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Rate Versus Rhythm Control Pharmacotherapy For Atrial Fibrillation: Where are We in 2008?

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Abstract

Atrial fibrillation (AF) is the most common sustainedcardiac rhythm disturbance encountered by physicians. The management of AF isfocused on control of heart rate, correction of rhythm disturbance, andrisk-determined prophylaxis of thromboembolism. The goals of AF therapy are, aswith other serious disorders, to reduce mortality (if possible) and morbidity(improve quality of life, [QOL]). To this end, several large studies haveexamined rhythm-control versus rate-control strategies. Although a survivaladvantage to using rhythm control with currently available antiarrhythmic drugshas not been proven, neither has there been a significant excess risk versusrate control. Therefore, using our current therapies, the results have notsupported rate control or rhythm control as being a preferable first-linetherapy for AF as regards survival; importantly, neither do they disprove the hypothesis thatmaintenance of sinus rhythm is preferable to the continuation of AF,particularly if rate control fails to restore adequate QOL. Many post-hocanalyses and substudies have assessed QOL, functional status, and exercisetolerance, with the majority demonstrating important benefits associated withachievement of rhythm control. This review examines rate and rhythm controloptions, the clinical outcomes of several important AF trials, discusses thelimitations in applying the major morbidity/mortality findings to everydayclinical practice, and summarizes the lessons learned.

Introduction

Atrial fibrillation (AF) is the most commonsustained cardiac rhythm disturbance encountered in clinical practice.[1] It is characterized by the absence of discreteorganized atrial activity on the electrocardiogram,uncoordinatedatrialactivation, disordered contraction of the atrium, and the deterioration ofatrial mechanical function. AF is currently estimated to affect between 2.3and 5.1 million people in the United States alone, with expected rates of 5.6to 15.9 million by the year 2050 as an even greater segment of our populationreach older age,[2,3] and marked multiples thereof worldwide. AFâ€™sprevalence has been estimated at 1% in the general population, with higherrates in both the elderly (>7% and >10% in women and men ≥80 yearsold, respectively) and in those with heart failure (HF) of progressivelyincreasing severity.[2,4] AF often is associated with underlying structuralheart disease, including hypertension (~50-80% of AF patients in all recentlarge clinical trials), coronary artery disease (25%), HF (23%-29%), andvalvular heart disease (17%).[5]

Symptoms of AF may include palpitations, angina,dyspnea, lightheadedness (and, rarely, syncope) [all of which may betachycardic related and/or secondary to the altered mechanics of AF]; chronicfatigue [which, in my experience, almost always requires restoration of sinusrhythm for resolution]; and/or impaired exercise tolerance.

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However, AF may beasymptomatic at all times in some patients and at some times in patients withotherwise symptomatic periods or episodes. Irrespective of symptoms, all-causemortality is increased 1.5- to 1.9-fold in association with AF compared withmortality rates in individuals in sinus rhythm.6This may be the consequence of interactions with underlying disorders,consequences of our therapeutic decisions, consequences of adversely alteredhemodynamics, and/or consequences of uncontrolled tachycardic rates or emboli.Concordantly with the above, AF can cause hemodynamic impairment with decreasedcardiac output; can induce cardiomyopathy and HF, particularly when ventricularrates are rapid; and can be associated with an increased risk of stroke inselected AF populations.[7-9] Health-related qualityof life (QOL) is adversely affected by the presence of AF in most patients,with patients potentially experiencing discomfort due to symptoms, functionalimpairment due to chronic fatigue, exercise intolerance, and/or the effect oftheir AF-related medications, and anxiety due to fear of anticoagulationtherapy and the potential for bleeding.[10, 11] Furthermore, AFis associated with a significant economic burden. Healthcare costs areapproximately 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 treatmentoptions (most notably, rhythm versus rate control strategies) and their successrates in patients with AF.[14-19] Although thestudies conducted to date with currently available therapies have not demonstrateda survival advantage using rhythm control strategies versus rate controlstrategies in AF, these results should not be interpreted to indicate that rate control is aspreferable a 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 inaddition to, and, perhaps, at a higher priority than, the issue of overallsurvival.Commonly, restoration of an acceptable QOL requires the pursuit ofsinus rhythm, despite the lack of any simultaneous beneficial survivaladvantage for the therapy employed. This review examines rate and rhythmcontrol approaches as well as the clinical outcomes of several important AFtrials, their limitations, and the lessons learned from them.

Patterns of AF and their impact on rate andrhythm control considerations

AF presents in specific patterns and can beclassified as paroxysmal (self-terminating) [with some authors adding thedictate that it last <7 days], persistent (not self-terminating) [with someauthors adding the dictate that it last >7 days], and permanent (lasting>1 year, being refractory to cardioversion, and/or with sinus rhythm nolonger to be pursued).20 Paroxysmal AF (PAF) andpersistent AF are not mutually exclusive as individuals may experience both atdifferent times. Treatment goals differ with presentation pattern (Table 1).

AF in patients without evidence of cardiopulmonarydisease, including hypertension, is generally referred to as lone AF. However,genetic factors that contribute to the development of lone AF are beingincreasingly recognized, as are associations between lone AF and sleepdisorders, autonomic contributors, and obesity Lone AF is more common inyounger patients with PAF than in older patients with persistent AF.[21] Although patients with lone AF have a lower riskof stroke and mortality, their risk for thromboembolic events andcardiovascular comorbidities increases with age.[22]

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

The rate and rhythm treatment approaches to PAF areto reduce symptoms during episodes (rate control) and to reduce the number andduration of episodes when QOL so demands (rhythm control with a chronicallyapplied 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 topersistent AF episodes are to reduce the symptoms during the episodes (ratecontrol) and to restore sinus rhythm such that permanent AF is not established(cardioversion, either by pharmacologic or electrical methods), as well as toreduce the frequency of episodes when QOL so demands (rhythm control with achronically applied regimen). Infrequent but tolerable persistent AF may betreated with intermittent cardioversion (which is especially attractive when itcan be attained pharmacologically) and does not necessarily require chronic suppressiveantiarrhythmic therapy (either drug or ablative). This is an important butcommonly overlooked treatment alternative, with oral class IC single dosetherapy being effective in up to 80% of patients with a mean conversion timeapproximating four hours.[25, 26]

Permanent AF, by definition, requires rate controlbut not the pursuit of rhythm control; however, recent reports of some successwith restoring sinus rhythm with ablational approaches even in some patientswith long-standing ongoing AF may cause us to revisit our definitions of andour approaches to therapy of â€œpermanentâ€&AF. Finally, rate control is needednot only to reduce tachycardic associated symptoms during AF events (seeabove), but also to prevent the development of a tachycardic inducedventricular myopathy, independent of whether the AF event is itself symptomaticor not.

Rate Control Therapies

Rate control, as has been well described 27 in many prior reviews, including themost recent ACC/AHA/ESC guidelines, 20 can beachieved pharmacologically in most patients using beta blockers, verapamil ordiltiazem, and digitalis, singly or in combination. Of these, only digitalisdoes not have the potential to simultaneously reduce blood pressure. Ingeneral, blood pressure is less likely to drop with beta blockers than withcalcium channel blockers in older patients. Clinical pearls concerning ratecontrol are relatively few, aside from knowing that: 1) clonidine can be usedto potentiate the effect of the other above-named agents, when blood pressureallows, thus enhancing the possibility for adequate rate control but with thelikewise enhanced risk of sinus nodal and AV nodal dysfunction if/when sinusrhythm reappears; 2) pindolol is less likely than verapamil, diltiazem, or anyother available beta blocker to produce worsened sinus node function inpatients with the brady-tachy syndrome, and hence, is the preferred agent inthis condition where its use may avoid the necessity of inserting a pacemakerto support the use of an alternative AV nodal blocking agent; 3) ablation of ordrug suppression of an antegradely conducting bypass tract is necessary inaddition to AV nodal blockade to attain rate control in patients withpreexcitation; 4) amiodarone can be effective in providing ventricular ratecontrol but is rarely indicated for this purpose alone given its toxic profile(whereas, the currently investigational and apparently less toxic derivative ofamiodarone, dronedarone, may be if and when it becomes available); [these twoagents can also provoke sinus nodal and AV nodal dysfunction in sinus rhythmwhen underlying dysfunction is present, and, in addition, amiodarone anddronedarone may effect pharmacological cardioversion beyond rate control, soanticoagulation management is needed if/when these agents are given to patientswith persistent AF or to patients with PAF of uncertain or protractedduration]; 5) when drug therapy is ineffective or not tolerated, ablation of AVconduction and implantation of a permanent pacemaker is an appropriate andeffective alternative approach to achieving rate control. Physiologically, thetarget for rate control should be the attainment of approximately the sameventricular rate for the same activity state as would be likely for the patientat 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 theventricular rate on the ECG. Rather, ambulatory ECG assessment, such as byHolter monitoring, is the optimal way to determine the status of rate controlin a patient in AF.[20] If only a resting ECG isperformed, it is not possible to tell whether residual symptoms during dailyactivity or exercise are due to inadequate rate control or whether they persistdespite rate control and will necessitate the pursuit of sinus rhythm
for their further resolution.

Rhythm Control Therapies

Rhythm control requires cardioversion in persistentAF and often requires an antiarrhythmic strategy (drug or ablation, +/- pacingin brady-tachy patients) for the maintenance of sinus rhythm in both persistentAF and PAF patients. It is beyond the scope of this review to discuss eitherthe available antiarrhythmic drugs used for this purpose or the current stateof ablative technology, approaches, and outcomes when used for AF patients. The interested reader is referred to the ACC/AHA/ESC management guidelines20 and other recent therapeutic reviews for more detailson specific therapies.

Restoration and Maintenance of Sinus Rhythm inPatients with AF

The treatment and management of AF are focused onfour main goals: management of any underlying contributing disorder andreduction of its pathophysiology when feasible, control of ventricular rate,correction of the rhythm disturbance when necessary, and prophylaxis ofthromboembolism.[20] Although it has often beendebated as to whether rate or rhythm control is a preferable strategy, thesestrategies are not mutually exclusive and the debate is often artificial. Ratecontrol is necessary even when a rhythm control strategy is being considered. Abolition of symptoms with rate control may eliminate the necessity forsuppression of AF, and, rate control will be needed if antiarrhythmic therapyfails to prevent all AF and recurrences occur. Nonetheless, the choice of oneover 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, andthe safety profiles of the treatments under consideration. Of note, prophylaxisof thromboembolism must be considered irrespective of treatment strategy; theneed for anticoagulation therapy is based on the overall risk of stroke –not on the restoration or maintenance of sinus rhythm, whether by pharmacologicor ablative approaches. [However, as anticoagulation is not a focus in thisreview it will not be covered further herein.

Defining Success in the Treatment of AF

The treatment of AF is ultimately aimed at reducingmorbidity and improving QOL in AF patients, and, if feasible, reducing any riskof mortality associated with AF in the given patient. However, AF therapy isnot required for all patients with

Table 1 AF Patterns and Treatment Approaches(excluding anticoagulation)

PAF
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)
Persistent AF
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.
After treatment of a precipitating cause such as acute myocardial infarction , cardiac or thoracic surgery, hyperthyroidism, pneumonia, or pericarditis
Permanent AF
Reduce symptoms and prevent tachycardia-induced cardiomyopathy (rate control)

AF.For example, infrequent, transient,minimally symptomatic episodes probably do not require treatment. Moreover,recurrences of this type during drug therapy may not constitute treatmentfailure. Hence, therapy (drug or otherwise) should be matched to presentation characteristicsand should be focused on appropriate target goals with a simultaneous concernfor minimizing the potential for adverse effects. In addition to survival andQOL, our current state of medical costs and payments necessitates a thirdtreatment goal: that of reducing the economic and societal burden of AF.

The determination of whether the pursuit andmaintenance of sinus rhythm should be the primary or default goal for mostpatients with AF has been the topic of several recent important trials (Table2).Between 2000 and 2003, five major prospective trials – AFFIRM, RACE,PIAF, HOT CAFE, and STAF – compared outcomes with rhythm- versusrate-control strategies.[14-19] In each of thesetrials attainment of a significant difference in the primary endpoint -- amortality benefit or a composite endpoint benefit (or a survival benefit whenassessable as part of a composite endpoint) -- associated with rhythm-controlstrategy over a rate control strategy using intention-to-treat (ITT) analysesproved to be elusive (see more detailed discussion below). However, theseresults should not be taken to suggest that a rate-control strategy isequivalent to maintenance of sinus rhythm. It merely suggests that, using anITT assessment of currently available antiarrhythmic therapies, the rhythm- andrate-control strategies appear to be equivalent with regard to length of lifeor composite assessments including survival. These trials do not disprove thehypothesis that if one were to attain and maintain sinus rhythm with safermethods than exist at present, NSR would be preferable to the continuation ofAF. Moreover, and importantly, becauserhythm control did not carry a statistically significant excess risk over ratecontrol in these studies, the results do not support rate control as asufficient strategy when it does not restore adequate QOL in patients with AF.

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

Table 2 | **Rate versus Rhythm Control Trials in Atrial Fibrillation**

No significant difference in survival or primary composite endpoint by ITT analysis
AFFIRM [16]
RACE [17]
STAF[18]
PIAF [44]
HOT-CAFÉ [19]
J-RHYTHM [36] Note : Sinus was associated with better event-free survival in PAF subgroup
AF-CHF [37]
Improved survival or primary composite endpoints in association with rhythm control (see text)
AFFIRM [30] Subanalysis indicated better survival in sinus rhythm offset by worse survival with antiarrhythmic drugs
RACE [33,34] Better survival with NSR if it was maintained, but not with antiarrhythmic drugs
DIAMOND Better survival if sinus rhythm was AF 15 attained and maintained
STAF [18] Despite balanced event rates between rate and rhythm control arms, 18 of 19 events occurred during AF; only 1 during sinus rhythm
CHF-STAT [35] Survival was greater in amiodarone-treated patients who attained and maintained NSR than those who remained in AF on amiodarone.

were in AF or sinus rhythmor whether they actually received and continued the therapy they wererandomized to receive. Once assigned to a treatment arm, all patients wereanalyzed as though they were fully compliant with their therapy and did notcross over to the alternative treatment, whether or not this was the case.Outcomes in clinical trials such as these are further biased by the innateproperties and adverse effects of the treatments. While the ITT approach may bestatistically desirable and provide information on the likelihood of a givenoutcome if a particular treatment strategy is chosen, it does not necessarilyprovide information on what actually happens if patients take and continuetherapy. When discontinuation or compliance rates differ markedly between twotherapies, this type of analysis is biased. (For instance, a comparison of drugand nonpharmacologic therapies would inherently be biased to show greaterefficacy 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 outcomesfor patients who actually initiate and continue without interruption theirassigned therapy. These analyses provide information on the likelihood of aparticular outcome when a therapy is administered and complied with, but not onthe likelihood of overall outcomes for therapeutic strategies being compared(i.e., the ITT population). Because some patients may be excluded from efficacyor on-therapy analyses, such as those never started on therapy, those who donot continue therapy, etc., unequal group sizes and durations of therapy (forexample) may arise and confound the interpretation of findings. The innateproperties and adverse-event profiles of the specific treatments also maycontribute to bias. For example, patients who discontinue their assignedtreatment early in a study, because of adverse events or insufficientefficacy create additional bias in the study results. In the case of AF, oneimportant contributing factor to the bias in an efficacy analysis is thatcurrently it is usually not realistic to expect that patients will always bemaintained in sinus rhythm in real-world clinical practice (given the efficacyand adverse event profiles of currently available drugs); thus, a stand-aloneefficacy analysis without the context of an ITT evaluation would be of limitedclinical usefulness.

Other important biases may apply to both the ITT andefficacy/on-therapy analyses; for example, the definition of treatment successand failure. Historically, a recurrence of AF has been interpreted as treatmentfailure in AF clinical trials, such as in time to first event endpoints. Inclinical practice, such a sole definition of success and failure is notappropriate. A change in the pattern of AF from "frequent and protracted" to"rare and briefâ" would constitute clinical success in actual practice. Forexample, in a patient with frequent PAF if two therapies both reduced episodesto 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**

1. Administer aspirin 81 to 325 mg daily for patients with no risk factors
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
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.
Moderate-risk factors include age ≥75 years, hypertension, heart failure, LV ejection fraction ≤35%, or diabetes mellitus
High-risk factors include prior stroke, transient ischemic attack or embolism, mitral stenosis, prosthetic heart value*
*If mechanical valve, the INR should be maintained between 2.5-3.5 Adapted from Fuster V et al [183]

or 6 months wouldbe of no real significance clinically. And, perhaps, it may not really matterif there were two versus three episodes that year. As with angina, a decreasein the incidence of AF recurrence should be considered a treatment success inAF trials. The complete absence of AF recurrence may be unachievable andimpractical, whereas fewer and shorter AF episodes would be a more realisticgoal from the standpoint of everyday clinical practice.

Additionally when assessing a treatment strategy,the definition of success may confound clinical and trial impressions. Despitemy discussion of a functionally clear assessment of attainment of adequate ratecontrol above, there have been substantial differences concerning rate controlassessment in different trials, and various target rates for resting and activestates have been used. The lack of a well-defined target rate may lead to lessaggressive titration of rate-control drugs, which can lead to underestimationof the adverse-event rates associated with these agents, and failure to fullyassess the optimum benefits attainable with these agents. [For example, lowerdoses of beta-blockers are associated with lower rates of adverse eventsbecause many of the events are dose dependent.] Furthermore, heart rate mayvary by activity level, time of day, and/or dosing schedule which can furthercomplicate interpretation of study results. Similarly, definitions ofeffective therapy endpoints are important in rhythm control assessments. Forexample, in patients with infrequent persistent AF or prolonged PAF episodes,termination by intermittent cardioversion, especially if by oral out-patientsingle dose pharmacologic conversion, may be more acceptable to the patientthan is the taking of daily suppressive therapy; yet, in trials such as AFFIRMand 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, lackof an adverse mortality profile associated with a therapy is an importantcriterion of success for any treatment. However, by itself, consideration ofsurvival alone is not a sufficient measure. QOL in patients with AF has beenshown to be poorer than that of the general population and even worse than thatof patients with coronary heart disease.[28] QOLis a subjective measure that is affected by many consequences of AF, as well asby its therapy and the patientâ€™s QOL can be affected on a daily basis by AFsymptoms, complications, and/or therapy. Thus, while a therapy that reducedsymptoms but increased mortality would not likely be acceptable, one with noeffect on QOL with a neutral effect on survival would also be clinicallyuseless. In addition, as with all medical decisions, costs associated withtherapies to be employed must also be considered, and reduced economic burdenis another important measure of treatment success. Economic burden can beinfluenced and measured by hospitalizations, treatment costs, and costs relatedto complications, QOL issues, and the functional status of patients.

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

Effects on Mortality

AFFIRM

The AFFIRM study (N=4060) compared rhythm and ratecontrol in patients with AF and a high risk of stroke or death.[16] 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-controlgroup (P=0.08). Interestingly, the ratesof cardiovascular death (9% and 10%, respectively) and vascular death (3% and3%, respectively) were comparable between the two treatment arms, whereasnoncardiovascular deaths were significantly higher in the rhythm-control group(12% vs 8% for rate control; P=0.0008),[29] driven primarily by pulmonary and cancer-relateddeaths. The drug used most commonly in the rhythm-control arm was amiodarone(approximately 2/3 of the cases).

Rhythm- and rate-control strategy comparisons inAFFIRM were limited by the constraints of the prespecified ITT analysis.[16] In AFFIRM, many patients randomized to therhythm-control arm remained in AF rather than attaining and maintaining sinusrhythm (17.6%, 26.7%, and 37.4% at

1, 3, and 5 years), while many patients inthe rate-control arm were in sinus rhythm for some or most of the time evenwithout an antiarrhythmic drug (34.6% at 5 years), having suffered only PAF. Thus, AFFIRM compared treatment algorithms based on currently availabletherapies and strategies, not outcomes based on whether a patient was in AF orin sinus rhythm. Two additional observations made in AFFIRM are also importantto 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 relatedto drug toxicity (see above). Notably, in AFFIRM, after adjusting for thepresence of sinus rhythm, sinus rhythm was associated with a better survivalrate (P<0.0001). Importantly,however, this analysis included patients in the rate control arm with PAF whowere in sinus rhythm during follow up visits without the use of anantiarrhythmic agent. The above results suggest that the antiarrhythmic drugsused in AFFIRM were neither highly efficacious nor safe, at least in thepatient population enrolled in AFFIRM. Extrapolation of these results to otherpopulations, such as younger patients and those without associated riskfactors, in which therapy options other than those used in AFFIRM might beconsidered, would/could be hazardous/inappropriate. Approximately 60% of theAFFIRM population was male, and most had persistent AF (69%) rather than PAF(31%). Very few had lone AF (12%).16 About 23% ofpatients also had HF. The mean age approximated 70 years. A subanalysis of datafrom AFFIRM suggests that younger patients (<65 years of age) and those witha history of HF may derive a greater survival benefit with rhythm-control drugs.31 Additionally one cannot exclude from AFFIRM thata survival benefit with rhythm control might occur were the trial to be doneagain with therapies that possesses a better safety profile, should some becomeavailable. The role of rhythm control in AF patients with HF is being furtherinvestigated in the AF-CHF study (see below).32 Notably,the other factor that was associated with better outcome in AFFRIM wasanticoagulation. The incidence of stroke, some of which were fatal, wassomewhat lower in the rate control than the rhythm control treatment arm.Importantly, most strokes occurred in patients who had terminatedanticoagulation therapy or were receiving subtherapeutic levels of warfarin. Thesefindings have been taken to suggest that all patients with AF with risk markersfor stroke should receive anticoagulation therapy irrespective of treatment andrhythm outcome.

RACE

The RACE trial (N=522) studied patients withpersistent AF and mild to moderate HF who were rate controlled vs cardiovertedand assigned a rhythm control therapy.[17] Acomposite outcome measure that included cardiovascular death, hospitalizationsfor HF, thromboembolic complications, severe hemorrhage, pacemakerimplantation, and severe adverse events was the primary endpoint. Overall, nodifference in the primary endpoint was observed between the treatment arms.Moreover, in a subanalysis, patients who remained in sinus rhythm whilereceiving rhythm control and anticoagulation did not have a better prognosisfor survival.[33] However, a post-hoc analysisshowed that those in sinus rhythm compared with patients in AF at the end ofthe study had lower rates of cardiovascular mortality (0% vs 9.5%), progressionof 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% vs7.1%) and adverse drug effects (8.5% vs 3.6%).[34] These datasuggest that several clinically important outcomes may improve when sinusrhythm is achieved and maintained. The trial was not adequately powered totruly assess mortality risk associated with treatment approach.

While AFFIRM and RACE taken together suggest that atpresent, a rhythm control approach has no survival benefit over a rate controlapproach 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 dofetilidevs placebo in heart failure patients. An AF substudy in DIAMOND, DIAMOND AF(N=506), investigated the potential of dofetilide to restore and maintain sinusrhythm 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% ofplacebo-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 nosignificant difference in mortality between the two therapies, regardless oftreatment, the mortality rate was significantly lower in patients whoexperienced restoration and maintenance of sinus rhythm than in those who didnot 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 controlin 200 patients with persistent AF.[18] There wasno 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 therhythm-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 ofthe benefit seen in DIAMOND AF if sinus rhythm were established on dofetilide,and to the AFFIRM substudy regarding the maintenance of sinus rhythm (seeabove). The above data sets taken in combination do not appear to indicatethat rate control is as good as rhythm control with respect to survival, butrather, that the benefit of sinus rhythm may be obscured by the adverse effectsof some of our rhythm control therapies, at least in some patient populations. There remains much still to learn.

PIAF and HOT-CAFE

TTwo additional small studies comparing rate versusrhythm control, similar in magnitude to STAF, were also performed at a similarpoint in time: PIAF and HOT-CAFE.[14,19] They, too,revealed no significant difference in their primary endpoints by a rate versusrhythm control strategy (using intention-to-treat analysis), were too small toassess mortality events, and are not detailed further here. However, relevantinformation on quality of life derived from these trials is explored below in asubsequent section of this manuscript.

PIAF and HOT-CAFE

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CHF-STAT

TThe CHF-STAT trial, which compared ICD treatment,amiodarone, and best medical therapy in specific patient types with heartfailure, included a subgroup of 103 patients who had both AF and HF atbaseline. Deedwania and colleagues 35 reported theeffects of amiodarone versus placebo in converting and maintaining sinus rhythmrelative to survival patterns in this subgroup. Sixteen of 51amiodarone-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 inmortality rate was noted between the two treatment groups overall, the survivalrate was significantly higher among amiodarone-treated patients who convertedto and remained in sinus rhythm (n=16) than for amiodarone-treated patients whoremained in AF (n=35; P=0.04).The small numbers involved in this report are too insignificant to weighimportantly in their own right, but they are consistent with the sinus rhythmsurvival benefit story built from the AFFIRM substudy, the trend based uponreduced 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, wasassessed using the Atrial Fibrillation Quality of Life Questionnaire. While thenumber of patients who completed the questionnaire was not reported when resultswere presented at the Heart Rhythm Society meeting in 2007, 36 maintenance of sinus

rhythm occurred more frequently in the rhythm controlgroup than in the rate control group (P=0.0027)and resulted in greater improvements in the frequency and duration of symptomsamong patients with PAF. The severity of symptoms and AF-related anxiety andlimitations of activity were similar in the two therapeutic arms.

Maintenance of Sinus Rhythm and Progression of AF

Although results from the studies reviewed hereinsuggest, but do not yet prove, that there are benefits to achieving sinusrhythm with respect to overall mortality, and almost uniformly suggest thatsinus rhythm is associated with a better QOL than is AF inmost patients, it ismore difficult to assess the important issue as to the role of sinus rhythmcontrol in preventing the progression of AF from the initial episode topermanent AF. Dittrich and colleagues 48 showedthat maintenance of sinus rhythm at 1 month after cardioversion was more likelyin patients with an AF duration of <3 months than in those with AF durationof >12 months (P<0.05). This isconsistent with the hypothesis that there is greater potential for reverse remodelingand long-term maintenance of normal sinus rhythm when normalization is achievedearly in the course of treatment. In addition, the PAF 2 trial showed thatpharmacologically controlled sinus rhythm after ablation and pacing therapylowered the risk of progression from PAF to permanent AF by 57% (P=0.02).49 Similarly,RACE demonstrated that maintenance of sinus rhythm was associated with reducedatrial size (remodeling) and improved left ventricular function (P<0.05)50 and in HOTCAFE, only patients in the rhythmcontrol group had an increase in leftventricular fractional shortening (P<0.001).[19]

Just as the results of these studies are consistentwith a progressive model of AF pathophysiology and suggest a possible role forearly intervention to reverse and/or prevent the progression of AF, so too arethe observations in several drug and ablation studies which have shown thatatrial size can regress toward normal and atrial function can improve with theattainment of sinus rhythm. However, complete normalization of size and fullrestoration of function do not generally occur and further investigation intothese remodeling issues is required, and, in addition, little data existregarding restoration of atrial secretory function and reduction in biochemicalthrombogenic factors in patients who achieve and maintain normal sinus rhythm.Thus, discontinuation of anticoagulation should not be considered at this timefor AF patients with a significant CHADS2 score despite theirconversion to and maintenance of sinus rhythm.

One additional observation

There are several additional important AF trialsbeyond those cited above. They have not been explored herein as they did notcompare rate versus rhythm control strategies, did not assess mortality as atarget (alone or part of a composite) in their primary endpoint, and/or did notprovide additional important analyses re quality of life outcomes. However,two, the RAFT and ERAFT trials, pivotal to the approval of sustained releasepropafenone for the maintenance of sinus rhythm in AF patients,51,52 are worth mention for one additional purpose. RAFTwas a prospective, double-blind, placebo-controlled trial designed to test theefficacy and safety of 225 mg, 325 mg, and 425 mg bid in reducing the frequencyof symptomatic recurrences in patients who were in sinus rhythm but had ahistory of symptomatic AF. ERAFT was a prospective, double-blind,placebo-controlled trial designed to test the efficacy and safety of 325 and425 mg bid (but not 225 mg) efficacy in reducing recurrent symptomaticparoxysmal AF in patients with prior symptomatic AF who were in sinus rhythm atdrug initiation. Both trials documented a superior efficacy for sustainedrelease propafenone over placebo (and contributed to FDA approval of theproduct) but the relative efficacy rates of identical doses were different inthe two trials. In RAFT, the median time to the occurrence of a primaryoutcome event was 41 days for placebo, 291 days for 325 mg bid, and >300days for 425 mg bid (the latter being a non-exact number because a largepercentage of patients did not have any recurrence on the 425 mg bid dose). InERAFT, the median time to occurrence of a primary outcome event was 9 days forplacebo, 35 days for 325 mg bid, and 44 days for 425 mg bid. Why is there sucha discrepancy in the time to first recurrence with the same drug and dose inthe two trials and what lesson is there to learn from this? The major reasonis the difference in

the patient demographics, with the ERAFT patients having amuch longer AF history and more frequent prior events than the patients inRAFT. The lesson to be learned is that one cannot safely or effectivelycompare the magnitude results of drug outcomes across different trials, evenwhen using the same agent in the same dose(s). Only direct comparisons in asingle trial with a single population can be considered accurate. Furthermore,because beta blockers and, to some extent, verapamil, through sympatholyticactions, can enhance the electrophysiologic and antiarrhythmic effects ofantiarrhythmic drugs (such as by preventing their reversal during times ofspontaneous increased sympathetic activity, e.g., stress, exercise),differences in concomitant rate control drugs across different clinical trialsmay also confound accurate assessment of magnitude of antiarrhythmic drugeffects in different trials, and even, at times, within a single trial. Nonetheless, directional similarities across trials do provide importantobservations.

Conclusions: Lessons Learned

The clinical trials conducted to date in patientswith AF do not show an advantage to a strategy of rhythm control over ratecontrol. However, based on the available data, clear and thorough comparisonsof outcomes between patients who achieve normal sinus rhythm and those whoachieve rate control are not possible because of the variety of limitationsdiscussed above. For example, use of the ITT approach to data analysis is notparticularly relevant to everyday practice, but is the primary method –and sometimes the only method – of analysis reported in peer-reviewedpublications. Also problematic is the fact that many patients will remain in AFdespite treatment with the currently available antiarrhythmic drugs, and thislack of efficacy is frequently accompanied by adverse-event profiles that areless than ideal. In contrast, it is important to note that several non-ITTanalyses have found reductions in mortality and improvements in QOL, functionalstatus, and exercise tolerance when sinus rhythm was achieved and maintained.From a theoretical standpoint, early restoration and maintenance of sinusrhythm also may result in reversal of atrial remodeling and in slowing or preventingAF disease progression, and this merits some consideration. Therefore, whenconsidering the currently available options for treatment, it should beremembered that no single strategy is universally beneficial, and treatmentmust be individualized for each patient. The development of new antiarrhythmicdrugs with improved efficacy and tolerability profiles and additional dataconcerning the absolute and comparable value of ablative approaches shouldfacilitate a more meaningful and detailed assessment of the benefits of sinusrhythm control strategies in patients with AF.

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