Vargas et al. *HCA Healthcare Journal of Medicine* (2023) 4:5
https://doi.org/10.36518/2689-0216.1564

Clinical Review

Atrial Fibrillation: Rate Versus Rhythm Control

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Abstract

Description

Atrial fibrillation (AF) remains the most common arrhythmia worldwide and is expected to affect approximately 12 million individuals in the United States alone by 2030. Thromboembolic events remain a feared complication of AF and should be treated and risk-stratified utilizing the CHA_2DS_2-VASc scoring system. Other complications of AF span a wide spectrum from impaired quality of life (QoL) to an increase in all-cause mortality. Rate control strategies consist of controlling the ventricular rate and have been shown to be a safe and effective strategy for asymptomatic AF patients. In patients who are plagued with symptoms leading to impaired QoL or a decrease in exercise capacity, rhythm control with antiarrhythmic drugs or catheter ablation may be suitable options. Mortality benefits when comparing rate versus rhythm control remain equivocal when comparing multiple studies over the past decade.

Keywords

atrial fibrillation (AF); rate control; rhythm control; anti-arrhythmic drugs; electrical cardioversion; catheter ablation; atrial fibrosis; quality of life (QoL)

Introduction

Atrial fibrillation (AF) is a consequence of uncoordinated electrical conduction in the atria and is characterized on the electrocardiogram as the absence of consistently conducted P waves and irregular R-R intervals.[1,2] The estimated lifetime risk of developing AF is 22-26%, making it the most common arrhythmia worldwide, estimated to affect 12.1 million individuals in the United States alone by 2030.[2,3] Several clinical types of AF exist and should be classified in clinical practice as follows: first diagnosed (initial AF episode), paroxysmal (AF that terminates within 7 days of onset, either following intervention or spontaneously), persistent (continuous AF lasting ≥7 days regardless of termination), long-standing persistent (continuous AF for >12 months), and permanent AF (acceptance from patient and physician that termination of AF will not be pursued).[1]

Notable complications of AF include impaired quality of life (QoL), heart failure, increased hospitalization, mortality, and subsequent medical costs.[2,3] Thromboembolic events, mainly ischemic stroke, remain some of the most debilitating complications of AF. These complications may be mitigated by using the CHA_2DS_2-VASc scoring system, which several studies have validated to determine a patient's risk of ischemic stroke.[4,5] In patients without absolute contraindications who are high risk (CHA_2DS_2-VASc score ≥2 men, ≥3 women), treatment with anticoagulation is recommended.[6] The HAS-BLED score, which determines a patient's risk of adverse bleeding events, should not exclude patients from anticoagulation but rather guide clinicians to monitor patients closely.[4,5,7-9]

Treatment of concomitant comorbidities, such as hypertension, diabetes mellitus, obesity, obstructive sleep apnea, pulmonary disease,

and cardiomyopathies can reduce the lifetime risk of acquiring AF.[10,11] Although these disease states have been traditionally viewed as risk factors for the development and recurrence of AF, advancements in basic science and genetics have gained insight into primary atrial myopathy as a leading substrate for AF.[12,13]

Current AF guidelines from both the European Society of Cardiology and the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society recommend rate-control as first-line therapy, reserving rhythm control (ie, restoration of sinus rhythm) for patients with persistent symptoms.[1,14-16] In this brief review, we aim to summarize the state of the most current literature regarding AF management options, as newer studies have revealed that some benefits of rhythm control are superior to rate control, specifically when comparing patient QoL.

Rate Control

Rate control is commonly achieved using atrioventricular (AV) nodal blocking agents, such as beta-blockers, non-dihydropyridine calcium channel blockers, or digoxin.[1] When employing rate control strategies, lenient (resting heart rate <110 bpm) vs strict (resting heart rate <80 bpm) control were compared in the RACE-II trial.[17] Results of that study revealed no differences in mortality, stroke, or heart failure-related hospitalizations when comparing lenient versus strict control for patients with permanent AF.

Beta-blockers are preferred in patients with AF complicated by a left ventricular ejection fraction (LVEF) of less than 40%. Due to their negative inotropic effects, non-dihydropyridine calcium channel blockers are contraindicated in patients with a LVEF of less than 40% but remain a suitable option in other AF cases.[18] Digoxin may be used in combination with either beta-blockers or non-dihydropyridine calcium channel blockers in patients with difficult to control ventricular rates by increasing parasympathetic tone in the AV node.[18] Limitations of digoxin include a narrow therapeutic index, the need to monitor serum levels frequently, long onset of action (>1 hour), inability to maintain goal heart rate when the patient is not at rest, and no benefit in mortality.[15,18,19]

In patients with difficult-to-control ventricular rates that remain refractory to medical therapy, catheter ablation of the AV node and ventricular pacing may be required. Various trials have shown that AV node ablation and cardiac resynchronization therapy improved patient symptoms and QoL.[20,21] Modification of the AV node and subsequent ventricular pacing, however, can rarely lead to sudden cardiac death with an estimated risk of 2.1%.[22] Risk factors for sudden cardiac death after an ablate-and-pace approach include mitral stenosis, dilated cardiomyopathy, and QRS morphology (narrow QRS or right bundle branch block).[23] This risk is lowered when patients are initially paced at a ventricular rate of 90 bpm and gradually decreased to a normal resting heart rate of 60 bpm in comparison with those who were decreased to ventricular rates of 60 bpm immediately following AV node ablation.[20,24]

In summary, when using rate control strategies for patients with AF, medical therapy with beta blockers or non-dihydropyridine calcium channel blockers, depending on the LVEF, are considered first-line agents. Digoxin can be added to existing therapies, while ablation of the AV node is helpful in controlling symptoms and QoL in refractory cases.

Rhythm Control

Rhythm control consists of restoring normal sinus rhythm by either electrical or pharmacologic cardioversion with antiarrhythmic medications and/or catheter ablation of ectopic atrial electrical activity. The effect of restoration of normal sinus rhythm on mortality and other markers of morbidity has been widely debated in the literature.

A significant reduction in all-cause mortality and hospitalization when pursuing rhythm control has not been reported in several randomized controlled trials; however, other benefits of rhythm control include improved QoL, exercise capacity, and longer 6-minute walk distance.[25-31] The AFFIRM trial, in which rhythm and rate control were compared, revealed no survival advantage with rhythm control and no difference between the incidence of stroke and cardiac arrest.[32] In addition, a meta-analysis of early observational studies failed to show significant differences in all-cause mortality with

2 other trials reflecting similar outcomes.[31,33,34] Furthermore, restoration of normal sinus rhythm becomes difficult the longer AF persists and is associated with increased all-cause mortality, myocardial infarction, and heart failure.[35,36]

Electrical Cardioversion

Synchronized direct current cardioversion (DCCV) is used emergently in hemodynamically unstable patients with AF and rapid ventricular response. In contrast to its critical use, DCCV can also be utilized electively to restore normal sinus rhythm. Non-vitamin K oral anticoagulant is mandatory for 3 weeks prior to elective DCCV in the absence of a mechanical valve or valvular AF, in which warfarin is indicated. Non-vitamin K oral anticoagulants are also indicated when the duration of AF is greater than 48 hours due to the increased risk of thrombus formation within the left atrium and left atrial appendage.[15,16] Alternatively, transesophageal echocardiogram can be used to exclude thrombus in these locations if elective cardioversion is desired prior to completing the recommended oral anticoagulation duration.[16] Oral anticoagulation should continue 4 weeks after successful DCCV.[15]

Methodological nuances have been linked to successful cardioversion. In a single center randomized trial, comparing maximally fixed shocks (360-360-360 J) to low-escalating shocks (125-150-200 J), the maximally fixed shocks were more effective in achieving normal sinus rhythm with similar safety endpoints to low-escalating shocks.[37] Electrode placement has also been highlighted in recent research. Electrodes placed in the anterior-lateral position were shown to be superior to the standard anterior-posterior approach for achieving normal sinus rhythm after one shock in AF.[38] Additionally, manual pressure applied to electrodes in the anterior–lateral position may increase the efficacy of DCCV.[39,40]

The optimal timing of DCCV remains unclear. Early DCCV in comparison to a watch-and-wait approach has been studied. A watch-and-wait approach, which consisted of treating patients diagnosed with AF with rate control medications and waiting 48 hours for spontaneous cardioversion, was non-inferior to early DCCV in achieving the primary endpoint of normal sinus rhythm at 4 weeks.[41]

Several comorbidities, however, have been associated with AF recurrence and progression to persistent AF. Prior history of COPD, ischemic stroke, valvular heart disease, left atrial enlargement, heart failure, obesity, older age, uncontrolled hypertension, and hyperthyroidism are risk factors for recurrence.[35,42] Optimization of these conditions can increase the likelihood that once normal sinus rhythm is achieved, it will be sustained.[43]

Antiarrhythmics

In this section, the role of antiarrhythmic drug therapy to solely maintain normal sinus rhythm in AF patients will be discussed. Flecainide is a class Ic sodium-channel blocker and remains an effective treatment strategy in pharmacologic cardioversion of AF. Flecainide has a rapid onset of action (2-4 hours) and is relatively free of complications in those without structural heart disease.[44-46] Flecainide has a high use-dependence effect, meaning its efficacy increases at higher heart rates due to increased ion channel binding, making it useful in atrial tachyarrhythmias, such as AF.[47] Results from the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that the use of flecainide to treat asymptomatic or mildly symptomatic ventricular arrhythmias in patients with left ventricular dysfunction after myocardial infarction carried a higher risk of mortality, for which the United States Food and Drug Administration issued a black box warning.[48] Contrary to this belief, recent data utilizing coronary flow capacity detected on positron emission tomography found that patients with occult coronary artery disease who were taking flecainide did not have an increased number of adverse events.[49]

Propafenone is another Ic medication that, in the absence of structural heart disease, is effective at restoring normal sinus rhythm in patients with AF. For individuals with a high health literacy who can identify symptoms of AF recurrence, a single oral dose of either propafenone (600 mg) or flecainide (300 mg) may be used as a “pill-in-the-pocket” for pharmacologic cardioversion in the outpatient

setting.[46,50,51] This approach may reduce hospital readmission rates in patients who are able to self-identify and treat their episodic AF.[52]

Sotalol is a class III antiarrhythmic drug that is utilized in the maintenance of normal sinus rhythm instead of acute cardioversion of AF.[53] Limitations to sotalol use are that patients require a creatinine clearance greater than 40 mL/min, normal QT-interval at baseline, normal serum potassium, and absence of asthma as a comorbidity.[54] Routine electrocardiography is required when prescribing sotalol to monitor the QT-interval, and the drug should be discontinued if the duration is either greater than 500 ms or a greater than 60 ms increase from baseline.[1,15] In a large meta-analysis, which included 59 randomized control trials comparing various antiarrhythmic drugs, it was found that sotalol was associated with a 2-fold increase in death compared to placebo.[55] Although sotalol is effective at maintaining normal sinus rhythm (ie, reducing AF recurrence), the risks incurred may not outweigh the benefit.

Ibutilide, a class III AAD with the pharmacologic properties of both sodium and potassium channel blockers, is an effective agent in cardioverting AF with higher cardioversion successes in atrial flutter. The proarrhythmic effects of ibutilide include torsade de pointes, which requires close monitoring in an intensive care unit after intravenous administration, typically in conjunction with magnesium.[53,56]

Dronedarone exhibits antiarrhythmic properties of all 4 Vaughn-Williams classes and is a very well-studied antiarrhythmic drug with several positive trials.[57] Dronedarone has been shown to reduce the incidence of AF recurrence in paroxysmal AF and persistent AF. The ATHENA trial confirmed these findings and showed that dronedarone reduced hospitalizations and death.[58] Importantly, results from PALLAS and ANDROMEDA highlighted the negative effects of dronedarone, which were mainly an increase in morbidity, mortality, and adverse outcomes in patients with permanent AF and concomitant heart failure, respectively.[59]

Antiarrhythmics in Structural Heart Disease

In the presence of structural heart disease, the use of antiarrhythmic drugs to treat AF is limited. Dofetilide is a class III antiarrhythmic drug effective in pharmacologic cardioversion of AF in patients with structural heart disease.[53,60-62] Initiation of dofetilide requires in-hospital administration to monitor for the occurrence of malignant arrhythmias, which remains the major limitation to its use.[60]

One of the most widely used antiarrhythmic drugs is amiodarone. Letelier et al found that amiodarone was effective for converting AF to sinus rhythm in a wide range of patients.[63] Amiodarone decreased proarrhythmic effects compared with other antiarrhythmic drugs, such as flecainide, making it more suitable for those with structural heart disease, coronary artery disease, and heart failure. Due to its high iodine content, amiodarone notoriously effects the thyroid gland, but these affects are usually reversible with either dose reduction or cessation.[64] Screening tests recommended prior to initiation of amiodarone include pulmonary function testing, thyroid and liver function tests, and interval reassessment to ensure that no organ involvement has occurred, including annual eye examinations.[65] In summary, amiodarone and dofetilide are the antiarrhythmic drugs recommended to restore normal sinus rhythm in patients with AF and structural heart disease.[66]

Antiarrhythmics: Morbidity and Mortality

The role of antiarrhythmic drugs should be focused on relieving patient symptoms as the effects on mortality have been equivocal. A study completed nearly 2 decades ago showed that in patients older than 65 years with 1 additional risk factor for ischemic stroke, the overall mortality did not differ when comparing either rate or rhythm control with more adverse drug effects occurring in the latter.[32] Registry data found that patients over 65 treated with antiarrhythmic drugs, most commonly amiodarone, experienced more frequent falls within the first 2 weeks.[67] In a comparison study of conventional rate control strategies, antiarrhythmic drugs failed to show a significant difference in the primary endpoints of all-cause mortality and heart failure hospitalization.[68] In contrast to these results, restoration of sinus rhythm by either catheter ablation or anti-arrhythmic drugs within 1 year of diagnosis reduced the risk of ischemic stroke.[28] In a recent meta-analysis,

individuals greater than or equal to 75 years old, failed to show a benefit of rhythm control in decreasing the risk of ischemic stroke.[31,34] AF has been associated with cognitive impairment regardless of ischemic stroke history.[34] Several studies have shown a reduction in cerebral gray and white matter and elevated levels of serum neurofilament, a biomarker of neuronal injury that is inversely related to cognitive function, in patients with AF.[69]

Catheter Ablation

Catheter ablation therapies are usually reserved for patients who are unable to tolerate or fail anti-arrhythmic drug treatment. Although ablative technologies for AF have evolved into several different modalities, the principles remain the same with all techniques focused on delivering energy to the area of the myocardium responsible for arrhythmia formation.[70] Utilizing these therapies for the restoration of normal sinus rhythm can be an effective and durable strategy; however, a small percentage of patients may require multiple procedures.[71] Risk factors for failed catheter ablation include older patients, female sex, persistent AF, valvular AF, and left atrial diameter greater than 50mm.[72,73] Although rare, complications are inherent with any invasive procedure and include cerebrovascular accident, transient ischemic attack, pericardial effusion, and atrial-esophageal fistula.[74,75]

Catheter Ablation: Morbidity and Mortality

In patients who are relatively young and healthy, radiofrequency catheter ablation appears to be more effective than medical therapy as a first-line treatment strategy for improving QoL and reducing the recurrence of paroxysmal AF when compared with antiarrhythmic drug therapy.[30,74,76,77] In patients older than 75 years, however, lower success rates have been observed when persistent AF is treated with cather ablation.[78,79] Other benefits of catheter ablation are a decreased risk of dementia and cognitive decline in comparison to conventional antiarrhythmic pharmacotherapies for AF.[80,81] Results from a study by Mohanty et al showed a significant decrease in the Montreal Cognitive Assessment (MoCA) score in AF patients treated with catheter ablation and left atrial appendage occlusion devices (eg, Watchman™).[82] In all, ablative therapies seem to be a safe and reliable approach to improve symptoms, QoL, and possibly mitigate cognitive decline in patients with paroxysmal AF but should be avoided in older patients.

Individuals who have AF complicated by heart failure experience increased mortality.[66,83] Multiple studies have revealed lower mortality rates when patients pursuing a rhythm-control strategy were treated with catheter ablation in comparison to antiarrhythmic drugs.[28,31,84-86] Data from a 2018 meta-analysis showed that in individuals with AF and LVEF of less than 40%, catheter ablation decreased mortality, reduced recurrence, and improved left ventricular systolic function compared to conventional management.[87] Other studies have echoed this result with the additional benefit of reduced heart failure hospitalizations and a low rate of complications when restoring normal sinus rhythm with catheter ablation-based therapy in patients with systolic heart failure.[85,88,89] These benefits were amplified in patients treated with catheter ablation in the first year of incident AF, compared to medical therapy.[28,77,89,90] Lower all-cause mortality was observed in AF patients with preserved ejection fraction who were treated with catheter ablation.[91]

In contrast, the recent RAFT-AF trial showed that AF patients with concomitant heart failure, treated with catheter ablation therapy, did not significantly differ in all-cause mortality or heart failure events when compared to conventional management. The same research group found improvement in the catheter ablation-treated arm in parameters such as increased LVEF while NT-proBNP decreased.[29] Other statistically significant benefits of the RAFT-AF trial included an improvement in 6-minute walking distance, Minnesota Living with Heart Failure Questionnaire, and, as previously mentioned, QoL.

Atrial Myopathy

The longer a patient remains in AF, contractile remodeling of the atria occurs. In their reviews, Rivner et al and Kallergis et al concluded that this remodeling results in atrial systolic and diastolic dysfunction leading to an increase in thrombus formation, atrial dilation, and, consequently, stabilization of the arrhythmia.[13,92] As

time progresses, structural remodeling ensues giving rise to atrial fibrosis through accumulation of fibrillar collagen deposits. Several growth factors (eg, connective tissue growth factors, extracellular matrix proteins) as well as angiotensin-II play a critical role in these developments.[12,92] Together, these substrates enable an accumulation of fibrillar collagen deposits, causing significant disarray between cardiomyocyte connections and electrical properties.[92] Epicardial adipose tissue has also been proposed to promote inflammation and fibrosis by the release of adipokines, which in turn affect the surrounding myocardium.[13]

Atrial stretch overload-induced fibrosis can advance by both angiotensin-II-dependent or independent mechanisms. The angiotensin-II-dependent pathway appears to be linked to mitogen-activated protein kinase, which increases TGF-β1 and stimulates collagen production.[93,94] Animal models have revealed differences between atrial and ventricular remodeling responses to overload. As such, there was a more rapid atrial angiotensin II response and associated mitogen-activated protein kinase-induced activation.[93] Rapid increases in mitogen-activated protein kinase were associated with significant increases in the profibrotic TGF-β1.[93] In accordance with these findings, atrial biopsies obtained from patients with permanent AF suggested that the aberrant collagen synthesis was linked to impaired metalloproteinase regulation and upregulation of the TGF-β1/Smad2 pathway.[94]

Recent research has focused on potential pharmacological treatments that may intervene in atrial overload-remodeling. In 2018, Kondo et al suggested that rivaroxaban could play a role in pressure overload-induced atrial remodeling, working via factor Xa inhibition.[95] More recent work by Emig et al elucidated how myocytes respond to their mechanical environment via stretch-activated Piezo1.[96] Piezo1 activation of atrial fibroblasts led to human atrial cell stiffness, suggesting that Piezo1 could be a future pharmacological target.[96] Given the nonlinear relationship between atrial fibrosis and AF, questions regarding whether a threshold exists and the specific causative role that fibrosis plays in AF promotion remain topics of intense research.

Conclusion

Atrial fibrillation continues to be the most prevalent arrhythmia worldwide. Complications of the disease span the spectrum of fatigue, poor QoL, debilitating thromboembolic events, and increased mortality. In this updated review of the literature, we found that rate and rhythm control have specific indications as to when they should be utilized. Rate control is a reasonable approach to patients experiencing AF without symptoms, with elderly patients benefiting the most. In patients with reduced LVEF of less than 40%, beta-blockade remains the safest option. In symptomatic AF patients, a rhythm control strategy with antiarrhythmic drugs can offer reduced morbidity. Patients who are unable to tolerate or who remain refractory to antiarrhythmic drugs may be candidates for ablative procedures to relieve persistent symptoms. Mortality benefits have not been supported in recent studies, and at best remain equivocal, when pursuing rhythm control with either antiarrhythmic drugs or ablative therapies. It is our recommendation that patients found to have new onset symptomatic AF be referred to an electrophysiologist for specialized care in this seemingly routine and simple disease state.

Conflicts of Interest

Dr Alexander discloses speaking honoraria from Janssen Pharmaceuticals.

Drs Ahmed, Bhatnagar, Flynn, and Vargas declare no conflicts of interest.

Drs Vargas and Alexander are employees of Corpus Christi Medical Center, a hospital affiliated with the journal's publisher.

Dr Bhatnagar is an employee of MountainView Hospital, a hospital affiliated with the journal's publisher.

Dr Ahmed is an employee of HCA Houston Healthcare Kingwood, a hospital affiliated with the journal's publisher.

Dr Flynn is an employee of HCA Healthcare Graduate Medical Education, an organization affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare-affiliated entity. The views

expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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