Pharmacological and electrical conversion of atrial fibrillation to sinus rhythm: Is it worth it?

Pharmacological and Electrical Conversion of Atrial Fibrillation to Sinus Rhythm Is Worth the Effort

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Current treatment guidelines for atrial fibrillation (AF) base decisions on the triad of prevention of symptoms and protection from stroke and tachycardia-mediated cardiomyopathy. Conceptually, all of these objectives could be satisfied by either timely cardioversion and subsequent rhythm control, or the admittedly easier (for the patient and the physician) rate control strategy. We feel strongly that pharmacological or electrical cardioversion is worth the effort and should in fact usher in a new paradigm for AF disease management, rather than the passive and defeatist approach currently in place.

Response by Wyse on p 1443

AF is the most frequent arrhythmia in clinical practice and a major cause of morbidity and mortality. More than 100 years after Sir James Mackenzie first described a pulse irregularity associated with disappearance of the “a” wave from the jugular pulse and paralysis of the atria, the pathophysiology of AF remains incompletely understood. However, over the last half century it was realized that electrical, contractile, and structural remodeling are fundamental contributors to the disease process of AF, potentially allowing improved and more specific therapies. Traditional therapy for AF consists of empirically tested ion channel blockers, offered without a real understanding of the pathophysiologic basis of the disease. It is therefore not surprising that pharmacological therapies for AF are neither as effective nor as safe as we would like. In major clinical trials, which have traditionally based success on absence of symptoms alone, antiarrhythmic drugs (AADs) prevent recurrent AF in 50% to 65% over short-term follow-up. It is largely due to frustration from current AADs that studies comparing rate control with rhythm control were conducted. Although the debate of rhythm versus rate control continues, it is important to realize that with either therapy, mortality trends in patients with AF remained unabated. In a longitudinal cohort study of patients with newly diagnosed AF, modern treatment provided no change in the overall age and gender-adjusted mortality over a 21-year period, even after adjustment for various comorbidities. This observation is particularly alarming in the face of the rapidly growing prevalence of AF in the United States. Our goal, therefore, should not be replacing one failed therapy with another, but finding new therapies that improve the natural history and survival of patients with AF.

AF is commonly associated with other cardiovascular diseases such as coronary artery disease or heart failure, but the causative relationship between these conditions has not
been fully determined. Although this association can be explained by the presence of common risk factors such as age, hypertension, diabetes mellitus, obesity, and valvular and nonvalvular structural heart disease, AF confers a poorer prognosis, even after adjusting for these risk factors.4–10 Thus, at a time when better therapies for coronary artery disease and heart failure result in improved longevity, the independent prognostic role of AF could be much higher. This observation also highlights the contrast between the progress we made in understanding and treating coronary disease and heart failure as opposed to AF. Up until a decade ago, therapy for heart failure largely consisted of pharmacological inotropic support, a therapy that made complete physiological sense in the failing heart with a reduced cardiac output. Similar to the therapy of AF with currently available AADs, treatment of heart failure with digoxin resulted in symptomatic improvement without conferring a survival benefit.11 Not until groundbreaking research established the fundamental role of neuroadrenegic activation in heart failure did disease-modifying therapies became available. In a similar manner, better understanding of mechanisms underlying the development and progression of AF is crucial for advancement in therapeutic options. Elucidation of the mechanisms and pathways involved in remodeling the left atria may set the stage for a new era in the therapy of AF. Selective interference in the remodeling process may halt the progression of AF or even prevent its appearance in high-risk groups of patients.

Left Atrial Remodeling in AF
Remodeling is an adaptive regulatory process of cardiac myocytes that occurs over time in order to maintain homeostasis against external stresses.12 Adaptive remodeling may occur at the ionic, genomic, cellular, and extracellular levels.13–15 If the stressor is removed early enough, this process can be reversible. However, if left untreated, irreversible cellular and extracellular changes such as apoptosis, necrosis, and fibrosis can occur as early as after 1 month. Moreover, changes in gene expression, hormone regulation, distribution of cellular ionic channels, and recalibration of energy production and expenditure all synergize to promote a self-perpetuating cascade of reactions, which leads to irreversible and deleterious maladaptive remodeling of the left atrium.

Electrical Remodeling
With the onset of AF, electrical remodeling of the left atria begins, as does the inexorable progression from paroxysmal to persistent AF. In a landmark study, Wijffels et al16 were the first to demonstrate in an experimental animal model that AF provokes structural and functional alterations that favor perpetuation of the arrhythmia. The repetitive induction of AF in goat hearts using rapid pacing induced longer-lasting episodes of AF, higher vulnerability for induction, and lower likelihood of spontaneous conversion to sinus rhythm. This phenomenon can be partially explained by the following model: At rapid atrial rates, inward calcium current significantly increases myocyte calcium load. Because high intracellular calcium concentrations can be toxic, adaptive mechanisms rapidly reduce the load to protect the cell. Early in the remodeling process, the membrane channel responsible for calcium entry becomes less active and is eventually down-regulated.17–18 These changes ultimately reduce the inward calcium current, which shortens action potential duration. Hence adaptive mechanisms that respond to intracellular calcium loads ultimately shorten the atrial refractory period, promoting functional re-entry and perpetuation of AF.19

Structural Remodeling
Structural remodeling in AF is characterized by atrial dilatation and interstitial fibrosis.20 In recent years, atrial fibrosis has been recognized as the hallmark of arrhythmogenic structural remodeling.15 Tissue fibrosis results from an accumulation of fibrillar collagen deposits, occurring most commonly as a reparative process to replace degenerating myocardial parenchyma with concomitant reactive fibrosis.20–22 Although atrial fibrosis occurs as a convergent pathological end point in a variety of cardiovascular conditions, increased collagen deposition has been documented also in patients with lone AF, highlighting the critical association between atrial fibrosis and AF.23 In the dog model, atrial fibrosis causes localized regions of conduction slowing and increased conduction heterogeneity, providing the substrate for AF.15 Although the precise mechanism of atrial fibrosis is not entirely clear, data from animal models implicate angiotensin-converting enzyme and angiotensin II as upstream regulators of profibrotic molecules such as transforming growth factor β1.24–26 These findings may have therapeutic implications, as attenuation and reversal of atrial fibrosis with angiotensin-converting enzyme–I, angiotensin II type 1 receptor blockers seems to inhibit fibrosis and result in lower susceptibility to develop AF in animal models.26–31

Prevention of Left Atrial Fibrosis
Although remodeling of the left atrium may not necessarily be the underlying cause of AF, there is substantial evidence to support its fundamental role in the cascade of events leading to the development of persistent AF. Because remodeling is a dynamic process with a wide range of pathophysiological changes occurring in a stepwise manner, interventions to remove the inciting stimuli can slow, arrest, or even reverse this process. However, if left untreated, cellular and structural changes may become irreversible, and the arrhythmia perpetuates. Data from studies in humans is limited to retrospective analyses of clinical trials with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, and 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors. These studies have demonstrated a reduction in the risk to develop AF in patients at the highest risk of structural remodeling.32 Several ongoing prospective studies promise to clarify the
effects of these drugs on atrial remodeling and the propensity to develop AF. Although these observations are early, and our ability to interrupt the pathophysiologic processes incomplete, we feel that they warrant fresh evaluation of our working paradigm. Treatment of AF should start with prevention of atrial remodeling. This can be achieved with treatment of hypertension, sleep apnea, obesity, or hyperthyroidism. Once AF occurs, early restoration of sinus rhythm can disrupt progression of atrial remodeling, whereas the addition of disease-modifying agents may possibly lead to reversal of this process.

**Risk of Stroke**

AF is the single most important cause of ischemic stroke. The rate of ischemic stroke among patients with nonrheumatic AF averages 5% per year, which is between 2 and 7 times that of individuals without AF. Moreover, the risk of stroke increases with age; in the Framingham Heart Study, the annual risk of stroke attributable to AF increased from 1.5% in participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years. Multiple studies have demonstrated that adjusted-dose warfarin reduces this risk by approximately 60%, at the cost of a small increase in serious bleeding, including intracranial hemorrhage. Although warfarin therapy is effective, the lifetime residual risk of stroke and complications of anticoagulant therapy may still be substantial.

This fact exposes the important logical inconsistency of judging therapies using the myopic lens of clinical trials. AF is potentially a lifelong disease process, with escalating risk as patients age. Although it could be argued that passive therapies work out acceptably over a 2- to 3-year time frame, it is difficult to justify allowing the inexorable progression of a process that is very likely to cause harm over the course of decades.

**Rhythm Versus Rate Control**

Timely cardioversion only makes sense in the context of appropriate therapies to maintain sinus rhythm. Randomized trials comparing rhythm and rate control strategies over a short time frame have consistently failed to demonstrate a mortality benefit with rhythm control. Moreover, the recently published Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial showed that an initial strategy of rhythm control was not superior to rate control even in patients with heart failure, in whom the theoretical benefit of rhythm control would seem to be higher.

In contrast, the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) studies, a series of trials assessing the efficacy and safety of dofetilide to treat AF, showed that patients who maintained sinus rhythm, either with or without AADs, had a superior prognosis compared with patients with continued AF. Thus it is possible that actual presence or absence of sinus rhythm itself, rather than treatment strategy, is responsible for outcome. In this regard, analysis of the AFFIRM: survival by actual rhythm

![Figure 1. An “on-treatment” analysis of the AFFIRM study allowed for the inclusion of time-dependent variables, such as the presence or absence of sinus rhythm. Multivariable analysis demonstrated that the presence of sinus rhythm is either an important determinant of survival or a marker for other characteristics associated with survival that were not captured in the model. The positive impact of sinus rhythm is essentially equal and opposite of that of AAD therapy. CAD indicates coronary artery disease; HF, heart failure. Reproduced from Corley et al with permission of the publisher. Copyright © 2004, the American Heart Association.](image-url)

Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial according to actual treatment revealed that presence of sinus rhythm was associated with a considerable reduction in the risk of death, consistent with the findings of the DIAMOND study (Figure 1). However, because of the retrospective and nonrandomized nature of the analyses, neither the DIAMOND study nor the AFFIRM study can distinguish whether sinus rhythm is an important independent determinant of survival or a marker for other factors associated with increased survival.

The results of these studies, although valuable, are often overinterpreted and applied without consideration of inherent limitations. The problem with a short-term assessment of a lifetime disease process has already been stated. Although it was standard of care at the time, these trials took a casual approach to monitoring for AF recurrence. Epochs of undetected AF expose patients to the risk of AAD treatment without benefit. Most participants were older (65 to 75 years) and relatively asymptomatic, with risk factors for stroke that were often incompletely treated. In contrast, a smaller group of younger patients (age <40 years) with valvular heart disease and AF showed a significant benefit of rhythm control with respect to reduction of mortality and improvement of functional capacity and quality of life (QOL).

One of the main reasons to initiate rhythm control therapy in patients with AF is to control symptoms. Patients with AF exhibit a wide variety of clinical symptoms, ranging from none to disabling symptoms. The most common symptoms include palpitations, dizziness, and chest pain. However, more subtle symptoms such as anxiety and fatigue are common as well and could potentially remain undetected.
unless specifically addressed. Many patients who have “asymptomatic” AF feel much better after successful cardioversion. Several hemodynamic derangements, including rapid ventricular rates, loss of organized atrial contraction, irregularity of cardiac rhythm, and bradycardia (resulting particularly from sinus pauses when AF episodes terminate) may explain some of the symptoms related to AF. Although the true percentage of symptomatic patients with AF is unknown, the impact of atrial fibrillation of health-related QOL may shed some light on this subject. The available data suggest that QOL is considerably impaired in patients with AF compared with that of age-matched controls. Moreover, some studies show that restoration of sinus rhythm is associated with improved QOL and better exercise performance.46,51–54 The effect of AF on QOL was assessed in a substudy of the Canadian Trial of Atrial Fibrillation (CTAF).55 The original study was a multicenter, prospective, and randomized clinical trial of amiodarone compared with either propafenone or sotalol in patients with recent onset of AF. The results of the CTAF substudy indicated that QOL, measured by the most widely validated generic health scale available, was significantly lower among patients with AF compared with healthy controls. Because the patients were relatively young and healthy (most had normal left ventricular function, and there was a low incidence of comorbid illnesses such as ischemic heart disease or diabetes mellitus), this suggests that AF per se was responsible for QOL impairment. Furthermore, the majority of patients were receiving medications to control ventricular response at baseline. In addition to symptoms directly attributable to the arrhythmia itself, general well-being, physical and social function, and vitality were substantially impaired in patients with AF, who perceived themselves more often as having “heart disease.” After restoration of sinus rhythm, there was substantial improvement, particularly in physical role functioning, vitality, social functioning, and symptoms frequency and severity. Although this improvement may have been the result of a drug effect or adjustment of other therapies (including rate-controlling agents), the improved QOL in patients who did not have any recurrence over patients with such a recurrence signifies the role of rhythm control in these patients.

New-onset AF is of particular pathophysiological, clinical, and prognostic importance and hence deserves special therapeutic considerations. New-onset AF is associated with a significantly higher risk for death compared with no AF or persistent AF. In a 21-year community-based cohort study of patients with newly diagnosed AF, the mortality risk was substantially higher within the first 4 months, with a hazard ratio of 9.62 (95% CI, 8.93 to 10.32) as compared with a hazard ratio of 1.66 (95% CI, 1.59 to 1.73) thereafter.3 Similarly, in an analysis of the Carvedilol Or Metoprolol European Trial (COMET), new-onset AF, but not baseline AF, was an independent predictor of all-cause mortality.8 This observation was also confirmed in the Framingham Heart Study.56 Few plausible mechanisms may explain why new onset of AF is associated with a worse outcome. First, as discussed above, the first appearance of AF set multiple pathophysiological mechanisms in motion, favoring remodeling of the left atria and thereby promoting the conversion of paroxysmal AF into persistent AF. Emerging data also demonstrate that acute-onset AF is associated with a prothrombotic state that includes activation of platelets, decreased endocardial nitric oxide synthase expression, and increased expression of plasminogen activator inhibitor 1.57,58 These events occur at a local cardiac level before manifesting in the peripheral circulation and are due to AF per se and not the rapid ventricular rate seen during the arrhythmia. Second, the adequacy of rate control, achieved either naturally over time or by medications, is usually better than ventricular rates accompanying a new presentation of AF. Third, the potential for treatment with harmful antiarrhythmic medications is highest at the beginning of AF. Lastly, initiation of warfarin therapy, especially in elderly patients, carries considerable risk for both under and over anticoagulation, despite adherence to well-established warfarin initiation protocols.59 Although it is likely that progression to persistent AF also requires a substrate beyond a pure electrical burden, it seems reasonable to attempt early cardioversion in order to disrupt this vicious cycle. Many patients maintain sinus rhythm for prolonged periods after an initial cardioversion, even without antiarrhythmic treatment, especially if precipitating factors are identified and treated.

Catheter Ablation

AFFIRM demonstrated that the favorable influence of sinus rhythm may be counterbalanced by the harm caused by currently available AADs.49 Radiofrequency catheter ablation is a new but widely adopted technique for the treatment of AF that provides an alternative approach for maintaining sinus rhythm.60–63 Several small randomized trials have consistently demonstrated the superiority of catheter ablation over antiarrhythmic therapy.64–67 Typically these trials have been much more stringent in the electrocardiographic detection of AF recurrence than has been the case with AAD trials. Stabile et al68 randomized 137 patients with drug-refractory AF to ablation with AAD or AAD alone. At 1 year, freedom from AF was achieved in 65.9% of patients randomized to catheter ablation combined with AAD, as compared with 8.7% in patients receiving only AAD. Pappone et al67 randomized 198 patients with long-standing paroxysmal AF who failed AAD therapy to either catheter ablation or maximal tolerable doses of another AAD. At 1 year, 93% and 35% of the catheter ablation and AAD groups, respectively, were free of atrial tachyarrhythmias. Wazni et al65 randomized symptomatic patients who had not received prior treatment for AF (aged 18 to 75 years) to undergo either catheter ablation or receive AAD therapy. At 1-year follow-up, only 13% of the patients who underwent catheter ablation had recurrence of symptomatic AF as compared with 63% of those randomized to AAD. Catheter ablation was also associated with a significantly
better QOL. In a recent meta-analysis of studies comparing catheter ablation with AAD therapy, in which the results were weighted to reflect the size of the trial, ADT indicates antiarrhythmic drug therapy; CPVA, circumferential pulmonary vein ablation. Reproduced from Noheria et al.68 with permission of the publisher. Copyright © 2008, the American Medical Association.

Conclusions

As the population continues to age, partially because of better therapies for atherosclerosis and heart failure, and becomes increasingly overweight, AF will not only become more prevalent, its effect on morbidity and mortality is likely to become even more important. We should therefore focus on therapies that improve prognosis rather than embracing remedies that are, at best, noninferior to current standard of care. Recent research has led to better understanding of basic mechanisms involved in the development and perpetuation of the arrhythmia. Although present merely as an electrical pathology, AF is a dynamic disease, with a well-characterized pattern of progression. Therapy for AF should be active rather than passive, particularly early in the disease process (Figure 3). The underlying pathophysiology suggests that there is a window period where therapy may yield substantial benefit broother demographics, and longer follow-up), such as the Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment (RAAFT),69 the Catheter Ablation for the Cure of Atrial Fibrillation (CACAF-2),70 and the Catheter Ablation versus ANtiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) will clarify the role of catheter ablation in the disease management of AF. The proposed CABANA study plans to enroll 3000 subjects with a similar demographic as the AFFIRM study, who will be randomized to either catheter ablation or best drug therapy (which includes both rate control and rhythm control). The primary end point is mortality over 3 years, whereas secondary end points include stroke, serious bleeding, freedom from AF, symptoms, and QOL.

Figure 2. A Forest plot of the 4 randomized trials comparing catheter ablation versus AAD therapy, in which the results were weighted to reflect the size of the trial. See text for further discussion. ADT indicates antiarrhythmic drug therapy; CPVA, circumferential pulmonary vein ablation. Reproduced from Noheria et al.68 with permission of the publisher. Copyright © 2008, the American Medical Association.

Figure 3. A new paradigm for treatment of AF, similar to the staged approach for treatment of heart failure. This figure expresses (1) the need for risk factor modification before disease expression, (2) the window period of opportunity for aggressive rhythm control therapy at early stages of the disease, and (3) the probable failure of aggressive attempts at rhythm control in advanced stages of the atrial remodeling process after irreversible remodeling is established. CAD indicates coronary artery disease; SR, sinus rhythm.
(Table); later in the process, when widespread atrial fibrosis has already occurred, aggressive therapy is no longer warranted. Treatment should start with prevention of the atrial remodeling and progressive fibrosis. This can be achieved by treating hypertension, sleep apnea, obesity, coronary disease, and heart failure. Once AF occurs, early restoration of sinus rhythm followed by maintenance rhythm control therapy is recommended, particularly in patients who can reasonably be expected to live longer than the 2 to 3 years of follow-up that current trials have provided. Combined with risk factor control, this strategy provides the highest chance for halting disease progression and, if successful and started early in the process, even reverse remodeling. Properly monitored AAD therapy may be useful in selected patients to maintain sinus rhythm after cardioversion. Although more research is clearly needed, catheter ablation appears to be safe and more effective than AADs, at least in highly selected patients (arguably the ones who have the most to gain) when performed at experienced centers. New therapies based on the first fruits of experienced centers. New therapies based on the first fruits of AF disease progression and, if successful and started early in the process, even reverse remodeling. Properly monitored AAD therapy may be useful in selected patients to maintain sinus rhythm after cardioversion. Although more research is clearly needed, catheter ablation appears to be safe and more effective than AADs, at least in highly selected patients (arguably the ones who have the most to gain) when performed at experienced centers. New therapies based on the first fruits of greater pathophysiological understanding of the AF disease process will undoubtedly be discovered and applied in the immediate future.

The frequently offered excuse that we have imperfect tools no longer, in our opinion, carries the day. We think that fighting the good fight with our currently available armamentarium may prevent a hopeless situation in the future when better therapies are available.

Disclosures

None.

References


I enjoyed reading the article of Drs Anter and Callans on the topic of cardioversion for atrial fibrillation (AF), particularly their scholarly review of the pathophysiology of AF. I do challenge their assertion that progression from paroxysmal to persistent/permanent AF is “inexorable.” There is little evidence that such a progression occurs in all or even the majority of humans with AF. We share a longing for a better understanding of pathophysiology and agree it will lead to better therapies. I suspect we agree more than we disagree. The results of the trials of pharmacologic rate versus rhythm control have been interpreted by many. For example, the American College of Physicians’ guidelines inappropriately assert that rate control should be the initial approach for all patients. The trials showed no clear superiority of one approach over another. Rhythm management approaches need to be individualized. There are many situations in which rhythm control is the most appropriate initial therapy. We agree that the first episode of AF is such an instance wherein a holistic approach, including aggressive treatment of associated conditions such as hypertension and sleep apnea, is an important part of the therapy. We agree that cardioversion only makes sense when sinus rhythm can be effectively maintained when new therapies are ultimately evaluated.
Pharmacological and electrical conversion of atrial fibrillation to sinus rhythm: Is it worth it?

Cardioversion of Atrial Fibrillation for Maintenance of Sinus Rhythm
A Road to Nowhere
D. George Wyse, MD, PhD

Nowadays people know the price of everything, and the value of nothing.
—Oscar Wilde, The Picture of Dorian Gray

It is often never entirely clear or particularly important when something was done “first.” The provenance for cardioversion of atrial fibrillation (AF) can be approximated, however. In PubMed, the earliest publication about quinidine for the treatment of AF appeared in 1948,1 so one can speculate that pharmacological cardioversion of AF was “discovered” in the 1940s. The original description of electrical cardioversion is usually attributed to Bernard Lown and colleagues in a 1962 publication.2 It is interesting, therefore, that we are still discussing whether or not conversion of AF is “worth it.”

Response by Anter and Callans on p 1452

Consequences of AF are determined from measurable clinical outcomes associated with it. An association is not necessarily a consequence, however. AF may be a risk factor (causative) or a risk marker (bystander) for clinical associations. If AF is a risk factor, terminating it would reasonably be expected to have an impact on the clinical outcome; if AF is a risk marker, terminating it would not be expected to have an impact on the clinical outcome. Candidate outcomes for measuring the impact of conversion and maintenance of sinus rhythm include death, stroke, ventricular function/heart failure, and symptoms.

In spite of a lack of evidence, many physicians continue to believe that restoring and maintaining sinus rhythm has a positive impact on the risk of death and stroke and removes the need for anticoagulation.3 Indeed, until recently, the standard for regulatory approval of a new treatment for AF was the demonstration that the treatment was superior to placebo with respect to maintenance of sinus rhythm. In reality, the worth of the cardioversion and maintenance of sinus rhythm must be measured in terms of its impact on the consequences of AF.

Cardioversion

It would be difficult to defend the position that all cardioversions are worthless. Certainly there are acute clinical situations in which conversion, particularly electrical cardioversion, provides rapid results that are important to a good clinical outcome. However, such acute situations are proba-
bly relatively uncommon. The need for speed often has more to do with getting the patient out of the emergency department and avoiding hospital admission, an important economic outcome from a societal healthcare perspective, but not necessarily the best approach for the patient.

It is true that AF in some instances is “situational,” particularly first episodes, and conversion in itself is a means to an end. For these patients, correction or removal of the circumstances leading to AF may leave the patient free of further episodes of AF for months or years or perhaps forever. Freedom from future AF is more likely when the AF has self-terminated, however, indicating the absence of a well-developed substrate for maintenance of AF. Among patients presenting to the emergency room with AF as the primary diagnosis, at least 50% will spontaneously convert to sinus rhythm over the next 48 hours. When the first episode of AF spontaneously terminates, nearly 40% of patients will not have a recurrence during the next 5 years. These data suggest that there is useful information to be obtained when there is a period of watchful waiting to determine whether AF will self-terminate.

The immediate success rate of electrical cardioversion using current technology is high, approaching or slightly exceeding 90% in those enrolled in randomized trials. It may be lower than that in unselected study populations, but is probably still more than 80%. Urgently terminating AF has at least 1 other potential drawback. One of the scourges of electrical cardioversion is immediate or early recurrence of AF. It turns out, somewhat unexpectedly, that immediate or early recurrence of AF is more common the sooner after the onset of AF that one is electrically cardioverted. There is also no advantage of immediate cardioversion in terms of progression to permanent AF. These data argue against urgency to cardiovert when the patient is clinically stable in AF.

The success rate for pharmacological cardioversion is more difficult to pinpoint. Conversion success is at least partly dependent on the agent being used and the route of administration. Distinguishing between AF and atrial flutter may also be a determinant of success. Time is also an important covariate for at least 2 reasons. First, pharmacological cardioversion with many drugs is most likely to be successful when AF has been present for a short period of time. Second, because of the confounding effect of spontaneous conversion, it is necessary to specify a brief period of time within which conversion reasonably can be attributed to drug therapy.

The literature on pharmacological cardioversion is vast and cannot be reviewed here. Common drugs used for pharmacological cardioversion in North America are propafenone, flecainide, or amiodarone. Flecainide and propafenone are only available in an oral formulation, whereas amiodarone is available in both an oral and intravenous form. Cardioversion by amiodarone is delayed for at least 6 to 8 hours, and the class I drugs are superior for conversion within 1 to 2 hours. It is often difficult to estimate the net effect of drugs because of the confounding problem of spontaneous conversion in the placebo-treated group. One crude approach is to subtract the conversion rate in the placebo group from that in the treatment group. Doing so in the case of intravenous amiodarone, the net conversion rate is 28% at 24 hours. Given orally, the net conversion rate for amiodarone at 24 hours is 52%. For a single, large, oral dose of flecainide or propafenone, conversion is expected within 3 hours, and the net effect compared with placebo is 38%. The only other intravenous drug currently available for pharmacological cardioversion in North America is ibutilide. Using 90 minutes, the net conversion rate with this drug is 44%.

Certainly compared with electrical cardioversion, these results are not particularly impressive. Pharmacological cardioversion does, however, essentially eliminate the problem of immediate or early recurrence of AF. It is associated with a number of other problems, including torsade des points ventricular tachycardia, bradycardia, hypotension, atrial flutter with 1:1 atioventricular conduction, and others. Nevertheless, demonstration of efficacy for pharmacological cardioversion has led to the so-called “pill-in-the-pocket” outpatient approach to therapy. In my opinion, “pill-in-the-pocket” pharmacological cardioversion is applicable to a vanishingly small number of highly selected patients and begs to be compared with the “pill-in-the-pocket” approach using rate-controlling drugs.

The most feared complication of cardioversion is stroke or systemic embolism. The risk of stroke or systemic embolism is less of an issue for pharmacological cardioversion, because this therapy is usually applied very early after the onset of AF. Unfortunately, estimates of the risk are derived from observational data sets and have many limitations. The major limitation is that the data sets contain patients with (or without) a variety of stroke risk factors and who are being treated (or not) with a variety of antithrombotic therapies that may (or may not) be continued. Some of the key results of 1 such recent data set are illustrated in Figure 1. The overall risk is approximately 0.7% but can be 3-fold higher when the international normalized ratio is below the therapeutic range of 2.0 to 3.0. Other findings of interest in this observational data set is that the risk is similar for atrial flutter and AF, and the point estimate of risk is 0.3% when anticoagulation is not continued in those cardioverted within 48 hours of the onset of AF. The latter estimate is of interest because the current treatment guidelines suggest it is permissible to cardiovert patients without continued anticoagulation in those for whom it is known that the duration of AF is <48 hours.

The discussion so far has viewed the tip of the iceberg—a comparison of the efficacy and risks of the process of cardioversion of AF itself in all patients. If that were the end of it, one could reasonably conclude that efficacy was high, at least for electrical cardioversion, and risk is acceptably low. The problem is that the majority of patients who really require cardioversion (non–self-terminating [persistent] AF) will have recurrences of AF on an ongoing basis. Therefore, the implication of doing a cardioversion is that one is...
committing to the strategy of maintaining sinus rhythm and all that entails. The main therapy for maintaining sinus rhythm in the majority of patients at this time is the use of antiarrhythmic drugs. There is a fairly robust amount of evidence comparing such a strategy to the much simpler strategy of administering treatments that primarily are aimed at controlling the heart rate during AF and do little or nothing for the maintenance of sinus rhythm. The main reason for adopting the point of view that cardioversion is not worthwhile arises from the evidence of the futility of rhythm control with respect to superiority for hard clinical outcomes. This evidence will be briefly outlined below.

**Maintaining Sinus Rhythm Does Not Reduce the Risk of Death**

There are individual instances where one can see how AF might lead to death; a cardioembolic stroke can result in death, and AF can lead to ventricular fibrillation. Are such events common enough in the general population with AF that one can demonstrate an impact on death by converting it and attempting to maintain sinus rhythm? There is ample evidence, at least in patients with structural heart disease, that AF is associated with an increased risk of death. Is AF a common cause of death or is it merely a marker of increased risk? So far the data suggest the latter rather than the former.

Three randomized controlled trials were large enough and enrolled patients sufficiently enriched for risk of death to produce a plausible answer to the question concerning an impact on mortality. These 3 trials all enrolled older patients with other risk factors for death or stroke. The key results of the 3 trials with respect to death are reproduced in Figure 2. In 1 trial, there was a modest trend for increased risk of death with rhythm control (Figure 2A). In another, the Kaplan-Meier curves are nearly identical (Figure 2B). The latter study enrolled only patients with heart failure and reduced left ventricular function. One might have expected the greatest impact on death in such patients. Both of these studies had relatively long follow-up (up to 5 years) and specified criteria for heart rate control in the control arm. The third trial enrolled patients similar to those in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and compared dronedarone with placebo. This third trial had a much shorter duration of follow-up (up to 2 years) and no specific targets for heart rate control when AF recurred are reported. It did, however, show a weak “trend” for reduced mortality with rhythm control (Figure 2C). Before anyone attributes this effect of dronedarone to restoration of sinus rhythm, it should be pointed out that amiodarone, the predominate drug used in the other 2 trials, is more effective at maintenance of sinus rhythm than dronedarone. From these 3 trials, it seems reasonable to conclude that cardioversion and pharmacological maintenance of sinus rhythm has no impact on mortality.

Believers in a favorable impact of maintenance of sinus rhythm on mortality have based their faith on 2 points. The points are as follows: (1) drugs are not very effective in maintaining sinus rhythm, and (2) adverse effects of antiarrhythmic drugs offset the favorable effects of maintenance of sinus rhythm. The evidence for either of these suppositions is relatively weak and surely must be discounted in the face of the primary evidence. Amiodarone is reasonably effective for the maintenance of sinus rhythm. In the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Trial, for example, the prevalence of sinus rhythm in the rhythm control arm over the 5 years of follow-up was approximately 80%.

Defenders of rhythm control approach have placed much reliance on a single publication from AFFIRM. In that post hoc secondary analysis, all the AFFIRM patients in both arms were combined, and statistical adjustment was made for baseline and time-varying parameters thought to have an impact on death. That analysis found that sinus rhythm was associated with survival, and antiarrhythmic drug use was associated with death. There are several problems with relying on these data. First, exposure over time was actually an estimate rather than a precise measurement. Second, the analysis does not account for variables that were unmeasured, even if known to have an impact on death. Third, the analysis does not account for variables that have an impact on death that has yet to be discovered. Finally, such an analysis can only demonstrate associations and does not establish cause and effect. Specifically, it cannot determine whether AF is a risk factor or a risk marker for death. Anomalies in the data should be a warning. For example, there was an association with digoxin use and death, a common association in statistical models but one disproved in randomized trials. A more sophisticated but similar analysis of the AF-CHF data demonstrated a complete lack of any favorable association between sinus rhythm and survival.

Defenders of the rhythm control approach have hypothesized that the adverse drug effects with respect to mortality in the treatment of AF will be overcome by the use of transcu-
taneous catheter ablation treatments. Until such a benefit is demonstrated in appropriate randomized trials enrolling patients at risk for death, such a supposition remains a hypothesis. At this point in time, it can be said that there is no credible evidence that converting and maintaining sinus rhythm has any favorable impact on mortality.

Maintaining Sinus Rhythm Does Not Reduce the Risk of Stroke/Systemic Embolus

There is a known mechanistic reason, and atrial fibrillation is associated with increased risk of stroke/systemic embolus in those with stroke risk factors. Anticoagulation reduces this risk. The proportion of thrombotic strokes in contemporary patients with AF that is cardioembolic (embolus from the left atrium) is unknown, however. One estimate, based on 20-year-old data, suggests that 65% of strokes in AF patients are cardioembolic in origin. Maintaining sinus rhythm can only impact cardioembolic strokes. The annual stroke rate in contemporary AF patients on antithrombotic therapy, approaching 1.5% per year, is a barrier to obtaining accurate and believable data on this point. The available data are imperfect, but not encouraging.

In the 2 largest randomized trials comparing pharmacological rhythm control with rate control, the incidence of thrombotic stroke was compared in the 2 treatment arms (Figure 3). Patients in both arms were taking warfarin. In AFFIRM, the use of warfarin ranged from 85% to 95% over the 5 years of follow-up in the rate control arm, but after the fourth month fell to 70% to 75% in the rhythm control arm. A key and sobering finding of that analysis was that the majority of strokes occurred in patients who discontinued warfarin or whose international normalized ratio was subtherapeutic. There was no overall difference in the stroke rate between arms (Figure 3A) in spite of the difference in warfarin usage. An optimist might argue this result suggests a stroke prevention benefit for maintenance of sinus rhythm because of the lower usage of warfarin in that arm. However, a similar analysis from AF-CHF is shown in Figure 3B. In this trial, the use of warfarin was the same in both arms at approximately 90% throughout the trial. There was no stroke-prevention advantage detected in the rhythm control arm. Thus it has been conclusively demonstrated in patients with stroke risk factors that maintenance of sinus rhythm has no additional impact on the risk of stroke in patients already taking antithrombotic therapy. Such an effect would have been anticipated if there was a stroke-preventing effect of maintaining sinus rhythm. Admittedly, the event rate for stroke is low; maintaining sinus rhythm...
can only have an impact in 65% of the strokes, and a type II error cannot be excluded.

Nevertheless, on the basis of the evidence, any benefit for prevention of stroke possibly achievable by cardioversion and attempting to maintain sinus rhythm is not worth the effort in patients with stroke risk factors. Anticoagulation is the preferred method of preventing stroke. Given the known "silent" recurrence rate of AF after pulmonary vein ablation,32,33 one should not expect a different outcome with this form of therapy.

A Favorable Impact of Maintaining Sinus Rhythm for Congestive Heart Failure Is Questionable

Another outcome for which it might be expected that conversion and maintenance of sinus rhythm would be a superior treatment is ventricular function, specifically congestive heart failure. A positive effect on heart failure should be most easily demonstrated in patients who have congestive heart failure and poor left ventricular function. The impact of pharmacological maintenance of sinus rhythm on worsening heart failure in such patients enrolled in the AF-CHF trial is illustrated in Figure 4.21 As can be seen, incident worsening heart failure in the rhythm and rate control arms of this trial was not significantly different. An optimist will note the slight separation in the 2 Kaplan-Meier curves. To eradicate any notion that there is a "trend" favoring maintenance of sinus rhythm, it is important to point out a flaw in the data. Leaving aside the outcomes of death and stroke, interpretation of the clinical outcomes in such unblinded trials is complicated by the problem of ascertainment bias. It is important to remember that the patients and evaluators know which treatment has been assigned to individual patients. Thus if one believes that sinus rhythm improves outcome with respect to congestive heart failure, there is a tendency to overrate its impact. Ascertainment bias probably explains the observation that congestive heart failure was the commonest reason given for crossing over from the rate control to the rhythm control strategy.21

There is probably an argument to be made for conversion and maintenance of sinus rhythm for treatment of heart failure in the case of isolated diastolic dysfunction. Diastolic dysfunction is an important factor in the pathophysiology of AF24 and a common coexisting finding, partly because of interrelationships between hypertension, diastolic dysfunction, and AF. Atrioventricular synchrony may be more important with respect to heart failure in the case of isolated diastolic dysfunction. The value of conversion and maintenance of sinus rhythm for heart failure in isolated diastolic dysfunction with AF has not been evaluated in an appropriately designed randomized trial.

Early results of studies of pulmonary vein ablation in congestive heart failure, although thought by many to be
promising, are hampered by the aforementioned problem of ascertainment bias and other limitations of the outcome measures used.\textsuperscript{35} In summary, at this point in time, the evidence for a favorable effect of conversion and maintenance of sinus rhythm compared with other therapies for treatment of congestive heart failure is not convincing.

**Maintaining Sinus Rhythm Has a Trivial Impact on Symptoms and Quality of Life for Most Patients**

Relief of symptoms is probably the single indication for conversion and maintenance of sinus rhythm, for which there is some evidence for superiority to other treatments. Its impact, however, has probably been overrated. First, it should be noted that only approximately 33\% of patients with AF have class 3 to 4 symptoms; the remainder are less symptomatic, and 40\% are asymptomatic or minimally symptomatic.\textsuperscript{36} The impact on symptoms should be greatest in the most symptomatic one third and little advantage to the majority.

The impact of conversion and maintenance of sinus rhythm compared with rate control on quality of life and functional capacity was examined in the AFFIRM trial, and the key results are shown in Figure 5. AF usually has its greatest impact on physical symptoms. As can be seen, there was absolutely no difference in these scores between the 2 treatment arms in an intention-to-treat analysis.\textsuperscript{37} Furthermore, there was no difference in these scores when examined according to the presence or absence of sinus rhythm.\textsuperscript{37} A common misconception is that the patients enrolled in AFFIRM were asymptomatic at enrollment and explains the lack of an effect of conversion and maintenance of sinus rhythm. In fact, only 6\% of patients enrolled in AFFIRM were asymptomatic.\textsuperscript{38} Furthermore, it can be seen in Figure 5A that the average SF-36 scores for patients in AFFIRM were lower than the age-adjusted norms for the American population without AF.

In Figure 5B, data from AFFIRM depicting distance walked in a 6-minute walk test are displayed.\textsuperscript{39} In this instance we see that there is a potential superiority of conversion and maintenance of sinus rhythm; however, the magnitude of the effect is vanishingly small. The difference between the 2 groups is less than a 10\% increase. When one considers the caveat about unblinded evaluation and biased ascertainment, it could be argued that the observed result is equivocal.

Other studies\textsuperscript{40,41} have been used to support the notion of a superior impact of maintenance of sinus rhythm on symptoms and exercise capacity. It should be pointed out that these studies compounded the problem of ascertainment bias by excluding from evaluation patients being treated to maintain sinus rhythm who had relapsed into AF. Any differences noted in such evaluations are more likely due to the nature of the underlying disease, rather than the rhythm management strategy. The data suggest that the superiority of maintaining sinus rhythm for symptoms is rather small in the case of pharmacological treatment and accrues to a minority of patients.

It seems likely that transvenous catheter ablation procedures may give better relief of symptoms in highly symptomatic patients with paroxysmal AF,\textsuperscript{42} even allowing for ascertainment bias from unblinded evaluation. However, the risks of the procedure\textsuperscript{43} and problems with widespread applicability limit its usefulness in this regard.

**Maintaining Sinus Rhythm Is More Expensive**

Finally, a literal interpretation of “worth” could be incremental cost. When stringent economic analysis is applied to compare the strategy of maintaining sinus rhythm to the simpler heart rate control strategy, the financial advantage clearly resides with the heart rate control strategy.\textsuperscript{44} Given the lack of efficacy of the treatment in preventing death, when economic data are examined in a cost-effectiveness analysis, there is no benefit from this approach (Figure 6).

**Conclusions**

Conversion of AF to sinus rhythm is easily achievable in the short term, with an acceptably low complication rate. However, in the absence of a correctable or reversible cause, AF will return in most patients with persistent AF. Once AF
becomes recurrent, the real question is: what benefits accrue to the patient from conversion and maintenance of sinus rhythm? Such an approach has no benefit in terms of preventing death and no credible evidence for reduction of stroke risk. It also has little demonstrable effect for reduction of the likelihood of worsening heart failure. The approach is more expensive and has a modest benefit for a small number of patients for improving symptoms.

In conclusion, for the majority of patients with recurrent AF, conversion and maintenance of sinus rhythm is not “worth it.” Going forward, it might be more fruitful to examine means of preventing AF rather than converting it.

Disclosures

Dr Wyse has been a paid consultant on research planning committees or Data and Safety Monitory Boards for randomized controlled trials sponsored by the National Institutes of Health, Boerhinger Ingelheim, Medtronic, SanofiAventis, Bristol-Myers Squibb, Biotronik, and Boston Scientific.

References


Response to Wyse

Elad Anter, MD; David J. Callans, MD

Dr Wyse’s article, paired with ours, presents an eloquent and cogent reasoning for treatment strategies in patients with atrial fibrillation. It is clear that the abundance of conflicting data precludes a universal treatment strategy and rather commences a patient-based therapy. We agree that available data do not allow us to conclude whether atrial fibrillation is a “causative factor” or a “risk marker” of poor clinical outcome. Nevertheless, ample evidence suggests that the onset of atrial fibrillation sets the trigger for structural and electrical remodeling processes; some become irreversible with time. This vulnerable period might be a window of opportunity to prevent atrial remodeling. Studies comparing rhythm with rate control enrolled patients with well-established atrial fibrillation (paroxysmal and persistent), and therefore, the majority of these patients had already presumably irreversible changes. This may also explain their poor response to antiarrhythmic medications (∼55% to 65%). Patients presenting for the first time with atrial fibrillation are therefore a unique subset of patients in whom, although the theoretical benefit of attempting rhythm control seems high, no clinical trials have been attempted. There are many situations in which rate control is indeed the most appropriate strategy, such as in asymptomatic, elderly, and inactive patients. Finally, we both agree that the treatment paradigm for atrial fibrillation should start years before its clinical appearance. Prevention and control of risk factors may not only halt atrial fibrillation but also clearly leads to an improved cardiovascular outcome.
Cardioversion of Atrial Fibrillation for Maintenance of Sinus Rhythm: A Road to Nowhere
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