REVIEWS

Rhythm Control Strategies and the Role of Antiarrhythmic Drugs in the Management of Atrial Fibrillation: Focus on Clinical Outcomes

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Atrial fibrillation (AF) is a common disorder that significantly impacts the lives of affected patients. The restoration of sinus rhythm may prevent AF progression and reduce the occurrence of negative sequelae; however, available antiarrhythmic drugs (AADs) have largely failed to demonstrate significant benefit relative to rate control with respect to morbidity and mortality outcomes. The review commentary will address current knowledge regarding the pathologic mechanisms of AF, current trials that investigate rate and rhythm strategies, and future therapies that may change treatment approaches based on preliminary evidence suggesting a more favorable safety profile. The observed outcomes are likely a reflection of the limited efficacy plus poor safety and tolerability of available AADS. However, data from patients who attained and maintained sinus rhythm in a number of clinical studies demonstrate that the achievement of normal sinus rhythm can indeed reduce AF-associated morbidity and mortality. Furthermore, the results of trials designed to assess specific morbidity and mortality outcomes such as cardiovascular death hospitalization suggest that the development of safer AF therapies, whether pharmacologic or nonpharmacologic, can potentially improve clinical outcomes.

KEY WORDS: atrial fibrillation; drugs; ablation; stroke; heart failure; outcomes.

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Atrial fibrillation (AF) is the most frequent of all sustained arrhythmias; its prevalence is increasing in parallel with the aging of the population.¹ Between 0.4–1% of the general population and 10% of the population >80 years of age have AF.² Analysis of data from 1980–2000 in Olmstead County, Minnesota ($n=4,618$) indicate that the incidence of new onset AF increased 12.6% ($P=0.014$) during this time period despite adjustment for age.¹ Should this trend continue, it is estimated that 15.9 million Americans will have AF in 2050. Common conditions associated with aging such as diabetes, obesity, hypertension, heart failure, coronary artery disease,

valvular heart disease, cardiac surgery; and smoking may predispose individuals to AF development and progression.³

Patients with AF experience a variety of symptoms that impact quality of life (Fig. 1). Although variable, arrhythmia progression is common; nearly one-quarter of patients with paroxysmal AF will progress to persistent AF and up to 29% of patients with paroxysmal or persistent AF develop permanent AF in a population observed over 30 years. Disease progression can occur even in the absence of new or worsening underlying heart disease although this typically only develops in a minority of patients.⁴ Patients that have coexistent cardiovascular disease such as hypertension, obstructive sleep apnea, heart failure, and valvular heart disease have a much higher increased risk for arrhythmia progression.

AF increases the risk of adverse long-term cardiovascular outcomes in patients with and without structural heart disease in observational studies.⁵ Similarly, in patients with heart failure and an ICD, both chronic and new onset AF increase the risk of heart failure hospitalization, ICD shocks, and death.⁶ The presence of AF also increases total mortality in patients with heart failure without an ICD.⁷ Based upon these observations it is reasonable to surmise that aggressive rhythm management with maintenance of sinus rhythm would improve long-term cardiovascular outcomes. However, a strategy of rhythm control has never been shown to reduce morbidity and mortality when compared to treatment with rate control therapies. Multiple large randomized trials (Table 1) have failed to demonstrate a rhythm strategy including: Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)⁸, How to Treat Chronic Atrial Fibrillation (HOT-CAFÉ and CAFÉ II)^{9,10} Pharmacological Intervention in Atrial Fibrillation (PIAF)¹¹, Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)¹², Strategies of Treatment of Atrial Fibrillation (STAF)¹³, and Atrial Fibrillation and Congestive Heart Failure Investigation (AF-CHF)¹⁴. Furthermore, a trend towards increased mortality with rhythm control was seen in AFFIRM and RACE. Table 2 shows investigational agents for the potential management of AF.

Subset analyses of these trials have raised the question whether sinus rhythm is a surrogate of a better prognosis or whether there is a cause and effect relationship.^{15–18} For example, in the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) study, dofetilide had no effect on all-cause mortality; however, the restoration and maintenance of sinus rhythm (regardless of study treatment) did improve survival by 66%.¹⁸ In addition, subanalysis of the AFFIRM trial showed improved survival in patients who maintained normal sinus rhythm, even though there was no mortality benefit by intention to treat analysis.¹⁵ It is also likely

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Figure 1. Broad consequences of atrial fibrillation.

that patient characteristics such as age and concomitant conditions such as CHF influence clinical outcomes. For example, subset analysis of AFFIRM demonstrated that younger patients (≤ 65 years of age) and patients without a history of CHF benefited more (had better survival) from rate versus rhythm control therapy.¹⁷ These trials highlight the relative risks of AF itself when compared to antiarrhythmic therapy. In this commentary, we address the pathologic mechanisms of AF, current trials that investigate rate and rhythm strategies, and future therapies that may change treatment approaches based on preliminary evidence suggesting a more favorable safety profile.

THE CLINICAL IMPLICATIONS OF DISEASE PROGRESSION

AF develops when electrical triggering occurs in the presence of an appropriate substrate to sustain re-entry. In patients with left ventricular dysfunction, the shortening of the atrial cellular effective refractory period may provide this substrate.^{19,20} AF progression appears to result from electrical, contractile, and structural remodeling that occurs when the arrhythmia is permitted to persist.²¹ Electrical remodeling occurs rapidly and is characterized by shortened atrial refractoriness and loss of normal rate adaptation, which promotes AF occurrence. Contractile remodeling develops more insidiously and appears to arise from altered calcium transport and uptake and subsequent depression of the L-type calcium current.²² Structural changes develop over a longer period of time and are characterized by diffuse scarring and chamber enlargement. Contractile and structural remodeling interferes with both atrial and ventricular function, and may be directly related to negative outcomes (e.g., thromboembolism, heart failure). Whereas electrical remodeling is typically reversible upon restoration of sinus rhythm, contractile and structural remodeling may persist. The longer the duration of AF, the

more difficult it becomes to restore normal sinus rhythm, likely because the electrical, contractile, and structural changes that create an optimal environment for AF propagation.²³ These structural observations with durable AF imply a question: does aggressive upfront restoration of sinus rhythm with either nonpharmacologic or pharmacologic interventions improve outcomes?^{23,24}

The potential consequences of AF and AF-associated remodeling are significant (Fig. 1). The hemodynamic consequences of atrial fibrillation may give rise to symptoms (e.g., discomfort, palpitations, breathlessness, syncope, dizziness, reduced exercise tolerance, and chronic fatigue) that can significantly reduce quality of life and impact health care resources.^{25,26} In patients with new onset HF, one study showed a yearly risk of 3.3% of developing AF.²⁷ Chronic tachycardia from AF can result in significant left ventricular dysfunction and HF.²⁸ This bidirectional relationship likely results in the high prevalence of HF (up to 42%) in epidemiologic studies of AF.^{29,30}

Similarly atrial dilation and reduced contractility can result in hemostasis and thrombus formation in the left atrium and left atrial appendage increasing risk of stroke.³¹ Approximately 15% of all strokes are due to AF.³² The risk of stroke is directly proportional to the presence of other cardiovascular risk factors in patients with AF (age >75 years, hypertension, congestive heart failure, diabetes, and prior stroke). However, across all of these disease states, the persistence of AF increases the stroke risk further.⁵

AF is also a frequent cause of hospitalization. During a 15-year period between 1985 and 1999, the number of hospitalizations in the US with AF as the principle diagnosis increased approximately 144%.³³ In part the increased rate of hospitalization for AF was attributed to higher rates of coexistent cardiovascular diseases such as hypertension, ischemic heart disease, heart failure and diabetes. However, there persists an increase in AF hospitalization that cannot be explained by adjustment for these variables and age. Hospitalization is costly and contributes to the financial burden of AF.³⁴ In the UK, the cost of AF hospitalization increased 123% between

Table 1. Clinical Trials for AF Evaluating Rate Versus Rhythm

Trial	Population	Rate control	Rhythm control	Sinus rhythm at study end
AFFIRM ⁸ (n=4060)	Age>65 Other stroke risk factors	Digoxin (71%) BB (68%) CCB (46%)	Amiodarone (63%) Sotalol (41%) Propafenone (15%)	Rhythm (63%) Rate (35%)
HOT-CAFÉ ^{9,10} (n=205)	Persistent AF CCB (8%) Digoxin (43%)	BB (89%) Propafenone (37%) Sotalol (24%)	Amiodarone (57%)	Rhythm (64%) Rate (not specified)
PIAF ¹¹ (n=252)	Persistent AF	BB (9%) Digoxin (7%) CCB (100%)	Amiodarone (100%)	Rhythm (56%) Rate (10%)
RACE ¹² (n=522)	Persistent or recurrent AF/AFL	Not specified	Sotalol (initial agent)	Rhythm (39%) Rate (10%)
STAF ¹³ (n=200)	Persistent AF	BB (45%) CCB (22%) Digoxin (75%)	Amiodarone (42%) Sotalol (22%) Class 1 (12%)	Rhythm (38%) Rate (9%)
AF-CHF ¹⁴ (n=1376)	Persistent AF Ejection Fraction (<35%)	*BB (88%) *Amiodarone (7%) *CCB (3%)	*Amiodarone (82%) *Sotalol(2%) *Dofetilide (<1%)	Rhythm (73%) Rate (30-41%)

*Medication use at 12 months

Abbreviations: BB (beta adrenergic blocker), CCB (calcium channel blocker)

1995 and 2000.³⁴ It has been estimated AF increases direct costs of medical care by more than fivefold.³⁵

We are to some extent faced with a “paradox”. On one hand there is extensive evidence demonstrating the adverse effects of atrial fibrillation upon mortality, morbidity and the progression of many diseases. Despite this, well designed clinical trials have failed to demonstrate any benefit from strategies aimed at maintaining sinus rhythm. Whether future improvements in rhythm control strategies will result in better outcomes in comparison to the approach of rate control remains to be discovered as well as the best means to measure therapeutic efficacies.

IMPACT OF ANTIARRHYTHMIC THERAPY ON CLINICAL OUTCOMES

In the widely publicized AFFIRM trial,⁸ rhythm-control strategies were no better than rate-control strategies with respect to mortality (23.8% versus 21.3% at 5 years; $p=0.08$). Patients in the rhythm-control strategy group required more hospitalizations ($p<0.001$) and experienced more adverse effects (pulmonary events, gastrointestinal events, bradycardia, QT prolongation, and other; all $P\leq 0.001$) than did patients in the rate-control strategy group. Data from the HOT-CAFÉ and CAFÉ II^{9,10}, PIAF¹¹, RACE¹², STAF¹³, and AF-CHF¹⁴ trials similarly failed to demonstrate clinical meaningful benefits for rhythm-control versus rate-control strategies.

It is likely that multiple factors contributed to the general lack of clinical benefit observed in these trials. As a group, currently available AADs are not highly effective. Recurrence rates during therapy are high (44% to 67% at 1 year; data pooled from multiple studies).³⁶ The lack of efficiency of AADs to maintain sinus rhythm is manifest in the AFFIRM trial, in which approximately 63% of the rhythm control arm was in sinus rhythm at 5 years.^{8,15} The true percentage is likely even lower as subclinical episodes of AF are common. Lack of efficacy, however, does not

Table 2. Investigational Agents for the Potential Management of AF—Adapted from Wyse⁶⁴ and Naccarelli⁶⁵

Atrial selective	Cardiac channel
Vernakalant	Kur, Kto, Na, KACH
Ranolazine	Na
AZD7009	Kr, Kto, Kur, Na
AVE0118	Kur, Kto, KACH
AVE1231	Kur, KACH
ATI2042	Kr, Ks, Ca, Kto
S9947	Kur
S20951	Kur
Tertiapin	KACH
NIP-142	Kur, KACH
Diphenylphosphine oxide-1 (DPO-1)	Kur
Amiodarone analog	
Dronedarone	Kr, Ks, Ca, Kto, Na, β , α
Celivarone	Kr, Ks, KACH, Kv1.5, Ca, Kto, Na, β , α
Novel Class III	
Azimilide	Kr, Ks, Ca, Na
Tedisamil	Kr, Ks, Kto, KATP, Na, Kur
Ersentilide	Kr, β 1
EMD60263	Ca, Kr, Na
JTV-519	Na, KACH, Kr
Gap junction modulators	
Rotigaptide (connexin modulator)	
AAP10 (connexin modulator)	
Adenosine A1 agonists	
Tecadenoson	
Selodenoson	
Other mechanisms	
GsMTx4 (stretch receptor antagonist)	
KB-R7943 ($\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor)	
CP-060S ($\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor)	
Cariporide (Na^+/H^+ exchange inhibitor)	
Piboserod (5-HT4 receptor antagonist)	
GsMTx4 (SAC blocker)	
Non-antiarrhythmics	
Angiotensin converting-enzyme inhibitors	
Angiotensin receptor blockers	
3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors	
Omega-3 fatty acids/fish oil	

Abbreviations: Potassium (K): r(rapid), s(slow), to(transient outward), ATP (adenosine triphosphate sensitive), ACh(acetylcholine sensitive), Sodium (Na), Calcium (Ca), Beta (β), Alpha (α)

tell the entire story. In the recently published AF-CHF trial¹⁴, which involved a higher risk population of HF patients, approximately 80% of patients were in sinus rhythm at study completion in the rhythm control arm. These patients were most often on amiodarone and required frequent cardioversions. Despite this vigorous approach to maintain sinus rhythm there still was no apparent advantage to rhythm control. As with the other trials, there are multiple confounding factors including a significantly higher use of beta blockers in the rhythm control group that may have also influenced outcomes.

A second possibility is that adverse effects of currently used AADs may negate or offset the potential beneficial effects of maintaining sinus rhythm. Adverse events and side effects are common with AADs and likely contribute to poor adherence. Up to 23% of premature discontinuations from AAD therapy are due to adverse effects and up to 7% are due to proarrhythmia.³⁶ The negative inotropic effects of antiarrhythmics may have detrimental effects in some patients, such as those with left ventricular dysfunction.³⁷ Furthermore, permanent pacemaker implantation may be necessary despite AAD therapy. This may be an important risk factor in patients with underlying left ventricular dysfunction who develop congestive heart failure related to asynchrony from right ventricular apical pacing. In RACE, permanent pacemaker implantation was required in 6% of patients in the rhythm-control groups versus no patients in the rate control group.³⁸

A third possibility is that the lack of rhythm control benefit may reflect study design (Fig. 2); namely the focus on the effects of the treatment strategy (rate-control strategy versus rhythm-control strategy) rather than on the impact of sinus rhythm. It is possible that increased mortality among AAD users masked the positive effects of sinus rhythm in clinical studies. In AFFIRM, AF persisted in many patients in the rhythm-control arm (17.6%, 26.7%, and 37.4% at 1, 3, and 5 years) and normal sinus rhythm was attained (and maintained) by many patients in the rate control arm (34.6% of patients in the rate-control group were in sinus rhythm at 5 years).⁸ Although the use of antiarrhythmic drugs increased the risk of death by 49% ($p=0.0005$), adjustment for the presence of sinus rhythm demonstrated a benefit for sinus rhythm attainment ($p<0.0001$).¹⁵ Similarly in RACE, post-hoc analysis demonstrated several clinically important benefits of sinus rhythm achievement and

maintenance, including reduced cardiovascular mortality (0% vs. 9.5%), progression of HF (2.1% vs. 4.8%), bleeding (0% vs. 4.8%), and pacemaker implantation (2.1% vs. 6.0%).³⁸ Examination of patients who experienced a primary outcome event in STAF revealed that only 1 of the 19 patients was in sinus rhythm at the time of the event ($p=0.049$).¹³ In CHF-STAT, 31.4% of amiodarone-treated patients and 7.7% of placebo-treated patients (7.7%) converted to and remained in sinus rhythm for the duration of the study ($p=0.002$).³⁹ Within the amiodarone group, survival was greater among the sinus rhythm subset ($p=0.04$). Although all trials require analysis according to intention to treat, subanalysis by presence or absence of sinus rhythm raises the question if the rhythm status is a surrogate versus cause and effect. If it is the later, these findings highlight the need for better methods of achieving and maintaining sinus rhythm. If the observations are related to confounders, and those that are in sinus rhythm are a lower risk group, then the findings highlight the need for appropriate patient selection for available and future therapeutic options.

A fourth possibility that may confound a potential positive effect of rhythm control in these trials is the inconsistent use of concomitant pharmacologic therapies such as anticoagulants. For example, patients who achieved sinus rhythm in AFFIRM⁸ and RACE¹² and maintained may have had their anticoagulant therapy discontinued based upon the perception that the rhythm control strategy was working effectively. Consequently in AFFIRM, the majority of strokes occurred in patients who terminated anticoagulation therapy or were receiving subtherapeutic levels of warfarin.⁸ This could have been the consequence of recurrent atrial fibrillation in these patients or the presence of underlying risk factors for stroke irrespective of whether in sinus rhythm or not. Similarly, there was variability of use of other medications known to improve outcomes in patients with cardiovascular disease such as ACE inhibitors, beta blockers, HMG-CoA reductase inhibitors, and aspirin.

Lastly eligible patients for these trials were a selected group who were able to tolerate AF sufficiently so as to allow randomization. Highly symptomatic patients and patients with reduced left ventricular compliance (e.g., hypertrophic cardiomyopathy, severe left ventricular hypertrophy, diastolic heart failure, etc) were underrepresented, thus complicating the interpretation of study results and their applicability to the general population of patients with AF.

Figure 2. Evolution of clinical trials of AF therapies.

DEFINING FUTURE APPROACHES

Clinical outcomes remain the primary focus of ongoing antiarrhythmic drug research. One recent expert consensus identified seven main outcome domains that could be used to evaluate the benefits of agents that have demonstrated the ability to maintain sinus rhythm: death, stroke, symptoms and quality of life, rhythm, left ventricular function, cost, and emerging parameters (e.g., surrogate markers based on blood levels and histology).⁴⁰ Such outcomes may provide more insight into the overall impact of AF therapies than traditional outcomes such as time to arrhythmia recurrence. The lack of solid data regarding secondary outcomes has resulted in a lack of consensus regarding an optimal treatment approach.^{41–43} The ACC/AHA/ESC guide-

lines⁴¹ currently advocate an individualized approach based on symptoms, duration and pattern of AF, comorbidities, and short and long-term treatment goals. Furthermore, these guidelines recommend that, when maintenance of sinus rhythm is desired, the selection of therapy include consideration of concomitant conditions such as hypertension, coronary artery disease, and heart failure. A recent summary of the 2nd AFNET-EHRA conference advocated improving rhythm control monitoring as a means to improve outcomes and allow continuous therapy.⁴⁴

Fortunately, new avenues and options of therapies continue to emerge. Recently, the ATHENA trial studied dronedarone, an analogue of amiodarone without iodine moieties, was studied in the ATHENA trial to assess the efficacy in prevention of cardiovascular hospitalization or all cause mortality.⁴⁵ In this study, the primary endpoint was cardiovascular hospitalization or death which was reduced by 24% during a mean follow-up period of 21 months. Similarly, dronedarone reduced the risk of first hospitalization due to cardiovascular events by 26% (primarily for AF), the risk of first hospitalization for AF 37%, and the risk of first hospitalization for acute coronary syndrome by 30%. It also reduced the risk of death from cardiovascular causes by 29% and the risk of death from cardiac arrhythmia by 45%. In post hoc analysis a reduction in stroke was also noted in the ATHENA trial in those randomized to dronedarone.⁴⁶ These data are important as they show a positive benefit in newly specified clinical outcomes as well as AF symptomatology. These data complimented those previously collected that showed dronedarone reduced time to AF recurrence compared to placebo in the DAFNE, EURIDIS, and ADONIS trials.^{47,48} Dronedarone is contraindicated in patients with advanced (class III-IV) heart failure (a cohort not studied in ATHENA) based on the findings of the ANDROMEDA trial which was discontinued prematurely due to increased mortality in this group of patients.⁴⁹ It has been speculated that drug toxicity (increased serum creatinine) may have resulted in the discontinuation of or failure to initiate treatment with ACE inhibitors or ARBs in patients with advanced heart failure. Nonetheless, the exact mechanisms of the increased mortality are largely unknown and direct drug toxicity is also plausible. Based on the finding of increased mortality among patients with advanced CHF, clinicians should not use dronedarone in this patient population.

An interesting aspect to dronedarone is that as a class III antiarrhythmic it has modest efficacy.⁵⁰ Recurrence of AF occurs more commonly among patients treated with dronedarone than among those receiving amiodarone.⁵⁰ An important observation is that this new medication with modest efficacy and few side effects shows a clear favorable impact on mortality in those without severe heart failure.

A number of potential new AF therapies are in various stages of development (Table 1). Atrial selective agents in advanced stages of development such as vernakalant⁵¹ and AZD7009^{52,53} may convert AF to sinus rhythm with a limited risk of proarrhythmia. Additionally, vernakalant may suppress arrhythmia recurrence when administered orally as maintenance therapy.⁵⁴

ABLATION

Due to the variable efficacy of currently available antiarrhythmic medications, investigators have developed nonpharmacologic

approaches for maintenance of sinus rhythm. These approaches are predicated upon pulmonary vein involvement in the pathophysiology of AF⁵⁵ and many different ablative approaches at or near the orifice of the PV have demonstrated substantial therapeutic success. Currently, these are second-line options for the treatment of medically refractive paroxysmal or persistent AF.⁴¹ In a worldwide survey of catheter ablation for AF, 8745 patients ($n=8,745$) from 90 centers (27.3% required >1 procedure), 52.0% became asymptomatic without drugs and another 23.9% became asymptomatic in the presence of formerly ineffective antiarrhythmic drugs. At least 1 major complication was reported in 6.0% of patients.⁵⁶ Although these early outcome data are favorable, the success rate and low complication rates were primarily driven by a few high volume centers. Also, given the moderate efficacy in patients with more advanced forms of AF, AADs will continue to play a central role of arrhythmia management as these nonpharmacologic approaches continue to be refined.

The role of catheter ablation in AF remains to be determined. Pulmonary vein isolation was superior to drug therapy in suppressing AF and improving symptoms, exercise capacity, and quality of life in patients with AF resistant to at least 1 antiarrhythmic drug in the A4 study.⁵⁷ In another comparative trial, pulmonary vein isolation significantly reduced the frequency of symptomatic recurrences relative to antiarrhythmic drug therapy during the 1-year follow-up period (13% vs. 63%; $P<.001$).⁵⁸ Pulmonary vein isolation compared to nodal ablation with biventricular pacing in patients with symptomatic, drug-resistant AF and heart failure, was associated with longer 6-minute walk times and mean ejection fraction at 6 months.⁵⁹ Data from the recently approved NHLBI sponsored trial Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) will provide much needed long-term outcome data. In addition to ablation therapies directed at restoring sinus rhythm, atrioventricular junctional ablation plus pacemaker implantation reduced symptoms and improved quality of life to a greater extent than drug therapy in patients with symptomatic AF not controlled by pharmacologic therapy.⁶⁰

Pacemakers are also routinely placed in patients with tachy-brady syndrome and allow more aggressive rhythm and/or rate control. Device programming is required to minimize the impact of chronic right ventricular pacing. Nonetheless, pacemakers are commonly used in a combination of both pharmacologic and nonpharmacologic therapies. Upcoming trials will define a subset of patients for whom nonpharmacologic interventions may be appropriate as first line therapies.

Other available nonpharmacologic approaches include the open-heart surgical Maze procedure. Long-term data utilizing the Cox III lesion set are impressive; 90% of patients remain in sinus rhythm at 10 years.⁶¹ Recently a mini-maze procedure has been developed that has less procedural risk and shorter recovery times. Rather than cutting the atrium, energy delivery sources such as cryothermal and radiofrequency (unipolar and bipolar) are used. This strategy reduces procedure time, but also decreases success rates comparable to those achieved through catheter-based approaches, although direct comparison is limited due to patient characteristics.⁶² These surgical approaches in general share the common benefit of removing the left atrial appendage that may reduce stroke risk. Also, similar to catheter ablation frequent modifications of approach limit understanding of which procedure with current tools may

optimize outcomes.⁶³ Although nonpharmacologic approaches have favorable efficacy and durability, as AF becomes more prevalent globally due to the aging population, they will not be sufficient alone to meet the clinical need as they are time consuming, require unique physician training, and demand significant nonmonetary and monetary resources.

SUMMARY

AF can significantly impact the lives of affected patients. Restoration of normal sinus rhythm may prevent AF progression and reduce the occurrence of associated sequelae that contribute to the overall burden of this condition. The general failure of currently available AADs to improve clinical outcomes goes beyond rhythm versus rate control strategies alone and has implications in the initial experimental design, drug toxicities and efficiencies, and drug compliance. Recent trials suggest that safer AF therapies, whether pharmacologic or nonpharmacologic, can potentially improve clinical outcomes and as such provide incentive to continue to explore the benefits of aggressive rhythm control strategies.

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