Editorial Comment

Rhythm or Rate Control Management of Atrial Fibrillation: An Overrated Dilemma

Antonis S. Manolis

Third Department of Cardiology, Athens University School of Medicine, Athens, Greece

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Address:
Antonis Manolis

Third Department of Cardiology
Athens University School of Medicine
asm@otenet.gr

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence of 1-2% – or higher if we include those who suffer from silent AF.[1,2] The prevalence of AF is related to age, reaching 6-10% in the elderly.[3,4] The adjusted relative mortality risk is approximately 20% higher in patients with AF in all age-gender strata compared with those without AF,[5] and may be higher in asymptomatic AF patients compared with symptomatic patients.[6] Recent awareness of cognitive decline in AF patients is another important and worrisome adverse effect, and this association may be strongest for younger patients, particular those with longer exposure to AF.[7-10]

The rate versus rhythm control saga

The two major randomized controlled studies, AFFIRM[11] and RACE,[12] comparing AF management strategies of "rate vs. rhythm control", published in 2002, found that rhythm control with antiarrhythmic drugs and cardioversion offered no survival benefit over rate control. The use of rhythm-control strategies in the US declined significantly in the first few years after publication of these two studies,[11,12] a trend which was reversed by the year 2005 with the advent of catheter ablation for AF, which was probably responsible for the shift back to rhythm-control interventions.[13-15] Although rate control is not inferior to rhythm control with regard to morbidity and mortality (AFFIRM and RACE), long-term maintenance of sinus rhythm by a rhythm-control approach may be preferable in terms of improvement of quality of life and subjective general well-being, and may even mitigate mortality rate.[16,17]

According to a review and meta-analysis of 10 studies (n=7867) that compared rate- and rhythm-control strategies using drug therapy, morbidity and in-hospital mortality were not different between groups, while rates of rehospitalization were much lower with a rate-control strategy.[17] However, in patients younger than 65 years, a rhythm-control strategy was superior to rate control in the prevention of all-cause mortality (p=0.0007).

According to population-based administrative databases from Quebec, Canada,[18] among 26,130 AF patients aged ≥66 years, followed for a mean period of ~3 years, after a small increase in mortality for patients treated with rhythm control in the 6 months following treatment initiation, the mortality was similar between the 2 groups until year 4 but decreased steadily in the rhythm-control group after year 5. Thus, rhythm-control therapy seems to be superior in the long-term.

The data from the epidemiological study (ODYSSEY) in a Greek cohort of 1545 AF patients, reported in the current

issue of the Hellenic Journal of Cardiology by Vardas et al,[19] give credence to this latter concept. This multicenter, countrywide, 24-month observational prospective study indicated that, although there was no difference in cardiovascular morbidity between rhythm- and rate-control therapies, there was significantly lower total mortality in the first and second year of the study with the rhythm control approach.

Teleologically, sinus rhythm is the optimal rhythm and all therapies should aim at its maintenance. In patients with AF, restoration and maintenance of sinus rhythm is often needed to control symptoms; however, an alternative strategy for AF is appropriate rate control, particularly if sinus rhythm cannot be maintained with current therapies or when these therapies are unsafe or not tolerated. Rate control is safe in older patients (≥65 years), at least according to studies with a follow up of a few years.[20] The therapeutic approach should be individualized, considering the patient's comorbidities and preferences. Over recent years, catheter ablation has evolved as an effective non-pharmacological alternative that may be a second-line or occasionaly even a first-line treatment.[14,15,21-26] Often, therapies can achieve reduction of the frequency, severity and duration of AF episodes, rather than elimination, and this may be sufficient for many patients, resulting in a significant improvement in quality of life. Adequate rate control, importantly during both rest and activity, is necessary in order to allay symptoms but also to prevent tachycardia-mediated cardiomyopathy.[27] Thus, rate control is necessary for all patients, whereas maintenance of sinus rhythm with drugs or catheter ablation should be individualized based on the patient's profile, needs, preferences, and comorbidities.[15]

In a predefined analysis of the RACE study, in 261 patients with mild to moderate congestive heart failure, rate control was not inferior to rhythm control.[28] However, if sinus rhythm could be maintained, outcomes might be improved. In another analysis of 335 patients from the same trial,[29] echocardiographic findings were compared between patients randomized to rate control (n=160) and rhythm control (n=175), and in the rhythm control group, between patients with AF versus sinus rhythm at the end of the study. The results showed that routine rate control prevented deterioration of left ventricular function, while maintenance of sinus rhythm was associated with improvement of left ventricular function and reduction of atrial size. Indeed, in patients with left ventricular dysfunction or heart failure, where a much higher incidence of AF is noted,[30] one may err on the side of a strategy that maintains sinus rhythm rather than just achieving rate control, in order to avoid an increased risk for mortality and heart failure progression.[31] This view is further supported by the recent EORP-AF Pilot Registry data, focused on management practices among European cardiologists, which showed that despite the high prescription of oral anticoagulants (OAC), annual mortality and morbidity remain high in AF patients, particularly from heart failure and hospitalizations. [32] Also, recently accumulated evidence of cognitive decline in AF patients further urges for strategies to maintain sinus rhythm.[7]

Catheter ablation

Antiarrhythmic drug therapy has provided disappointing results in maintaining sinus rhythm, plagued by inefficacy and side-effects.[33,34] Over recent years, catheter ablation has emerged as a viable alternative for both paroxysmal and persistent AF, albeit at a cost of moderate success and a still significant complication rate.[22-24] Compared with drug therapy, catheter ablation therapy appears superior in decreasing AF recurrences;[14,24-26] however, it is still dubious whether AF elimination by catheter ablation improves cardiovascular outcomes.[35] The ongoing CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) and EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) trials may help to provide such data.[14]

The 2012 European AF guidelines recommend catheter ablation for *symptomatic paroxysmal AF*, performed by an experienced operator, in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy and who prefer further rhythm control therapy (class I; level of evidence [LOE] A).[36] Ablation of *persistent symptomatic AF* that is refractory to antiarrhythmic therapy is a class IIa (LOE B) indication. Currently, there is no evidence to recommend catheter ablation of AF in asymptomatic patients. According to the 2014 American guidelines, AF catheter ablation is useful for *symptomatic paroxysmal AF* refractory or intolerant to at least one class I or III antiarrhythmic medication when a rhythm control strategy is desired *(*class I; LOE A*)*.[37] The guidelines emphasize that, prior to consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended (class I; LOE C). A class IIa (LOE A) indication concerns selected patients with

symptomatic *persistent AF* refractory or intolerant to at least one class I or III antiarrhythmic medication. Finally, in patients with recurrent symptomatic paroxysmal AF, catheter ablation may be a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after the risks and outcomes of drug and ablation therapy have been weighed (class IIa; LOE: B). The Canadian guidelines recommend catheter ablation of AF performed by highly experienced electrophysiologists in patients who remain symptomatic after an adequate trial of antiarrhythmic drug therapy and in whom a rhythm control strategy is still desired.[38] Also, catheter ablation as first-line therapy for relief of symptoms is recommended only in highly selected patients with symptomatic, paroxysmal AF. All guidelines agree that pulmonaty vein isolation (PVI) is the aim of the ablation procedure. Indeed, according to the recent European Snapshot Survey on Procedural Routines in Atrial Fibrillation Ablation (ESS-PRAFA),[21] PVI remains the main strategy for AF ablation. Unfortunately, procedure-related complications seem not to have declined, hovering around 5%.[21]

Rate control in chronic AF

A good number of patients remain in chronic or permanent AF and are managed with a "rate control only" strategy that aims to control symptoms and prevent excessive tachycardia and thus the development of tachy-cardiomyopathy,[27] with its attendant heart failure risk. However, target heart rates are not well established, as clinical trials to date have not convincingly demonstrated a benefit of strict (<80 bpm) versus lenient (<110 bpm) rate control.[39] Guidelines provide divergent recommendations with regard to rate control. The US guidelines recommend more-strict rate control (heart rate <80 bpm: class IIa recommendation; LOE B), while the European Society of Cardiology guidelines propose lenient rate control (heart rate <110 bpm: class IIa recommendation; LOE B). The recent results of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) trial,[40] a prospective US registry of AF patients in the community, indicated that, among patients with permanent AF, there is a J-shaped relationship between heart rate and mortality, suggesting that patients in community practice routinely (70%) achieved more-stringent rate control (<80 bpm) and that the associated outcomes were more favorable so long as heart rate was ≥65 bpm. The only caveat pertaining to this situation relates to the use of digoxin, as a recent accumulation of data, albeit mostly from observational studies, points to a possible mortality increase with digoxin and cautions against the routine use of this 200-year-old remedy.[41]

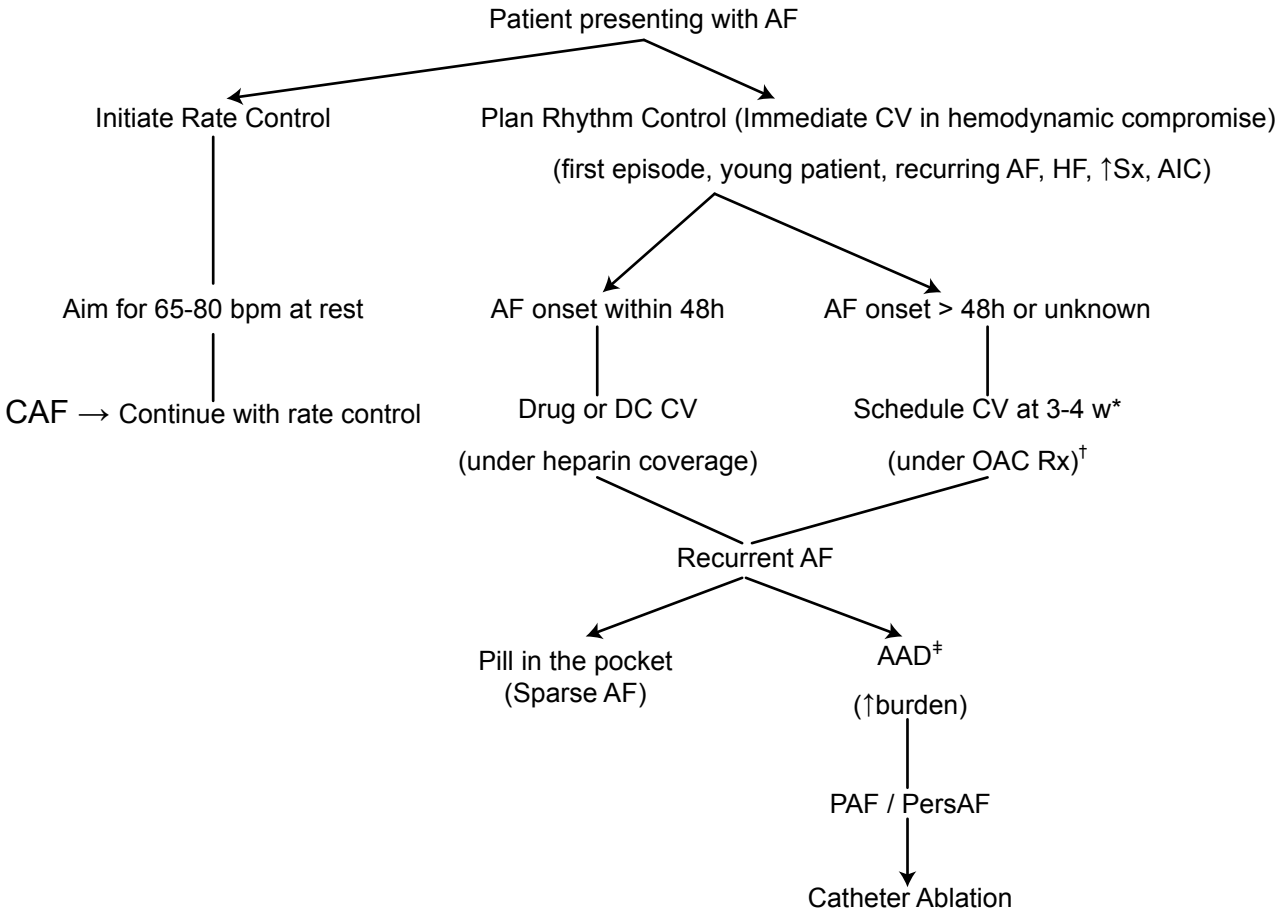
Optimal anticoagulation

Another issue raised by the present study relates to suboptimal OAC therapy. Specifically, patients managed with rhythm control were those with the lowest percentage of OAC treatment. At baseline, a total of ~70% of patients received OAC, but this percentaged dropped to ~51% in the rhythm-control group, whereas in the rate-control group ~84% of patients received OAC.[19] Recent registry data indicate that the percentage of AF patients receiving OAC is increasing in Europe, though compliance with guidelines still remains suboptimal.[32] However, there is evidence showing that even in those receiving OAC therapy, the time in therapeutic range (TTR) often remains suboptimal.[42] An average TTR of the INR >65-70% is recommended for optimal efficacy and safety in patients treated with a vitamin K antagonist (VKA). The SAMe-TT2R2 score – Sex; Age (<60 years); Medical history (at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease); Treatment (interacting drugs, e.g. amiodarone for rhythm control) (all 1 point); and current Tobacco use (2 points) and Race (non-Caucasian; 2 points) – has recently been proposed, based on the results of a prospective "real-world" cohort of 459 patients with AF receiving acenocoumarol, to identify those patients who can respond well to VKA therapy.[43] Thus, patients with poor quality anticoagulation could benefit from additional strategies for improving anticoagulation control with VKAs or alternative OACs.

Conclusion

AF is the commonest cardiac arrhythmia, having an age-dependent prevalence and conferring an increased risk of morbidity and mortality. The pharmacological management of AF has yielded only modest success, with an increased rate of side-effects, among which proarrhythmia (for all drugs) and extracardiac toxicity (for amiodarone) predominate. However, when sinus rhythm is maintained, quality of life and

other indices of well-being are improved. Despite the "rate vs. rhythm" control controversy, the teleological aim of maintaining sinus rhythm remains in focus, albeit elusive in several cases. The current report in a Greek cohort of AF patients lends further support to accumulating evidence that a rhythm control strategy, when feasible, may indeed be the preferred strategy, at least in selected patient groups (Figure 1). Over the past several years, catheter ablation, despite its limitations, has been brought to center stage as a practical rhythm-control strategy. Advances in ablation techniques have improved results in symptomatic patients with both paroxysmal and persistent forms of AF and, despite being far from optimal, they are probably responsible for a shift back to rhythm control interventions. Thus, the dilemma of rate vs. rhythm control, if not obsolete, is at least overrated. Of course, additional goals for long-term AF control in these patients focus on optimizing anticoagulation therapy and on the management of other medical comorbid conditions and risk factors associated with AF. Finally, ongoing studies evaluating the long-term cardiovascular outcomes of catheter ablation will shed further light on the dilemma at hand.



*When planning to maintain patient on AAD, start AAD 5 T½ (or ~2 weeks for amiodarone) prior to CV / for earlier CV →use TEE.

†When using VKA, maintain INR 2.0-3.0 for at least 3 weeks prior to CV and preferably at 2.5-3.0 for the last 2 weeks prior to CV / Continue OAC per the CHA_2DS_2-VASc score.

‡Use IC agents only in the absence of structural heart disease, otherwise resort to amiodarone.

Figure 1. Flow-chart proposing an algorithm for a current approach to rate vs. rhythm control management in patients with atrial fibrillation (AF). AAD – antiarrhythmic drug; AIC – arrhythmia-induced cardiomyopathy; bpm – beats per minute; CAF – chronic atrial fibrillation; CV – cardioversion; DC – direct current; HF – heart failure; INR – international normalized ratio; OAC – oral anticoagulant; PAF – paroxysmal atrial fibrillation; persAF – persistent atrial fibrillation; Rx – therapy; Sx – symptoms; TEE – transesophageal echocardiogram; T½ – (drug) half-life; VKA – vitamin K antagonist.

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