Modern management of atrial fibrillation

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ABSTRACT – Atrial fibrillation (AF) continues to offer a management challenge to physicians. The incidence of this arrhythmia is rising and the cost to the healthcare system is vast. Much of this health burden relates to the high risk of stroke and thromboembolism associated with AF. This review covers common treatment strategies employed in AF management, discusses relevant drug therapy and the role of electrophysiology or surgery.

KEY WORDS: antiarrhythmic drugs, atrial fibrillation, stroke, thromboembolic prophylaxis

Introduction

As the most common arrhythmia encountered in clinical practice and with rapidly evolving treatment strategies, atrial fibrillation (AF) continues to offer a management challenge to the physician. This emerging health epidemic is reflected by AF now consuming approximately 1% of NHS expenditure.

Cross-sectional studies have shown that the prevalence and incidence of AF continues to surge, correlating in particular with the advancing age of Western populations. In those over 65, approximately 5% have AF, while in those aged over 80 years, this figure rises to 10%.

This review focuses on management of AF with reference to the National Institute for Health and Clinical Excellence (NICE) evidence-based clinical guidelines published in June 2006.[1] In addition, the American College of Cardiology/American Heart Association/European Society of Cardiology consensus guidelines for the management of patients with AF have also now been updated.[2]

Box 1. Common risk factors for developing atrial fibrillation (AF).

- Age
- Male sex
- Body mass index
- Excess alcohol
- Hyperthyroidism
- Respiratory disease (eg chronic lung disease, carcinomatosis, pulmonary embolus)
- Diabetes
- Cardiovascular (eg ischaemic heart disease, hypertensive heart disease, valvular/structural heart disease, heart failure and cor pulmonale, intracardiac masses/tumours, pericardial disease, cerebrovascular disease, peripheral vascular disease)
- Recent surgery

Risk factors for atrial fibrillation

Many risk factors for AF have been identified. As well as advancing age, there is a strong link with hypertension, ischaemic heart disease, structural/functional heart disease, valvular heart disease and hyperadrenergic states (such as thyrotoxicosis or illicit drug use), to name but a few. In some patients, alcohol excess may provide an adequate trigger for acute AF.

In fact, the array of associations with AF is enormous (Box 1) and in part explains why a detailed knowledge of this condition is essential for both the generalist and specialist alike; not only will cardiologists frequently encounter AF, but so will colleagues in other specialties.

Symptoms and presentation

The incidental finding of asymptomatic AF remains relatively common, often detected for example during preoperative assessment. Increasingly, though, AF is diagnosed during investigation for symptoms such as palpitations, dyspnoea, dizziness or syncope. This list is by no means exhaustive and it is increasingly recognised that AF contributes to or exacerbates numerous complaints, including lethargy, fatigue and anxiety. Additionally, it is important to remember that other conductive or atrioventricular nodal diseases may coexist with AF and in those who complain of syncopal episodes this should be considered as a co-diagnosis. Box 2 illustrates the most common symptoms reported in association with AF.

Classification

The classification of AF has been through a period of change. Most are now agreed on a clinical classification system, based on the temporal patterns of AF, summarised as follows:[3]

- recent onset AF (within 48 hours)
- paroxysmal AF

Box 2. Common symptoms reported in atrial fibrillation (AF).

- Palpitations
- Dyspnoea
- Poor exercise capacity
- Dizziness/syncope
- Fatigue
- Anxiety

- persistent AF (lasting seven days or more, but potentially cardiovertable)
- permanent AF (refractory to cardioversion attempts).

Regardless of classification, the management of patients with AF should be guided by many considerations, including symptoms, the presence or absence of haemodynamic compromise, and associated comorbidities. The (sometimes artificial) classification system purely gives an idea of the time course of the AF but not the ultimate clinical outcome, and re-emphasises the fact that the management of AF should be guided by symptoms.

The clinical subtypes of AF can help define the objectives of management and therapeutic strategies.[4] For example, the management objective in paroxysmal AF is the reduction of paroxysms and the long-term maintenance of sinus rhythm, and hence antiarrhythmic drugs (or non-pharmacological approaches) are used. In persistent AF, the management objective is sinus rhythm restoration, and hence cardioversion is attempted. In permanent AF, the objective is heart rate control. This is generally achieved with antiarrhythmic drugs, however, non-pharmacological approaches may be required in some patients. In all patients with AF, appropriate antithrombotic therapy use is mandatory, based on risk factors for stroke and thromboembolism.

Investigation of the patient with atrial fibrillation

As discussed, the potential causes for AF are many and the symptom profile is potentially complex. Thus, assessment of the patient with AF needs to be methodical. A thorough history taking and clinical examination are essential, as they will not only alert the physician to any potential trigger for AF, but it will also help guide any further investigation and the treatment strategy to be pursued.

A 12-lead electrocardiogram (ECG), blood investigations (including full blood count, electrolytes and thyroid function tests), chest X-ray and echocardiogram are essential. Other tests such as 24-hour (or sometimes, seven-day) Holter monitoring or exercise testing may be required in certain patients – often for those where a diagnosis of paroxysmal AF is suspected but not initially apparent or to assess the AF burden as part of risk assessment for anticoagulation. Box 3 summarises relevant investigations for AF.

Rate control or rhythm control

Much of the current dilemma for the physician is deciding whether to pursue a rate control or rhythm control strategy.

Box 3. Investigating the patient with atrial fibrillation (AF).

History
- Symptoms and severity
- Risk factors for AF (including symptoms of thyroid disease)
- Drugs (and alcohol)

Examination
- Pulse (rate is better assessed apically in AF)
- Abnormal cardiac or respiratory findings

12-lead electrocardiogram
- Confirmation of rhythm
- Rate (at rest)
- Detection of pre-excitation arrhythmias
- Evidence of left ventricular hypertrophy (usually secondary to hypertension or aortic stenosis)
- Signs of ischaemic heart disease

Chest X-ray
- Screen for carcinomatosis and chronic lung disease

Blood investigations
- Full blood count
- Electrolyte profile
- Thyroid function tests

Echocardiogram
- Structural/hypertensive/valvular heart disease
- Left atrial size
- Left ventricular size and function
- Pericardium

The following may be useful in some patients:

Holter monitor
- Useful to assess rate control
- Assessment of AF burden in paroxysmal AF

Exercise test
- Exercise/ischaemia induced AF
- Assessment of rate control during exercise

Theoretically, restoration of sinus rhythm in all patients seems ideal, as this should allow improved haemodynamics and provide symptom relief while potentially reducing the thromboembolic tendency and stroke risk. However, the trend in many patients with AF is to have recurrences (often asymptomatic), even if a rhythm control strategy initially succeeds. Despite the use of potent antiarrhythmics and an aggressive serial cardioversion strategy for early relapse, for example, only approximately 50% of patients remain in sinus rhythm at one year.[5] At five years, the figures are dire, with only 25% remaining free of AF,[5] bringing into question whether it is appropriate to stop thromboembolic prophylaxis even if rhythm control initially succeeds.

This knowledge presents a dilemma. Should all patients be offered rhythm control, or would it be more prudent to accept that many patients will eventually succumb to permanent AF, and adopt a rate control strategy for all? This subject has been addressed by several randomised controlled trials. The largest of these, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, investigated 4,060 participants with

recurrent AF and one or more risk factors for stroke;[6] this trial showed no difference in the primary endpoint of overall mortality at five years in those randomised to rate or rhythm control strategies. Furthermore, there was no significant difference in the composite secondary outcome measure of death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest between the two study arms. Notably, a rhythm control strategy was associated with a higher rate of hospitalisations and more frequent adverse drug reactions associated with antiarrhythmic drug use. In a, post hoc, analysis of the predictors of the AFFIRM trial, anticoagulation use and sinus rhythm emerged as significant predictors of survival. However, a higher mortality was associated with the use of antiarrhythmic drugs which offset the survival advantage of being in sinus rhythm.[6] Nonetheless, some caution should be exercised before extrapolating the data from the rate control versus rhythm control trials to the entire AF population. In these trials, a large proportion of patients in the rhythm control arms did not maintain sinus rhythm, but were continued in that arm of the trial for the 'intention to treat' analysis. Most participants were older patients with risk factors for stroke and more than likely other comorbidities as well, or who had previous failed attempts at rhythm control. Crossing over from rhythm control to rate control treatment was also common.

The NICE guidelines on AF have systematically reviewed the evidence and provided guidance for which treatment strategy (rhythm control or rate control) is most appropriate (Box 4). These indications are not mutually exclusive, and in appropriate circumstances, the possibility of restoring sinus rhythm (eg using catheter ablation) can be considered, especially in symptomatic patients.

Drug management of atrial fibrillation

Acute atrial fibrillation

The strategy for management of acute AF owes much to an accurate assessment of the patient's haemodynamic status and cardiac stability, as well as any associated complications such as angina or heart failure. In patients with life-threatening features, emergency electrical cardioversion should always be considered, irrespective of duration of AF. Some patients with AF and an uncontrolled ventricular response develop acute decompensation with peripheral or pulmonary oedema. Although the fast ventricular response has clearly played a major role, these patients often have underlying cardiac disease and rapid improvement can be achieved by reducing ventricular rate. These patients may include those with recent onset AF, those with paroxysmal AF who present with a fast paroxysm, and those with previously stable persistent/permanent AF who have become tachycardic.

Until relatively recently, the mainstay of drug therapy for AF was the cardiac glycoside, digoxin; however, this drug is of limited efficacy in the context of thyrotoxicosis, fever, perioperatively and most importantly during exercise. As such, it is only in the elderly sedentary patient that digoxin monotherapy is likely to offer adequate rate control. A rate-limiting calcium antagonist or beta-blocker should be tried as first line in stable patients, but where these are inappropriate (eg pulmonary oedema), intravenous amiodarone (ideally through central access) is preferred.

In other patients, particularly those who are younger without any structural heart disease, it is important to consider Wolff-Parkinson-White syndrome, as fast AF may be the initial presenting rhythm in this condition. Atrioventricular node-blocking agents (such as diltiazem, verapamil, or digoxin) should not be used as these may exacerbate the ventricular rate and could be dangerous. Here it would be appropriate to consider intravenous flecainide for attempting pharmacological cardioversion.

Box 4. Rate or rhythm control for atrial fibrillation (AF)?

A rate control strategy should be the preferred initial option in the following patients with persistent AF:

- over 65
- with coronary artery disease
- with contraindications to antiarrhythmic drugs
- unsuitable for cardioversion
- without congestive heart failure.

A rhythm control strategy should be the preferred initial option in the following patients with persistent AF:

- symptomatic
- younger
- presenting for the first time with lone AF
- AF secondary to a treated/corrected precipitant
- congestive heart failure.

Rate control in atrial fibrillation

Clearly optimal cardiovascular status is best achieved by restoration of sinus rhythm; however, this is not always feasible or successful and in these circumstances the ventricular rate should be controlled to that where cardiac output is optimal and the patient's symptoms are adequately controlled. It is generally accepted that a resting heart rate below 90 bpm is optimal, while on exertion the heart rate should not exceed 110 bpm in the sedentary patient or '200 minus age' in the ambulatory patient.[7] Beta-blockers are effective at controlling ventricular rate and are increasingly being used as first-line agents. Beta-blockers also offer some protection against recurrence following successful cardioversion (be it spontaneous, pharmacological or electrical) and are used as first-line prophylactic agents in paroxysmal AF. They are also useful in the perioperative setting, to reduce the likelihood of developing AF in those deemed at risk. As AF commonly coexists with hypertension or heart failure due to systolic dysfunction, beta-blockers may be part of the therapeutic management in such patients.

The rate-limiting, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are also frequently used to optimise rate control in those unable to take or tolerate a beta-blocker. Although digoxin is no longer considered first line in

most patients, it remains a useful adjunct in those who remain tachycardic at rest and can be used in combination with either a beta-blocker or calcium channel blockers (the so-called 'hybrid' approach).

A small minority of patients continue to have poor control of ventricular rate or in the case of paroxysmal AF may suffer frequent distressing relapses. This sub-group of patients tend to be very symptomatic and other agents such as amiodarone are sometimes useful. Side effects with amiodarone are, however, common, particularly with prolonged exposure, when hepatic, ophthalmic, pulmonary or thyroid complications may occur. Thus, it is important to keep these patients under long-term follow-up with regular assessment usually under the care of a cardiologist.

Rhythm control in atrial fibrillation

Rhythm control aims to restore, and achieve long-term maintenance of sinus rhythm. Potential candidates for a rhythm control strategy are: younger patients; those with lone AF, or AF secondary to a corrected precipitant (eg alcohol); patients with symptoms despite optimal rate control; patients with heart failure.

In persistent AF, cardioversion can be performed electrically or pharmacologically. Electrical cardioversion may be successful in 75–93% of patients, but success rate depends on duration of AF, left atrial size and coexisting structural heart disease.[8] The outcome is significantly lower in patients with AF duration of more than one year. The rate of recurrence of AF after electrical cardioversion is high and maintenance of sinus rhythm may improve by concomitant administration of antiarrhythmic drugs, such as amiodarone or sometimes beta-blockers.

Pharmacological cardioversion can be achieved using a number of drugs including disopyramide (class IA), flecainide and propafenone (class IC), dofetilide, ibutilide, sotalol and amiodarone (class III). Those most commonly prescribed in the UK are flecainide, sotalol and amiodarone. As with electrical cardioversion, earlier administration improves the chance of success, with (generally) little to choose between oral and intravenous administration, except speed of conversion. In fact, successful cardioversion is reported in up to 80% with oral antiarrhythmic drugs, rising to approximately 90% with intravenous administration.

As relapse following cardioversion is common, antiarrhythmic drugs are used in both persistent and paroxysmal AF to enhance long-term maintenance of sinus rhythm. The class IC and III drugs are preferred to class IA drugs, in view of their better safety profile.[9] A number of studies have demonstrated that flecainide and propafenone are effective for preventing recurrence of AF.[10–12] The effectiveness of flecainide is comparable to quinidine, but with fewer side effects. Propafenone is more effective at maintaining sinus rhythm than quinidine, and is as effective as sotalol. Given the relatively high risk of proarrhythmia, class IC drugs should not be used in patients with ischaemic heart disease or left ventricular dysfunction.

All current class IA, IC, and III antiarrhythmic drugs have significant side effects. Major complications include proarrhythmia and noncardiovascular effects. Most antiarrhythmic medicines prevent or terminate AF by alteration of function of potassium or sodium channels of atrial cells. Blocking of potassium channels prolongs repolarisation and the refractory period that may cause QT and QRS prolongation. QT prolongation with potassium-channel blockers may result in the life-threatening proarrhythmia (such as torsades de pointes) in up to 5% of patients.[13] Factors known to enhance risk for development of torsades de pointes are hypokalaemia or hypomagnesemia, congenitally prolonged QT intervals, bradycardia, congestive heart failure, female gender, and pauses associated with the conversion of AF to sinus rhythm. The risk of QT prolongation and torsades de pointes may be further increased by concomitant use of wide range of medications, especially ones, which interfere with the hepatic metabolism of antiarrhythmic drugs. It is therefore advisable that these drugs are not prescribed to patients taking other substances known to promote QT prolongation (such as erythromycin) and that a 12-lead ECG be requested after starting treatment.

In some, particularly in the presence of renal impairment, class IC drugs can turn AF into atrial flutter with 1:1 atrioventricular nodal conduction and haemodynamic instability. For this reason, the concomitant use of atrioventricular nodal blocking agents, such as beta-blockers and rate-reducing calcium antagonists, is recommended.

Non-pharmacological approaches

For those who continue to be heavily symptomatic or where antiarrhythmic drugs are ineffective or intolerant, non-pharmacological options can be considered. It has long been recognised that the pulmonary veins appear to have a crucial role in the aetiology of AF.[14] This has led to the emergence of non-pharmacological approaches to AF management.

Catheter approaches. Ablation of the atrioventricular (AV) node with permanent pacemaker implantation is an established and effective option that ensures good rate control, alleviates symptoms and improves quality of life.[15] This technique is particularly useful in those with poor rate control despite multi-drug therapy.

In some, AV node modification rather than ablation may be attempted. This technique involves preferential ablation of the electrical inputs to the AV node with the shortest refractory period, thereby implying an upper limit to ventricular rate response.[16] Of course, there is a significant incidence of complete heart block requiring subsequent pacing and also risk of AF recurrence, limiting the feasibility of this approach.

Pulmonary vein isolation has been used as first-line management for recurrent AF, with impressive results. Häissaguerre *et al*[17] reported that 94% of ectopic triggers for AF were located in the myocardial tissue around the pulmonary veins. Ablation of these foci prevented AF recurrence in 62% of patients. Unfortunately, the procedures are long and arduous, and often two or more attempts are required to achieve success.

Furthermore, complications (eg pulmonary stenosis) remain relatively common and can occur in up to 6% of patients.[18] In addition, some go on to have recurrent episodes of AF, which may be asymptomatic and difficult to detect clinically, thus making an absolute assessment of stroke risk difficult.[19,20] More recently, Pappone *et al*[20] demonstrated that robotic magnetic navigation was feasible for AF ablation. This allowed circumferential pulmonary vein ablation from a remote operator and illustrates the potential for expansion of catheter techniques.

Surgery. Prior to the expansion of ablation techniques, surgical procedures allowed the potential to offer a cure. The 'corridor' procedure,[22] introduced in 1985, involves surgical isolation of the atrial-free walls from the septum through a series of sutures. In the remaining corridor, a conduction pathway between the sinus and AV nodes is maintained. Unfortunately, later development of other atrial arrhythmias is common and affects up to 27% after five years.[23]

Subsequent work by Cox *et al*[24] led to the development of the 'maze' procedure which involves a series of incisions within the atria with subsequent fibrosis, thereby creating lines of conduction block. This later evolved into the Maze III operation, which involves excision of the left and right atrial appendages, isolation of the pulmonary veins and several additional incisions to prevent atrial re-entry. This is now the surgical procedure of choice for medically refractory AF. However, because of the requirement for an invasive approach, these techniques are probably best reserved for those undergoing thoracotomy for other reasons, for example, those requiring coronary artery bypass grafting or valve surgery.

Antithrombotic therapy

The presence of AF increases the risk of stroke by up to five-fold across all age groups; indeed, AF accounts for up to 10–15% of all ischaemic strokes.[25] This association continues to strengthen with age and in those over 80 AF accounts for nearly 35% of strokes, especially in the presence of comorbidities.[25] Of greater concern is that those with AF who have a stroke have a significantly worse outcome in terms of morbidity and mortality.

A recent meta-analysis of 13 trials (n=14,423) showed that adjusted-dose warfarin compared to placebo offered significant absolute reduction in risk of ischaemic stroke or systemic embolism.[26] As expected, the absolute risk reduction for all stroke was far greater for secondary stroke prevention (NNT for one year to prevent one stroke=12) when compared with primary prevention (NNT=37). A target INR (international normalised ratio) of 2.0–2.5 should be maintained in most patients, as the risk of stroke increases two-fold in those with INR 1.5–2.0, and even higher with INRs <1.5.[27]

Meta-analysis of the six main randomised controlled trials of aspirin versus placebo has shown that aspirin treatment offers a significant stroke risk reduction of 22% (95% CI 2–38).[28] This 22% is similar to that seen for stroke reduction with antiplatelet therapy use in vascular disease patients, and the aspirin effect may simply reflect this. In fact, a recent Cochrane review of antithrombotic therapy in AF concluded that aspirin only provided a modest reduction in stroke risk, at best this approached 25%.[29] Indeed, much of the evidence in favour of aspirin eminates from the Stroke Prevention in Atrial Fibrillation (SPAF) I clinical trial,[30] which initially reported a 42% stroke risk reduction with aspirin versus placebo. In this trial, aspirin-eligible AF patients were divided into two groups: Group I (anticoagulation eligible) patients were randomised to warfarin, aspirin (n=206) or placebo (n=211), while Group II patients (anticoagulation ineligible, based on safety considerations or patient refusal) were randomised to aspirin (n=346) or placebo (n=357). In Group I, there were 1 and 18 events in the aspirin and placebo arms, respectively, implying a significant risk reduction of 94% ($p<0.001$), while in Group II, there were 25 and 28 events in the aspirin and placebo arms respectively, equivalent to only a 8% risk reduction ($p=0.75$); the pooled analysis of Groups I and II events (with some inconsistency between the two groups) gives a 42% risk reduction with aspirin for the whole trial ($p=0.02$).[29] More importantly, strokes in aspirin-treated AF patients are usually more severe, with greater inpatient mortality and disability. Thus, aspirin should therefore be considered an inferior substitute in terms of stroke prevention among high-risk subjects with AF.

Despite the evidence, there is a tendency for physicians to shy away from prescribing anticoagulation. In particular, anticoagulation is less likely to be offered to the elderly and those with a history of falls, recent history of bleeding, or poor compliance. Each of these patient factors is more common in the elderly, but it is this very patient group that is also at the highest risk from thromboembolic events. Additionally, there appears to be a clustering of embolic events around the time of AF onset in some patients and therefore a decision regarding anticoagulation should not be excessively delayed.

In addition, the greater application of percutaneous coronary intervention (PCI) for ischaemic heart disease has led to debate regarding the optimal choice for anticoagulation in this setting. For PCI, generally aspirin and clopidogrel are recommended, to reduce the risk of stent thrombosis, however, the efficacy of these drugs for stroke prevention in AF is questionable, while triple therapy with aspirin, clopidogrel, and warfarin is associated with more bleeding events.[31] Various suggestions regarding treatment have been made, however these are based upon assumptions regarding risk of stroke and subsequent cardiac events. It is clear that for this common clinical scenario, guidelines formulated from evidence based on clinical trials are urgently required.[31] Of course, the main concern about anticoagulation is of significant haemorrhage. Indeed, anticoagulation is associated with an increased risk of haemorrhagic stroke and other bleeding events. Additionally, the requirement for regular therapeutic monitoring, lifestyle restrictions (especially alcohol) and compliance all play a role in the decision whether or not to anticoagulate.

Of note, up to 40% of patients would prefer not to receive warfarin[32] and thus, pressurise the doctor advocating the (inappropriate) use of aspirin. Many patients see a moderate–severe stroke as a fate worse than death.[33] Indeed, the importance of compliance should be stressed to each patient, as an erratic INR

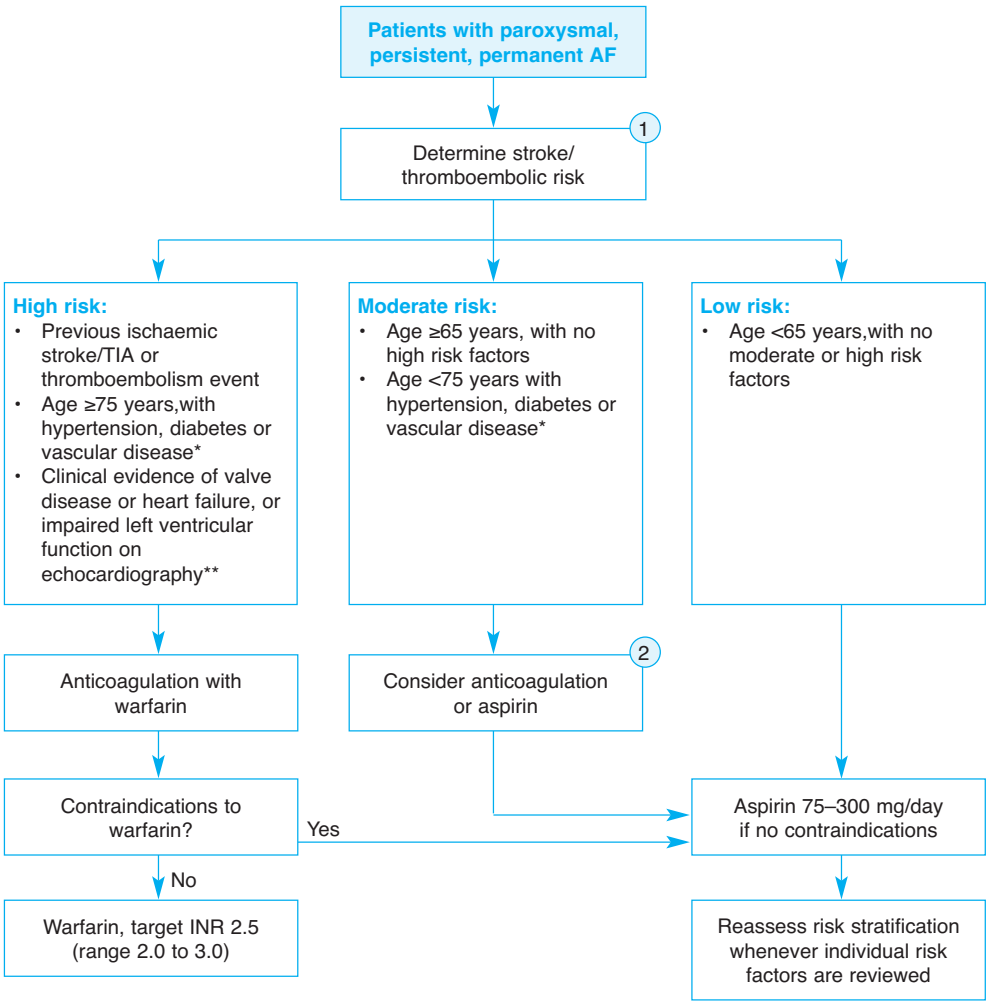

Fig 1. Practical guidelines for antithrombotic therapy in non-valvular atrial fibrillation. (1) The risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis appears similar to other aetiologies of atrial fibrillation (AF), antithrombotic treatments should be chosen based on the presence of validated stroke risk factors. (2) Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risk and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more risk factors. Referral and echocardiography may help in cases of uncertainty. *Coronary arery disease or peripheral artery disease. **An echocardiogram is not needed for routine assessment, but refines clinical risk stratification in the case of moderate or severe left ventricular dysfunction and valve disease. INR = international normalised ratio; TIA = transient ischaemic attack.

leads to an excessive risk of bleeding events. Furthermore, a 10% increase in time out of the therapeutic INR range can be associated with an increased risk of mortality, ischaemic stroke and hospitalisation among those patients anticoagulated for AF.[34]

Numerous risk stratification schema have been proposed in an effort to identify high-risk patients with AF who should be targeted for anticoagulation. None of the published schemes are ideal, with marked variability of patients categorised as low- or high-risk. It is recognised that AF commonly associates with other risk factors for stroke and investigators have proposed combining these to form a scoring system. For example, in the $CHADS_2$ scoring system, one point is assigned for the presence of congestive heart failure, hypertension, age >75 years and diabetes mellitus, while two points are assigned for a history of stroke or transient ischaemic attack. The stroke risk per 100 patient years increased by a factor of 1.5 for each one-point increase in the score, highlighting the importance of accurate risk stratification.[35] The current NICE guideline favours a more practical and pragmatic algorithm-based risk stratification approach, which is shown in Fig 1. The $CHADS_2$ score and NICE risk stratification schema (the latter based on the Birmingham risk stratification schema[25]) have a similar predictive value for stroke and vascular events, when tested in a prospective cohort of AF patients.

Conflict of interest statement

GL 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 to the atrial fibrillation management NICE Guideline Development Group.[1] TW and ES: none declared

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