INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia where uncoordinated atrial electrical activity results in ineffectual atrial mechanical action and irregular ventricular response. AF is the commonest sustained arrhythmia and its prevalence increases with age. AF is often associated with underlying structural or functional heart disease, but there may not be any detectable heart disease in a significant minority of patients. Apart from symptoms of AF per se, AF is notorious to engender haemodynamic and thromboembolic complications. In the following brief overview, I shall highlight the contemporary issues in the medical management of AF, eg, pharmacological cardioversion, strategies for maintaining sinus rhythm, the burning issue of rate versus rhythm control, strategies for rate control, risk assessment for thromboembolic complications and the prophylaxis of thromboembolism.

CLASSIFICATION OF AF

To classify AF is not a straightforward job as AF is a highly complicated arrhythmia with a broad spectrum of pathophysiological, clinical, haemodynamic, therapeutic and prognostic variations. However, the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) have formulated a practical and relatively simple scheme of classification of AF mainly considering its temporal pattern of occurrence.\(^1\)

This is as follows-

1. **First detected AF**: The first documentation of AF is important. Many a treatment strategy depends on this. One must recognize that it may be asymptomatic and just a chance detection. It may be self-limited (and usually so). It does not tell about the duration of that particular episode, and neither does it preclude undetected episodes before the index episode.

2. **Paroxysmal AF**: Self-terminating AF is called paroxysmal AF. The definition includes self-termination within up to 7 days, though more strictly, it means termination within 48 hours. From therapeutic angle, this time frame is important, as after 48 hours, chance of self-termination drastically falls and pre-conversion anticoagulation becomes necessary.

3. **Persistent AF**: If AF lasts for more than 7 days or is cardioverted by electrical or pharmacological means before that, it is termed as persistent AF.

4. **Permanent AF**: A persistent AF which has lasted for more than one year and could not be cardioverted or was deemed not for cardioversion, is termed as permanent AF.

It is understandable that even this classification is not full-proof as AF tends to change its pattern with time.

Lone AF is a term reserved for AF in person below 60 years of age with no clinical or echocardiographic problem and no hypertension as well. Generally lone AF is more benign in prognosis.

PHARMACOLOGICAL MANAGEMENT STRATEGY FOR FIRST DETECTED AF

As mentioned before, the first detected episode of AF may be paroxysmal or persistent. If it is paroxysmal and the patient has no significant symptom or haemodynamic
compromise, then no treatment is warranted except possibly anticoagulation as will be discussed later.

If the first detected AF proves to be persistent, then first thing to be decided is whether a cardioversion will be attempted or rate-control strategy is to be adopted. This will be discussed later. In either case, anticoagulation should strongly be considered.

**PHARMACOLOGICAL MANAGEMENT STRATEGY FOR RECURRENT PAROXYSMAL AF**

Here management strategy is not different from the first detected paroxysmal AF except the need for maintenance antiarrhythmic drugs to prevent recurrence. In case the drug treatment fails, AF ablation should be considered.

**PHARMACOLOGICAL MANAGEMENT STRATEGY FOR PERSISTENT AF**

Here again it is to be decided if the patient is a candidate for cardioversion, electrical or pharmacological. If not, rate control and anticoagulation are to be implemented. If cardioversion is considered, then anticoagulation and maintenance antiarrhythmic therapy are to be instituted. If cardioversion is attempted and fails on repeated occasions, (either no conversion or quick recurrence), then AF ablation and surgical intervention are the options.

**PHARMACOLOGICAL CARDIOVERSION**

Before any attempt to cardioversion, pharmacologic or electric, appropriate anticoagulation must be instituted to prevent thromboembolic complication as left atrial thrombus which may have been formed during ineffectual contraction of left atrium due to AF tends to go into circulation as soon as left atrium starts contracting in sinus rhythm.

Ideally, oral anticoagulation with vitamin K antagonist (VKA) must be on board for 3 weeks prior to and 4 weeks after cardioversion, maintaining an international normalized ratio (INR) of prothrombin time between 2.0 and 3.0.

However, if a transoesophageal echocardiogram can exclude any thrombus in the left atrial appendage, then cardioversion can be done immediately under heparin coverage.

If the AF is undoubtedly of less than 48 hours duration, role of anticoagulation is controversial. In case of acute onset AF with haemodynamic compromise or severe symptoms, urgent cardioversion is recommended. Here, cardioversion should be preceded by intravenous (iv) unfractionated heparin or subcutaneous (sc) low molecular weight heparin, to be followed by adequate oral anticoagulation for 4 weeks.

The drugs with class I (level of evidence A) recommendation for cardioversion are oral dofetilide, oral or iv flecainide (2mg/kg over 10 min), iv ibutilide (1mg over 10 min), and oral or iv propafenone (2 mg/kg over 10 min) and iv vernakalant (3 mg/kg over 10 min); whereas oral or iv amiodarone (5 mg/kg over 1 hour) has got class Ila (A) recommendation. Class Iib (B) agents are iv disopyramide, iv procainamide and oral quinidine.

Intravenous flecainide and propafenone are the preferred agents in absence of underlying structural heart disease, whereas iv amiodarone is the drug of choice in its presence. The oral dosages and the side effect profiles of these agents are summarized in table I.

If the AF persists for more than 7 days, then cardioversion becomes relatively more difficult. In this situation, only

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (oral)</th>
<th>Adverse reaction / contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>100-25 mg tid</td>
<td>HF, cautiously with QT prolonging drugs, glaucoma, dry mouth, urinary retention</td>
</tr>
<tr>
<td>Flecainide</td>
<td>100-200 mg bid</td>
<td>HF, IHD, renal impairment</td>
</tr>
<tr>
<td>Propafenone</td>
<td>150-300 mg tid</td>
<td>HF, IHD, renal impairment</td>
</tr>
<tr>
<td>d, I-Sotalol</td>
<td>80-160 mg bid</td>
<td>HF, LVH, QT prolongation, hypokalemia, Renal impairment</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>600 mg odx4wks, then 400 mg odx4 wks Then 200 mg od</td>
<td>Photosensitivity, pulmonary toxicity, polyneuropathy, hepatic toxicity, corneal pigmentation, dysthyroidism, arrhythmia</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>400 mg bid</td>
<td>HF, renal impairment</td>
</tr>
</tbody>
</table>
class IA agent is oral dofetilide. Amiodarone and ibutilide enjoy a class IIa(A) recommendation whereas disopyramide, flecainide, propafenone, quinidine and procainamide have class IIb recommendation.

Drugs also play an important role as pretreatment for successful electrical cardioversion and to prevent an immediate recurrence of AF. They are amiodarone, flecainide, ibutilide, propafenone and sotalol; whereas the role of beta-blockers, diltiazem, verapamil, disopyramide, dofetilide and procainamide are less certain for this purpose.

Another interesting concept here is the “pill-in-the-pocket” strategy. In patients with frequently recurring AF, a single self-administered oral dose of propafenone or flecainide may terminate the AF. Before advocating this, the efficacy and safety of the strategy must be tested in the hospital.

In the case of adrenergic AF, ie, AF precipitated by exertion or excitement, beta-blocker is the drug of choice, and amiodarone is no so effective.

On the other hand, in vagal AF which typically disturbs sleep by palpitation and precipitates in early morning (and almost never occurs between breakfast and lunch time), antiarrhythmic with anticholinergic effects, eg, disopyramide is the most effective drug.

MAINTENANCE OF SINUS RHYTHM AFTER CARDIOVERSION
Chance of maintaining sinus rhythm after successful cardioversion depends on the duration of AF, presence and extent of underlying heart disease, any precipitating cause which is permanently cured, and the efficacy and the tolerability of the selected maintenance antiarrhythmic agent.

The recommended drugs for this purpose are orally instituted amiodarone (100-400mg/d), disopyramide (400-750mg/d), dofetilide (500-1000mcg/d), flecainide (200-300mg/d), propafenone (450-900mg/d) and sotalol (160-320mg/d).

RATE CONTROL VERSUS RHYTHM CONTROL IN PERSISTENT AF
Much debate has occurred on this issue over the last few decades. Many randomized trials compared outcomes of rhythm vs. rate control strategies in patients with AF. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) found no difference in all cause mortality or stroke rate between the two strategies.4 The Rate Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trial had similar results. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial observed no difference in cardiovascular mortality between patients with an LVEF ≤35% randomized to rate or rhythm control, or in the secondary outcomes including all-cause death and worsening of HF.

Not only the hard cardiovascular outcomes, the AFFIRM, RACE, the Pharmacologic Intervention in Atrial Fibrillation (PIAF) trial6, and the Strategies of Treatment of Atrial Fibrillation (STAF) trial5 found no differences in quality of life with rhythm control compared with rate control. However, one must consider how optimum the assessment was in these trials.

New-onset HF was not different between rate control and rhythm control therapy groups in the AFFIRM, RACE, or AF-CHF trials. A post-hoc analysis of the AFFIRM database has suggested that deleterious effects of antiarrhythmic drugs (a mortality increase of 49%) may have offset the benefits of sinus rhythm (which was associated with a 53% reduction in mortality).

Rhythm control therapy is reasonable to ameliorate symptoms, but should not result in cessation of antithrombotic therapy, rate control therapy, or therapy of underlying heart disease. In younger patients with active lifestyle and severe symptoms persisting after adequate rate-control and if there is no underlying cardiac or extracardiac condition which may preclude reasonable chance of conversion to and subsequent maintenance of sinus rhythm, electrical or pharmacological cardioversion is definitely indicated.

If any new antiarrhythmic drug proves to be effective as well as safe for long-term use, then the indication for rhythm control will broaden.

RATE CONTROL STRATEGIES
Pharmacological control of ventricular rate during AF is the mainstay of therapy for most persistent and permanent cases of AF. Both at rest heart rate and exercise-induced heart rate should be within the physiological range. HF and accessory pathway as co-morbidities influence the rate-control strategy. In acute AF with no accessory pathway and HF if blood pressure is maintained then iv esmolol, metoprolol, propranolol, diltiazem and verapamil are the first-choice agents. In acute setting the target ventricular rate should be 80-100 bpm.
In presence of HF, iv digoxin (if no accessory pathway) and amiodarone are the first-line agents. Digitalis is more effective in controlling the resting heart rate. Digitalis may be combined with a beta-blocker or diltiazem or verapamil for adequate rate control. Intravenous amiodarone is useful in difficult cases. In presence of an accessory pathway, electrical cardioversion is the treatment of choice with iv procainamide or ibutilide as a reasonable alternative. Radiofrequency ablation of AV node / accessory pathway may be warranted in appropriate situations. In non-acute settings, oral metoprolol, propranolol, diltiazem and verapamil are suitable drugs; whereas in presence of HF, oral digoxin, beta-blockers and amiodarone (only drug to be used in presence of accessory pathway) are the recommended agents. In nonpermanent AF and in absence of advanced HF, oral dronedarone may be used.

**RISK STRATIFICATION AND PROPHYLAXIS FOR THROMBOEMBOLIC COMPLICATIONS IN AF**

Ischaemic cerebrovascular accident (CVA) is the main concern in AF related thromboembolism. Controversy exists regarding the proper identification of the high-risk population. However, so far, most clinicians followed the CHADS2 risk score as originally introduced in 2001. Here, each of 4 parameters (Cardiac failure, Hypertension, Age>75 years, Diabetes mellitus) has 1 point and previous Stroke (CVA and transient ischaemic attack) has 2 points. If the score is 0 or 1, then only oral aspirin therapy 81-325 mg daily is recommended. Same is true for patients in whom oral anticoagulation is contraindicated. If the CHADS2 score is 2 or higher then oral anticoagulation with a VKA is warranted keeping the INR between 2.0 to 3.0. However, risk for bleeding needs to be carefully evaluated. INR should be checked at least weekly during dose stabilization and then monthly. The CHADS2 score is applicable to AF in absence of valvular heart disease. All valvular heart disease patients in AF are very high risk for CVA and should have long-term oral anticoagulation therapy. Prior CVA, systemic embolism, rheumatic mitral stenosis and mechanical prosthetic heart valve are the most high-risk categories of AF for thromboembolism.

For nonvalvular AF, with age 65-74, or female sex, or coronary artery disease, aspirin or VKA may be given considering the risk of bleeding, suitability of INR testing and patient’s preference. In any case, if the patient refuses to take oral anticoagulation therapy, then combination of aspirin and clopidogrel should be offered. In the elderly, bleeding risk of aspirin is considered to be similar to that of VKA.

If a patient of AF presents with a stroke/TIA, cerebral imaging must be done immediately. If it is a TIA, oral anticoagulation therapy must be started immediately. If it is an ischaemic stroke, then anticoagulation should start after 2 weeks (and longer in case of a massive stroke). In case of a haemorrhagic stroke, anticoagulation is naturally precluded.

From time to time, the situation should be reappraised. Before dental or surgical procedures oral anticoagulation may be withheld for upto 7 days if desired by the surgeon, provided that there is no mechanical prosthetic heart valve. In case longer drug-free interval is required, it is better to cover that period with unfractionated or low molecular weight heparin. Post-operatively, usual maintenance dose of the VKA should be resumed on the same evening, if not surgically contraindicated.

After coronary revascularization, low dose aspirin and initially clopidogrel as well, are added to ongoing VKA therapy. Bare metal stents are preferred to drug-eluting stents in situations of PCI with AF, because then dual antiplatelet on top of VKA will be needed for shorter duration. Long-term therapy will consist of VKA with either aspirin or clopidogrel for a minimum of 1 year. After an acute coronary syndrome, whether stent is deployed or not, dual antiplatelet therapy in addition to VKA is recommended for 3-6 months, followed by dropping one of the antiplatelet agents. Radial approach for PCI is preferred in patients on long term anticoagulation. Whenever, antiplatelet agent is added to VKA, target INR may be reset to 2.0 to 2.5. If patients on VKA with INR 2.0-3.0 develop ischaemic CVA or systemic embolism, then target INR should be reset to 3.0-3.5, rather than adding an antiplatelet agent.

In presence of pregnancy, unfractionated heparin or low molecular heparin are to be used in the first trimester and in the last one month; the rest of the pregnancy period can be protected by VKA. In lone AF of persons below 60 years of age, long-term anticoagulation is not indicated.

In 2010, ESC has introduced a modification of the CHADS2 scoring system. This is CHA2DS2-VASc, where first A depicts age 75 or more and carries a score of 2, whereas the second A depicts age 65-74 and carries a score of 1. The V stands for vascular disease (prior myocardial infarction, peripheral vascular disease or aortic plaque) and Sc means sex category (female), each carrying 1 point. Here again, the stroke risk rises sharply above score 1.
Several new anticoagulant drugs—especially, the oral direct thrombin inhibitors (e.g., dabigatran etexilate) and the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban)—are being developed for stroke prevention in AF.

In the RE-LY study, dabigatran 110 mg b.i.d. was non-inferior to VKA for the prevention of stroke and systemic embolism with lower rates of major bleeding, whilst dabigatran 150 mg b.i.d. was associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage, compared with VKA. The AVERROES study was stopped early due to clear evidence of a reduction in stroke and systemic embolism with apixaban compared with aspirin in patients intolerant of or unsuitable for VKA, with an acceptable safety profile.

A bleeding score has also been introduced called HAS-BLED [7] (H=hypertension, A=abnormal renal or liver function, S=stroke, B=bleeding, L=labile INR, E=elderly >65 years and D=drug or alcohol). It is prudent to assess the bleeding risk and to weigh the risk-benefit ratio of chronic oral anticoagulation in every individual.

**UPSTREAM THERAPY**

This term has been applied to prevent development of AF (primary) or to reduce relapses (secondary) by treating the underlying predisposing heart disease proactively.

**NEWER AND EXPERIMENTAL AGENTS**

Currently available anti-AF agents are generally only moderately effective and associated with extracardiac toxicity and/or a risk for development of life-threatening ventricular arrhythmias. Included among current investigational strategies for improving the effectiveness and safety of anti-AF drugs is the development of: 1) Agents that produce atrial specific or predominant inhibition of IKur, IK-ACh, or INa; eg, vernakalant; 2) “Upstream therapies” discussed above; 3) Derivatives of “old” anti-AF drugs with an improved safety pharmacological profile; eg, dronedarone and 4) Gap junction therapy aimed at improving conduction without affecting sodium channels, eg, Cx40, Cx43.2

**CONCLUSION**

Pharmacological management of AF is an evolving field with a lot of issues to be addressed simultaneously. Management policy should be discussed with the patients in details. From time to time, the policy needs to be re-assessed. Close monitoring for drug side-effects, INR and patients’ compliance are important. In appropriate situations, the patient should be referred for invasive electrophysiological evaluation / management or for surgical intervention.

**REFERENCES**