Recent Advances in Management of Atrial Fibrillation

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INTRODUCTION

Atrial Fibrillation (AF) is one of the most common arrhythmias.It currently affects about 1% of the population. The overall prevalence of AF is significantly greater among men than women. The prevalence of AF increases with age, from 0.1% among those younger than 55 years to 9% among individuals 80 years of age and older. AF represents a significant and growing health burden emphasizing the need for preventive strategies and effective therapies[1].

In 70-80% cases it is associated with structural heart disease.Apart from structural heart disease it also occurs in hyperthyroidism, Chronic obstructive pulmonary disease, hypertension, alcoholism and ischaemic heart disease. In 30% cases it can be idiopathic or what is termed as 'lone atrial fibrillation'[2]. AF can be isolated or associated with other arrhythmias, often atrial flutter or atrial tachycardia. Novel risk factors like obesity and sleep apnoea have also been associated with AF[3].This article reviews the various management strategies of Atrial fibrillation.

CLASSIFICATION OF ATRIAL FIBRILLATION :

1. CAUSALITY BASED:

i) IDIOPATHIC : when no cause or heart disease is found.

ii) SECONDARY : when associated with heart disease or a known cause eg. Hyperetnsion.

2. ONSET & RESPONSE BASED:

i) SINGLE EPISODE OR LONE: single episode without any cause

ii) RECURRENT: 2 or more episodes

iii) PAROXYSMAL: Recurrent AF when terminated spontaneously

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iv) PERSISTENT:Sustained AF irrespective of termination by pharmacological therapy or electrical cardioversion.

v) PERMANENT or CHRONIC: Long standing AF i.e. greater than 1 year in which cardioversion has neither been indicated nor attempted.

Classification of AF is very important in deciding the management strategy. Another important decision making factor is whether the patient is symptomatic or asymptomatic.

MANAGEMENT OF ATRIAL FIBRILLATION

The treatment of Atrial Fibrillation is based on following 3 issues :

1. Anticoagulation
2. Rate control
3. Rhythm control

Anticoagulation in AF :

The rate of ischemic stroke among patients with nonrheumatic AF averages 5% per year, which is 2 to 7 times the rate for people without AF. All patients with AF should receive antiplatelet therapy or anticoagulation therapy as warranted by clinical situation.The need for anticoagulation is always decided by assessing the risk for stroke in patients.The risk factors for stroke include; i)Age>75 years ii)Previous history of stroke or TIA or systemic embolization, iii)congestive heart failure, iv)hypertension, v) Diabetes mellitus, vi)Left ventricular dysfunction, vii) Left atrial enlargement>5 cm, viii)Mitral stenosis, ix)spontaneous ECHO contrast.

Low risk for stroke : Aspirin can be given in low dose.However Aspirin offers only modest protection against stroke for patients with AF. The effect is less consistent than that of oral anticoagulation .Aspirin might be more efficacious for AF patients with hypertension or diabetes[5].

High risk patients: Oral anticoagulation with warfarin should be done.It should be started in a dose of 5 mg /day

and uptitrated to maintain an INR (International normalized ratio) between 2 and 3. The new anticoagulants apixaban, rivaroxaban and dabigatran were developed with the goal of avoiding these problems. Dabigatran has already been approved for thromboembolism prophylaxis for patients with atrial fibrillation. All three substances do not require routine control blood tests[6].The target INR involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications. It is important to target the lowest adequate intensity of anticoagulation to minimize the risk of bleeding, particularly for elderly AF patients. Maximum protection against ischemic stroke in AF is probably achieved with an international normalized ratio (INR) of 2 to 3, whereas an INR range of 1.6 to 2.5 appears to be associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher intensity anticoagulation[7].

Anticoagulation is a must before restoring the patient to sinus rhythm and must be continued for at least 1 month after restoration of sinus rhythm.

In acute cases anticoagulation can be achieved by parenteral heparin where low molecular weight heparin is preferred over unfractionated heparin. Patient can receive heparin for 7- 10 days before starting oral anticoagulation.

In patients in whom anticoagulation is contraindicated, cardioversion can be done with maintainance of sinus rhythm using Antiarrhythmic drugs.In patients who cannot tolerate arrhythmic drugs, the need for chronic anticoagulation can be curtailed by use of left atrial appendectomy or left atrial isolation using left atrial occluding device.

Rate control :

There is always a difficulty in deciding about rate or rhythm control in AF, leading to a rate vs. rhythm control debate. A rate-control strategy should be the preferred initial option in the following patients with persistent AF: Age over 65 years,long standing AF with repeated failed attempts at cardioversion,large left atrial size, with coronary artery disease with contraindications to antiarrhythmic drugs, unsuitable for cardioversion, without congestive heart failure.

Acute rate control : This is usually achieved by intravenous administration of any one of the following drugs[8] :

Adenosine 6-18 mg rapid bolus: Given usually in patients undergoing revascularization or cardiac surgery

Esmolol 500 µgm/kg over 1 minute as bolus dose followed by 50 µgm/kg/min infusion till rate is controlled.Usually given in AF associated with thyrotoxicosis, Hypertension or CAD or valvular heart disease.

Diltiazem 0.25 mg/kg over 3-5 minutes followed by 5-15 mg/hour maintainance.Indications are same as that for Esmolol.

Amiodarone 15 mg/min over 10 min followed by 1 mg/min for 6 hours as maintainance dose.Given in patients unresponsive to above drugs and in those patients where pharmacological restoration to sinus rhythm is contemplated.

Digoxin 0.5 mg bolus dose followed by 0.25 mg /day maintainance dose.Not used now a days due to late onset of action and toxicity. But it is more effective in rheumatic AF especially if associated congestive heart failure is present.

Ibulitide 1mg over 10 min. This is a newer drug which is more effective and may be used in selected patients to facilitate termination with direct current cardioversion.

Chronic rate control : This can be achieved by β-blockers like metoprolol or calcium channel blockers like Diltiazem or Verapamil.However a close ECG monitoring and evaluation for exercise induced increments in heart rate should be done. A prorhythmic effect of drug should also be taken into account Combination therapy can also be given with Digoxin.

Rhythm control:

A rhythm-control strategy should be the preferred initial option in the following patients with persistent AF: those who are symptomatic, younger patients, those presenting for the first time with lone AF, those with AF secondary to a treated/corrected precipitant, those with congestive heart failure or haemodynamic decompensation due to AF.A schematic algorithm for management of chronic AF is shown in Figure No.1[9]

Rhythm control can be achieved by 3 ways: Pharmacological or Electrical or Catheter/ surgical ablative therapy.

Pharmacological therapy

Pharmacological therapy for rhythm control includes

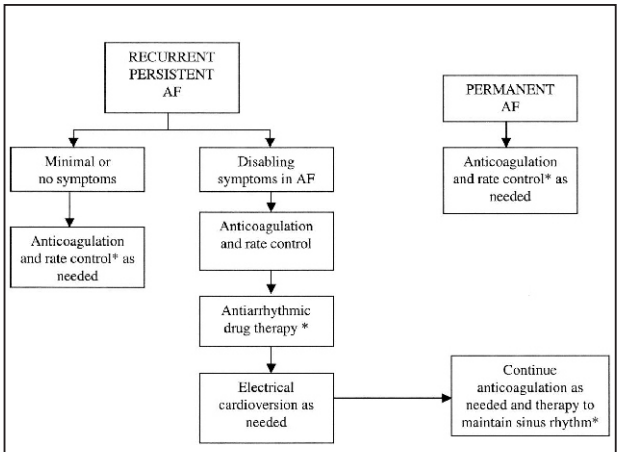


Figure No. 1 Algorithm for management of Chronic Atrial Fibrillation'

oral drugs like doefelitide, flecainide,propafenone,amiodarone. These drugs or Ibulitide can be used intravenously. Pharmacological cardioversion is more effective in AF of less than 7 days duration.Antiarrhythmic drugs may have to be given for a long time and adverse effects should be considered.The newer promising drugs are as follows:

Dronedarone has been widely studied with several completed trials related to AF therapy. In a pooled analysis of results from two international phase III trials (EURIDIS and ADONIS) of dronedarone in maintenance of sinus rhythm in 1250 patients, with either paroxysmal (70%) or persistent AF, the first year data showed that compared with placebo the time of AF recurrences was 2.3-2.7 times longer after treatment with dronedarone 400 mg twice daily. Safety data were promising but patients with a heart failure were excluded from the trials[10].

Celivarone It is another non-iodinated amiodarone derivative undergoing phase II human trials. It exhibits eletro-physiological and hemodynamic properties characteristic of dronedarone[11].

Azimilide is a selective Class-III AAD (Antiarrhythmic drugs) that blocks both rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium current. It prolongs cardiac APD and refractory period. Its long half life (up to four days) allows one daily dosing and limits major fluctuations in blood concentration [12].

Tedisamil is an antianginal agent possessing multiple ion channel effects including blockade of transient outward current I_{to}, in addition to I_{Kr}, I_{Ks}, I_{Kur}, $I_{K\text{-}ATP}$ and even I_{Na} also causes reverse, rate dependant QT interval prolongation.In a multicenter, double blind, randomized placebo controlled study in 175 patients with symptomatic recent onset AF or atrial flutter, 41-51% of patients receiving tedisamil (0.4 or 0.6 mg/kg I.V.) converted to sinus rhythm in an average time of 35 minutes with two instances of (1.8%) of possible proarrhythmia [13].

Rotigaptide (ZP 123) is a specific gap-junction facilitating drug. Gap junctions are specialized pores that coordinate cell-to-cell transmission of electrical impulses essential for synchronized contraction. Gap-junction modulation may present a novel therapeutic target in some forms of currently being studied in a phase II trial on rotigaptide[14].

Vernaklant (RSD 1235) is in the most advanced phase of investigation and its IV) formulation has recently been recommended for approval for pharmacological conversion of AF. An oral formulation of Vernakalant is under development for long term maintenance of NSR following cardioversion[15].

Besides there are many other molecules undergoing trials in the management of AF. Combining AADs and non-AADs such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may increase effectiveness of AADs in patients with AF[16].

Recently it has been shown that sinus rhythm achieved after conversion of AF may be prolonged by certain non-antiarrhythmic drugs such as ACEIs, corticosteroids, aldosterone antagonists, statins and omega 3-PUFA. Rate of AF recurrence was lower when amiodarone combined with ACEI than with amiodarone alone[17].

Electrical cardioversion :

Termination of AF associated with severe symptoms and haemodynamic collapse is done as an emergency procedure. Direct current transthoracic cardioversion using a 200 J biphasic shock synchronously with QRS is done under short acting anaesthesia.The success rate with cardioversion is more than 90%.Antiarrhythmic drugs may have to be given later to maintain sinus rhythm.

Catheter ablative Therapy :

The long-term medical treatment of AF with antiarrhythmic drug therapy is associated with a failure

rate of 50% at one year and up to 84% at two years [18,19].

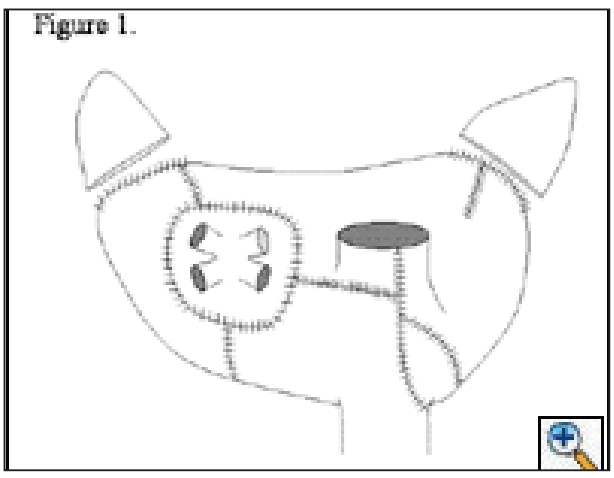
As a part of rate control strategy AV nodal ablation with implantation of activity sensor pacemaker is done.This 'ablate and pace' treatment is associated with complications like LV dysfunction and dyssynchronization.

Ablative therapy for rhythm control is done in patients with symptomatic recurrent AF. The atrial muscle sleeves around the pulmonary veins as they enter the left atrium have been identified as the most common site of trigger for AF.Hence catheter ablative therapy targets this area. The source of energy used can be radiofrequency waves, laser, ultrasound or cryoprobes.The success rate of catheter ablative procedures is 50-80%.It can be useful in most severe form of persistent AF and also where LA size is large. The complications of catheter based ablation procedure are pulmonary vein stenosis, systemic embolization, fistula formation, perforation of atria or phrenic nerve injury. But the risk is very low.

Recently Calo L. etal observed that in a selected population of vagal paroxysmal AF, the anatomic ablation of Ganglionic Plexuses in the RA is effective in about 70% of patients. These results confirm that atrial vagal denervation can abolish AF, as suggested by experimental and clinical data [20].

SURGICAL THERAPY

The outstanding results of the Cox-Maze III procedure justify its status as the 'gold standard' surgical procedure for AF. Cox and colleagues report an overall success rate of 99% in curing patients of AF. No instances of sinus node damage have been identified. Left and right atrial function have been documented in 93 and 99% of patients, respectively. High rates of freedom from AF have been reported by other investigators performing the Cox-Maze III procedure. Despite this high degree of success, the procedure has not gained widespread clinical application due to its perceived complexity [21,22,23].



In an attempt to make the procedure simpler, less time-consuming, and potentially obviate the need for cardiopulmonary bypass, a number of investigators have developed so-called partial Maze procedures. Kress and colleagues have validated one such left atrial lesion set for the treatment of atrial fibrillation [24]. These procedures have generally focused on the left atrium, with the pulmonary veins being isolated by a series of lesions and the left atrial appendage being either excluded or excised Cryoablation is performed with a nitrous oxide cooled probe that when applied to atrial tissue at -60 degrees C for 2 minutes reliably produces transmural lesions that block atrial conduction. An advantage of this technique is that there is no tissue vaporization or charring and the endocardial surface remains smooth following cryoablation. Cox and colleagues were the first to incorporate this modality into surgery for AF and it remains an important component of the Cox-Maze III procedure.Cox and colleagues have subsequently published results for the 'cryo-Maze' procedure in which the lesions of the Cox-Maze III operation are performed solely by cryoablation[25]. As new procedures are developed that effectively treat AF, have low morbidity, and are minimally invasive, they will be increasingly utilized to restore sinus rhythm permanently in patients afflicted with AF.

To conclude Atrial Fibrillation is one of the most distressing arrhythmia for patient as well as physician to treat.However based on clinical judgement and guidelines given above an effective strategy can be planned .

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