from the ACTIVE-W trial[63] showed a clear superiority of warfarin over aspirin plus clopidogrel combination therapy for stroke prevention. Furthermore, aspirin plus clopidogrel reduced the rate of ischaemic stroke by 28% compared with aspirin alone.[64] Of note, the risk of major bleeding with aspirin plus clopidogrel was 2% per year, which was more than 50% higher compared with aspirin alone, and similar to major bleeding rates recorded with warfarin. In view of a modest effect of aspirin plus clopidogrel, this combination could be used in patients with atrial fibrillation who refuse any oral anticoagulation (or have difficulties with anticoagulation monitoring, if warfarin is used), provided that they are not at significant risk of bleeding.[4] Aspirin plus clopidogrel is also used after acute coronary syndrome and angioplasty or stenting, but in patients with atrial fibrillation at moderate to high risk of stroke, oral anticoagulation is still needed as part of an initial triple therapy regimen.[55,65]

In an individual patient meta-analysis,[66] the risk of stroke (and vascular events) in patients with atrial fibrillation rose with increasing age, from age 65 years upwards; however, as patients aged, the absolute beneficial effect of oral anticoagulation remained whereas the effect of aspirin decreased greatly. Serious bleeding showed a small rise with increasing age, with no substantial difference between oral anticoagulation and aspirin, which accords with findings from other trials.[67,68]

The approach to provision of thromboprophylaxis in atrial fibrillation has changed with the availability of new oral anticoagulant drugs that do not need monitoring (figure 2). An analysis using a Markov state transition decision model showed that use of these new drugs could lower the threshold for anticoagulation to a stroke rate of 0·9% per year, when balancing ischaemic stroke risk against intracranial haemorrhage risk.[69] In a large real-world nationwide cohort study, Olesen and colleagues[70] showed that the net clinical benefit balancing ischaemic stroke against intracranial haemorrhage for warfarin was only negative at a CHA_2DS_2-VASc score

	Score
$CHADS_2$ acronym	
Congestive heart failure	1
Hypertension	1
Aged ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA_2DS_2-VASc acronym	
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (previous MI, PAD, or aortic plaque)	1
Aged 65–74 years	1
Sex category (ie, female sex)	1
Maximum score	9

TIA=transient ischaemic attack. TE=thromboembolic. LV=left ventricular. MI=myocardial infarction. PAD=peripheral artery disease.

Table 1: **Definition and scores for $CHADS_2$ and CHA_2DS_2-VASc**

	Adjusted stroke rate (% per year)
$CHADS_2$ score*	
0	1·9%
1	2·8%
2	4·0%
3	5·9%
4	8·5%
5	12·5%
6	18·2%
CHA_2DS_2-VASc score†	
0	0%
1	1·3%
2	2·2%
3	3·2%
4	4·0%
5	6·7%
6	9·8%
7	9·6%
8	6·7%
9	15·2%

*Adjusted stroke rate scores based on data from Gage and colleagues.[46] These stroke rates are based on data for hospitalised patients with atrial fibrillation and published in 2001. Because stroke rates are decreasing, actual rates of stroke in contemporary non-hospitalised cohorts might vary from these estimates. †Adjusted stroke rate scores based on data from Lip and colleagues.[50] Actual rates of stroke in contemporary cohorts might vary from these estimates.

Table 2: **Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores**

of 0, indicating the truly low-risk state of these patients. Furthermore, patients in this study with a high HAS-BLED score had a greater net clinical benefit with warfarin, since those at higher risk of bleeding are also at high stroke risk, and would have have a greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. Balancing of stroke prevention and bleeding risk also needs consideration of patient values and preferences (webappendix p 6).[71–79]

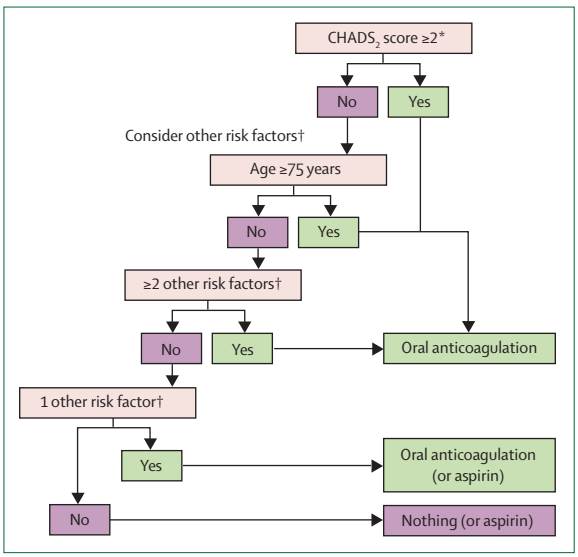

Figure 2: **Clinical flowchart for the use of oral anticoagulation for stroke prevention in atrial fibrillation**
*Congestive heart failure, hypertension, age ≥75 years, diabetes (all 1 point); stroke/transient ischaemic attack/thromboembolism (2 points). †Other clinically relevant non-major risk factors: age 65–74 years, female sex, vascular disease. Adapted from European Society of Cardiology guidelines.[3]

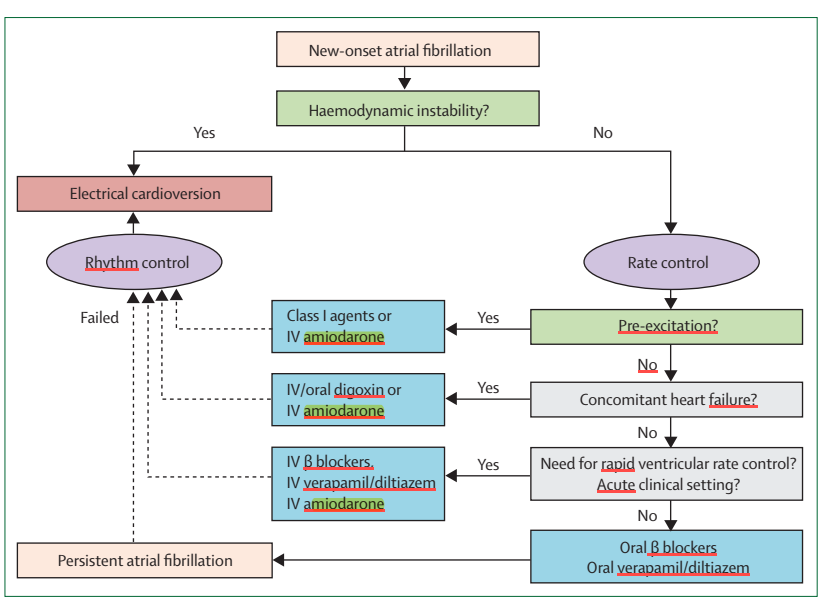

Figure 3: **Treatment approach in patients presenting with new-onset atrial fibrillation**
IV=intravenous.

The new oral anticoagulant drugs can be divided into two broad categories: the oral direct thrombin inhibitors and oral factor Xa inhibitors. In a comparison of the oral direct thrombin inhibitor dabigatran etexilate (150 mg and 110 mg twice per day) with warfarin, dabigatran 150 mg was better than warfarin for the reduction of stroke, with a similar rate of major haemorrhage, whereas dabigatran 110 mg was non-inferior to warfarin for efficacy, with significantly less major bleeding.[80] Intracranial haemorrhage was significantly less with both doses of dabigatran than with warfarin. A network meta-analysis[81] indirectly compared dabigatran etexilate with antiplatelet therapy and placebo and showed that dabigatran 150 mg twice per day significantly reduced the risk of any stroke compared with placebo by 77%, aspirin monotherapy by 63%, and aspirin plus clopidogrel by 61%. Intracranial or extracranial haemorrhage significantly increased with dabigatran compared with antiplatelet therapy.

In patients who were deemed unsuitable for, or declined, warfarin, the AVERROES trial[82] randomly assigned patients to the oral factor Xa inhibitor apixaban or to aspirin 81–325 mg. This trial was stopped early because apixaban was superior to aspirin for stroke prevention, and the rates of major bleeding (and intracranial haemorrhage) did not differ significantly between apixaban and aspirin. Furthermore, aspirin was significantly less well tolerated than apixaban, as indicated by the rate of permanent discontinuations. In the double-blind ROCKET-AF trial,[83] the oral factor Xa inhibitor rivaroxaban was non-inferior to warfarin for efficacy in reduction of stroke and systemic embolism, but did not reach statistical superiority based on the conservative intention-to-treat analysis (although superiority of rivaroxaban over warfarin was achieved based on the on-treatment analysis). Rates of major haemorrhage did not differ significantly between groups, but rivaroxaban had significantly less intracranial haemorrhage than did warfarin. In the double-blind ARISTOTLE trial,[84] the oral factor Xa inhibitor apixaban was superior to warfarin for efficacy in reduction of stroke and systemic embolism (driven by a substantial reduction in haemorrhagic stroke, although the rate of ischaemic stroke did not differ to that with warfarin), with a significant reduction in major haemorrhage and intracranial haemorrhage. Additionally, there was a significant 11% reduction in all-cause mortality. Findings from other clinical trials in progress might provide further evidence for edoxaban (ENGAGE-AF[85]).

Rate and rhythm control

Initial management of atrial fibrillation

In patients presenting with newly diagnosed atrial fibrillation, the short-term treatment goal should be control of their symptoms with rate or rhythm control therapies.[4–6] Except for the need of emergency cardioversion to restore sinus rhythm in patients with haemodynamic instability due to very rapid ventricular rates or presence of structural heart disease, the initial therapeutic approach

should include assessment for the underlying causes of atrial fibrillation and ventricular rate control to improve haemodynamic status and relieve symptoms (figure 3).

The choice of drugs for control of ventricular rate depends on the presence of coexisting pre-excitation due to Wolff-Parkinson-White syndrome, congestive heart failure, other comorbid disorders, patient's symptoms, and haemodynamic status.[4,5] In patients with atrial fibrillation with pre-excitation due to Wolff-Parkinson-White syndrome, the use of atrioventricular nodal blocking agents alone can trigger ventricular fibrillation because of very rapid ventricular rates. These patients should initially be given a class I antiarrhythmic drug such as procainamide or flecainide, or the class III agent ibutilide,[86] to slow the conduction across the accessory pathway. In Wolff-Parkinson-White syndrome, intravenous amiodarone can lead to ventricular fibrillation because it slows atrioventricular nodal conduction before it affects the accessory pathway.[87] In patients with decompensated congestive heart failure, digoxin is preferable over β blockers or non-dihydropyridine calcium-channel blockers to avoid further deterioration in haemodynamic status.

Intravenous amiodarone is a safe and effective alternative in critically ill patients with severe heart failure or hypotension, in whom other agents are ineffective or contraindicated for ventricular rate control. For patients with stable atrial fibrillation with rapid ventricular rates, an initial target resting heart rate of less than 100 beats per min should be achieved with verapamil and diltiazem, β blockers, and digoxin given intravenously or orally. In the acute setting, when patients cannot take oral drugs or when a more rapid ventricular rate control is needed, intravenous administration of atrioventricular nodal blocking agents might be necessary, rather than oral therapy. Table 3 shows the dose, side-effects, and indications for different atrioventricular nodal blocking agents.

Cardioversion of atrial fibrillation

Up to 50% of patients with recent onset atrial fibrillation convert back to sinus rhythm spontaneously.[4,5] If the patient does not convert spontaneously, pharmacological or electrical cardioversion can be considered, especially for those who remain symptomatic despite ventricular rate control. Electrical cardioversion is often faster, more

	Dose	Efficacy	Adverse effects
Digoxin			
Intravenous	0·5–1 mg bolus	Effective for rate control at rest	Drug interaction, heart block and ventricular tachyarrhythmias, gastrointestinal upset, change in vision
Oral	0·0625–0·25 mg once per day	As above	As above
Metoprolol			
Intravenous	2·5–5 mg bolus at 5 min interval up to 15 mg	Effective with high adrenergic tone and myocardial ischaemia	Hypotension, heart block, heart failure, airway obstruction
Oral	25–200 mg once per day	As above	As above
Esmolol			
Intravenous	0·5 mg/kg infusion loading, then followed by a maintenance infusion of 0·05–0·2 mg/kg per min	Effective with high adrenergic tone and myocardial ischaemia	Hypotension, heart block, heart failure, airway obstruction
Propranolol			
Intravenous	1–3 mg at a rate not exceeding 1 mg per min	Effective with high adrenergic tone and myocardial ischaemia	Hypotension, heart block, heart failure, airway obstruction
Oral	80–240 mg three times per day	As above	As above
Diltiazem			
Intravenous*	0·25 mg/kg bolus then 5–20 mg/h	Effective for rate control in acute setting	Hypotension, heart block, heart failure, gastrointestinal upset, drug interaction
Oral	30–60 mg three times per day	As above	As above
Verapamil			
Intravenous	5–20 mg bolus	Effective for rate control in acute setting	Hypotension, heart block, heart failure, gastrointestinal upset, drug interaction
Oral	40–80 mg three times per day	As above	As above
Amiodarone			
Intravenous	5 mg/kg in 1 h then 0·5–1 mg per min	Effective for rate control in critical ill setting and heart failure	Phlebitis, hypotension, bradycardia, QT prolongation, rarely torsades de pointes, drug interaction
Oral	100–200 mg per day	As above	As above

*Limited availability.

Table 3: **Pharmacological agents for rate control, by method of administration**

effective, and more efficient than pharmacological cardioversion. Panel 1 shows the potential advantages and disadvantages of pharmacological versus electrical cardioversion.

***Panel 1:* Methods of cardioversion**

Pharmacological cardioversion

Advantages

- No need for conscious sedation or anaesthesia
- Might enhance subsequent electrical cardioversion

Disadvantages

- Needs continuous medical supervision and electrocardiogram monitoring during drug administration
- Proarrhythmia
- Thromboembolic
- Low success rate for longstanding atrial fibrillation

Electrical cardioversion

Advantages

- High success rate: greater than 90% even for longstanding atrial fibrillation, especially with biphasic defibrillation

Disadvantages

- Needs conscious sedation or anaesthesia
- Skin burn
- Proarrhythmia
- Thromboembolic
- Potential interference with medical device

	Route and dose	Efficacy	Adverse effects
Flecainide*			
<7 days	Intravenous: 2 mg/kg; oral: 200–300 mg†	67–92% (1–6 h), usually 0·5 h	Hypotension, atrial flutter with high ventricular rate, Tdp
Propafenone*			
<7 days	Intravenous: 2 mg/kg; oral: 450–600 mg†	41–91% (2–6 h), usually 0·5–2 h	Hypotension, atrial flutter with high ventricular rate, TdP
Amiodarone			
<7 days	Intravenous: 5 mg/kg in 1 h, then 0·5–1 mg per min	34–95% (slower onset), usually >24 h	Phlebitis, hypotension, bradycardia, QT prolongation, rarely Tdp
>7 days	As above	15–40%	As above
Ibutilide‡			
<7 days	Intravenous: 1–2 mg	50–71% (~90 min), usually 30 min	QT prolongation, Tdp
>7 days	As above	As above	As above
Dofetilide‡			
<7 days	Oral: 125–500 µg twice per day (based on CrCl)	44–85% (24–36 h)	QT prolongation, Tdp
>7 days	As above	30–40%	As above
Vernakalant*§			
<7 days	Intravenous: 3–5 mg	45–62%	Nausea, sneezing, dysgeusia, QT prolongation, hypotension, bradycardia, rarely Tdp

Tdp=torsade de pointes. CrCl=creatinine clearance. *Not effective for atrial flutter. †Can be used as a so-called pill-in-the-pocket approach. ‡Limited availability. §Not yet appaoved outside Europe.

***Table 4:* Pharmacological agents for chemical cardioversion, by duration of atrial fibrillation**

For atrial fibrillation of less than 7 days' duration, oral or intravenous administration of class Ic (flecainide and propafenone) or III (amiodarone, ibutilide, dofetilide) antiarrhythmic drugs, or the atrial selective agent vernakalant, can achieve conversion to sinus rhythm in 34–95% of patients within 24 h (table 4).[88,89] For atrial fibrillation of more than 7 days' duration, only 15–40% of patients convert to sinus rhythm with pharmacological cardioversion alone, and thus electrical cardioversion is more likely to be needed for these patients.[87] In patients with structural heart disease, such as coronary artery disease and impaired left ventricular ejection fraction (LVEF), class I antiarrhythmic drugs, including flecainide and propafenone, are contraindicated because of the potential increased risk of proarrhythmia.[4,5] In selected patients without structural heart diseases but infrequent episodes of symptomatic and haemodynamic stable atrial fibrillation, a so-called pill-in-the-pocket approach with administration of oral loading of flecainide or propafenone is a safe and effective therapy for self-conversion to sinus rhythm (table 4). Nevertheless, concomitant atrioventricular nodal blocking agents should also be used, because flecanide or propafenone can convert atrial fibrillation to atrial flutter with rapid ventricular rates.

Vernakalant is a novel class of antiarrhythmic drug with atrial selective properties by blockade of ultra-rapid delayed rectifier potassium current (I_{Kur}), which is mainly expressed in the atria. Furthermore, it is a multichannel blocker that affects the sodium channel and muscarinic acetylcholine receptor-operated potassium channel ($I_{K\text{-}Ach}$).[88,89] However, this drug has limited efficacy for conversion of atrial flutter and atrial fibrillation lasting more than 7 days. Intravenous vernakalant has been approved in Europe for rapid conversion of recent-onset atrial fibrillation lasting 3 days or less for surgical patients and 7 days or less for non-surgical patients. In a trial in which 254 patients were recruited from countries outside the USA,[89] intravenous vernakalant was more effective than was intravenous amiodarone (51·7% *vs* 5·7% by 90 min after start of treatment; p<0·0001) for the rapid conversion of atrial fibrillation. Vernakalant is contraindicated in patients with hypotension, severe congestive heart failure, significant valvular heart diseases, prolonged QT interval, and bradycardia. In patients with significant structural heart disease, intravenous amiodarone is the only available treatment, and cardioversion usually occurs several hours later than with other antiarrhythmic drugs.

Randomised trials have not shown any difference in rates of all-cause and cardiovascular mortality and stroke between rate control versus rhythm control in patients with atrial fibrillation,[90–96] including patients with heart failure and LVEF less than 35%.[96] Nevertheless, most patients recruited into these trials were elderly patients with coexisting cardiovascular diseases and few symptoms. On the basis of these findings, guidelines[29,97]

recommend that specific patient subgroups should adopt an initial rate control approach, whereas a rhythm control strategy might be appropriate for patients in whom maintenance of sinus rhythm is expected to be successful and beneficial (panel 2).

The considerations for long-term choice of atrioventricular nodal blocking agents for ventricular rate control should include the patient's lifestyle and comorbidities. Generally, β blockers or non-dihydropyridine calcium-channel blockers are the initial choice of drugs for ventricular rate control of atrial fibrillation in most patients (figure 4). Furthermore, digoxin should be reserved for those who are sedentary; it can be added to β blockers or non-dihydropyridine calcium-channel blockers in patients with atrial fibrillation and with uncontrolled ventricular rates. In patients with stable congestive heart failure and impaired LVEF, β blockers should be first-line therapy because they reduce mortality, whereas digoxin can be added to achieve ventricular rate control.

For long-term control of ventricular rate, findings from one trial[98] suggest an initially lenient approach, allowing a resting heart rate of less than 110 beats per min. In patients who have impaired LVEF or remain symptomatic after lenient ventricular rate control, a stricter approach (resting heart rate <80 beats per min and a heart rate <110 beats per min during moderate exercise) guided by 24-h Holter monitoring and exercise testing is needed (figure 4). This approach is recommended by guidelines.[4,97,99]

Maintenance of sinus rhythm

Clinical guidelines[4,42,97] recommend that flecainide, propafenone, or sotalol are first-line agents in patients with lone atrial fibrillation or minimal structural heart disease. Amiodarone is reserved for patients with congestive heart failure or significant left ventricular hypertrophy, or as a second-line agent after failure of other antiarrhythmic drugs, because of its potential serious extra-cardiac side-effects (table 5, figure 5).

Dronedarone is a derivative of amiodarone in which iodine has been removed and a methane sulphonyl group has been added to not only reduce the iodine-related organ toxicity and to shorten the half-life by decreasing lipophilicity, but also to reduce the antiarrhythmic efficacy of dronedarone.[88] In one trial, dronedarone reduced the frequency of the combined endpoint of cardiovascular hospitalisation and death (by 24%; $p<0\cdot001$)[100] and stroke (in a secondary analysis)[101] in patients with non-permanent atrial fibrillation with other cardiovascular risk factors (age >70 years, hypertension, diabetes, previous cerebrovascular accident, left atrial diameter ≥50 mm, or LVEF <40%). In a meta-analysis[102] and one short-term clinical trial,[103] dronedarone was less effective than was amiodarone in maintenance of sinus rhythm but had more favourable short-to-medium term side-effects. A reduction of ventricular rate during atrial fibrillation recurrence and the blood-pressure-lowering effect of dronedarone might also contribute to the improved clinical outcomes recorded in patients with atrial fibrillation.[104,105] However, in patients with decompensated or New York Heart Association (NYHA) class III–IV congestive heart failure, dronedarone was associated with increased mortality.[106] Nevertheless, subgroup analyses[107] suggest that only patients with NYHA class IV or unstable class II–III congestive heart failure were at risk of adverse clinical outcomes with dronedarone. More recently, the PALLAS study (Permanent Atrial Fibrillation Outcome Study Using Dronedarone On Top Of Standard Therapy) was designed to investigate whether dronedarone would improve cardiovascular outcomes in patients with permanent atrial fibrillation and pre-existing cardiovascular diseases or multiple risk factors. However,

***Panel 2:* Choices between rate versus rhythm control strategy**

Rate control

- Aged >65 years*†
- No history of congestive heart failure*†
- Failure or contraindications to antiarrhythmic drugs*†
- Hypertension*
- Patient preference*
- Coronary artery disease†
- Unsuitable for cardioversion†

Rhythm control

- Symptomatic patients*†
- Aged <65 years*†
- Newly detected lone atrial fibrillation*†
- No hypertension*
- Congestive heart failure triggered by atrial fibrillation*
- No previous failure of antiarrhythmic drugs*
- Patient preference*
- Atrial fibrillation secondary to a treated/corrected precipitant†

*Canadian guideline.[47] †UK National Institutes of Health and Clinical Excellence (NICE) guideline.[26]

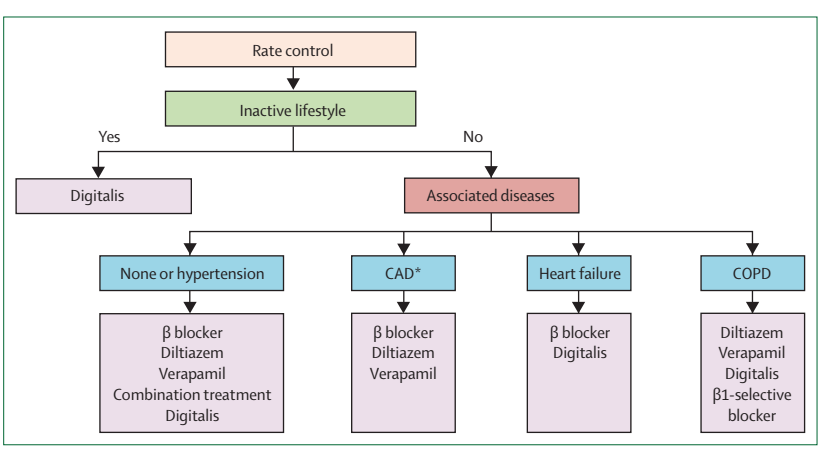

***Figure 4:* Treatment approaches for rate control in atrial fibrillation**
CAD=coronary artery disease. COPD=chronic obstructive pulmonary disease. *Recommended by Canadian guideline.[97] Adapted from Camm AJ, et al. ESC guideline 2010.[4]

	Indications	Route and dose	Efficacy	Adverse effects
Flecainide	AF in patients without, or with minimal, heart diseases	Oral: 100–300 mg in two divided doses	19–51%, no effect on VR	Proarrhythmia, bradycardia, negative inotropic effect, CNS effects; avoid in patients with heart failure, coronary artery disease, and CrCl <50 mg/mL
Propafenone	AF in patients without, or with minimal, heart diseases	Oral: 450–900 mg in three divided doses	54–70%, mild effect on VR	Proarrhythmia, bradycardia, modest negative inotropic effect, gastrointestinal system effects; uncertain safety in patients with heart failure and coronary artery disease
Sotalol	AF in patients without, or with minimal, heart diseases; or coronary artery diseases	Oral: 80–240 mg in two divided doses	51–63%, similar to β-blocker effect on VR	Sinus bradycardia, atrioventricualr block, negative inotropic, Tdp if hypokalaemic; avoid in patients with congestive heart failure
Amiodarone	AF in patients with significant heart diseases or in those who did not respond to other medication	Oral: loading at 600–800 mg daily and maintenance at 100–200 mg daily	37–73%, modest effect on VR	Many side-effects including pulmonary fibrosis, gastrointestinal upset, thyroid dysfunction, eye and skin changes; Tdp uncommon; dose of warfarin and digoxin should be reduced
Dronedarone	AF in patients with or without heart diseases	Oral: 400–800 mg in two divided doses	35–63%, modest effect on VR	Nausea, vomiting, diarrhoea, and rash; Tdp uncommon; need dose adjust for CrCl, body size, and age; dose of warfarin and digoxin should be reduced

AF=atrial fibrillation. VR=ventricular rate. CrCl=creatinine clearance. Tdp=torsade de pointes.

Table 5: **Pharmacological agents for maintenance of sinus rhythm**

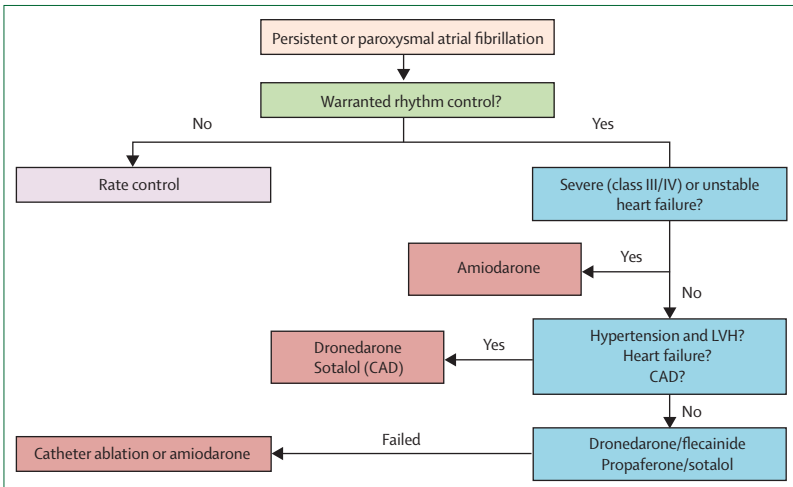

Figure 5: **Treatment approach in patients with recurrent paroxysmal or persistent atrial fibrillation**
LVH=left ventricular hypertrophy. CAD=coronary artery disease.

the study was prematurely terminated after initial enrolment of 3236 patients because dronedarone was associated with a doubling in the risk of death, stroke, and heart failure admission in patients with permanent atrial fibrillation. In PALLAS,[108] the first coprimary outcome (stroke, myocardial infarction, systemic embolism, or cardiovascular death) was increased with dronedarone (HR 2·29, 95% CI 1·34–3·94; p=0·002), with more cardiovascular deaths (HR 2·11, 95% CI 1·00–4·49; p=0·046), arrhythmic deaths (3·26, 1·06–10·00; p=0·03), stroke (2·32, 1·11–4·88; p=0·02), and heart failure hospitalisations (1·81, 1·10–2·99; p=0·02) in patients given dronedarone than in those given placebo. Therefore, dronedarone should be avoided in patients with permanent atrial fibrillation.[108]

Dronedarone should not be prescribed to patients with severe renal dysfunction (creatinine clearance <30 mg/mL); it is associated with potential drug–drug interaction with CYP-3A inhibitors (eg, ketoconazole, rifampin), and increases the drug serum concentrations of common cardiovascular drugs such as statins and warfarin. Furthermore, its long-term safety with regard to liver and pulmonary toxicities needs to be confirmed.[109] After reports of potentially severe cases of liver toxicity, including two patients needing liver transplantation, after the use of dronedarone, regular monitoring of liver function is now recommended.[109]

Clinical guidelines[4,97,99] have recommended dronedarone as a first-line agent for patients with non-permanent atrial fibrillation and no or minimal structural heart diseases. In European guidelines,[4] dronedarone is recommended for the maintenance of sinus rhythm; however, the 2011 focused update guideline from the American College of Cardiology Foundation, American Heart Assosocation, and Heart Rhythm Society recommends use of dronedeaone to decrease admissions and cardiovascular events in patients with paroxysmal atrial fibrillation or after conversion of persistent atrial fibrillation. Furthermore, the European guideline[4] recommends dronedarone as the first-line agent in hypertensive patients with left ventricular hypertrophy and in those with NYHA class I–II congestive heart failure, but this recommendation is not mentioned in the 2011 focused update guideline.

Several novel compounds[88]—including different derivatives of amiodarone (eg, budiodarone and celivarone), atrial selective agents (eg, oral preparation of vernakalant, xention, and AVE1231 derivatives), and other multichannel blocker agents—are being developed. The safety and clinical efficacy of these new antiarrhythmic drugs for treatment of atrial fibrillation will emerge as clinical trials progress.

Non-pharmacological therapies for atrial fibrillation

Cardiac pacing

In patients with atrial fibrillation who do not respond or are intolerant to atrioventricular blocking agents for ventricular rate control, atrioventricular nodal ablation with permanent pacemaker implant improves symptoms and quality of life.[110,111] After atrioventricular nodal ablation, biventricular pacing might be preferable to right ventricular pacing, especially in patients with impaired LVEF, to prevent deterioration of cardiac function.[112,113] However, cardiac resynchronisaton therapy can prevent

the progression of atrial fibrillation in selected patients with heart failure.[114,115] In patients with symptomatic sick sinus syndrome and paroxysmal atrial fibrillation, atrial-based pacing with avoidance of unnecessary ventricular pacing reduces the risk of persistent atrial fibrillation by 40% (p=0·009).[116] However, there are no data to lend support to any atrial pacing method or sites that can prevent the onset or progression of atrial fibrillation.

Catheter ablation

The aim of catheter ablation for atrial fibrillation is to eliminate the triggers or substrate that initiates and maintains the disorder, to maintain sinus rhythm. In patients with paroxysmal atrial fibrillation, most triggers originated in or around the pulmonary veins, and only about 10% were detected at the left atrial posterior wall, interatrial septum, coronary sinus, superior vena cava, and crista terminalis. As a result, electrical isolation of pulmonary veins alone with different energy sources is the cornerstone of the catheter ablation procedure for the treatment of paroxysmal atrial fibrillation, and can achieve clinical success in 64–71% of patients.[117–119] However, the clinical efficacy of catheter ablation for persistent atrial fibrillation is less favourable even with additional ablation approaches, including complex fractionated electrogram and multiple linear left atrial ablations to target atrial substrate (22–56%).[117–120] Findings from several multicentre prospective clinical trials,[117–119] systematic reviews, and meta-analyses[120–123] have consistently shown that catheter ablation is more effective than antiarrhythmic drug therapy for maintenance of sinus rhythm, especially in patients with paroxysmal atrial fibrillation who did not respond to initial treatment with antiarrhythmic drugs. Furthermore, successful catheter ablation of atrial fibrillation to maintain sinus rhythm was associated with improved symptoms and quality of life.[124,125]

Nonetheless, catheter ablation is a complex interventional procedure that requires skilled operators and technological advances. The use of three-dimensional electroanatomical mapping systems, sometimes combined with robotic navigation, can provide a more accurate anatomical guidance to target the ablation in the atria and reduce the patient's and physician's exposure to radiation. However, advances in catheter ablation technology—such as the circular and balloon ablation system and different energy sources, including bipolar and irrigated radiofrequency energy, cryoablation, microwave, and laser ablations—are promising techniques to improve the safety and efficacy of atrial fibrillation ablations. Nevertheless, the best technique for catheter ablation is still unknown.[126]

Catheter ablation is associated with a risk of major complications (about 3–4%), and several procedures are often needed to control recurrent atrial fibrillation or postablation atrial tachycardia.[127] Studies[128] suggest that a substantial proportion of patients develop late recurrence of atrial fibrillation after catheter ablation, and there is no evidence to suggest that catheter ablation reduces stroke or mortality beyond rhythm and symptom control. Whether catheter ablation can improve long-term clinical outcomes will be addressed in ongoing trials (webappendix p 10).

Recurrences are often asymptomatic, and the proportion of asymptomatic paroxysms after ablation is increased.[129] As a result, clinical guidelines[4,97,99] have recommended catheter ablation to patients with paroxysmal atrial fibrillation and minimal structural heart diseases who remain symptomatic after initial antiarrhythmic drug therapy. In patients with structural heart diseases or persistent atrial fibrillation, catheter ablation should be reserved for those who are refractory or intolerant to at least one antiarrhythmic drug or used as an alternative to amiodarone therapy.

Left atrial appendage occlusion

The left atrial appendage is considered to be the site of thrombus in many patients with atrial fibrillation. Thus, it can be excluded from systemic circulation at the time of cardiac surgery by excision, ligation, suturing, or stapling,[130] although this strategy is not uniformly effective and suboptimum results are evident.[131]

Guidelines support the use of left atrial appendage ligation as an adjunctive procedure during mitral valve surgery.[132] Closure devices for percutaneous left atrial appendage have been developed, the first being the percutaneous left atrial appendage transcatheter occlusion (PLAATO) device (ev3, Plymouth, MN, USA).[133] A trial in which 707 patients were randomly assigned to percutaneous closure of left atrial appendage by the WATCHMAN device (Atritech, Plymouth, MN, USA) or warfarin showed non-inferiority (rate ratio 0·62, 95% CI 0·35–1·25) of a device approach compared with warfarin, but an increased rate of periprocedural complications (eg, pericardial effusion requiring intervention in 5% of patients).[134]

Conclusions

The management of atrial fibrillation has had substantial new developments. The limitations of aspirin (including its potential for bleeding, especially in elderly people) and the availability of new oral anticoagulant drugs that overcome the inherent drawbacks associated with warfarin would allow more widespread use of oral anticoagulant drugs, which would improve stroke prevention in atrial fibrillation. Stroke risk stratification, with comprehensive risk factor assessment, has led to a shift towards improved identification of truly low-risk (CHA_2DS_2-VASc score of 0) patients with atrial fibrillation who do not need antithrombotic therapy, and thus, all patients with one or more stroke risk factors (CHA_2DS_2-VASc score ≥1) can be treated with oral anticoagulation therapy.

New antiarrhythmic drugs have provided some additional approaches for rhythm control in atrial fibrillation. Nonetheless, the approach to management of

atrial fibrillation is increasingly patient-centred and symptom directed. Lenient or strict rate control strategies might not provide great differences in outcomes, whereas the availability of non-pharmacological approaches has allowed additional possibilities for the management of atrial fibrillation in patients who are unsuitable or intolerant of pharmacological therapy.

Contributors

All authors contributed to drafting and revisions of this Seminar.

Conflicts of interest

GYHL has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. He was Clinical Adviser for the UK National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management. He was on the writing committee of the 2010 ESC guidelines on atrial fibrillation, and is Deputy Editor (content expert) for the 9th American College Chest Physicians guidelines on antithrombotic therapy for atrial fibrillation. HFT has received funding for research, educational symposia, consultancy, or lecturing from different manufacturers of devices (Cordis Webster, St Jude Medical, and Medtronic) and drugs (Bayers, Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo Sankyo) used for the treatment of atrial fibrillation. DAL has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis (Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Bayer), and is a panellist on the American College Chest Physicians guidelines for the antithrombotic management of atrial fibrillation.

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