Medical Management of Atrial Fibrillation: State of the Art

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Medical Management of Atrial Fibrillation. Predominantly a disease of advancing age, atrial fibrillation (AF) is the most common sustained arrhythmia. Its prevalence is rising as the proportion of elderly people in the population continues its inexorable rise. Without more effective therapeutic interventions, AF-related cardiovascular and cerebrovascular morbidity and mortality will also continue to rise. Antiarrhythmic drugs are an essential tool in the management of AF and may be used as premedication before cardioversion; together with cardioversion to help or assist cardioversion; or given afterward to prevent recurrence. If AF recurs after one or two cardioversions, then it is usual to adopt a rate control strategy; highly symptomatic patients who fail cardioversion may benefit from ablation therapy. We are already on the threshold of a large expansion in the use of ablation therapy, a strategy that has potential to deliver dramatic improvements in outcome. Not only can AF be cured by ablative therapy, but there is also evidence that it confers functional improvement as well. It will not, however, be appropriate for all AF patients and pharmacological therapies will continue to have an important place in the management of AF. The plethora of antiarrhythmic drugs currently available for the treatment of AF is a reflection that none is wholly satisfactory, each having limited efficacy combined with poor safety and tolerability. Improved class III antiarrhythmic agents, such as dronedarone; new classes of antiarrhythmic agents, such as atrial repolarization delaying agents; and upstream therapies dealing with substrate represent potential sources of new pharmacological therapies for AF. (J Cardiovasc Electrophysiol, Vol. 17, pp. S2-S6, Suppl. 2, September 2006)

atrial fibrillation, antiarrhythmic drugs, rhythm control, rate control

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia with a heterogeneous presentation; it can occur in the absence of structural heart disease (lone AF) or, more commonly, in association with conditions such as hypertension, heart failure, and valvular heart disease. There are also temporal differences in AF, characterized by first-detected episodes and recurrent episodes. Recurrent arrhythmias, usually classified according to the 3-P system, include paroxysmal AF in which episodes terminate spontaneously, persistent AF which requires electrical or pharmacological cardioversion to normal sinus rhythm, and permanent AF in which restoration of normal sinus rhythm is considered impossible or inappropriate. With advances in ablation therapy, however, it is questionable whether AF is truly permanent and, instead, might be more accurately described as accepted AF, in which there is an acceptance by both physician and patient that the patient will remain in atrial fibrillation (Fig. 1).

Although AF can affect younger individuals, it is predominantly a disease of advancing age. Prevalence of AF increases sharply with age, affecting fewer than 1% of people aged <60, to about 5% of those aged 70–79, and approaching 10% in people aged 80 and older. About half of all AF patients are aged 75 or older, many of whom have asymptomatic AF. Data from the Cardiovascular Health Study have shown that with increasing age, irrespective of gender, there is an increasing likelihood that AF will be completely asymptomatic with a prevalence at least comparable to that of symptomatic AF (Fig. 2). In fact, evidence from the use of implantable devices suggests that there is far more asymptomatic AF, both in terms of numbers of patients and burden of disease, than symptomatic AF. As the proportion of elderly people in the population continues its inexorable rise, the prevalence of AF, both asymptomatic and symptomatic, will continue to increase. Without more effective therapeutic intervention, we will continue to see AF-related increases in cardiovascular and cerebrovascular morbidity and mortality. Since 1980, there has been an average 5% annual increase in the age-adjusted death rate from AF as well as a 2- to 3-fold increase in the rate of hospitalization.

Against a background of rising prevalence of AF and associated increases in AF-related morbidity and mortality, this review looks at current approaches to the management of AF and briefly discusses how treatment strategies may evolve to address the current unmet need.

Strategic Objectives in the Treatment of AF

Today, management of AF is multidimensional, taking account of the presence of underlying comorbid disease and degree of thromboembolic risk before deciding whether to pursue a strategy of maintenance of sinus rhythm or control of ventricular rate, in an attempt to prevent, or even reverse, atrial remodeling. Appropriate anticoagulation is essential to prevent thromboembolic complications. A number of scoring systems are used to define the risk of thromboembolism...

Dr. Camm received travel expenses and an honorarium from Sanofi-Aventis to present material from this study at a symposium.

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and to assess the need for anticoagulation. A detailed discussion of this is beyond the scope of this article.

Until recently, the decision to control rhythm or rate was largely empirical. Publication of a series of prospective rhythm versus rate control trials, of which the U.S. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and the European RAte Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (AFPR) studies were the largest, has shed some important light on the merits of these two approaches to the management of AF (Table 1). In essence, all of the studies showed no significant advantage for either strategy with respect to primary clinical endpoints that included mortality. A meta-analysis of the combined study results did show that the primary rate control strategy was associated with a significantly reduced risk of the combined endpoint of all-cause death and thromboembolic stroke (odds ratio 0.85, 95% CI 0.73–0.98, P = 0.03), but not of either endpoint alone, nor of major bleeding or systemic embolism. Interestingly, a subanalysis of patients assigned to rate control in the AFFIRM trial, published since the primary endpoint data, failed to show any relationship between achieved ventricular rate and key clinical outcomes, including survival (Fig. 3), quality of life (QoL), and functional status. No association was seen between a lower achieved heart rate at rest or during exercise and higher functional status, improvement in QoL, or indeed, survival free from hospitalization, total cardiovascular hospitalization, and overall survival, a paradox that clearly needs further investigation.

Although there was no statistically significant difference between rhythm and rate control strategies with respect to overall mortality in those trials in which it was an outcome measure, a trend toward greater mortality was seen with the rhythm control strategy over time. In the AFFIRM trial, for example, all-cause mortality was lower at follow-up, albeit not statistically significantly, with the rate control strategy than with the rhythm control strategy. In this trial, 2,033 patients were randomized to a rhythm control strategy and 2,027 to rate control. At an average follow-up of 3.5 years, 356 patients (24%) on rhythm control therapies had died compared with 310 (21%) of those on rate control therapies (P = 0.08 based on Kaplan-Meier estimates at 5 years). This was widely assumed to be due to the adverse proarrhythmic effect of the antiarrhythmic drugs used for the maintenance of sinus rhythm. However, a subsequent analysis by Steinberg et al. has shown that the excess mortality in the rhythm control arm of the trial was in fact due to noncardiovascular rather than to cardiovascular causes (Fig. 4). Fatal noncardiovascular events, mainly cancer and pulmonary events, occurred in 169 patients (47.5% of all deaths) in the rhythm control arm and 113 patients (36.5% of all deaths, P = 0.0008) in the rate control arm. As yet, there is no clear explanation for the increased risk of noncardiovascular death among patients assigned to the rhythm control strategy in the AFFIRM trial. As Steinberg et al. conclude, any explanation for these findings is handicapped by the very design of the trial, which compared treatment strategies (rhythm control vs rate control) rather than drug therapies.

In light of data from the rhythm versus rate control trials, which failed to show an advantage for the rhythm control strategy and, indeed, suggested a trend toward increased mortality, it is tempting to conclude that rhythm control has little place in the current management of AF. Such a conclusion, however, fails to take account of the fact that the rhythm versus rate control trials did not attempt to show whether maintenance of sinus rhythm was in fact better than allowing AF to continue unimpeded. In the AFFIRM trial, 62.6% of patients assigned to rhythm control were still in sinus rhythm after 5 years compared with 34.6% of those assigned to rate control (Table 1). Among patients who remained in sinus rhythm following cardioversion, evidence from subgroup analyses of the AFFIRM trial suggests that outcome is significantly improved; sinus rhythm emerged as either an important determinant of, or marker for other factors associated with, survival. This is consistent with data from the earlier Danish Investigators of Arrhythmia and Mortality on Dofetilide trial. Antiarrhythmic therapy with dofetilide proved significantly more effective than placebo at restoring and maintaining sinus rhythm in patients with AF, which translated into improved clinical outcome (reducing the risk of hospitalization for worsening heart failure). Outcome is improved in patients in whom sinus rhythm is maintained as well as in those receiving concomitant warfarin therapy for thromboprophylaxis. Conversely, use of digoxin and antiarrhythmic drug therapy can have a deleterious effect on outcome. Although the incidence of proarrhythmic events associated with antiarrhythmic drug therapy in the AFFIRM trial was relatively low, the potential for serious and occasionally life-threatening side effects must always be borne in mind when deciding whether or not to initiate antiarrhythmic therapy for a patient with AF.
TABLE 1
Key Features of the Major Trials That Investigated Rate Versus Rhythm Control Strategies in the Management of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Type and duration of AF</th>
<th>Etiology</th>
<th>Mean follow-up</th>
<th>Patients in SR (rhythm vs rate)</th>
<th>Primary endpoints</th>
<th>Outcome (rate control vs rhythm control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF</td>
<td>252</td>
<td>Persistent symptomatic 7 days–1 year</td>
<td>HTN 49%, CHD 23%, VHD 16%, CHF 10%, Lone 15%</td>
<td>1 year</td>
<td>56% vs 10%</td>
<td>Symptom improvement</td>
<td>No significant difference in primary endpoint (60.8% vs 55.1%, P = 0.32)</td>
</tr>
<tr>
<td>STAF</td>
<td>200</td>
<td>Persistent &gt;4 weeks–1 year</td>
<td>HTN 62.5%, CHD 43.5%, VHD 13%, CHF 12.5%, Lone 10%</td>
<td>19.6 months</td>
<td>26% vs 11% at year 1; 3% vs 0% at year 2; 1% vs 0% at year 3</td>
<td>Composite (all-cause mortality, cerebrovascular event, cardiorespiratory resuscitation, systemic embolism)</td>
<td>No significant difference in primary endpoint (9% vs 10%)</td>
</tr>
<tr>
<td>RACE</td>
<td>522</td>
<td>Persistent 24 hours–1 year</td>
<td>HTN 55% vs 43%, CHD 26% vs 29%, CHF 7% vs 11%, Lone 21% vs 21%</td>
<td>2.3 years</td>
<td>39% vs 10%</td>
<td>Composite (cardiovascular death, hospitalization for heart failure, thromboembolic complication, severe bleeding, pacemaker, severe adverse effects of therapy)</td>
<td>No significant difference in primary endpoint (17.2% vs 22.6%, P = 0.11)</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>4,060 (&gt;65 years) and paroxysmal 6 hour–6 months (1 in last 12 weeks)</td>
<td>Persistent (&gt;69%) and paroxysmal 6 hour–6 months (1 in last 12 weeks)</td>
<td>HTN 51%, CAD 26%</td>
<td>3.5 years</td>
<td>62.6% vs 34.6% at 5 years</td>
<td>All-cause mortality</td>
<td>No significant difference in primary endpoint (21.3% vs 23.8%, P = 0.08)</td>
</tr>
<tr>
<td>HOT CAFE</td>
<td>205</td>
<td>Persistent 7 days–2 years</td>
<td>HTN, CHD, nonsevere VHD, tone</td>
<td>1.7 years</td>
<td>63.5% in rhythm control arm</td>
<td>Composite (all-cause mortality, thromboembolic events, major bleeding)</td>
<td>No significant difference in primary endpoint (odds ratio 1.98, 95% CI 0.28–22.3, P &gt; 0.71)</td>
</tr>
</tbody>
</table>

AFFIRM = atrial fibrillation follow-up investigation of rhythm management; HOT CAFE = how to treat chronic atrial fibrillation; PIAF = pharmacologic intervention in atrial fibrillation; RACE = rate control versus electrical cardioversion for persistent atrial fibrillation; STAF = strategies of treatment of atrial fibrillation.

While it is sensible to attempt to restore and maintain sinus rhythm in patients experiencing a first episode of AF, physicians are faced with a more difficult decision of whether to adopt a rate or rhythm control strategy in patients with recurrent AF. As the treatment algorithm in Figure 5 illustrates, rhythm control is usually appropriate for paroxysmal AF, particularly in younger patients. Rate control too is an option for patients with paroxysmal AF. Similarly, for patients with permanent AF, rate control is usually considered first-line therapy. However, as mentioned previously, if that fails, then attempts to restore sinus rhythm are worth pursuing. Persistent AF presents a greater therapeutic challenge. Generally, cardioversion is tried in most cases; but where patients are asymptomatic and have other features suggesting that cardioversion will not work, then rate control may prove more successful.

Antiarrhythmic drugs are an essential tool in the management of AF and may be used as premedication before cardioversion; together with cardioversion to help or assist cardioversion; or given afterward to prevent recurrence. If sinus rhythm is achieved, but then defaults to AF, cardioversion may be repeated. However, if AF recurs after one or two cardioversions, then it is usual to adopt a rate control strategy; highly symptomatic patients who fail cardioversion may benefit from ablation therapy. Any treatment strategy should take account of the substrate and any underlying disease. The large array of antiarrhythmic drugs currently available for the treatment of AF is a reflection that none is wholly satisfactory, having limited efficacy combined with poor safety and tolerability. Amiodarone is arguably the most effective of the antiarrhythmic agents, consistently superior to placebo and

Figure 3. Mortality in the AFFIRM study. Left panel: Overall mortality rates observed in primary analysis.9 Reproduced with permission. Copyright © 2002 Massachusetts Medical Society. Right panel: Relationship between survival and achievement of target heart rate among patients assigned to rate control.14 Reprinted with permission from Excerpta Medica, Inc.

Figure 4. Causes of death in patients assigned to rhythm and rate control strategies in the AFFIRM trial (data from ref. 15).
other agents in comparative studies. Sotalol, flecainide, and propafenone may, however, yield excellent results in individual cases. AF commonly (20–50% of cases) occurs after cardiothoracic surgery, most probably because of perimyocardial inflammation. The arrhythmia may complicate the postoperative course and extend the patient’s hospital stay. It is apparent that much of the postoperative AF may be prevented by maintaining preoperative treatment with beta blockade, i.e., not exposing patients to increased catecholamine sensitivity at this critical time. Of the many antiarrhythmic strategies that have been tried, amiodarone beginning 6 days preoperatively and extending for 6 days postoperatively is probably the most effective.

Rate control therapy is relatively easily administered. Usually a nondihydropyridine calcium antagonist or beta-blocker is used as monotherapy, except in sedentary patients where digoxin treatment may be all that is needed. In active individuals, the rate reduction induced by digoxin, generally exerted via its effects on the parasympathetic nervous system, is overwhelmed by sympathetic stimulation and the treatment is generally ineffective. Combinations of digoxin with beta blockade or rate-limiting calcium antagonists may be needed. Amiodarone is often used as a rate control agent, usually because its prescription continues for rate control when its rhythm control efficacy has been expended. However, it is associated with too many complications to be used routinely for this purpose. Very occasionally, rate control is difficult to achieve pharmacologically and in such circumstances AV node/His bundle ablation and pacemaker implantation can be utilized. This is a highly effective therapy that allows very precise rate control without the need for additional medical treatment.

Bridging Current Treatment Gaps

While debate continues on the relative merits of controlling ventricular rate versus cardioversion and maintenance of sinus rhythm as strategies for management of AF, approaches to treatment continue to evolve. Pharmacological research activity is currently focused on three areas: upstream therapies dealing with substrate, an expansion of conventional class III antiarrhythmic agents, and the development of new classes of antiarrhythmic agents, such as atrial repolarization-delaying agents. Nonpharmacological strategies, already state of the art, can be expected to grow in parallel with new pharmacological approaches to treatment. Already we are on the threshold of a large expansion in the use of ablation therapy, a strategy that has the potential to deliver dramatic improvements in outcome. Not only can AF be cured by ablation therapy, but there is evidence that it also confers functional improvement as well. It will not, however, be appropriate for all cases of AF, and pharmacological therapies will continue to have an important place in the management of AF.

Upstream therapies include a diverse array of agents from drugs, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which target the renin–angiotensin system, to aldosterone antagonists, statins, corticosteroids, and N-3 polyunsaturated fatty acids. A recent meta-analysis has provided convincing evidence that ACE inhibitors and ARBs are highly effective in preventing AF recurrence, independent of their antihypertensive effects and irrespective of underlying conditions, such as congestive heart failure, hypertension, myocardial infarction, or AF itself. Evidence also supports the use of ARBs in conjunction with antiarrhythmic agents as a more effective strategy for preventing AF recurrence than antiarrhythmic drugs alone.

With respect to conventional antiarrhythmic agents, the search continues for more effective and safer drugs. Because of their propensity to increase mortality, development of new class I antiarrhythmics has essentially ceased and, instead, the focus has been on the development of new and improved class III agents, such as dronedarone, with encouraging results.

Conclusion

In the management of AF, the aim of therapy is the termination of arrhythmia and the prevention of AF recurrence. Despite progress in understanding the pathogenesis, electrophysiological mechanisms, and triggering factors of this disease, we are still some way from meeting this goal. Today, treatment of AF mostly consists of anticoagulant prophylaxis and antiarrhythmic drug therapy to maintain sinus rhythm after cardioversion or control of ventricular rate together with life-long anticoagulation. Prospective clinical trials that compared rhythm control with rate control strategies have shown that they produce equivalent clinical outcomes, including mortality. Results from these trials, however, are not necessarily applicable to all AF patients. Moreover, they have revealed little about what constitutes optimal rate control. As subgroup analyses have shown, where sinus rhythm can be successfully maintained in AF patients, there is evidence of improved outcome. AF remains a condition for which there is still significant unmet need. Increased use of ablative therapy will help to bridge current treatment gaps, as will greater use of upstream therapies and new antiarrhythmic drugs. As well as meeting efficacy targets, the success of new antiarrhythmic drugs will be determined by their atrial electrophysiological selectivity, freedom from nonelectrophysiological adverse cardiac effects, and overall safety profile.

References


