The prevalence of atrial fibrillation (AF), already the most common sustained cardiac arrhythmia, is constantly rising, even after adjusting for age and presence of structural heart disease. AF increases the risk of stroke sixfold and is associated with a twofold increase in mortality, which remains above 1.5-fold after adjusting for co-morbidity, predominantly caused by cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. The adverse haemodynamic effects of AF are well described and relate not only to loss of atrial contraction, but also to the accompanying rapidity and irregularity of ventricular contraction. Although AF may be asymptomatic, up to two thirds of patients report that the arrhythmia is disruptive to their lives. Finally, the treatment of AF and its associated complications creates a significant and increasing economic burden. This article focuses predominantly on the pathophysiology of the arrhythmia and its pharmacological treatment. Anticoagulation for prevention of thromboembolism, a fundamental principle in the management of this arrhythmia, electrical cardioversion, percutaneous ablation techniques, and surgery for AF are not discussed in any detail.

CLASSIFICATION

AF may be classified based on aetiology, depending on whether it occurs without identifiable aetiology in patients with a structurally normal heart (lone AF), or whether it complicates hypertensive, valvar, or other structural heart disease.

A classification system based on the temporal pattern of the arrhythmia has been recently recommended. Patients presenting to medical attention may have a first detected episode of AF or, if previous episodes have been documented, recurrent arrhythmia. Episodes themselves may be paroxysmal, if they terminate spontaneously, usually within seven days, or persistent if the arrhythmia continues requiring electrical or pharmacological cardioversion for termination. AF that cannot be successfully terminated by cardioversion, and longstanding (> 1 year) AF, where cardioversion is not indicated or has not been attempted, is termed permanent (fig 1).

PATHOPHYSIOLOGY AND MECHANISMS

Hypertensive, valvar, ischaemic, and other types of structural heart disease underlie most cases of persistent and permanent AF, whereas lone AF accounts for approximately 15% of AF cases. Familial AF is well described, although at present considered rare. A region on chromosome 10 (10q22-q24) was originally identified as containing the gene responsible for AF in families in which the arrhythmia segregated as an autosomal dominant trait. However, familial AF appears to be a heterogeneous disease. A family with a mutation in the gene encoding the pore forming α subunit of the cardiac I\textsubscript{ca} channel on chromosome 11 that results in increased function of this channel, with affected members developing persistent AF probably caused by a reduction in refractoriness, has more recently been described.

The pathogenesis of AF is now thought to involve an interaction between initiating triggers, often in the form of rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate capable of maintaining the arrhythmia. Although structural heart disease underlies many cases of AF, the pathogenesis of AF in apparently normal hearts is less well understood. Although there is considerable overlap, pulmonary vein triggers may play a dominant role in younger patients with relatively normal hearts and short paroxysms of AF, whereas an abnormal atrial tissue substrate may play a more important role in patients with structural heart disease and persistent or permanent AF.

Focal initiators of AF

It is now known that foci of rapid ectopic activity, often located in muscular sleeves that extend from the left atrium into the proximal parts of pulmonary veins, play a pivotal role in the initiation of AF in humans. Less frequently, focal initiation of AF may be result from ectopic activity that arises from muscular sleeves in the proximal superior vena cava, from the ligament of Marshall, or other parts of the right and left atria. Initiation of AF by rapid focal activity has been demonstrated
not only in patients with structurally normal hearts and paroxysmal AF, but also during the process of reinitiation of persistent AF after electrical cardioversion, both in the presence and absence of associated structural heart disease.¹

Muscular sleeves that extend into the proximal pulmonary veins are present in the normal heart. The mechanisms involved in the production of ectopic activity by these sleeves in patients with AF, as well as the exact mechanism of initiation of AF by the rapid activity, remain to be elucidated. Proposed mechanisms for generation of abnormal focus activity include increased automaticity, triggered activity, and micro-reentry. Changes in autonomic tone around the time of AF: key points

Forum 1 Temporal classification of atrial fibrillation (AF). An incident episode of AF presenting to medical attention may be the first ever detected episode of the arrhythmia, or represent recurrence of previously recognised arrhythmia (left). The episode may prove to be self terminating (paroxysmal), persistent (continuing until medical intervention such as DC cardioversion), or permanent (continuing for longer than one year or despite medical intervention such as DC cardioversion) (right).

Electrophysiological remodelling

AF in itself can cause progressive changes in atrial electrophysiology such as substantial refractory period shortening, which further facilitate perpetuation of the arrhythmia. In animal studies, changes in ion channel function and shortening of refractory periods start within minutes of AF onset and, by 24 hours, sufficient atrial remodelling has occurred to increase the likelihood of AF persisting. However, restoration of sinus rhythm does occur in humans with established AF, this may no longer be possible after very prolonged periods of AF and thus restoration and maintenance of sinus rhythm in these patients is often difficult.

PHARMACOLOGICAL TREATMENT

In patients with short paroxysms of AF, therapeutic strategies should generally concentrate on providing control of the arrhythmia itself. In patients with persistent AF, however, the clinician is often faced with the dilemma as to whether to try and restore and then maintain sinus rhythm (rhythm control), or to accept the arrhythmia (as in the case of permanent AF) and control the ventricular rate (rate control). Regardless of the
arrhythmia pattern or the therapeutic strategy chosen, and in
the absence of contraindications, patients should be consid-
ered for anticoagulation if they have one or more risk factors
for thromboembolism (fig 2). Patients at low or intermediate
risk, and higher risk patients in whom warfarin is contra-
indicated, may benefit from antiplatelet treatment.15

Rate versus rhythm control
There is still no consensus regarding whether patients with
persistent AF are best managed using strategies that target the
arrhythmia itself, or those that accept the arrhythmia and
control the ventricular rate. With rate control strategies, the
arrhythmia is allowed to continue, and symptomatic improve-
ment is achieved solely because of better control of the
ventricular rate. As the atria continue to fibrillate, the risk of
thromboembolism persists and ventricular filling occurs only
passively, without the active contribution of atrial contraction.
Rhythm control, on the other hand, aims to restore sinus
rhythm and thus synchronised atrioventricular contraction. In
theory, this strategy should also help slow or prevent the pro-
gression to permanent AF and reduce the risk of thromboem-
bolism, although there is as yet no evidence to support the lat-
ter assumption. Another important consideration, however, is
the propensity for drugs used for rhythm control to cause
serious proarrhythmia.

In a randomised open label pilot trial comparing rate
control, predominantly using diltiazem, and rhythm control,
predominantly using amiodarone with or without direct cur-
rent (DC) cardioversion in patients with AF, the two strategies
produced similar improvements in quality of life. A significant
improvement in exercise tolerance as assessed by a six minute
walk test was demonstrated in the rhythm control group, even
though only 56% of the patients in this group achieved sinus
rhythm. However, hospital admissions, predominantly for DC
cardioversions, were higher in the rhythm control group.

The results of the much larger AFFIRM (atrial fibrillation
follow-up investigation of rhythm management) trial have
recently been reported.16 The study enrolled more than 4000
patients with predominantly persistent AF. Enrolled patients
(mean age 70 years) had at least one risk factor for stroke or
death accompanying AF and could symptomatically tolerate
the arrhythmia at baseline. Approximately 50% of patients
randomised had a history of hypertension, whereas 25% had
 coronary artery disease or heart failure. Patients randomised
to rate control received digoxin, β blockers, or calcium antago-
nists, whereas those randomised to rhythm control received
amiodarone, sotalol or propafenone and, if necessary, DC car-
dioversion. At follow up, sinus rhythm was achieved in only
60% of patients in the rhythm arm, whereas satisfactory rate
control was achieved in 80% of patients in the rate control
arm. The primary end point of the study, all cause mortality,
was not significantly different between the two groups,
although there was a trend favouring rate control. There were
also no differences in secondary end point components,
including stroke rate, quality of life, or functional status and,
although a trend favouring rate control was once again noted,
anticoagulation was discontinued in more patients in the
rhythm than in the rate control group. The majority of strokes
in both groups occurred in patients with subtherapeutic levels
of anticoagulation, or after warfarin had been stopped. In the
pre-defined group of patients who were under the age of 65,
which accounted for approximately a quarter of patients
included in the study, a trend favouring rhythm control was
noted.

These results suggest that, at least in this elderly population
of patients with AF and risk factors for stroke or death, rate
control is at least as good as rhythm control. It should,
however, be emphasised that these conclusions are not neces-
sarily applicable to different patient populations, including
younger patients with structurally normal hearts, or patients
who are unable to tolerate the arrhythmia despite reasonable
rate control. The results of AFFIRM also appear to be at odds
with the results of a DIAMOND (Danish investigations of
arrhythmia and mortality on dofetilide) substudy, in which
patients (mean age 72 years) with heart failure or recent
myocardial infarction and AF had been randomised to
treatment with dofetilide or placebo. In this study, dofetilide
was shown to be moderately effective at restoring sinus
rhythm, but had no demonstrable effect on mortality. How-
ever, in a multivariate model, restoration of sinus rhythm,
regardless of whether this was achieved pharmacologically,
spontaneously, or electrically, was associated with a notable
reduction in mortality.16

Restoration of sinus rhythm
Restoration of sinus rhythm in patients with AF may improve
symptoms and cardiac haemodynamics, reverse the atrial
remodelling associated with continuing arrhythmia, and, at
least in theory, reduce the risk of thromboembolism. It has
been demonstrated that restoration of sinus rhythm is associ-
ated with improvements in exercise capacity and peak oxygen
consumption, both in patients with structural heart disease
and in those with normal hearts.17

Since there is an important inverse association between
duration of AF and likelihood of successful cardioversion or
recurrence of arrhythmia, it is important that attempts to
restore sinus rhythm are made as soon as this is possible and
safe. However, although most guidelines suggest that cardio-
version, be it pharmacological or electrical, within 48 hours of
arrhythmia onset has a low risk of thromboembolism even
without anticoagulation, the authors’ policy is not to electively
cardiovert patients who have been in AF without anti-
coagulation for longer than 12–24 hours.

For patients who have been in AF for longer, or in whom the
duration of the arrhythmia is not clear, a minimum period of
anticoagulation of three weeks is recommended before
cardioversion. An alternative approach, particularly useful if
there is clinical urgency to restore sinus rhythm, is to perform
transoesophageal echocardiography in an attempt to exclude
the presence of atrial thrombus before cardioversion. However,
even if transoesophageal echocardiography has demonstrated
Figure 2 Therapeutic goals in patients with atrial fibrillation
Principles of AF management: key points

- Assessment of thromboembolic risk and antithrombotic treatment for patients at risk
- A choice of:
  - Restoration and maintenance of sinus rhythm (rhythm control)
    - using electrical cardioversion, drugs, ablation, or surgery may be particularly useful in younger patients with structurally normal hearts and paroxysmal AF, or persistent AF of recent onset
    - surgery suitable even in long standing AF, but associated with substantial morbidity and mortality
  - Acceptance of the arrhythmia and control of the ventricular rate (rate control)
    - using drugs (usually β or calcium channel blockers with or without digoxin), or occasionally atrioventricular node ablation and implantation of a permanent pacemaker
    - may be more appropriate in elderly patients with hypertension or structural heart disease and persistent or permanent arrhythmia, especially if this can be tolerated symptomatically

Ventricular rate control

Digoxin is widely used for ventricular rate control during AF. Although generally safe to use even in patients with poor ventricular function, it appears to be less effective than other agents at controlling ventricular rate, particularly during acute or paroxysmal AF, exercise, or critical illnesses. The efficacy of digoxin at controlling the ventricular rate in AF is also limited during acute paroxysms of AF, and use of the drug may prolong the duration of paroxysms. Diltiazem is effective at controlling ventricular rate in patients with AF and fast ventricular rates. Both diltiazem and verapamil are superior to digoxin at controlling ventricular rates during exercise and allow modest improvements in exercise capacity, without causing resting bradycardia or pauses. The benefits of calcium channel blockers as well as of β blockers over digoxin appear to be particularly pronounced in patients with impaired diastolic filling, such as those with mitral stenosis. Combinations of digoxin with calcium channel blockers or β blockers may not only improve ventricular rate control, both at rest and during exercise, but may also improve exercise capacity, even in patients with underlying ventricular dysfunction.

In patients with impaired ventricular function, chronic administration of amiodarone, in addition to reducing AF burden, significantly reduces the ventricular rate. Intravenous amiodarone may also be moderately effective at controlling the ventricular rate in critically ill patients with AF.

Common mistakes

Anticoagulation

In clinical practice, physicians are often less keen to prescribe anticoagulation for patients with paroxysmal AF than for those with persistent AF. Although the risk of thromboembolism may indeed be higher in patients with persistent AF, thromboembolic risk may be substantial even in patients with paroxysmal AF. Therefore decisions regarding anticoagulation should be predominantly based on the presence or absence of well established risk factors for thromboembolism, including previous stroke or transient ischaemic attack, valvar or other
structural heart disease, hypertension, diabetes, age more than 65 years, and echocardiographic parameters such as left ventricular function and left atrial size, rather than on the temporal pattern of the disease.

Rate control
It is common for physicians to prescribe digoxin alone in attempts to control the ventricular response to AF. β Blockers or calcium antagonists are more effective.

Rhythm control
It is also common for physicians to prescribe digoxin to cardiovert patients. Digoxin has no effect on the likelihood of cardioversion, whereas class I antiarrhythmic drugs or amidarone are often effective.

CONCLUSIONS
AF is a common and increasingly prevalent arrhythmia that is associated with substantial morbidity and mortality. Because of the limited efficacy of catheter based treatments, especially for patients with persistent AF, and the substantial morbidity and mortality associated with surgery for the arrhythmia, pharmacological therapy remains the mainstay of treatment for the majority of patients. The optimum treatment strategy for patients with persistent AF remains controversial, with some clinicians favouring rhythm control and others rate control. Ultimately, treatment needs to be individualised, based on symptomatology and the likelihood of maintenance of sinus rhythm. Regardless of these controversies in arrhythmia management, antiarrhythmia or antiplatelet therapy for stroke prevention form an integral part of treatment of patients with AF and risk factors for thromboembolism.

The predominant focus of recent developments in pharmacological therapy for AF has been the development of novel class III antiarrhythmic agents, each with characteristic effects on potassium channels. In general, these agents have proven moderately efficacious but carry a significant risk of proarrhythmia. While research in this field continues, other drugs such as specific serotonin receptor antagonists continue to be developed. Further developments in catheter ablation technologies may greatly facilitate safe isolation of multiple pulmonary veins for patients with predominantly paroxysmal AF, whereas improvements in linear catheter ablation technologies, accompanied by three dimensional atrial mapping and catheter navigation, may facilitate creation of linear left atrial lesions, which appear to be critical for the successful treatment of patients with persistent arrhythmia.

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REFERENCES
14 An in-depth review of antithrombotic treatment for patients with AF.
17 The first large randomised trial comparing strategies to restore and maintain sinus rhythm versus accepting the arrhythmia and controlling the ventricular rate in patients with AF. There was no significant difference between the two groups, either in the primary end point of death or in the composite secondary end point that included death, disabling stroke, and major bleeding. Although a trend favouring rate control was noted, anticoagulation was more frequently stopped in the rhythm control group and the majority of strokes in both groups occurred in patients with subtherapeutic anticoagulation or after discontinuation of warfarin. A trend favouring rhythm control was observed in patients under the age of 65.
19 Among patients with cardiac failure enrolled in the DIAMOND study, a group of around 500 patients had atrial flutter or fibrillation at baseline. This substudy demonstrates the efficacy of dofetilide at restoring and maintaining sinus rhythm, as well as the risk of pro-arrhythmia. Although not a predefined end point, the study suggests that, at least in this group of patients, restoration of sinus rhythm, regardless of how it is achieved, is associated with reduced mortality.

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