Rate or Rhythm Control for Atrial Fibrillation: Update and Controversies

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ABSTRACT

Atrial fibrillation is associated with increased mortality and considerable morbidity, including stroke, heart failure, and diminished quality of life. Despite these adverse outcomes, rhythm control has not demonstrated benefit in clinical trials. Antiarrhythmic medications, including recently developed agents, have limited efficacy in achieving durable sinus rhythm and substantial toxicity. A rate-control strategy is therefore more attractive for minimally symptomatic patients, but younger and more symptomatic patients may benefit from restoration of sinus rhythm. Catheter ablation is more effective than medications in preventing arrhythmia recurrence, avoids adverse effects associated with antiarrhythmic drugs, and should be considered early in symptomatic patients when success is likely. However, more definitive data are needed from randomized trials assessing long-term outcomes after ablation, including stroke risk and mortality. Clinical decision tools help select the appropriate management for individual patients. Lenient rate management is easy to achieve and seems reasonably safe for certain patients, although the optimum rate varies with individual comorbidities. Because safer and more effective pharmacologic and interventional therapies are now available, an individualized approach to atrial fibrillation management is essential.
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Atrial fibrillation is the most commonly encountered sustained arrhythmia and is associated with substantial morbidity and mortality. In population studies such as the Man-

itoba Follow-up, patients with atrial fibrillation have demonstrated significantly worse overall and cardiovascular survival.[1] In addition, atrial fibrillation is associated with a 5-fold incremental risk of stroke,[2] an approximately 3-fold risk of heart failure,[1] diminished quality of life,[3] and substantial health care costs.[4] There also is increasing evidence that patients with atrial fibrillation have a higher incidence of various types of dementia, including Alzheimer's disease.[5] Despite these consequences, whether to restore and maintain sinus rhythm ("rhythm control") or allow atrial fibrillation to continue while controlling ventricular rate ("rate control") remains a key decision steeped in controversy. Although only anticoagulation in appropriate patients has been shown to reduce mortality, safer antiarrhythmic medications and superior efficacy associated with catheter ablation have extended the potential advantages of rhythm control. The increasing prevalence of atrial fibrillation in the setting of the aging population and emerging therapeutic advances make understanding contemporary treatment strategies essential. This review addresses management for pa-

tients with atrial fibrillation in the context of novel rate control, antiarrhythmic drugs, and ablation strategies.

THE MODERN ERA OF RHYTHM CONTROL AND THE EXPANDING ROLE OF ABLATION

Given the poor outcomes associated with atrial fibrillation,[1-2,6] rhythm control makes intuitive sense. However, it remains unclear whether atrial fibrillation causes death or is simply a marker of risk. Despite the association of atrial fibrillation with excess morbidity and mortality, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and multiple other studies failed to demonstrate reduction in death, stroke, or hospitalization with rhythm control compared with rate control, assuming appropriate anticoagulation as part of either strategy (Table 1).[7-11] Even in patients with systolic dysfunction and clinical heart failure, in whom atrial fibrillation is a predictor of death and frequent cause of decompensation, the Atrial Fibrillation and Congestive Heart Failure trial identified no difference in overall survival, cardiovascular death, worsened heart failure, or stroke at 37 months with rhythm control.[12]

> ### CLINICAL SIGNIFICANCE
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> - In symptomatic or young patients with few comorbidities, rhythm control is often warranted.
> - Ablation is more effective than pharmacotherapy for maintenance of sinus rhythm and has the potential to improve outcomes.
> - Antiarrhythmic drug options have expanded, but inadequate efficacy and toxicity continue to limit the benefit of pharmacologic rhythm control.
> - Lenient rate management is easy to achieve and seems safe; however, optimum rate varies between patients.

The apparent discrepancy between the poor outcomes associated with atrial fibrillation in epidemiologic studies and the failure of multiple trials to demonstrate a substantial benefit from a rhythm-control strategy reflect the limited efficacy and adverse effects of the available antiarrhythmic medications used in these studies to maintain sinus rhythm. The proportion of patients actually achieving sinus rhythm with antiarrhythmic drugs in randomized trials, ranging from 26% to 63%,[7,11] illustrates this limited efficacy. Nearly all antiarrhythmic medications carry a risk of ventricular proarrhythmic toxicity. In addition, the predominant antiarrhythmic drug in these studies, amiodarone (used in 62.8% of patients in the rhythm control arm of AFFIRM[7] and in 82% of patients in Atrial Fibrillation and Congestive Heart Failure[12]), has substantial extracardiac toxicity, including pulmonary and hepatic toxicity, thyroid dysfunction, and bradycardia (Table 2). Furthermore, because the "rate versus rhythm control" trials generally involved older patients with comorbidities, the results cannot be extrapolated to younger, healthier patients who would face the consequences of atrial fibrillation for longer periods with a rate-control strategy. The results of these studies should therefore not be interpreted as a lack of benefit of restoring sinus rhythm, but rather that the toxicity and limited efficacy of available antiarrhythmic medications make their routine use no better than rate control to achieve freedom from stroke and death. In support of this concept, a post hoc analysis of AFFIRM demonstrated that sinus rhythm was associated with a lower risk of death independently of the medications used compared with the presence of atrial fibrillation, and after adjustment for the rhythm, antiarrhythmic medications increased mortality.[13]

Catheter ablation of atrial fibrillation may improve mortality and stroke rates by more effectively restoring sinus rhythm without antiarrhythmic drug–related toxicities, although this is unproven. Ablation has consistently shown greater efficacy in maintaining sinus rhythm and more robust improvements in symptoms and quality of life than antiarrhythmic medications. In 1 randomized, multicenter comparison in patients with paroxysmal atrial fibrillation, freedom from symptomatic recurrence after 9 months was reduced by 70% with ablation compared with antiarrhythmic drugs.[14] In a recent international multicenter registry of 1273 patients who underwent ablation, atrial fibrillation-free survival was achieved in 85% of patients with paroxysmal atrial fibrillation and 72% of patients with persistent atrial fibrillation (76% and 60% off antiarrhythmic drugs, respectively) at a mean follow-up of 3.1 years, and freedom from atrial fibrillation was the strongest predictor of stroke-free survival (hazard ratio, 0.30; $P < .001$). Of note, rates of death and stroke were significantly lower in patients undergoing ablation compared with a separate cohort of patients with medically managed atrial fibrillation and were reduced to levels similar to those in a matched cohort of patients without atrial fibrillation (Figure 1).[15] However, whether rhythm control using ablation to restore sinus rhythm will actually lead to reductions in stroke and mortality has not been demonstrated in prospective studies. Ongoing randomized trials, including the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, and Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation, aim to more definitively address potential long-term improvements in meaningful outcomes after atrial fibrillation ablation.

The primary goal of ablation for atrial fibrillation involves complete electrical isolation of the pulmonary veins, which prevents recurrence in most patients with paroxysmal atrial fibrillation. Patients with persistent atrial fibrillation typically require additional substrate modification and ad-

Table 1   Rate Versus Rhythm Control Trials

Trial	Patient (n)	Age (Mean ± SD)	Mean Follow-up (y)	Rhythm Control Use of Amiodarone	Comorbidities	Patients in NSR in Rhythm Control	Ischemic Stroke/ Thromboembolism*	Hospitalization*	Mortality*
PIAF (2000)	252	61 ± 10 y	1.0	100%	HTN 49% CAD 23% CHF 50% VHD 16%	56% (at 1 y)	NR	24% vs 69%, P = .001	NR
AFFIRM (2002)	4060	69.7 ± 9.9y	3.5	63%	HTN 70.8% CAD 38% CHF 26% VHD 5%	63% (at 5 y)	5.5% vs 7.1%, P = .79	73% vs 80%, P <.001	26 vs 27%, P = .08
RACE (2002)	522	68 ± 9 y	2.3	NR	HTN 49% CAD 27% CHF 50% VHD 17%	39% (at study end)	5.5% vs 7.9%, P = NS	NR	7.0% vs 6.8%, P = NS
STAF (2003)	200	66 ± 8 y	1.6	42%	HTN 63% CAD 44% DCM 13% VHD 16%	26% (at 2 y)	2% vs 5%, P = NS	26% vs 54%, P <.001	8% vs 4%, P = NS
HOT CAFÉ (2004)	205	61 ± 11 y	1.7	56%	HTN 64% CAD 44% CHF 63% VHD 15%	64% (at study end)	1% vs 3%, P = NS	12% vs 74%, P <.001	1% vs 3%, P = NS
AF-CHF (2008)	1376	67 ± 1 y	3.1	82%	HTN 50% CAD 48% CHF 100% VHD 5%	42% (at study end)	4% vs 3%, P = NS	59% vs 64%, P = .06	33% vs 32%, P = .68

AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-Up Investigation of Rhythm Management; CAD = coronary artery disease; CHF = congestive heart failure; DCM = dilated cardiomyopathy; HOT CAFÉ = How to Treat Chronic Atrial Fibrillation; HTN = hypertension; NR = not reported; NS = not significant; NSR = nonsinus rhythm; PIAF = Pharmacologic Intervention in Atrial Fibrillation; RACE = Rate Control Versus Electrical Cardioversion of Persistent Atrial Fibrillation; SD = standard deviation; STAF = Strategies of Treatment of Atrial Fibrillation; VHD = valvular heart disease.

*Comparison between rate control and rhythm control arms, respectively.

Table 2 Commonly Used Antiarrhythmic Medications and Their Toxicities

Drug	Adverse Effects
Amiodarone	Pulmonary toxicity, hepatic toxicity, thyroid dysfunction, photosensitivity, visual dysfunction, polyneuropathy, GI upset, bradycardia, torsades de pointes
Disopyramide	Torsades de pointes, heart failure, glaucoma, urinary retention
Dofetilide	Torsades de pointes
Flecainide	Ventricular tachycardia, heart failure
Propafenone	Ventricular tachycardia, heart failure
Sotalol	Torsades de pointes, heart failure, bradycardia, bronchospasm

GI = gastrointestinal.

ditional procedures. More data are needed regarding the long-term efficacy of ablation, which may be limited by pulmonary vein reconnection and iatrogenic atrial tachycardias caused by incomplete lines of ablation.[16] Although the risk is low in experienced centers, potential complications include pulmonary vein stenosis, thromboembolism, tamponade, injury to the esophagus or phrenic nerve, and death.[16] In most comparisons, however, major treatment-related adverse effects are more frequent with antiarrhythmic drugs than ablation.[14] Emerging technologies, including safer energy sources, esophageal temperature monitoring, advanced imaging, and real-time catheter guidance, may further improve safety and efficacy.

The superiority of ablation over antiarrhythmic medications prompts consideration of ablation as initial therapy for symptomatic patients with paroxysmal atrial fibrillation; in a small randomized study of first-line ablation versus antiarrhythmic drugs, ablation substantially reduced atrial fibrillation recurrence (13% vs 63%, $P<.001$), decreased hospitalizations (9% vs 54%, $P<.001$), and improved quality of life at 1 year.[17] In US practice guidelines, ablation is considered a reasonable alternative to antiarrhythmic medications in symptomatic patients with little left atrial enlargement, regardless of underlying heart disease.[18] In patients with heart failure, a nonrandomized study demonstrated improvement in ventricular size and function, symptoms, and exercise capacity after ablation.[19] The 2010 European Society of Cardiology guidelines, observing that the risk of major complications associated with atrial fibrillation ablation compares favorably with long-term antiarrhythmic drug therapy, recommend ablation over amiodarone. Because other antiarrhythmic medications are contraindicated in patients with heart failure, the European guidelines recommend ablation as a first-line treatment for patients with New York Heart Association class III and IV symptoms due to atrial fibrillation.[20] In a recent expert consensus statement produced with collaboration between the Heart Rhythm Society and the European Heart Rhythm Association (EHRA), ablation was considered reasonable as primary

strategy before the initiation of antiarrhythmic medications for symptomatic patients with paroxysmal atrial fibrillation (class IIa recommendation), although upfront ablation was given a less enthusiastic recommendation (class IIb) for patients with more persistent arrhythmia.[21]

COST CONSIDERATIONS

In the Registry on Cardiac Rhythm Disorders Assessing Control of Atrial Fibrillation (RECORD-AF), an international observational study assessing patients with atrial fibrillation managed with both rate and rhythm control, the lifetime costs associated with either strategy were similar, and the estimated incremental cost-effectiveness favored rhythm control.[22] In Cost of Care in Atrial Fibrillation, a prospective survey that evaluated the cost of care for patients with atrial fibrillation in the office setting, the major drivers of cost were hospitalizations (52%) and the use of class III antiarrhythmic medications.[4] Ablation may substantially affect the cost analysis because it is associated with considerable procedural expenditures but greater efficacy in maintaining sinus rhythm and therefore fewer subsequent hospitalizations and less medication use. The price of an atrial fibrillation ablation procedure is approximately $17,000, with follow-up costs after the procedure ranging from $200 to $1300/year, compared with approximately $4000/year for patients treated with antiarrhythmic drugs; the costs associated with the 2 strategies converge after approximately 5 years.[21,23] Ablation may be most cost-effective in younger patients and in those at intermediate stroke risk.[24] Essentially all cost analyses of ablation have estimated its incremental cost-effectiveness close to the threshold level of $50,000 per quality-adjusted life year typically accepted in the United States.[23] Such calculations will remain speculative, however, until the long-term effects
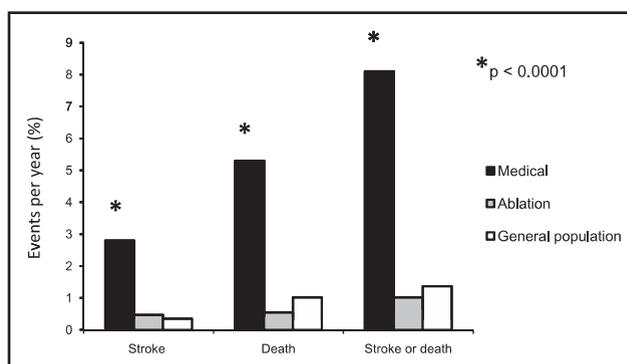

Figure 1   Ablation outcomes compared with medical therapy and controls. Outcomes after ablation of atrial fibrillation in a multicenter registry compared with patients treated medically in the Euro Heart Survey and a hypothetical cohort of matched controls without atrial fibrillation using mortality and stroke rates from UK national statistics. *Significant difference between the "medical" cohort and the other 2 groups.[15] License for republication obtained from BMJ Publishing Group Ltd, March 27, 2012 (license no. 2877291432685).

of atrial fibrillation ablation in terms of mortality and morbidity are clarified.

UPDATES IN PHARMACOLOGIC RHYTHM CONTROL

Because of the potential toxicity associated with antiarrhythmic medications, selection among them requires consideration of individual patient comorbidities. For patients without demonstrable heart disease, flecainide, propafenone, and sotalol are recommended as initial agents because they carry a relatively low risk of toxicity aside from proarrhythmia, an effect that occurs more commonly in patients with ischemic or structural heart disease. These agents also may be used as needed (the so-called "pill-in-the-pocket" approach) to further reduce toxicity. In patients with heart failure, the use of amiodarone or dofetilide is safest. Sotalol is preferred for patients with coronary artery disease, whereas patients with left ventricular hypertrophy may be prone to proarrhythmia, making amiodarone the prudent choice.[18] The worldwide RECORD-AF registry identified overuse of amiodarone for initial treatment of patients with coronary disease or lone atrial fibrillation.[25] Amiodarone use was more frequently discordant with guidelines at sites managing ≤ 10 patients with atrial fibrillation weekly.[25] In such situations, specialist referral may improve outcomes.

Dronedarone, introduced in 2009, has a pharmacologic profile similar to amiodarone, but it has structural differences resulting in a shorter half-life and less extracardiac

toxicity. Dronedarone is better tolerated than amiodarone, having demonstrated a trend toward fewer adverse thyroid, neurologic, dermatologic, and ocular events at 1 year,[26] but less effective in preventing recurrent atrial fibrillation. In the large, multicenter Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation trial comparing dronedarone with placebo in patients with paroxysmal atrial fibrillation, dronedarone reduced cardiovascular mortality (hazard ratio, 0.71; 95% confidence interval, 0.51-0.98) and the primary end point of death and cardiovascular hospitalizations.[27] However, in patients with systolic dysfunction and heart failure, dronedarone increased mortality during only 3 months of follow-up.[28] In addition, the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy trial of patients with at least a 6-month history of "permanent" atrial fibrillation was stopped early because of adverse cardiovascular outcomes in patients taking dronedarone.[29] The 2011 US practice guidelines, issued before the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy results became available, included dronedarone as a potential first-line antiarrhythmic for patients without heart failure or substantial left ventricular hypertrophy (**Figure 2**).[18] Dronedarone remains an option for patients with paroxysmal atrial fibrillation without heart failure, although its efficacy in maintaining sinus rhythm is limited.

Antiarrhythmic medications targeting ion channels primarily expressed in the atria may reduce ventricular proarrhythmic risk. Vernakalant is a novel atrial selective agent
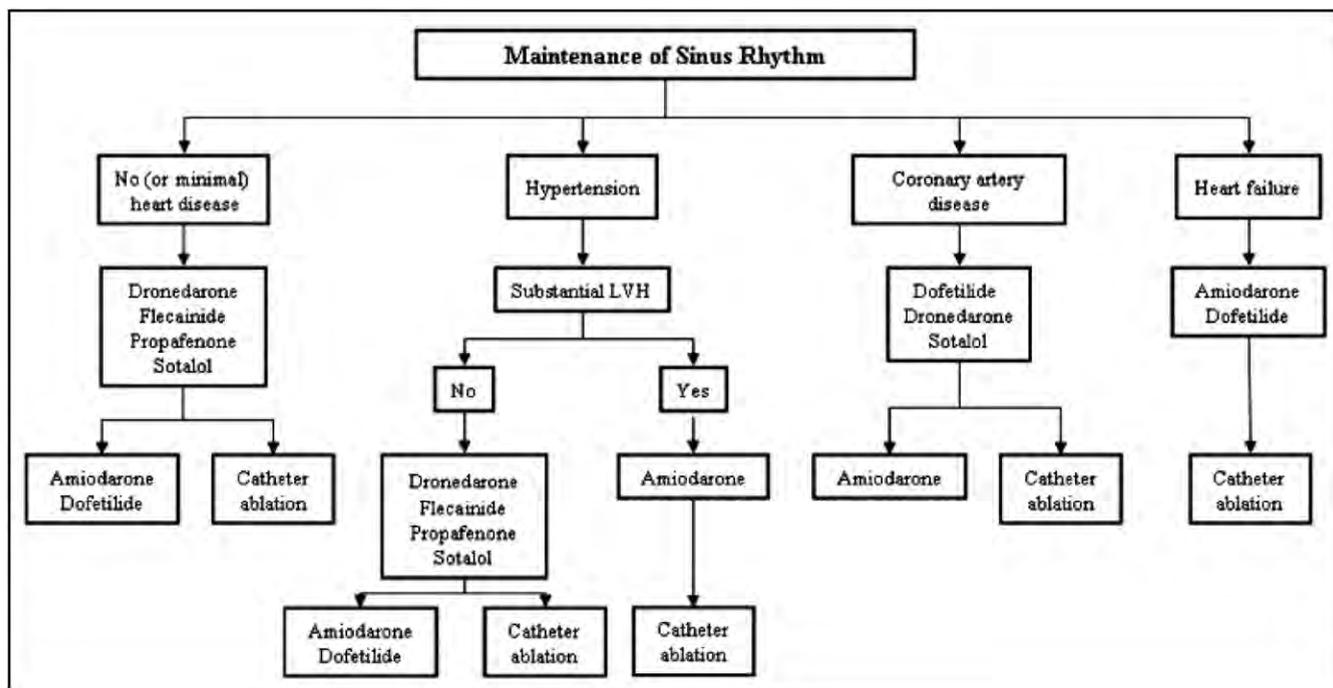

Figure 2   Treatment to maintain sinus rhythm in patients with paroxysmal or persistent atrial fibrillation. Adopted from the 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation. License for republication obtained from Elsevier, Inc, March 2011 (license no. 2676020822083).

approved in Europe for the rapid conversion of atrial fibrillation to sinus rhythm. Given intravenously, vernakalant demonstrated cardioversion rates greater than 50% with little ventricular proarrhythmic toxicity.[30] Oral vernakalant can maintain sinus rhythm after cardioversion with relatively few side effects,[31] although long-term safety and efficacy have not been established.

Better understanding of mechanisms underlying atrial fibrillation can promote the development of safer and more effective therapeutic approaches. Emerging approaches to prevent electrical and structural remodeling aim to limit progression from paroxysmal to persistent atrial fibrillation, at which point effective rhythm control is more difficult to achieve.[32] Although identification of specific mechanisms of atrial fibrillation in individual patients is challenging, doing so provides opportunity for targeted therapy.

DEVELOPMENTS IN RATE CONTROL

Ventricular rate control in atrial fibrillation may be achieved with negative dromotropic drugs. The clinical scenario and side effect profile of these medications should guide their selection in an individual patient (**Table 3**).

Lenient management of ventricular rate in atrial fibrillation may be preferred because it is relatively simple to achieve and requires fewer patient visits.[33] The Lenient versus Strict Rate Control in Patients with Atrial Fibrillation trial compared lenient (target resting heart rate < 110 beats/min) with "strict" control (target rate < 80 beats/min at rest and < 110 beats/min during exercise) in 614 patients with permanent atrial fibrillation; at 3 years, there was no difference in symptoms, hospitalizations, or the composite end point of cardiovascular death, heart failure hospitalization, stroke, thromboembolism, bleeding, or life-threatening arrhythmia.[33] However, studies of rate control have involved limited follow-up and outcome assessments. Optimum heart rates likely vary on the basis of patient comorbidities, and more aggressive control may benefit patients with mitral or tricuspid valve disease or diastolic dysfunction. In addition, cardiac function should be monitored when lenient rate control is used and stricter control adopted for those developing tachycardia-induced cardiomyopathy.

The "ablate and pace" strategy, achieving rate control through atrioventricular node ablation and permanent pacemaker implantation, improves quality of life in highly symptomatic patients[34] and may reduce healthcare resource use when pharmacologic therapy is limited by hypotension or intolerable side effects.[35] One limitation of this strategy is that permanent right ventricular pacing may promote dyssynchrony and impair cardiac function. The Left Ventricular-Based Cardiac Stimulation Post Atrioventricular Nodal Ablation Evaluation trial found that biventricular pacing after atrioventricular node ablation can improve functional capacity and systolic function compared with right ventricular pacing (ejection fraction 46% vs 41% at 6 months, $P = .03$), with the most pronounced improvements in patients with preexisting left ventricular dysfunction.[36] Cardiac resynchronization with biventricular pacing therefore should be considered in patients with impaired systolic function after atrioventricular node ablation. Another technique known as "atrioventricular node modification" attempts to ablate certain inputs to the atrioventricular node and slow the ventricular rate without pacemaker implantation.[37] Implementation of this procedure, however, has been limited by the risk of inadvertent complete atrioventricular block and a tendency for the ventricular rate to increase postablation.

DECIDING BETWEEN RATE AND RHYTHM CONTROL

Optimal management of atrial fibrillation warrants an individualized approach because symptoms, hemodynamic tolerance, and thromboembolic risk vary widely. The decision to attempt rhythm control is based mainly on atrial fibrillation–related symptoms, and practice guidelines recommend rate control for patients with minimal or no symptoms and restoration of sinus rhythm when symptoms are inadequately controlled.[18] Although symptoms associated with atrial fibrillation are common, occurring in 81% of patients in the RECORD-AF registry,[38] they are subjective, leaving vague the threshold at which atrial fibrillation becomes unacceptable for a given patient. The EHRA symptom severity scale may assist decision-making: In this scoring system, class I indicates no symptoms, class II indicates mild symptoms that do not interfere with daily activity, class III indicates severe symptoms that affect daily activity, and class IV indicates disabling symptoms.[20] The European

Table 3	Indications for Use of Rate Control Medications	
Medication	Indications in Atrial Fibrillation	Situations to Avoid
β-blockers	Chronic stable CHF, CAD, HCM, HTN, thyrotoxicosis, high adrenergic tone	Severe asthma/COPD, hypotension, hypoglycemia, decompensated CHF
Calcium-channel blockers	HTN, angina	Hypotension, severe LV dysfunction, decompensated CHF
Digitalis glycosides	Hypotension, CHF (stable or decompensated)	Renal insufficiency, electrolyte imbalance, recent MI, ventricular arrhythmias, hypermetabolic states, HCM, myocarditis

CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive lung disease; HCM = hypertrophic cardiomyopathy; HTN = hypertension; LV = left ventricular; MI = myocardial infarction.

Society of Cardiology guidelines suggest rate control as a reasonable strategy, particularly in elderly patients, when symptoms related to atrial fibrillation are acceptable (EHRA score ≤ 2), and a strategy of rhythm control with less toxic antiarrhythmic medications or ablation for younger patients with paroxysmal atrial fibrillation or those with higher EHRA scores.[20] Patients with diastolic dysfunction are particularly symptom prone when in atrial fibrillation as a result of the loss of atrial contraction and shortened diastolic filling times, and therefore they often benefit from restoration of sinus rhythm.[39]

In addition to symptoms, underlying substrate influencing the course of atrial fibrillation also varies between patients, and management decisions must weigh the risks and benefits of antiarrhythmic strategies against the likelihood of achieving durable sinus rhythm. A risk stratification model, the hypertension, age ≥ 75 years, transient ischemic attack or stroke [2 points], chronic obstructive pulmonary disease and heart failure [2 points] (HATCH) score, has been developed to predict progression from paroxysmal to persistent atrial fibrillation. Approximately 50% of patients with HATCH scores greater than 5 progressed to persistent atrial fibrillation, compared with 6% with scores of zero. In patients with higher HATCH scores, efforts to achieve sinus rhythm are likely to be unsuccessful despite antiarrhythmic therapy.[40]

Rhythm control avoids unfavorable electrical and mechanical remodeling and can improve cardiac function, symptoms, and quality of life. In older patients with minimally symptomatic atrial fibrillation (EHRA class ≤ II) and those with high HATCH scores, a rate-control strategy avoids antiarrhythmic drug–related toxicities and is sufficient to decrease hospitalizations. In younger, healthier patients who are more likely to maintain sinus rhythm or those with higher EHRA scores, a rhythm-control strategy should be strongly considered, and ablation should be discussed early with fully informed patients when the likelihood of success is high.

CONCLUSIONS

Atrial fibrillation is common and associated with considerable morbidity and mortality. However, substantial evidence associates antiarrhythmic medications with risk and supports rate control, particularly in elderly patients with tolerable symptoms. For younger or more symptomatic patients, the benefits of sinus rhythm should not be overlooked, and a more aggressive strategy may be warranted. In these cases, ablation is associated with greater success in restoring sinus rhythm than antiarrhythmic medications and may improve long-term outcomes in certain patients. Because safer and more effective therapies for atrial fibrillation are available, an individualized approach is essential.

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