**INTRODUCTION**

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by irregular, disorganized and chaotic atrial activation. It is the most common supraventricular arrhythmia (SVA), accounting for 34% of the hospitalized patients. AF predominantly occurs with other co-morbid clinical conditions such as valvular heart disease, cardiomyopathy, congestive heart failure (HF), myocardial infarction (MI) and determined by a number of factors such as age, diabetes, hypertension, thyrotoxicosis, pulmonary pathology and other infections. Rheumatic heart disease (RHD) with mitral stenosis used to be the commonest clinical condition precipitating AF. However, in recent years, the decrease in the prevalence of RHD has lead to other precursors taking a more prominent role as determinants of AF. Approximately two thirds of patients with HF are older than 65 years of age and thus have a high probability of AF presenting as co-morbidity. In the Framingham study, CHF was associated with a five- to six-fold increased risk of AF, which was higher than the risk related to valvular heart disease. The epidemiological survey of AF conducted in Asian countries such as mainland China and Malaysia have also shown similar results.

**MANAGEMENT OF AF**

The management of AF involves a) prevention of thromboembolism b) rate control c) rhythm control.

**Medical therapy**

Presently, medical therapy remains the mainstay for treatment of most patients with AF. Rate or rhythm management, antithrombotic therapy, and drug treatments not usually considered antiarrhythmic but that help to maintain sinus rhythm (ACE-inhibitors, statins, fish oils, and aldosterone antagonists) have become important aspects in the treatment of AF.

**Rate or Rhythm management**

Rate control in AF aims at controlling the heart rate at rest (<100bpm) and during activity (<130bpm), while rhythm management involves maintenance of sinus rhythm (SR) with the use of antiarrhythmic drugs and/or non-pharmacologic modalities. The superiority of either rate control or rhythm control has been a strong point of debate in the management of AF.

There have been seven published trials (Table 1) addressing the question and three published meta-analyses. On the whole, these studies concluded that in select group of patients rate control is not inferior to rhythm control strategy. Interestingly, most of the patient populations in these studies, like the AFFIRM and the RACE studies, were elderly, asymptomatic or minimally symptomatic, without risk factors for stroke, and without RHD. In this context, the CRRAFT (Control of Heart Rate vs Rhythm in Rheumatic Atrial Fibrillation Trial) and PAF2 (Paroxysmal Atrial Fibrillation 2) studies specifically evaluated rate control versus rhythm control in patients with RHD and AF. The CRRAFT study showed that at one year those who were in SR had a significant decrease in mortality, improvement in NYHA class, quality of life score and exercise time. These results were in contrast to the data from the other trials with the disparity primarily because the study patients had RHD and were younger (mean age: 39 years).

Therefore, in a select group of patients who are younger and asymptomatic with AF or those who develop cardiomyopathy with AF, the rhythm control is the essential strategy for symptom management. In these patients, the initial strategy involves the use of anti-arrhythmic drugs. The choice of antiarrhythmic agents depends on the associated co-morbidities (Table 2) with the three most commonly used agents being amiodarone, sotalol and propafenone and newer drugs like dofetilide, ibutilide and dronedarone.

The relative efficacy of the three most commonly used agents was compared in the CATAF trial, which proved the superiority of amiodarone over sotalol and propafenone. However, amiodarone is associated with increased incidence of pulmonary fibrosis, hypo- and hyperthyroidism, corneal opacification, skin discoloration, hepatitis etc. These long-term adverse effects of amiodarone make it an inappropriate choice for younger patients. Approximately 30% of patients started on amiodarone quit it due to adverse effects in the first year.

Dofetilide, a potassium channel blocker, has a modest conversion efficacy in AF but more effective in conversion of AF. Its significant limitation has been a linear relationship between plasma dofetilide levels and the QTc interval, which results in an overall 3.6% torsades de pointes VT incidence. Another factor limiting the use of dofetilide is the possibility of drug interaction with multiple agents including verapamil, hydrochlorothiazide, triamterene, etc. This results in an inadvertent increase in the bioavailability of...
Atrial Fibrillation – Advances in Treatment

Table 1: Overview of published trials of rate vs rhythm control in the management of atrial fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up</th>
<th>No. of Subjects</th>
<th>Atrial Fibrillation characteristics</th>
<th>Rhythm control</th>
<th>Rate control</th>
<th>Primary endpoints</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF (2000)</td>
<td>1 yr</td>
<td>252</td>
<td>Persistent: 7 d to 1 yr</td>
<td>Amio, ECV</td>
<td>Dit, BB, Dig, RFA</td>
<td>Proportion symptomatically improved</td>
<td>No difference in primary endpoint and QoL; rhythm = slightly ↓ functional capacity; rate = ↓ hospitalizations and adverse drug affects</td>
</tr>
<tr>
<td>PAF2 (2002)</td>
<td>1.3 yr</td>
<td>141</td>
<td>Paroxysmal, severely symptomatic</td>
<td>A, Pro, Flec, Sot, ECV, not allowed</td>
<td>RFA</td>
<td>Development of permanent AF</td>
<td>Rhythm = ↓ permanent AF; no difference in QoL and echo; rate = ↓ progression of CHF &amp; ↓ hospitalizations</td>
</tr>
<tr>
<td>AFFIRM (2002)</td>
<td>3.5 yrs</td>
<td>4,060</td>
<td>Persistent (&gt;69%) &amp; paroxysmal</td>
<td>BB, Dit, V, Dig, RFA</td>
<td></td>
<td>Death</td>
<td>No difference in 1° endpoint (trend favors rate) &amp; QoL; rate = ↓ hospitalizations and adverse drug effects; rhythm = slightly ↓ functional capacity</td>
</tr>
<tr>
<td>RACE (2002)</td>
<td>2.3 yr</td>
<td>522</td>
<td>Persistent (median 32 d) and recurrent after ECV</td>
<td>S, F, P; A; ECV (prescribed sequence)</td>
<td>BB, Dit, V, Dig, RFA</td>
<td>Composite of clinical events</td>
<td>Rate not inferior for primary endpoint; no difference in QoL; rate = ↓ hospitalizations and adverse drug effects</td>
</tr>
<tr>
<td>STAF (2003)</td>
<td>1.7 yr</td>
<td>200</td>
<td>Persistent &gt; 4 wk</td>
<td>A, P, F; ECV</td>
<td>BB, Dit, V, Dig, RFA</td>
<td>Composite of clinical events</td>
<td>No difference in primary or secondary endpoints; rate = ↓ hospitalizations</td>
</tr>
<tr>
<td>HOT CAFE (2004)</td>
<td>1 yr</td>
<td>205</td>
<td>Persistent: 7 d to 2 yr</td>
<td>ECV followed by P, S or Dis, repeat ECV, new drug or A for recurrence</td>
<td>BB, Dit, V, Dig, RFA</td>
<td>Composite of death and clinical events</td>
<td>No difference in primary endpoint; rate = ↓ hospitalizations; rhythm = ↓ exercise tolerance and slight ↓ in LVEF; all 3 strokes in rhythm</td>
</tr>
<tr>
<td>CRAAFT (2004)</td>
<td>1 yr</td>
<td>144</td>
<td>Average duration AF &gt; 5 yr</td>
<td>ECV alone (control group), A + ECV (rhythm control group)</td>
<td>Dit</td>
<td>Restoration and maintenance of SR at 12 mo</td>
<td>More patients in SR at 1 yr with amiodarone; other Comparisons included only rate control subjects to those in SR at 1 yr; SR = ↓ exercise tolerance, functional class, QoL, and ↓ deaths</td>
</tr>
</tbody>
</table>

**CAD** coronary artery disease, **CHF** congestive heart failure, **CV death** cardiovascular death, **EF** ejection fraction, **HR** hazard ratio, **LVEF** left ventricular ejection fraction, **HTN** systemic hypertension, **NNT** number needed to treat, **NYHA** New York Heart Association, **QoL** quality of life, **SR** sinus rhythm

Rhythm control therapies: A amiodarone, Dis disopyramide, ECV electrical cardioversion, F flecainide, P propafenone, S sotalol.

Rate control therapies: BB β-blockers, CCB calcium channel blockers, Dig digitalis, Dil diltiazem, RFA AV junction ablation, V verapamil.

Table 2: Choice of antiarrhythmic agents in the treatment of AF with associated co-morbidities

<table>
<thead>
<tr>
<th>Lone AF</th>
<th>CHF</th>
<th>CAD</th>
<th>LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>Amiodarone</td>
<td>Sotalol</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Dobutamide</td>
<td>Class Ia</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Class Ia</td>
<td>Dronedarone</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>2° Line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>Propafenone</td>
<td>Propafenone</td>
<td></td>
</tr>
</tbody>
</table>

Dofetilide which in turn may lead to increased QTc and possibility of torsades. Only providers closely familiar with this agent should use it in reliable and informed patients. The black box warning on the drugs dictates in-hospital initiation of this agent.

Ibutilide in intravenous form is moderately effective for conversion of AF but also much more effective for conversion of AFL. Its advantage is rapid effect (usually within 60 to 90 min) but is limited by QTc interval prolongation, which results in a 2.7% torsades de points VT incidence.10

Dronedarone, a benzofuran derivative with amiodarone like activity without the associated adverse effects, is effective to a certain extent in maintaining sinus rhythm. It also controls the ventricular rate in AF to a certain extent. Dronedarone is the first rhythm control drug to be associated with substantial improvement in cardiovascular survival of patients with AF; although associated with increased risk of mortality in patients with recent heart failure and ventricular dysfunction.11
Atrial specific drugs
Potassium channel-blocking drugs which cause selective block in the atria have been actively considered as a method of treating AF without prolonging the QT and causing torsades. The drugs which block “ultra-rapid” delayed rectifier potassium current (IKr) do allow such atrial selectivity, as IKr has not been reported in the human ventricle and the potassium channel gene that encodes for IKr is expressed much more extensively in atrium than in ventricle. Due to this, ventricular proarrhythmia will not result from IKr blockade for the treatment of AF.

However, despite these molecules being researched for over a decade, we still do not have any of these for clinical use.

The acetylcholine-dependent potassium current IK Ach also represents a novel atrial-specific target for AF therapy. Vagal influence on the atria, which results in hyperpolarization and shortening of the atrial action potential, has been implicated in precipitation of AF, so inhibition of this current could potentially treat AF. Even more important for this target is the potential to affect the remodeled atrium. A highly selective antagonist to this current has been shown to prolong atrial refractoriness and suppress tachyarrhythmias in the canine remodeled atrium, without affecting ventricular electrophysiology; this may provide a model for future atrial-specific drug development. Several standard antiarrhythmic agents, including amiodarone, flecainide, and quinidine, inhibit IK Ach, possibly accounting in part for their effectiveness in AF.

Stretch-activated ion channels (SACs) have been described, with both selective and nonselective conduction of calcium, potassium, and sodium. Atrial stretch is implicated as both a cause of and a result of AF; furthermore, computer models suggest that SACs could generate fast arrhythmias. Thus, the SAC might represent a novel target for the treatment of AF. However, despite these molecules being researched for over a decade, we still do not have any of these for clinical use.

Role of ACEI, ARB and Statins:
There is increasing evidence that inflammation and fibrosis may play a major role in initiation and maintenance of AF. Independent of its lipid lowering agents, statins are also known for their ‘pleotropic effects’ and may positively impact AF from this action. ACE-I and ARBs prevent atrial remodelling via suppression of renin–angiotensin system (RAS) Meta-analysis of six randomized controlled studies in 3557 patients has shown that the use of statins was associated with a 61% reduction in the incidence of recurrent AF. Meta-analysis of several retrospective reports as well as prospective studies in patients with congestive heart failure and hypertension has reported that therapy with ACE inhibitors and angiotensin receptor blockers reduced the risk of new onset AF by 20–30%. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in 15,000 hypertensive patients at high cardiovascular risk, new onset AF was less frequent in the valsartan-treated group than with the amlodipine-based regimen. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial (CHARM) which included AF as a pre-specified endpoint showed a 19% reduction in the incidence of new onset AF in patients with congestive heart failure and an ejection fraction of about 40% compared with placebo.

Anti-thrombotic therapy
The need for anticoagulation in AF is based on the presence of risk factors for thrombo-embolism. The risk factors include RHD, age > 65 years, severe left ventricular hypertrophy, congestive heart failure, hypertension, diabetes and prior transient ischemic attack or stroke. Presence of any of these would suggest the need for anticoagulation. In patients with RHD and AF, the risk for thrombo-embolism is 17-18% per year and therefore it is critical to ensure adequate anticoagulation. The superiority of adjusted-dose warfarin compared to aspirin in the primary and secondary prevention of ischemic stroke or systemic embolism in non-rheumatic AF has been confirmed in many randomized trials (Figure 1). Based on these studies, in non-valvular AF, CHADS2 scoring system predicts the necessity of warfarin for prevention of thromboembolism (See Table 2). Adjusted dose warfarin to maintain INR between 2 to 3 in non-valvular heart disease patients is recommended. Often in the elderly an INR level closer to 2 is maintained. Adjusted dose warfarin to maintain international normalized ratio (INR) between 2.5-3.5 in RHD and AF without prosthetic valve is recommended.

Despite the overwhelming evidence in favor of adjusted-dose warfarin for the prevention of stroke in patients with AF, numerous clinical observational studies have confirmed that fewer than half of all patients eligible for warfarin for AF actually receive it. This underutilization of anticoagulation for AF in clinical practice is due to multiple factors such as inconvenience of dosing and monitoring, limited availability of anticoagulation monitoring systems, and mis-perceived increased bleeding risk. Since the overall risk of bleeding due to warfarin ranges from 0.9 – 2.7% in majority of the patients with AF the benefit of warfarin far outweigh the risk of bleed associated with it provided adequate monitoring is performed. Regular reliable INR check is a major problem and is often not widely available in rural areas. This results in major morbidity and mortality arising from thrombosed prosthetic valves or thrombo-embolism secondary to under-anticoagulation or from excessive bleeding from over-anticoagulation. Hence, there is a need for a better anticoagulant, not requiring regular monitoring and without many drug-drug interactions.

In this context, the emergence of Dabigatran has been considered a promising development. Dabigatran etexilate is an orally available pro-drug that is converted to dabigatran, the active moiety. The RELY trial showed that dabigatran etexilate 150mg BID (twice daily) significantly reduces the risk of stroke and systemic embolism by 34% (p<0.001) in patients with atrial fibrillation compared to well-controlled warfarin without increasing the risk of major bleeding. Dabigatran etexilate 110mg BID also demonstrated similar reductions in stroke and systemic embolism compared to well controlled warfarin while delivering a 20% reduction (p=0.003) in major bleeding rates compared to warfarin; however, from currently available data, this effect may be highly dose dependent.
Radio-frequency ablation (RFA)

RFA procedures for atrial fibrillation are now a well-established therapeutic option for the management of AF. Over the past decade, multiple techniques have been developed for catheter ablation of AF that report similar success rates. These techniques focus on the elimination of mechanisms involved in the triggering and perpetuation of AF. The different approaches include pulmonary vein (PV) isolation, electrogram-based ablation or complex fractionated atrial electrograms (CFAEs) ablation, linear lesions within the left atria, autonomic ganglionated plexi ablation, and sequential ablation strategy. Various ablation strategies and targets used solo or in combination have been adopted for the ablation of AF. Overall, it appears that in persistent and long-lasting AF, the placement of additional lines of ablation, as well as targeting CFAEs in addition to standard PV isolation has been widely adopted and may add to the overall success rate of the procedure.

Lack of standardized protocol for the procedure, procedural endpoints as well as accepted method of follow up and definition of success has led to heterogeneity in the literature regarding the reported success rate of catheter ablation of AF in the short and long term. Reports of longer-term success rates have ranged from 45 to 95%. In a large meta-analysis combining all studies employing a wide-circumferential approach encircling the PVs in 15,455 patients, the overall success rate was 74% after >6 months follow-up in a wide range of patients (10% of these patients were taking antiarrhythmic drugs). Single center studies have typically reported higher success rates.

Cappato and colleagues surveyed complications of AF ablation performed between 1995 and 2002 in 8,745 patients (30% with multiple procedures) from 181 centers worldwide. The most serious complications included death (0.05%), cardiac tamponade (1.22%), permanent diaphragmatic paralysis (0.11%), pulmonary vein (PV) stenosis greater than 50% (1.63%, symptomatic in 40%), stroke or transient ischemic attack (0.94%), and pseudoaneurysm or atrioventricular (AV) fistula (0.95%).

Surgery

Surgery for AF in the Indian context should be utilized for patients with associated RHD undergoing valve surgery. Maze surgery and its modifications are extremely promising and have been successfully attempted by many investigators to restore SR in RHD and AF patients. Patwardhan et al. pioneered the technique of radiofrequency bi-polar maze for AF during valve surgery. The additional maze procedure required only 12 minutes of extra cross-clamp time. There was 80% freedom from AF at 5 months and resurgence of atrial transport function. Guang Y et al. have also had similar experience with radiofrequency maze during mitral valve surgery, with a longer follow-up of 3 years wherein 77% of patients remained in sinus rhythm.

Therefore, surgical therapy is advised when RFA fails or when the patient is having a concomitant cardiovascular surgery to treat patients with atrial fibrillation.

Pacemaker algorithm for AF prevention – rationale, results

Dual-chamber or atrial pacing has been evaluated as a means of decreasing the risk for AF in patients who require permanent pacing for sinus node dysfunction. A rate-adaptive atrial pacing algorithm (AF Suppression Algorithm, St. Jude Medical Cardiac Rhythm Management Division, Sylmar, California) was designed to provide a high percentage of atrial paced beats while allowing for the normal diurnal variation in the heart rate. The algorithm increases the pacing rate when the native rhythm emerges and periodically reduces the rate gradually to search for intrinsic atrial activity. The Atrial Dynamic Overdrive Pacing Trial (ADOPT) was designed to assess the clinical efficacy and safety of the AF Suppression Algorithm in patients with AF, sick sinus syndrome, and an indication for permanent pacing.

The ADOPT demonstrates that the AF Suppression Algorithm is
safe and effective in patients with symptomatic AF and sick sinus syndrome. Given the apparent safety of the algorithm as it was programmed in the ADOPT and because it is an incremental therapy that can be programmed on or off in patients who are receiving a pacemaker for another reason, this therapy is a suitable option for patients with the sick sinus syndrome and AF.

CONCLUSION

As AF is the most frequent arrhythmia which is primarily diagnosed with the need for hospitalized treatment, it demands a substantial share of institutional health care resources. Thus, as the prevalence of atrial fibrillation increases with our aging population, the number of hospitalizations and, consequently, the costs of treating patients with atrial fibrillation are expected to continue to increase. Further studies will also be required into the potential role of genetics as it pertains to identifying those at greatest risk of AF, as well as for the development of genetically directed pharmacotherapy. Other new drug approaches include those that are atrial selective and those that prevent atrial fibrosis, clearly a trigger for AF. Non-pharmacological management of AF will continue to have a rapid expansion of novel technologies for mapping and ablation, including cryoablation, high-frequency ultrasound, and laser ablation.

However, management of AF remains a challenging problem despite the advances in the armamentarium of treatment options. This is more so in the Indian context with RHD still constituting the major burden, non-availability of anti-arrhythmic drugs and monitoring anticoagulation being the stumbling blocks.

REFERENCES


