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Journal of Atrial Fibrillation

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Rate Control Strategy Elevated To Primary Treatment For Atrial Fibrillation: Has The Last Word Already Been Spoken?

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Abstract

In the last decade, we were able to see the light shed by several trials and observational studies that dealt with the appropriate manner of treating patients with atrial fibrillation (AF). Recently the AF management by cardiologists has become more aggressive, in part because of an improved comprehension of this rhythm disturbance, as well as, the availability of new treatment strategies. Increasing awareness of AF as a disease rather than as an acceptable alternative to sinus rhythm has led to search for clear arguments to support a certain strategy as a gold standard. In this respect, the decision of whether to restore sinus rhythm, or to control the ventricular rate and allow AF to persist is of critical importance. The results of randomized, controlled trials addressing this matter shed some light on the proper way of treatment for these AF patients. The AFFIRM and RACE trials and their respective sub-studies showed surprising results. The vast majority of physicians were surprised to learn that the rate control strategy was elevated to the position of primary treatment for the AF management instead of the all-time recognized rhythm control approach to restoration and maintenance of sinus rhythm. The use of anticoagulants in the trials was different in the treatment strategies. There was a greater anticoagulant use in the rate control arm because of the belief that anticoagulation can be discontinued in the rhythm control arm when sinus rhythm was restored and maintained for one month. On the other hand, only pharmacological agents were used to maintain sinus rhythm in those trials, however, there is increasing evidence that AF ablation can restore and maintain sinus rhythm in a great proportion of patients. Indeed, there are some limitations and several interesting aspects of these trials and other studies that will be discussed. The last word has not been spoken yet.

Introduction

It is well known that arrhythmias are generated by the presence of substrates, triggers, or modifying factors for arrhythmias. Since the beginning of this century, the debate on ectopic foci versus reentry as the mechanism underlying atrial fibrillation (AF) in humans has continued. It has been reported that ectopic foci from the pulmonary veins can initiate AF and can also act as drivers for maintaining AF. However, not all patients with atrial arrhythmias initiate AF. A substrate for atrial propensity to AF is required for AF initiation and maintenance. Clinical electrophysiological studies have focused on the properties of the electrophysiological substrates in the atrial muscle during sinus rhythm and on the atrial electrical responses elicited by programmed atrial stimulation.[1-3] For example, abnormal atrial electrograms recorded by endocardial mapping during sinus rhythm, abnormal responses of the atrium elicited by programmed stimulation, shorter atrial effective refractory periods, greater dispersion of atrial refractoriness and atrial conduction delay have been observed more frequently in patients with paroxysmal AF.[4-6] However, even if atrial electrical remodeling facilitates AF initiation and maintenance, the initiation of AF requires a trigger. Perhaps, the greatest recent advancement in our understanding of AF relates to the demonstration that ectopic foci from the pulmonary veins are the main triggers of AF. The mechanism of AF maintenance was shown to be a spiral wave of activation,[7,8] or a random multiple reentry[9,10] of independent wavelets wandering in the atria around arcs of refractory tissue[11,12] driven by focal activity originating mainly from the pulmonary veins[13-16] or the superior vena cava,[17] or ligament of Marshall.[18,19] Increasing awareness of atrial fibrillation as a disease rather than as an acceptable alternative to sinus rhythm has led to search for clear arguments to support a certain strategy as a gold standard. In the search to develop an appropriate treatment for adequately managing the clinical spectrum of symptoms and complications related to this disorder, several randomized clinical trials have been developed. The new emerging methods for restoring sinus rhythm have been accompanied by a search for methods of maintaining sinus rhythm. Furthermore, the risks of pro-arrhythmia with anti-arrhythmic agents, their limited efficacy, and the undesirability of long-term prophylactic

Key Words:
Atrial Fibrillation, Rate And Rhythm Control Therapy, Af Catheter Ablation, Atrial Vulnerability.

Disclosures:
None.

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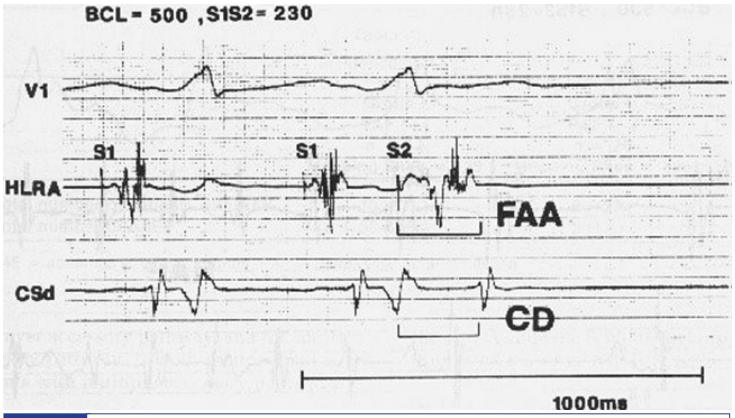

Figure 1: This is an example of the induction of fragmented atrial activity as a feature of atrial vulnerability. Surface electrocardiographic lead V1 is shown together with intracardiac electrograms from the high lateral right atrium (HLRA), and distal coronary sinus (CSd). S1 and S2 are, respectively, the driving and premature stimulus artefacts. The basic drive cycle length (BCL) was 500 ms and the coupling interval (S1–S2 interval) was 230 ms. There is a prolongation of the duration of atrial activity from 110 to 200 ms in the HLRA. CD indicates interatrial conduction delay. Reprinted with permission from Konoe et al. Pacing Clin Electrophysiol 1992;15:1040-1052.

administration have prompted interest in non-pharmacologic methods.[20] These include pacing strategies, radiofrequency catheter ablation and cardiac surgical procedures. Bi-atrial pacing has been developed as a technique for simultaneous activation of the right and left atrium to reduce the intra-atrial conduction delay.[21-24] This has been reported to prevent the recurrence of AF in paced patients with a marked intra-atrial conduction delay.[25] Thus, these facts indicate that the intra-atrial conduction delay can play an important role in the onset of AF. More recent additions include radiofrequency ablation "maze" procedures in which electrophysiologists try to perform a maze surgical-like operation with electrode catheters by a percutaneous ablation procedure. Moreover, there is great interest and good results with radiofrequency ablation of atrial and junctional tachycardias, and pulmonary veins or other ectopic foci that underlie some cases of atrial fibrillation. The development on implantable atrial defibrillators further expands the non-pharmacological options in the management of this rhythm disturbance.[26, 27] Therefore, there are some limitations and several interesting aspects of these different methods of AF treatment that will be discussed in this manuscript.

Electrophysiological Properties Of The Atrial Myocardium In Atrial Fibrillation

The well known complexity of the mechanism for developing AF accounts for the failure and relative success of the different therapeutic maneuvers in the management of AF. The AF mechanism is considered to be a spiral wave with a continuously changing pattern of the activation wave front,[7, 8] that is, a random multiple reentry[9, 10] of independent wavelets wandering in the atria around arcs of refractory tissue[11, 12] or the accentuation of focal activity originating mainly from the pulmonary veins[13-16] or the superior vena cava,[17] ligament of Marshall.[18, 19] Clinical electrophysiological studies have concentrated on the electrophysiological properties of the substrates in the atrial muscle during sinus rhythm, and on the atrial electrical responses elicited by premature stimulation method[1-3] (Figures 1 and 2). However, many fundamental aspects of this arrhythmia have been poorly understood until quite recently. Abnormal atrial electrogram during sinus rhythm and abnormal responses of the atrium elicited by programmed stimulation have been observed more frequently in patients with paroxysmal AF than in those without paroxysmal AF[4-6] (Figure 3). A shorter atrial refractoriness, greater dispersion of the atrial refractoriness and atrial conduction delay are also of electrophysiological significance in the genesis of AF. Electrical remodeling is likely to be a final common pathway that ultimately supervenes. Even if atrial electrical remodeling facilitates AF initiation and AF perpetuation, the initiation of AF requires a trigger. A wealth of new information has been published on the genesis of AF, especially arrhythmogenic pulmonary veins as the triggers of AF,[13-16] and on electrical remodeling[28-30] of the electrophysiological properties in the atrial muscle as modifying factors of AF (Figures 4, and 5). Furthermore, a possible genetic basis of AF has been suggested in some cases,[31] although little is known about its electrophysiology.

Adequate Therapeutic Management Of Atrial Fibrillation

In the search to develop an appropriate treatment to adequately manage the clinical spectrum of symptoms and complications related to this disorder, several randomized clinical trials have been developed.[32-36] The new emerging methods for restoring sinus rhythm have been accompanied by a search for methods of maintaining sinus rhythm. Furthermore, the risks of proarrhythmia with antiarrhythmic agents, their limited efficacy, and the undesirability of long-term prophylactic administration have prompted interest in non-pharmacologic methods. These include pacing strategies and cardiac surgical procedures. Bi-atrial pacing has been developed as a technique for simultaneous activation of the RA and left atrium to reduce the intra-atrial conduction delay[37-39] This has been reported to prevent the recurrence of AF in paced patients with a marked intra-atrial conduction delay.[40] Thus, these facts indicate that the intra-atrial conduction delay can play an important role in the onset of AF. Later additions include radiofrequency ablation "maze" procedures, in which electrophysiologists try to perform a maze surgical-like operation with electrode catheters by a percutaneous ablation procedure. The development on implantable atrial defibrillators further expands the non-pharmacological options in the management of this rhythm disturbance. Approaches to the

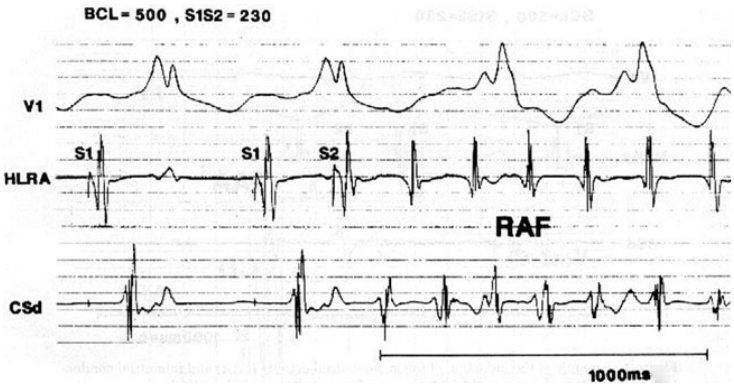

Figure 2: This is an example of the induction of repetitive atrial firing as a feature of atrial vulnerability. Surface electrocardiographic lead V1 is shown together with intracardiac electrograms from the high lateral right atrium (HLRA), and distal coronary sinus (CSd). S1 and S2 are, respectively, the driving and premature stimulus artefacts. The basic drive cycle length (BCL) was 500 ms and the coupling interval (S1–S2 interval) was 230 ms. Reprinted with permission from Konoe et al. Pacing Clin Electrophysiol 1992;15:1040-1052.

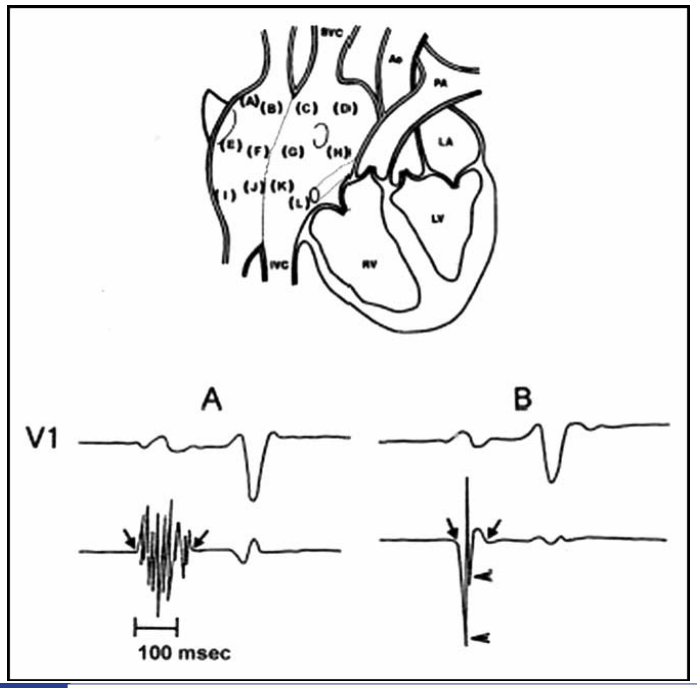

Figure 3: **(Top) Twelve endocardial mapping sites in the right atrium. Atrial endocardial electrograms were recorded in each patient from the anterior, lateral, posterior, and medial aspects of the high (a– d), mid (e– h), and low (i–l) right atrium.**
(Bottom) (A) Abnormal atrial electrogram with 10 fragmented deflections and 130 ms in duration versus (B) normal atrial electrogram with 2 fragmented deflections and 80 ms in duration.
Ao: aorta; IVC: inferior vena cava; LA: left atrium; LV: left ventricle;
PA: pulmonary artery; RV: right ventricle; SVC: superior vena cava.
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surgical management have improved and have provided information about the clinical determinants of AF.[11, 12, 41-43] Information has been obtained about post-operative AF and the response to implanted devices, such as both atrial pacemakers and atrial defibrillators.[44, 45] Further investigation into the electrophysiological properties in AF will be needed in order to contribute to the future development of an appropriate treatment.

For most patients with AF, the major problem is preventing recurrence of AF rather than restoring sinus rhythm. Maintenance of sinus rhythm is not always possible, and often, the attempt ceases to be worthwhile. In this setting, long-term anticoagulation and pharmacologic treatment with rate-control anti-arrhythmic agents can provide adequate symptom and risk control for most patients. However, the optimal heart rate at rest and during exercise for patients with AF is uncertain and susceptible to individual variations. Due to the loss of atrial kick and the presence of inefficient short ventricular cycles, the heart rate probably needs to be relatively faster than that during sinus rhythm to maintain cardiac output. The irregularity of the rhythm may itself be detrimental. Clear clinical evidence exits that abolishing AF makes patients feel better in the short to medium-term, however, data on the economic viability or long-term efficacy of such a strategy are scanty.

Among the several clinical trials that assessed the best way to treat a patient with AF, the most representative probably is the AFFIRM trial. This trial consisted of 4060 patients over 65 years of age with AF that was thought likely to be recurrent and to require long-term therapy.[32] The patients were randomly assigned to rate control using digoxin, beta blocker, and/or calcium antagonist and anticoagulation with warfarin; or to rhythm control with the most effective anti-arrhythmic drug. After a mean follow-up of 3.5 years, the following findings were observed. There was a trend toward an increase in incidence of the primary end point (all cause mortality) with rhythm control (27% vs 26%, hazard ratio 1.15, 95% CI 0.99 to 1.34). There was no significant difference in the composite secondary end point of death, ischemic stroke, anoxic encephalopathy, major bleeding, or cardiac arrest. There was a trend toward a higher risk of ischemic stroke with rhythm control (7.1% vs 5.5%); 72% of strokes occurred in patients receiving no or suboptimal anticoagulation. There was no significant difference in functional status or quality of life. The number of patients requiring hospitalization during follow-up was significantly greater in the rhythm control group than in the rate control group (80% vs 73%). The data from this trial, as well as the data from the RACE trial[33] confirm that both rate and rhythm control are acceptable approaches, depending upon the specific clinical individual circumstances. It may be stated that rate control is at least just as good if not even better than rhythm control in patients with AF over 65 years of age. However, this results can not be extrapolated to young adults with PAF, since this patients were not enrolled in these trials and also because the mechanism for development of AF may not be the same. The likelihood of firing pulmonary veins focus in the genesis of the AF in young adults makes radiofrequency ablation of these focuses an attractive first line definitive therapy.

We have also learned from these trials results that most patients with AF, regardless of whether a rate control or rhythm control strategy is chosen, should be chronically anti-coagulated with a target INR of 2.0 to 3.0. It is not safe to stop anticoagulation after successful

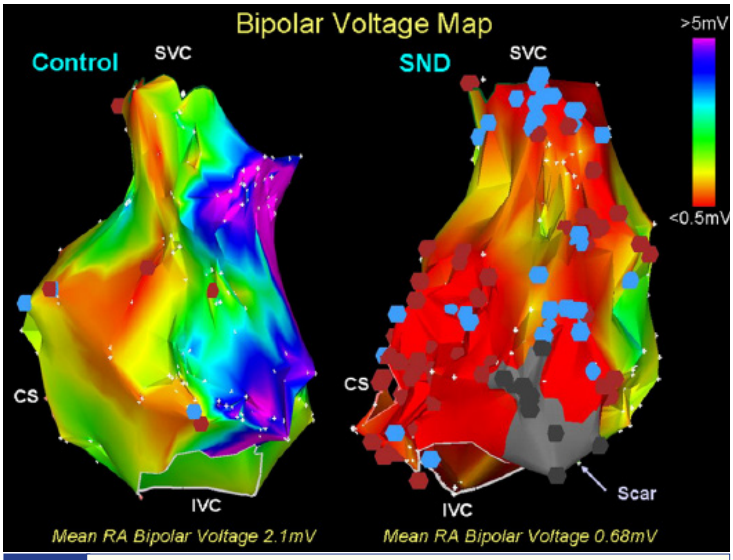

Figure 4: **Electroanatomic bipolar voltage mapping of the right atrium in a patient with evidence of diffuse atrial remodeling prone to develop atrial fibrillation (right) and an age-matched control patient (left). Note the widespread regions of low voltage (indicated in red) and scar (indicated in gray) in the patient with sinus node disease. In addition, the patient on the right has a greater number of points with fractionated signals (brown dots) and double potentials (blue dots). SVC indicates superior vena cava; IVC, inferior vena cava; CS, coronary sinus. Reprinted with permission from Sanders P et al. Circulation. 2004;109:1514–1522.**

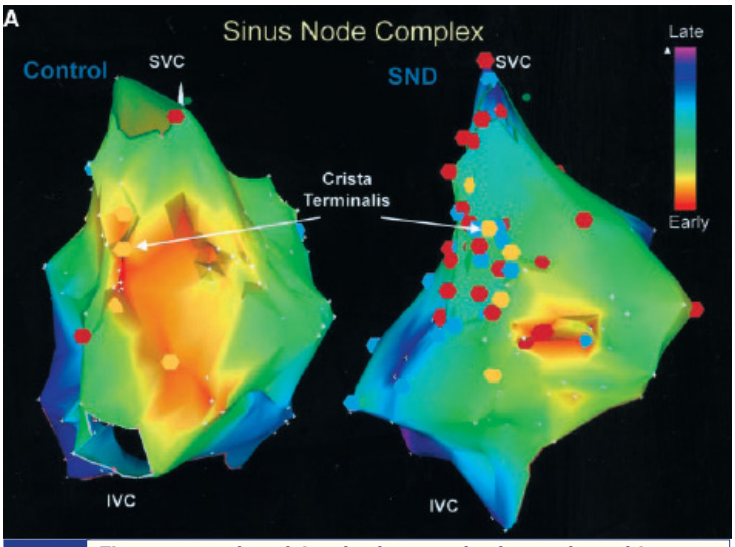

Figure 5: **Electroanatomic atrial activation mapping in a patient with evidence of diffuse atrial remodeling prone to develop atrial fibrillation (right) and an age-matched control patient (left). The patient in the right demonstrates significantly greater number of points with double potentials (blue dots) and fractionated signals (brown dots) and earliest activity (sinus node complex) over a greater extent of crista terminalis. SVC=Superior vena cava; IVC= Inferior vena cava.**
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AF cardioversion, even when there is strong documented evidence that sinus rhythm has been restored and maintained longer than one month. In addition, many symptomatic patients with AF present also asymptomatic episodes of paroxysmal AF after restoration to normal sinus rhythm. Therefore, symptoms are not enough to demonstrate AF recurrence with thromboembolic potential. Retrospectively, we have learned that even the patients that are treated with the rhythm control strategy should be kept on life-long anticoagulation. It is well known that coumadin or warfarin therapy significantly diminishes the incidence of stroke in AF patients compared to placebo. In this regard, the rate control group should have had lesser incidence of stroke because of permanent anticoagulation. Indeed, this thought is consistent with the trials results. There was a trend to excess of stroke and systemic embolism in the rhythm control strategy in AFFIRM,[32] RACE,[33] and STAF[36] trials. The PIAF study also noted an increased stroke rate in the rhythm control arm.[35] The use of anticoagulants in all trials was different in the two treatment strategies. There was a greater anticoagulant utilization in the rate control arm because of the belief that anticoagulation can be discontinued in the rhythm control group when sinus rhythm is restored and maintained for one month. We can imagine the danger for patients who alternate between AF and sinus rhythm in the absence of anticoagulation considering the likelihood of thrombus ejection in this setting. Considering that the incidence of stroke and systemic embolism should have played an important role in morbidity and mortality, ¿what would have happened with the incidence of total mortality in the rhythm control group if anticoagulation was not stopped and given lifelong? There is a possibility that the combination of sinus rhythm and permanent warfarin protection would diminish even further the incidence of stroke demonstrating superiority for the rhythm control strategy. Perhaps, the unequal conditions in anticoagulant therapy may have contributed to the surprising worse outcome in the rhythm control patients. Today, thanks to these trials results, we can say that it is unsafe to leave an elderly patient with AF without adequate anticoagulant protection even if sinus rhythm is restored and apparently maintained. In patients with symptomatic AF, rate control may be effective in reducing or eliminating symptoms. The adequacy of rate control should be assessed both at rest and with exercise, with defined maximal heart rates, for example 80 at rest and 110 with exertion. However, in patients who are highly symptomatic, such as those with diastolic dysfunction or hypertrophic cardiomyopathy, rate control may be insufficient to control symptoms. In this setting, rhythm control should be attempted more aggressively.

The trials results showed a very low incidence of maintenance of sinus rhythm, except for the AFFIRM trial that demonstrated a 60% maintenance of sinus rhythm in the long-term follow-up.[32, 46] However, this high percentage may be due to the fact that up to 35% of the patients had paroxysmal AF, while the other trials did not include this kind of patients. It might be argued that the rhythm control strategy failed to demonstrate superiority over the rate control strategy because maintenance of sinus rhythm could not be achieved in the long term. Whatever the case, it must be assumed that the strategies used to maintain sinus rhythm are far away of being adequate. This is the road we have to pave to find a proper solution to manage patients with AF in the near future. A long way has been traveled so far with radiofrequency ablation of ectopic focus of AF. Although this procedure has been tested primarily in young patients,[13-15] there are promising results utilizing this therapeutic modality with 3D electroanatomical mapping guidance in elderly patients with chronic AF.[47-50]

Percutaneous Catheter Ablation Of Atrial Fibrillation

Catheter ablation of AF has emerged from being a novel, largely unproven procedure to its role today as a very commonly performed procedure for treatment of patients with symptomatic AF.[51-57] Although, pulmonary vein isolation is increasingly utilized and currently is considered the cornerstone procedure for AF ablation, these procedures have not yet attained a high degree of perfection because of the controversy concerning ablation strategy, the relatively high recurrence rate, and specific complications.[58-63] Nevertheless, a recent study, which included 63 radiofrequency ablation studies, reported the outcomes of two meta-analyses of the safety and efficacy of catheter ablation of AF and anti-arrhythmic drug therapy.[64] The single-procedure success rate of ablation with no anti-arrhythmic drug therapy was 57%, the multiple-procedure success rate with no anti-arrhythmic drugs was 71%, and the multiple-procedure rate with anti-arrhythmic drugs or with unknown anti-arrhythmic drug usage was 77%. In comparison, the success rate for anti-arrhythmic therapy was 52%. There have been at least 7 prospective randomized clinical trials that compared the outcomes of AF ablation with anti-arrhythmic drug therapy.[65-74] A meta-analysis of 4 of these studies reported that 76% of patients treated with catheter ablation were free of AF compared with 19% of patients randomized to anti-arrhythmic drug therapy.[69] The study concluded that there was a more than 3.7-fold higher probability of remaining in sinus rhythm with catheter ablation than with anti-arrhythmic medications. Catheter ablation was deemed superior to medical therapy as a strategy for maintenance of sinus rhythm even in patients with persistent AF at 12-month follow-up in the SARA Study.[75]

Since many AF patients are sufficiently symptomatic and

inadequately compensated with the strategy of rate control, there is still a role for the development, and utilization of new methods that may be more effective in the long-term maintenance of sinus rhythm. This shall include novel atrial selective anti-arrhythmic agents and several non-pharmacologic procedures.[76] In this regard, more than 3000 eligible patients for the AFFIRM trial were not enrolled due to highly symptomatic AF. Hence, the results of these trials can not be extrapolated to these latter patients, neither to young symptomatic AF patients who may benefit from pulmonary vein radiofrequency ablation. Percutaneous catheter ablation was shown to be superior to medical therapy as a strategy for maintenance of sinus rhythm even in patients with persistent AF.[75]

Conclusion

There is considerable evidence available demonstrating that catheter ablation of AF is more effective than anti-arrhythmic drug therapy in controlling AF and that AF ablation improves quality of life. There is great interest in the development of new ablation technology that will improve even further the safety and efficacy of AF ablation. The decision as to weather restoring sinus rhythm is feasible and realistic in individual patients, and will remain a decision to be made on a case-by-case basis bearing in mind the light that recent trials and scientific works have shed in the management of this growing social problem. Until a new randomized controlled trial of rhythm and rate control strategy, with newer ablation methods for sinus rhythm restoration, and with equal and adequate anticoagulation is performed, we think that the proper way of managing the therapeutic maneuvers in AF patients remains to be determined, and for instance, the last word has not been spoken yet.

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