Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance encountered by physicians. The management of AF is focused on control of heart rate, correction of rhythm disturbance, and risk-determined prophylaxis of thromboembolism. The goals of AF therapy are, as with other serious disorders, to reduce mortality (if possible) and morbidity (improve quality of life, QOL). To this end, several large studies have examined rhythm-control versus rate-control strategies. Although a survival advantage to using rhythm control with currently available antiarrhythmic drugs has not been proven, neither has there been a significant excess risk versus rate control. Therefore, using our current therapies, the results have not supported rate control or rhythm control as being a preferable first-line therapy for AF as regards survival; importantly, neither do they disprove the hypothesis that maintenance of sinus rhythm is preferable to the continuation of AF, particularly if rate control fails to restore adequate QOL. Many post-hoc analyses and substudies have assessed QOL, functional status, and exercise tolerance, with the majority demonstrating important benefits associated with achievement of rhythm control. This review examines rate and rhythm control options, the clinical outcomes of several important AF trials, discusses the limitations in applying the major morbidity/mortality findings to everyday clinical practice, and summarizes the lessons learned.

Abstract

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance encountered in clinical practice. It is characterized by the absence of discrete organized atrial activity on the electrocardiogram, uncoordinated atrial activation, disordered contraction of the atrium, and the deterioration of atrial mechanical function. AF is currently estimated to affect between 2.3 and 5.1 million people in the United States alone, with expected rates of 5.6 to 15.9 million by the year 2050 as an even greater segment of our population reach older age. AF is currently estimated to affect 2.3 and 5.1 million people in the United States alone, with expected ages of 5.6 to 15.9 million by the year 2050 as an even greater segment of our population reach older age. AF’s prevalence has been estimated at 1% in the general population, with higher rates in both the elderly (>7% and >10% in women and men ≥80 years old, respectively) and in those with heart failure (HF) of progressively increasing severity. AF often is associated with underlying structural heart disease, including hypertension (~50-80% of AF patients in all recent large clinical trials), coronary artery disease (25%), HF (23%-29%), and valvular heart disease (17%).

Symptoms of AF may include palpitations, angina, dyspnea, lightheadedness (and, rarely, syncope) [all of which may be related to the altered mechanics of AF]; chronic fatigue [which, in my experience, almost always requires restoration of sinus rhythm for resolution]; and/or impaired exercise tolerance.
However, AF may be asymptomatic at all times in some patients and at some times in patients with otherwise symptomatic periods or episodes. Irrespective of symptoms, all-cause mortality is increased 1.5- to 1.9-fold in association with AF compared with mortality rates in individuals in sinus rhythm.6 This may be the consequence of interactions with underlying disorders, consequences of our therapeutic decisions, consequences of adversely altered hemodynamics, and/or consequences of uncontrolled tachycardic rates or emboli. Concordantly with the above, AF can cause hemodynamic impairment with decreased cardiac output; can induce cardiomyopathy and HF, particularly when ventricular rates are rapid; and can be associated with an increased risk of stroke in selected AF populations.7-9 Health-related quality of life (QOL) is adversely affected by the presence of AF in most patients, with patients potentially experiencing discomfort due to symptoms, functional impairment due to chronic fatigue, exercise intolerance, and/or the effect of their AF-related medications, and anxiety due to fear of anticoagulation therapy and the potential for bleeding.10,11 Furthermore, AF is associated with a significant economic burden. Healthcare costs are approximately 5 times higher for patients with AF than for those without it, and hospitalizations are a key contributor to this burden.12,13

Many studies have examined different treatment options (most notably, rhythm versus rate control strategies) and their success rates in patients with AF.14-19 Although the studies conducted to date with currently available therapies have not demonstrated a survival advantage using rhythm control strategies versus rate control strategies in AF, these results should not be interpreted to indicate that rate control is a preferable first-line therapy for AF as is the pursuit of sinus rhythm. Rather, QOL in AF and its daily impact on the patient must be considered in addition to, and, perhaps, at a higher priority than, the issue of overall survival. Commonly, restoration of an acceptable QOL requires the pursuit of sinus rhythm, despite the lack of any simultaneous beneficial survival advantage for the therapy employed. This review examines rate and rhythm control approaches as well as the clinical outcomes of several important AF trials, their limitations, and the lessons learned from them.

Patterns of AF and their impact on rate and rhythm control considerations

AF presents in specific patterns and can be classified as paroxysmal (self-terminating) [with some authors adding the dictate that it last <7 days], persistent (not self-terminating) [with some authors adding the dictate that it last >7 days], and permanent (lasting >1 year, being refractory to cardioversion, and/or with sinus rhythm no longer to be pursued).20 Paroxysmal AF (PAF) and persistent AF are not mutually exclusive as individual patients may experience both at different times. Treatment goals differ with presentation pattern (Table 1).

AF in patients without evidence of cardiopulmonary disease, including hypertension, is generally referred to as lone AF. However, genetic factors that contribute to the development of lone AF are being increasingly recognized, as are associations between lone AF and sleep disorders, autonomic contributors, and obesity. Lone AF is more common in younger patients with PAF than in older patients with persistent AF.21 Although patients with lone AF have a lower risk of stroke and mortality, their risk for thromboembolic events and cardiovascular comorbidities increases with age.22

AF often is a progressive disease, and electrical or pharmacologic conversion of AF to sinus rhythm becomes less likely and more challenging when the arrhythmia has persisted for more than 6-12 months. Between 14% and 24% of patients with PAF have progression to persistent AF, and persistent AF not infrequently progresses to permanent AF.22,23 Both PAF and persistent AF can result in poor QOL, but the symptoms that affect QOL often are different for these two AF variants. In the recently reported AFFECTS Registry palpitations, chest discomfort, and dizziness were found to be more commonly reported in patients with PAF while fatigue and exercise limitations were more commonly reported in patients with persistent AF.24

The rate and rhythm treatment approaches to PAF are to reduce symptoms during episodes (rate control) and to reduce the number and duration of episodes when QOL so demands (rhythm control with a chronically applied regimen). Patients whose symptoms during and pattern of PAF are-
acceptable to the patient, especially after rate control has been established, do not require chronic preventative antiarrhythmic therapy.

The rate and rhythm treatment approaches to persistent AF episodes are to reduce the symptoms during the episodes (rate control) and to restore sinus rhythm such that permanent AF is not established (cardioversion, either by pharmacologic or electrical methods), as well as to reduce the frequency of episodes when QOL so demands (rate control with a chronically applied regimen). Infrequent but tolerable persistent AF may be treated with intermittent cardioversion (which is especially attractive when it can be attained pharmacologically) and does not necessarily require chronic suppressive antiarrhythmic therapy (either drug or ablation). This is an important but commonly overlooked treatment alternative, with oral Class IC single dosetherapy being effective in up to 80% of patients with a mean conversion time approximating four hours. Permanent AF, by definition, requires rate control but not the pursuit of rhythm control; however, recent reports of some success with restoring sinus rhythm with ablational approaches even in some patients with long-standing ongoing AF may cause us to revisit our definitions of and our approaches to therapy of permanent AF. Finally, rate control is needed not only to reduce tachycardic associated symptoms during AF events (see above), but also to prevent the development of a tachycardic induced ventricular myopathy, independent of whether the AF event is itself symptomatic or not.

Rate Control Therapies

Rate control, as has been well described in many prior reviews, including the most recent ACC/AHA/ESC guidelines, can be achieved pharmacologically in most patients using beta blockers, verapamil or diltiazem, and digitalis, singly or in combination. Of these, only digitalis does not have the potential to simultaneously reduce blood pressure. In general, blood pressure is less likely to drop with beta blockers than with calcium channel blockers in older patients. Clinical pearls concerning rate control are relatively few, aside from knowing that: 1) clonidine can be used to potentiate the effect of the other above-named agents, when blood pressure allows, thus enhancing the possibility for adequate rate control but with the likewise enhanced risk of sinus nodal and AV nodal dysfunction if/when sinus rhythm reappears; 2) pindolol is less likely than verapamil, diltiazem, or any other available beta blocker to produce worsened sinus node function in patients with the brady-tachy syndrome, and hence, is the preferred agent in this condition where its use may avoid the necessity of inserting a pacemaker to support the use of an alternative AV nodal blocking agent; 3) ablation of or drug suppression of an antegrade conducting bypass tract is necessary in addition to AV nodal blockade to attain rate control in patients with preexcitation; 4) amiodarone can be effective in providing ventricular rate control but is rarely indicated for this purpose alone given its toxic profile (whereas, the currently investigational and apparently less toxic derivative of amiodarone, dronedarone, may be if and when it becomes available); [these two agents can also provoke sinus nodal and AV nodal dysfunction in sinus rhythm when underlying dysfunction is present, and, in addition, amiodarone and dronedarone may effect pharmacological cardioversion beyond rate control, so anticoagulation management is needed if/when these agents are given to patients with persistent AF or to patients with PAF of uncertain or protracted duration]; 5) when drug therapy is ineffective or not tolerated, ablation of AV conduction and implantation of a permanent pacemaker is an appropriate and effective alternative approach to achieving rate control. Physiologically, the target for rate control should be the attainment of approximately the same ventricular rate for the same activity state as would be likely for the patient at hand in sinus rhythm. Thus, since patients are rarely entirely sedentary, it is not appropriate to judge rate control only by the resting pulse or the ventricular rate on the ECG. Rather, ambulatory ECG assessment, such as by Holter monitoring, is the optimal way to determine the status of rate control in a patient in AF. If only a resting ECG is performed, it is not possible to tell whether residual symptoms during daily activity or exercise are due to inadequate rate control or whether they persist despite rate control and will necessitate the pursuit of sinus rhythm for their further resolution.
Rhythm Control Therapies

Rhythm control requires cardioversion in persistent AF and often requires an antiarrhythmic strategy (drug or ablation, +/- pacing in brady-tachy patients) for the maintenance of sinus rhythm in both persistent AF and PAF patients. It is beyond the scope of this review to discuss either the available antiarrhythmic drugs used for this purpose or the current state of ablative technology, approaches, and outcomes when used for AF patients. The interested reader is referred to the ACC/AHA/ESC management guidelines and other recent therapeutic reviews for more detail on specific therapies.

Restoration and Maintenance of Sinus Rhythm in Patients with AF

The treatment and management of AF are focused on four main goals: management of any underlying contributing disorder and reduction of its pathophysiology when feasible, control of ventricular rate, correction of the rhythm disturbance when necessary, and prophylaxis of thromboembolism. Although it has often been debated as to whether rate or rhythm control is a preferable strategy, these strategies are not mutually exclusive and the debate is often artificial. Rate control is necessary even when a rhythm control strategy is being considered. Abolition of symptoms with rate control may eliminate the necessity for suppression of AF, and, rate control will be needed if antiarrhythmic therapy fails to prevent all AF and recurrences occur. Nonetheless, the choice of one over the other as the primary strategy is a function of several factors, including the duration and pattern of AF, the type and severity of symptoms, the presence of cardiovascular disease, intrinsic AV node functionality, and the safety profiles of the treatments under consideration. Of note, prophylaxis of thromboembolism must be considered irrespective of treatment strategy; the need for anticoagulation therapy is based on the overall risk of stroke—not on the restoration or maintenance of sinus rhythm, whether by pharmacologic ablative approaches. However, as anticoagulation is not a focus in this review it will not be covered further herein.

Defining Success in the Treatment of AF

The treatment of AF is ultimately aimed at reducing morbidity and improving QOL in AF patients, and, if feasible, reducing any risk of mortality associated with AF in the given patient. However, AF therapy is not required for all patients with

<table>
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<tr>
<th>Table 1</th>
<th>AF Patterns and Treatment Approaches (excluding anticoagulation)</th>
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<tbody>
<tr>
<td><strong>PAF</strong></td>
<td>Reduce symptoms during episodes (rate control) and reduce the number and duration of episodes when QOL so demands (rhythm control with a chronically applied regimen)</td>
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<tr>
<td><strong>Persistent AF</strong></td>
<td>Reduce symptoms during episodes (rate control) and restore sinus rhythm to reduce symptoms and to avoid permanent AF (cardioversion) as well as to reduce the frequency of episodes when QOL so demands (rhythm control with a chronically applied regimen). Infrequent but tolerable persistent AF may be treated with intermittent cardioversion (preferably pharmacologically if possible) and does not necessarily require chronic suppressive drug or ablative therapy.</td>
</tr>
<tr>
<td></td>
<td>After treatment of a precipitating cause such as acute myocardial infarction, cardiac or thoracic surgery, hyperthyroidism, pneumonia, or pericarditis</td>
</tr>
<tr>
<td><strong>Permanent AF</strong></td>
<td>Reduce symptoms and prevent tachycardia-induced cardiomyopathy (rate control)</td>
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AF. For example, infrequent, transient, minimally symptomatic episodes probably do not require treatment. Moreover, recurrences of this type during drug therapy may not constitute treatment failure. Hence, therapy (drug or otherwise) should be matched to presentation characteristics and should be focused on appropriate target goals with a simultaneous concern for minimizing the potential for adverse effects. In addition to survival and QOL, our current state of medical costs and payments necessitates a third treatment goal: that of reducing the economic and societal burden of AF.

The determination of whether the pursuit and maintenance of sinus rhythm should be the primary or default goal for most patients with AF has been the topic of several recent important trials (Table 2). Between 2000 and 2003, five major prospective trials – AFFIRM, RACE, PIAF, HOT CARE, and STAF – compared outcomes with rhythm- versus rate-control strategies. In each of these trials attainment of a significant difference in the primary endpoint -- a mortality benefit or a composite endpoint benefit (or a survival benefit when assessable as part of a composite endpoint) -- associated with rhythm-control strategy over a rate control strategy using intention-to-treat (ITT) analyses proved to be elusive (see more detailed discussion below). However, these results should not be taken to suggest that a rate-control strategy is equivalent to maintenance of sinus rhythm. It merely suggests that, using an ITT assessment of currently available antiarrhythmic therapies, the rhythm- versus rate-control strategies appear to be equivalent with regard to length of life or composite assessments including survival. These trials do not disprove the hypothesis that if one were to attain and maintain sinus rhythm with safer methods than exist at present, NSR would be preferable to the continuation of AF. Moreover, and importantly, because rhythm control did not carry a statistically significant excess risk over rate control in these studies, the results do not support rate control as a sufficient strategy when it does not restore adequate QOL in patients with AF.

Different study design characteristics and approaches to analysis can contribute to the challenge in interpreting results and pragmatically applying them to patients in clinical practice. Most clinical trials use an ITT approach as their primary analyses to compare one strategy with another. For example, in the recent AF trials discussed herein, all patients were assigned to a therapeutic strategy, and the outcome was dependent on the therapy path chosen, not on whether patients

<table>
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<th>Table 2</th>
<th>Rate versus Rhythm Control Trials in Atrial Fibrillation</th>
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<tr>
<td><strong>No significant difference in survival or primary composite endpoint by ITT analysis</strong></td>
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<tr>
<td>AFFIRM 16</td>
<td></td>
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<tr>
<td>RACE 17</td>
<td></td>
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<tr>
<td>STAF 18</td>
<td></td>
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<tr>
<td>PIAF 44</td>
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<tr>
<td>HOT-CAFÉ 39</td>
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<tr>
<td><strong>J-RHYTHM 36 Note: Sinus was associated with better event-free survival in PAF subgroup</strong></td>
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<tr>
<td><strong>AF-CHEF 37</strong></td>
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<tr>
<td><strong>Improved survival or primary composite endpoints in association with rhythm control (see text)</strong></td>
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<tr>
<td>AFFIRM 30 Subanalysis indicated better survival in sinus rhythm offset by worse survival with antiarrhythmic drugs</td>
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<tr>
<td>RACE 33,34 Better survival with NSR if it was maintained, but not with antiarrhythmic drugs</td>
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<tr>
<td>DIAMOND Better survival if sinus rhythm was AF 15 attained and maintained</td>
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<tr>
<td>STAF 19 Despite balanced event rates between rate and rhythm control arms, 18 of 19 events occurred during AF; only 1 during sinus rhythm</td>
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</tr>
<tr>
<td>CHF-STAT 35 Survival was greater in amiodarone-treated patients who attained and maintained NSR than those who remained in AF on amiodarone.</td>
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</table>
were in AF or sinus rhythm whether they actually received and continued the therapy they were randomized to receive. Once assigned to a treatment arm, all patients were reanalyzed as though they were fully compliant with their therapy and did not cross over to the alternative treatment, whether or not this was the case. Outcomes in clinical trials such as these are further biased by the innate properties and adverse effects of the treatments. While the ITT approach may be statistically desirable and provide information on the likelihood of a given outcome if a particular treatment strategy is chosen, it does not necessarily provide information on what actually happens if patients take and continue the therapy. When discontinuation or compliance rates differ markedly between two therapies, this type of analysis is biased. (For instance, a comparison of drug and nonpharmacologic therapies would inherently be biased to show greater efficacy from the nonpharmacologic approach.)

In contrast to ITT analyses, efficacy analyses (also known as on-therapy or per-protocol analyses) can be used to evaluate outcomes for patients who actually initiate and continue without interruption their assigned therapy. These analyses provide information on the likelihood of aparticular outcome when a therapy is administered and complied with, but not on the likelihood of overall outcomes for therapeutic strategies being compared (i.e., the ITT population). Because some patients may be excluded from efficacy on-therapy analyses, such as those never started on therapy, those who do not continue therapy, etc., unequal group sizes and durations of therapy (for example) may arise and confound the interpretation of findings. The innate properties and adverse-event profiles of the specific treatments also may contribute to bias. For example, patients who discontinue their assigned treatment early in a study, because of adverse events or insufficient efficacy, create additional bias in the study results. In the case of AF, one important contributing factor to the bias in an efficacy analysis is that currently it is usually not realistic to expect that patients will always be maintained in sinus rhythm in real-world clinical practice (given the efficacy and adverse event profiles of currently available drugs); thus, a stand-alone efficacy analysis without the context of an ITT evaluation would be of limited clinical usefulness.

Other important biases may apply to both the ITT and efficacy/on-therapy analyses; for example, the definition of treatment success and failure. Historically, a recurrence of AF has been interpreted as treatment failure in AF clinical trials, such as in time to first event endpoints. In clinical practice, such a sole definition of success and failure is not appropriate. A change in the pattern of AF from “frequent and protracted” to “rare and brief” would constitute clinical success in actual practice. For example, in a patient with frequent PAF if two therapies both reduced episodes to two per year, whether the first event occurred at 5 months

Table 3  American College of Cardiology/American Heart Association/European Society for Cardiology Class I Indications for Treating Patients With Atrial Fibrillation With Antithrombotic Therapy

<table>
<thead>
<tr>
<th>American College of Cardiology/American Heart Association/European Society for Cardiology Class I Indications for Treating Patients With Atrial Fibrillation With Antithrombotic Therapy</th>
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<tr>
<td>1. Administer aspirin 81 to 325 mg daily for patients with no risk factors</td>
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<tr>
<td>2. Administer aspirin 81 to 325 mg daily or warfarin to maintain an INR between 2.0-3.0 for patients with 1 moderate-risk factor</td>
</tr>
<tr>
<td>3. Administer warfarin to maintain an INR between 2.0-3.0 for patients with any high-risk factor or more than 1 moderate-risk factor.</td>
</tr>
<tr>
<td>Moderate-risk factors include age ≥75 years, hypertension, heart failure, LV ejection fraction ≤35%, or diabetes mellitus</td>
</tr>
<tr>
<td>High-risk factors include prior stroke, transient ischemic attack or embolism, mitral stenosis, prosthetic heart value*</td>
</tr>
<tr>
<td>*If mechanical valve, the INR should be maintained between 2.5-3.5 Adapted from Fuster V et al [183]</td>
</tr>
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or 6 months would be of no real significance clinically. And, perhaps, it may not really matter if there were two versus three episodes that year. As with angina, a decrease in the incidence of AF recurrence should be considered a treatment success in AF trials. The complete absence of AF recurrence may be unachievable and impractical, whereas fewer and shorter AF episodes would be a more realistic goal from the standpoint of everyday clinical practice.

Additionally when assessing a treatment strategy, the definition of success may confound clinical and trial impressions. Despite my discussion of a functionally clear assessment of attainment of adequate rate control above, there have been substantial differences concerning rate control assessment in different trials, and various target rates for resting and active states have been used. The lack of a well-defined target rate may lead to less aggressive titration of rate-control drugs, which can lead to underestimation of the adverse-event rates associated with these agents, and failure to fully assess the optimum benefits attainable with these agents. [For example, low-doses of beta-blockers are associated with lower rates of adverse events because many of the events are dose dependent.] Furthermore, heart rate may vary by activity level, time of day, and/or dosing schedule which can further complicate interpretation of study results. Similarly, definitions of effective therapy endpoints are important in rhythm control assessments. For example, in patients with infrequent persistent AF or prolonged PAF episodes, termination by intermittent cardioversion, especially if by oral outpatient single dose pharmacologic conversion, may be more acceptable to the patient than is the taking of daily suppressive therapy; yet, in trials such as AFFIRM and RACE, this approach was not a focus of therapy or of endpoint analysis.

Benefits of Suppressing AF: More than Just Prolonging Survival

As with the treatment of any disorder, in AF, lack of an adverse mortality profile associated with a therapy is an important criterion of success for any treatment. However, by itself, consideration of survival alone is not a sufficient measure. QOL in patients with AF has been shown to be poorer than that of the general population and even worse than that of patients with coronary heart disease. QOL is a subjective measure that is affected by many consequences of AF, as well as by its therapy and the patient’s QOL. Reductions in symptoms, complications, and/or therapy. Thus, while a therapy that reduced symptoms but increased mortality would not likely be acceptable, one with no effect on QOL with a neutral effect on survival would also be clinically useless. In addition, as with all medical decisions, costs associated with therapies to be employed must also be considered, and reduced economic burden is another important measure of treatment success. Economic burden can be influenced and measured by hospitalizations, treatment costs, and costs related to complications, QOL issues, and the functional status of patients.

What Benefits Have We Demonstrated for Rhythm vs Rate-Control Therapy: A Contemporary Look at Classical Clinical Trials of AF

Effects on Mortality

AFFIRM

The AFFIRM study (N=4060) compared rhythm and rate control in patients with AF and a high risk of stroke or death. At 5 years, the ITT analysis showed an overall mortality rate (primary endpoint) of 23.8% in the rhythm-control group and 21.3% in the rate-control group (P=0.08). Interestingly, the rates of cardiovascular death (9% and 10%, respectively) and vascular death (3% and 3%, respectively) were comparable between the two treatment arms, whereas non-cardiovascular deaths were significantly higher in the rhythm-control group (12% vs 8% for rate control; P=0.0008), driven primarily by pulmonary and cancer-related deaths. The drug used most commonly in the rhythm-control arm was amiodarone (approximately 2/3 of the cases).

Rhythm- and rate-control strategy comparisons in AFFIRM were limited by the constraints of the prespecified ITT analysis. In AFFIRM, many patients randomized to the rhythm-control arm remained in AF rather than attaining and maintaining sinus rhythm (17.6%, 26.7%, and 37.4% at
1, 3, and 5 years), while many patients in the rate-control arm were in sinus rhythm for some or most of the time even without an antiarrhythmic drug (34.6% at 5 years), having suffered only PAF. Thus, AFFIRM compared treatment algorithms based on currently available therapies and strategies, not outcomes based on whether a patient was in AF or sinus rhythm. Two additional observations made in AFFIRM are also important to address. In AFFIRM, the use of antiarrhythmic drugs was associated with a 49% increase in the risk of death (P=0.0005), with the excess risk being non-cardiovascular deaths, presumed largely related to drug toxicity (see above). Notably, in AFFIRM, after adjusting for the presence of sinus rhythm, sinus rhythm was associated with a better survival rate (P<0.0001). Importantly, however, this analysis included patients in the rate control arm with PAF who were in sinus rhythm during follow-up visits without the use of an antiarrhythmic agent. The above results suggest that the antiarrhythmic drugs used in AFFIRM were neither highly efficacious nor safe, at least in the patient population enrolled in AFFIRM. Extrapolation of these results to other populations, such as younger patients and those without associated risk factors, in which therapy options other than those used in AFFIRM might be considered, would/could be hazardous/inappropriate. Approximately 60% of the AFFIRM population was male, and most had persistent AF (69%) rather than PAF (31%). Very few had lone AF (12%). About 23% of patients also had HF. The mean age approximated 70 years. A subanalysis of data from AFFIRM suggests that younger patients (<65 years of age) and those with a history of HF may derive a greater survival benefit with rhythm-control drugs.31 Additionally one cannot exclude from AFFIRM that a survival benefit with rhythm control might occur in the trial to be done again with therapies that possess a better safety profile, should some become available. The role of rhythm control in AF patients with HF is being further investigated in the AF-CHF study (see below).32 Notably, the other factor that was associated with better outcome in AFFIRM was anticoagulation. The incidence of stroke, some of which were fatal, was somewhat lower in the rate control than the rhythm control treatment arm. Importantly, most strokes occurred in patients who had terminated anticoagulation therapy or were receiving subtherapeutic levels of warfarin. These findings have been taken to suggest that all patients with AF with risk markers for stroke should receive anticoagulation therapy irrespective of treatment and rhythm outcome.

**RACE**

The RACE trial (N=522) studied patients with persistent AF and mild to moderate HF who were rate controlled vs cardioverted and assigned a rhythm control therapy.17 A composite outcome measure that included cardiovascular death, hospitalizations for HF, thromboembolic complications, severe hemorrhage, pacemaker implantation, and severe adverse events was the primary endpoint. Overall, no difference in the primary endpoint was observed between the treatment arms. Moreover, in a subanalysis, patients who remained in sinus rhythm while receiving rhythm control and anticoagulation did not have a better prognosis for survival.33 However, a post-hoc analysis showed that those in sinus rhythm compared with patients in AF at the end of the study had lower rates of cardiovascular mortality (0% vs 9.5%), progression of HF (2.1% vs 4.8%), bleeding (0% vs 4.8%), and pacemaker implantation (2.1% vs 6.0%) but higher incidence rates of thromboembolic complications (10.6% vs 7.1%) and adverse drug effects (8.5% vs 3.6%).34 These data suggest that several clinically important outcomes may improve when sinus rhythm is achieved and maintained. The trial was not adequately powered to truly assess mortality risk associated with treatment approach.

While AFFIRM and RACE taken together suggest that at present, a rhythm control approach has no survival benefit over a rate control approach in AF, several additional observations may provide “food for thought” about benefits if sinus rhythm is attained and maintained.

**DIAMOND**

The DIAMOND trials assessed the safety of dofetilide vs placebo in heart failure patients. An AF substudy in DIAMOND, DIAMOND AF (N=506), investigated the potential of dofetilide to restore and maintain sinus rhythm in patients with AF or atrial flutter in this population.15 Differences in favor of dofetilide were observed for the primary endpoint; cardioversion occurred in 44% of dofet-
ilide-treated patients and 14% of placebo-treated patients over the course of the study (P<0.001). The 1-year probabilities of maintainingsinus rhythm were 79% with dofetilide and 42% with placebo (P<0.001). Importantly, while there was no significant difference in mortality between the two therapies, regardless of treatment, the mortality rate was significantly lower in patients who experienced restoration and maintenance of sinus rhythm than in those who did not convert to sinus rhythm (risk ratio: 0.44; 95%; CI: 0.30-0.64; P<0.0001).

**STAF**

The STAF pilot trial compared rate vs rhythm control in 200 patients with persistent AF. There was no significant difference between the treatment groups in the primary endpoint, a composite of death, stroke or transient ischemic attack, systemic embolism, and cardiopulmonary resuscitation, occurring in 9 of 100 patients in the rhythm-control group and 10 of 100 in the rate-control group. Notably, however, only 1 of the 19 patients was in sinus rhythm at the time of the primary outcome event (P=0.049), reminiscent of the benefit seen in DIAMOND AF if sinus rhythm were established on dofetilide, and to the AFFIRM substudy regarding the maintenance of sinus rhythm (see above). The above data sets taken in combination do not appear to indicate that rate control is as good as rhythm control with respect to survival, but rather, that the benefit of sinus rhythm may be obscured by the adverse effects of some of our rhythm control therapies, at least in some patient populations. There remains much still to learn.

**PIAF and HOT-CAFE**

Two additional small studies comparing rate versus rhythm control, similar in magnitude to STAF, were also performed at a similar point in time: PIAF and HOT-CAFE. They, too, revealed no significant difference in their primary endpoints by a rate versus rhythm control strategy (using intention-to-treat analysis), were too small to assess mortality events, and are not detailed further here. However, relevant information on quality of life derived from these trials is explored below in a subsequent section of this manuscript.

**CHF-STAT**

The CHF-STAT trial, which compared ICD treatment, amiodarone, and best medical therapy in specific patient types with heart failure, included a subgroup of 103 patients who had both AF and HF at baseline. Deedwania and colleagues reported the effects of amiodarone versus placebo in converting and maintaining sinus rhythm relative to survival patterns in this subgroup. Sixteen of 51 amiodarone-treated patients (31.4%) and 4 of 52 patients receiving placebo (7.7%) converted to and remained in sinus rhythm for the duration of the study (P=0.002). Although no difference in mortality rate was noted between the two treatment groups overall, the survival rate was significantly higher among amiodarone-treated patients who converted and remained in sinus rhythm (n=16) than for amiodarone-treated patients who remained in AF (n=35, P=0.04). The small numbers involved in this report are too insignificant to weigh importantly in their own right, but they are consistent with the sinus rhythm survival benefit story built from the AFFIRM substudy, the trend based upon reduced mortality (when examined as one component of the composite endpoint) in RACE, the DIAMOND AF data, the STAF report, and the J-Rhythm trial (see below).

**J-Rhythm**

In the J-Rhythm trial, QOL, a secondary endpoint, was assessed using the Atrial Fibrillation Quality of Life Questionnaire. While the number of patients who completed the questionnaire was not reported when results were presented at the Heart Rhythm Society meeting in 2007, 36 maintenance of sinus...
rhythm occurred more frequently in the rhythm control group than in the rate control group (P=0.0027) and resulted in greater improvements in the frequency and duration of symptomatic symptoms among patients with PAF. The severity of symptoms and AF-related anxiety and limitations of activity were similar in the two therapeutic arms.

**Maintenance of Sinus Rhythm and Progression of AF**

Although results from the studies reviewed herein suggest, but do not yet prove, that there are benefits to achieving sinus rhythm with respect to overall mortality, and almost uniformly suggest that sinus rhythm is associated with a better QOL than is AF in most patients, it is more difficult to assess the important issue as to the role of sinus rhythm control in preventing the progression of AF from the initial episode to permanent AF. Dittrich and colleagues showed that maintenance of sinus rhythm at 1 month after cardioversion was more likely in patients with an AF duration of <3 months than in those with AF duration of >12 months (P<0.05). This is consistent with the hypothesis that there is greater potential for reverse remodeling and long-term maintenance of normal sinus rhythm when normalization is achieved early in the course of treatment. In addition, the PAF 2 trial showed that pharmacologically controlled sinus rhythm after ablation and pacing therapy lowered the risk of progression from PAF to permanent AF by 57% (P=0.02). Similarly, RACE demonstrated that maintenance of sinus rhythm was associated with reduced atrial size (remodeling) and improved left ventricular function (P<0.05) and in HOTCAFE, only patients in the rhythm control group had an increase in left ventricular fractional shortening (P<0.001).19

Just as the results of these studies are consistent with a progressive model of AF pathophysiology and suggest a possible role for early intervention to reverse and/or prevent the progression of AF, so too are the observations in several drug and ablation studies which have shown that atrial size can regress toward normal and atrial function can improve with the attainment of sinus rhythm. However, complete normalization of size and full restoration of function do not generally occur and further investigation into these remodeling issues is required, and, in addition, little data exist regarding restoration of atrial secretory function and reduction in biochemothrombogenic factors in patients who achieve and maintain normal sinus rhythm. Thus, discontinuation of anticoagulation should not be considered at this time for AF patients with a significant CHADS2 score despite their conversion to and maintenance of sinus rhythm.

**One additional observation**

There are several additional important AF trials beyond those cited above. They have not been explored herein as they did not compare rate versus rhythm control strategies, did not assess mortality as an endpoint, and/or did not provide additional important analyses of quality of life outcomes. However, two, the RAFT and ERAFT trials, pivotal to the approval of sustained release propafenone for the maintenance of sinus rhythm in AF patients, are worth mentioning for one additional purpose. RAFT was a prospective, double-blind, placebo-controlled trial designed to test the efficacy and safety of 225 mg, 325 mg, and 425 mg bid in reducing the frequency of symptomatic recurrences in patients who were in sinus rhythm but had a history of symptomatic AF. ERAFT was a prospective, double-blind, placebo-controlled trial designed to test the efficacy in reducing recurrent paroxysmal AF in patients with prior symptomatic AF who were in sinus rhythm at drug initiation. Both trials documented a superior efficacy for sustained release propafenone over placebo (and contributed to FDA approval of the product) but the relative efficacy rates of identical doses were different in the two trials. In RAFT, the median time to the occurrence of a primary outcome event was 41 days for placebo, 291 days for 325 mg bid, and 300 days for 425 mg bid (the latter being a non-exact number because a large percentage of patients did not have any recurrence on the 425 mg bid dose). In ERAFT, the median time to occurrence of a primary outcome event was 9 days for placebo, 35 days for 325 mg bid, and 44 days for 425 mg bid. Why is there such a discrepancy in the time to first recurrence with the same drug and dose in the two trials and what lesson is there to learn from this? The major reason is the difference in
the patient demographics, with the ERAFT patients having much longer AF history and more frequent prior events than the patients inRAFT. The lesson to be learned is that one cannot safely or effectively compare the magnitude results of drug outcomes across different trials, even when using the same agent in the same dose(s). Only direct comparisons in a single trial with a single population can be considered accurate. Furthermore, because beta blockers and, to some extent, verapamil, through sympatholytic actions, can enhance the electrophysiologic and antiarrhythmic effects of antiarrhythmic drugs (such as by preventing their reversal during times of spontaneous increased sympathetic activity, e.g., stress, exercise), differences in concomitant rate control drugs across different clinical trials may also confound accurate assessment of magnitude of antiarrhythmic drug effects in different trials, and even, at times, within a single trial. Nonetheless, directional similarities across trials do provide important observations.

Conclusions: Lessons Learned

The clinical trials conducted to date in patients with AF do not show an advantage to a strategy of rhythm control over rate control. However, based on the available data, clear and thorough comparison of outcomes between patients who achieve normal sinus rhythm and those who achieve rate control are not possible because of the variety of limitations discussed above. For example, use of the ITT approach to data analysis is not particularly relevant to everyday practice, but is the primary method—and sometimes the only method—of analysis reported in peer-reviewed publications. Also problematic is the fact that many patients will remain in AF despite treatment with the currently available antiarrhythmic drugs, and this lack of efficacy is frequently accompanied by adverse-event profiles that are less than ideal. In contrast, it is important to note that several non-ITT analyses have found reductions in mortality and improvements in QOL, functional status, and exercise tolerance when sinus rhythm was achieved and maintained. From a theoretical standpoint, early restoration and maintenance of sinus rhythm may result in reversal of atrial remodeling and in slowing or preventing AF disease progression, and this merits some consideration. Therefore, when considering the currently available options for treatment, it should be remembered that no single strategy is universally beneficial, and treatment must be individualized for each patient. The development of new antiarrhythmic drugs with improved efficacy and tolerability profiles and additional data concerning the absolute and comparable value of ablative approaches should facilitate a more meaningful and detailed assessment of the benefits of sinus-rhythm control strategies in patients with AF.

References


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