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Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Rate and Rhythm Management

Anne M. Gillis, MD, FRCPC,[a] Atul Verma, MD, FRCPC,[b] Mario Talajic, MD, FRCPC,[c] Stanley Nattel, MD,[c] Paul Dorian, MD,[d] and the CCS Atrial Fibrillation Guidelines Committee[e]

[a] *University of Calgary/Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada*

[b] *Southlake Regional Health Centre, Newmarket, Ontario, Canada*

[c] *Montreal Heart Institute, Université de Montréal and McGill University, Montreal, Québec, Canada*

[d] *St Michael's Hospital and University of Toronto, Toronto, Ontario, Canada*

[e] *For a complete listing of committee members, see Gillis AM, Skanes AC. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus. Can J Cardiol 2011;27:27-30.*

ABSTRACT

The goals of atrial fibrillation (AF) and atrial flutter (AFL) arrhythmia management are to alleviate patient symptoms, improve patient quality of life, and minimize the morbidity associated with AF and AFL. Arrhythmia management usually commences with drugs to slow the ventricular rate. The addition of class I or class III antiarrhythmic drugs for restoration or maintenance of sinus rhythm is largely determined by patient symptoms and preferences. For rate control, treatment of persistent or permanent AF and AFL should aim for a resting heart rate of <100 beats per minute. Beta-blockers or nondihydropyridine calcium channel blockers are the initial therapy for rate control of AF and AFL in most patients without a history of myocardial infarction or left ventricular dysfunction. Digoxin is not recommended as monotherapy for rate control in active patients. Digoxin and dronedarone may be used in combination with other agents to optimize rate control. The first-choice antiarrhythmic drug for maintenance of sinus rhythm in patients with non structural heart disease can be any one of dronedarone, flecainide, propafenone, or sotalol. In patients with abnormal ventricular function but left ventricular ejection fraction >35%, dronedarone, sotalol, or amiodarone is recommended. In patients

RÉSUMÉ

Les principaux objectifs du traitement de la fibrillation auriculaire (FA) et du flutter auriculaire sont d'atténuer les symptômes des patients, d'améliorer leur qualité de vie et de réduire au minimum la morbidité associée à la FA et au flutter auriculaire. Le traitement de l'arythmie consiste d'abord à ralentir la fréquence ventriculaire. La décision d'un traitement avec antiarythmiques de classe I ou III pour la conversion et/ou le maintien du rythme sinusal repose sur la présence de symptômes et les préférences du patient. L'objectif du contrôle de la fréquence ventriculaire pour la FA ou le flutter auriculaire persistant ou permanent est une fréquence cardiaque inférieure à 100/min au repos. Les béta-bloquants ou les inhibiteurs calciques (non-dihydropyridine) sont les médicaments de premier choix pour le contrôle de la fréquence ventriculaire de la FA et du flutter auriculaire chez la plupart des patients sans antécédent d'infarctus du myocarde ou dysfonction ventriculaire gauche. La digoxine n'est pas recommandée en monothérapie pour le contrôle de la fréquence ventriculaire chez les patients actifs. L'ajout de digoxine ou de dronédarone en combinaison avec d'autres agents peut être considéré pour optimiser le traitement. Chez les patients dont la fonction ventriculaire est normale, les anti-arythmiques de premier choix pour le maintien

Atrial fibrillation (AF) and atrial flutter (AFL) are often associated with rapid and irregular ventricular rates causing palpitations, dyspnea, fatigue, reduced exercise tolerance, other symptoms, and in some cases, left ventricular dysfunction and congestive heart failure. The approach to the management of AF and AFL includes, *in parallel*, identification and treatment of precipitating causes, antithrombotic therapy based on risk factors for stroke, drug therapy to control ventricular rates, and

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Corresponding author: Dr Anne M. Gillis, University of Calgary, Cardiac Sciences, 3280 Hospital Drive N.W., Calgary, Alberta, Canada T2N 4Z6. Tel: +1-403-220-6841, fax: +1-403-270-0313.

E-mail: amgillis@ucalgary.ca

The disclosure information of the authors and reviewers is available from the CCS on the following Web sites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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with left ventricular ejection fraction <35%, amiodarone is the only drug usually recommended. Intermittent antiarrhythmic drug therapy ("pill in the pocket") may be considered in symptomatic patients with infrequent, longer-lasting episodes of AF or AFL as an alternative to daily antiarrhythmic therapy. Referral for ablation of AF may be considered for patients who remain symptomatic after adequate trials of antiarrhythmic drug therapy and in whom a rhythm control strategy remains desired.

du rythme sinusal incluent la dronédarone, la flécaïnide, la propafénone ou le sotalol. Chez les patients dont la fonction ventriculaire est anormale mais avec fraction d'éjection ventriculaire gauche supérieure à 35 %, on recommande la dronédarone, le sotalol ou l'amiodarone. Chez les patients dont la fraction d'éjection ventriculaire gauche est inférieure à 35 %, seule l'amiodarone est recommandée. Un traitement anti-arythmique occasionnel ("pill-in-the-pocket") peut-être considéré comme alternative au traitement antiarythmique quotidien chez les patients symptomatiques qui présentent des épisodes de FA ou de flutter auriculaire infréquents mais de longue durée. L'ablation par cathéter doit être considérée chez les patients symptomatiques après échec du traitement antiarythmique et pour lesquels une stratégie de maintien du rythme sinusal demeure indiquée.

antiarrhythmic therapy as required to restore and/or maintain sinus rhythm with the major goal of alleviating patient symptoms and minimizing the morbidity associated with AF (Fig. 1).[1,2] Arrhythmia management usually commences with drugs to slow the ventricular rate. The addition of class I or class III antiarrhythmic drugs for restoration or maintenance of sinus rhythm is largely determined by patient symptoms and preferences as, to date, none of the large randomized trials has demonstrated that pharmacologic therapy to maintain sinus rhythm has improved survival or reduced the risk of stroke.[3-7]

AF may be classified as newly detected, paroxysmal (self-terminating episodes lasting <7 days), persistent (non–self-terminating episodes lasting >7 days), or permanent (no further attempts or no initial attempt to restore sinus rhythm to be undertaken).[8-9] The nature of AF is recurrent and frequently progressive (Fig. 2). Although a treatment strategy of rate control or rhythm control may be selected initially, the treatment strategy may change over time if the selected treatment strategy has been unsuccessful, as the arrhythmia progresses, or as the patient's condition changes (Fig. 1).[10] Thus, treatment strategies and their effectiveness, safety, and acceptability must be constantly reevaluated. Factors that might influence a decision for rate control versus rhythm control are summarized in Table 1.

AFL may also occur in the patient with AF or may present as an isolated arrhythmia. The goals of therapy and management approaches for AFL are similar to those for AF.

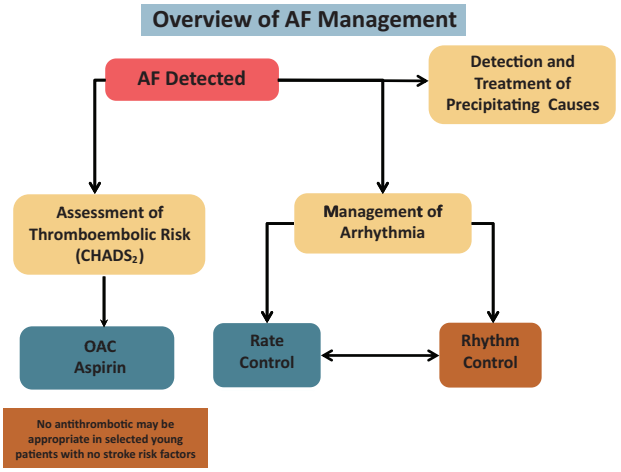

Figure 1. Overview of AF management. If a strategy of rate or rhythm control is not successful, crossover to the alternate strategy may be required. AF, atrial fibrillation; OAC, oral anticoagulation.

Goals of AF Arrhythmia Management

The major goals of AF and AFL arrhythmia management are to

- Identify and treat underlying structural heart disease and other predisposing conditions
- Relieve symptoms
- Improve functional capacity and quality of life (QOL)
- Reduce morbidity and mortality associated with AF and AFL, that is,
  - Prevent tachycardia-induced cardiomyopathy
  - Reduce or prevent emergency room visits or hospitalizations secondary to AF and AFL
  - Prevent stroke or systemic thromboembolism

RECOMMENDATION

We recommend that the goals of ventricular rate control should be to improve symptoms and clinical outcomes which are attributable to excessive ventricular rates (Strong Recommendation, Low-Quality Evidence).

We recommend that the goals of rhythm control therapy should be to improve patient symptoms and clinical outcomes and that these goals do not necessarily imply the elimination of all AF (Strong Recommendation, Moderate-Quality Evidence).

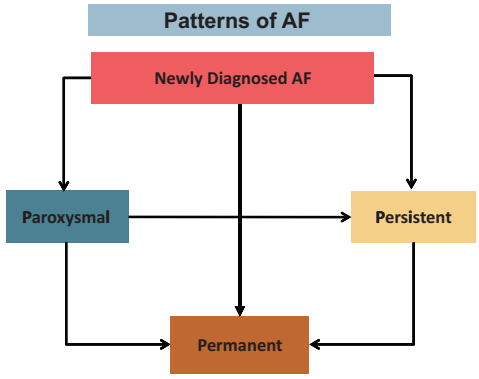

Figure 2. Interrelationships among categories of AF. Arrows indicate most common forms of progression. AF, atrial fibrillation. Adapted and reprinted with permission from Fuster V, et al.[8] Circulation 2006; 114(7):e257-e354. ©2006 American Heart Association, Inc.

Table 1. Factors favouring rate versus rhythm control

Favours rate control	Favours rhythm control
Persistent AF	Paroxysmal AF
	Newly detected AF
Less symptomatic	More symptomatic
Aged ≥65 years	Aged <65 years
Hypertension	No hypertension
No history of congestive heart failure	Congestive heart failure clearly exacerbated by AF
Previous antiarrhythmic drug failure	No previous antiarrhythmic drug failure
Patient preference	Patient preference

AF, atrial fibrillation.

Values and preferences. These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of class I or class III antiarrhythmic drugs compared with rate-control therapy.

Referral for Specialty Care

Most patients with a history of AF or AFL should be considered for referral to a cardiologist or an internist with an interest in cardiovascular disease for an expert opinion on management of AF or AFL, as well as any underlying cardiovascular conditions. Patients aged ≤35 years with symptomatic AF should be referred to an arrhythmia specialist to rule out other forms of supraventricular tachycardia that may trigger AF (so-called "tachycardia-induced tachycardia") and that would be best treated by radiofrequency ablation. Patients with isolated AFL may also be considered for referral for curative ablation therapy.[11] Patients who remain highly symptomatic despite multiple trials of antiarrhythmic drug therapy or who remain unresponsive to or intolerant of rate-controlling therapies should be referred to an arrhythmia specialist for an expert opinion on management alternatives.

Rate Control of AF and AFL

Rate control is an important part of therapy for all patients with AF or AFL. The primary goal of rate control is to improve symptoms and prevent deterioration of cardiac function associated with excessively rapid ventricular rates during AF or AFL. In addition, therapy for rate control should aim to improve exercise tolerance, QOL, and to avoid hospitalization. Tachycardia-induced cardiomyopathy refers to a condition characterized by reversible left ventricular systolic dysfunction occurring in patients with chronic rapid heart rates. This complication can occur in some patients with AF or AFL and very rapid ventricular rates (eg, >120/min for most or all of the time) and is totally or partially reversible and preventable with adequate rate control.[12]

Heart rate targets

In the past, *adequate heart rate control* had been empirically defined as ≤80 beats per minute (bpm) at rest.[3-6,8,13,14] A recent study randomized patients to strict (≤80 bpm at rest and ≤110 bpm during moderate exercise) or lenient (<110 bpm at rest) rate-control strategies.[15] No difference in the primary outcome (composite of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and arrhythmic events) was found, and the lenient strategy rate goal was achieved in a larger proportion of patients, with lower drug doses and fewer combinations of drugs, resulting in far fewer visits to achieve the intended target.[15] Relatively few patients randomized to lenient rate control had resting heart rates > 100 to 110 bpm. Furthermore, at the end of the first year, average resting heart rates were 86 ± 15 and 75 ± 12 bpm in the lenient and strict rate-control arms, respectively, and the difference of 10 to 11 bpm remained through the remainder of the trial. Thus, although the definition of lenient seems quite liberal, in the trial itself the difference in heart rates in the 2 groups was quite small. Since few patients had resting heart rates >100 bpm and previous studies cannot conclusively show the safety of resting heart rates >100 bpm, we recommend that a heart rate target of <100 bpm at rest be used for most patients. In all cases, the heart rate target may need modification based on patient symptoms and preferences. Patients with persistent or permanent AF or AFL who have exertional symptoms possibly due to excessive heart rates should have an assessment of rate response to exercise. Activity heart rate assessment can be achieved in a variety of ways, including recording heart rate after brisk hall walking or stair climbing, 24-hour ambulatory monitoring, or formal exercise testing. Correlation of symptoms and heart rate may also be achieved by patient-activated electrocardiogram (ECG) rhythm strips ("event recorders"). In all patients, it is reasonable to verify that symptoms are caused by rapid ventricular rates. Finally, it should be noted that rate control in paroxysmal AF is empirical, and heart rate targets are impractical for these briefer episodes of AF.

RECOMMENDATION

We recommend that ventricular rate be assessed at rest in all patients with persistent and permanent AF or AFL (Strong Recommendation, Moderate-Quality Evidence).

We recommend that heart rate during exercise be assessed in patients with persistent or permanent AF or AFL and associated exertional symptoms (Strong Recommendation, Moderate-Quality Evidence).

We recommend that treatment for rate control of persistent or permanent AF or AFL should aim for a resting heart rate of <100 bpm (Strong Recommendation, High-Quality Evidence).

Values and preferences. These recommendations place a high value on the randomized clinical trials and other clinical studies demonstrating that ventricular rate control of AF is an effective treatment approach for many patients with AF.

Heart rate control agents

Beta-blockers, nondihydropyridine calcium channel blockers (diltiazem, verapamil), and digitalis are the primary drugs used for ventricular rate control during AF or AFL. The approach to selection of rate-control agents is shown in Figure 3. The doses, adverse effects, and practical tips about the different rate-control agents are summarized in Table 2. All these drugs act by slowing atrioventricular (AV) nodal conduction and prolonging AV nodal refractoriness. Many

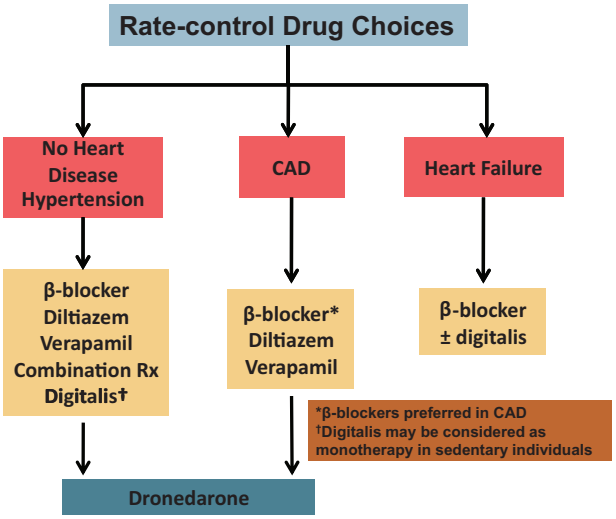

Figure 3. Selection of rate-control drug therapy is based on the presence or absence of underlying heart disease and other comorbidities. Combination therapy (Rx) may be required. CAD, coronary artery disease.

small comparative drug trials have been performed but have not shown major advantages of one agent over another.[13-19] In small, mostly blinded randomized trials, beta-adrenoceptor blockers led to lower heart rates at rest and exercise but no change or a decrease in exercise capacity.[14] Calcium channel blockers were less effective at heart rate lowering on exercise but led to an increase or no change in exercise capacity. In one study, beta-adrenoceptor blockers added to digoxin did not result in improved QOL, whereas calcium blockers resulted in small improvements in physical and emotional function.[20]

Digitalis prolongs AV nodal refractoriness by enhancing vagal tone. During exercise, vagal tone is withdrawn, and therefore digitalis controls the heart rate less effectively than beta-adrenoceptor blockers or calcium channel blockers during exercise. Digitalis should thus be avoided as the sole agent in active patients.[21,22] On its own, digoxin does not routinely control the heart rate and frequently has to be combined with another rate-slowing drug. Drug combinations are frequently effective when treatment with a single agent fails. Dronedarone is a newly released analogue of amiodarone with significant rate-controlling properties[23] which may also be useful in selected patients. Amiodarone has significant rate-controlling properties in addition to its antiarrhythmic actions and may be used in refractory patients. However, because of the risk of toxicity associated with long-term use, it should be used only when other rate-control strategies are not feasible or are insufficient.

Table 2. Drugs for heart rate control

Class	Dose	Adverse effects
Beta-blockers		
Atenolol	50-150 mg orally daily	Bradycardia, hypotension, fatigue, depression
Bisoprolol	2.5-10 mg orally daily	As per atenolol
Metoprolol	25-200 mg orally twice a day	As per atenolol
Nadolol	20-160 mg orally daily to twice a day	As per atenolol
Propranolol*	80-240 mg orally 3 times a day	As per atenolol
Calcium channel blockers		
Verapamil*	120 mg orally daily to 240 mg orally twice a day	Bradycardia, hypotension, constipation
Diltiazem*	120-480 mg orally daily	Bradycardia, hypotension, ankle swelling
Digoxin	0.125-0.25 mg orally daily	Bradycardia, nausea, vomiting, visual disturbances

*Sustained release preparations are available and generally preferred to prolong the dose interval and improve patient convenience or compliance.

RECOMMENDATION

We recommend beta-blockers or nondihydropyridine calcium channel blockers as initial therapy for rate control of AF or AFL in most patients without a past history of myocardial infarction or left ventricular dysfunction (Strong Recommendation, Moderate-Quality Evidence).

We suggest that digoxin not be used as initial therapy for active patients and be reserved for rate control in patients who are sedentary or who have left ventricular systolic dysfunction (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that digoxin be added to therapy with beta-blockers or calcium channel blockers in patients whose heart rate remains uncontrolled (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that dronedarone may be added for additional rate control in patients with uncontrolled ventricular rates despite therapy with beta-blockers, calcium channel blockers, or digoxin (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that amiodarone for rate control should be reserved for exceptional cases in which other means are not feasible or are insufficient (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations recognize that selection of rate-control therapy needs to be individualized on the basis of the presence or absence of underlying structural heart disease, the activity level of the patient, and other individual considerations.

Rate control in specific patient populations

Beta-blockers are preferred as a rate-control agent in patients after myocardial infarction and in patients with congestive heart failure.[24] Calcium channel blockers should be avoided in these populations but may be preferred in patients with chronic pulmonary disease and at risk of bronchoconstriction.[14,19] Digitalis may be useful as monotherapy in sedentary patients and is often useful in combination with beta-blockers or calcium channel blockers.

Practical tip. Carvedilol is a less-potent β-adrenergic blocking agent compared to metoprolol. Carvedilol is less effective for rate control of AF compared to metoprolol.[25]

RECOMMENDATION

We recommend beta-blockers as initial therapy for rate control of AF or AFL in patients with myocardial infarction or left ventricular systolic dysfunction (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a high value on the results of multiple randomized clinical trials reporting the benefit of beta-blockers to improve survival and decrease the risk of recurrent myocardial infarction and prevent new-onset heart failure following myocardial infarction, as well as the adverse effects of calcium channel blockers in the setting of heart failure.

Nonpharmacologic Treatment

Some patients may require the implantation of a permanent pacemaker to manage drug-exacerbated symptomatic bradycardia, particularly in patients with paroxysmal AF and sinus node disease associated with symptomatic sinus pauses, and thus safely allow adequate pharmacologic control of rapid ventricular rates. Isolated nocturnal pauses are often observed in asymptomatic patients with persistent or permanent AF and do not constitute an indication for pacing.

AV junction ablation requiring the implantation of a permanent pacemaker should be considered in patients with refractory symptoms associated with excessive heart rates despite adequate trials of rate-control drugs, including combination drug therapy. This procedure results in adequate rate control in virtually all patients and has been associated with improvements in clinical symptoms, exercise tolerance, QOL, and ventricular function.[26] Biventricular pacing should be considered after AV junction ablation in patients with left ventricular systolic dysfunction.[27] In selected patients, control of AF by left atrial or pulmonary vein catheter ablation to restore sinus rhythm can be considered as an alternative to AV nodal ablation requiring permanent pacing.[9,11]

Practical tip. As an alternative to AV junction ablation, an attempt at restoration of sinus rhythm via electrical or pharmacologic cardioversion may be warranted to control heart rate in cases in which this can be achieved, such as in the setting of persistent AF or AFL.

RECOMMENDATION

We recommend AV junction ablation and implantation of a permanent pacemaker in symptomatic patients with uncontrolled ventricular rates during AF despite maximally tolerated combination pharmacologic therapy (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the results of many small randomized trials and one systematic review reporting significant improvements in QOL and functional capacity as well as a decrease in hospitalizations for AF following AV junction ablation in highly symptomatic patients.

Rhythm Control of AF and AFL

It is important to emphasize that compared with rate control alone, the strategy of maintaining sinus rhythm has never been shown to decrease mortality or reduce the incidence of thromboembolic complications in AF patients compared to rate control alone.[3-7] Thus, the decision to pursue sinus rhythm maintenance should be directed to patients who remain symptomatic with AF or AFL despite adequate rate control (Table 1). Symptoms may include palpitations, fatigue, exercise intolerance, or symptoms of heart failure. In these patients, restoration and maintenance of sinus rhythm can alleviate these symptoms and improve QOL. Improvement in patient QOL and function, and not the total elimination of AF, should always be the focus of rhythm control. The benefits of any antiarrhythmic drug therapy must also be balanced against the side effects and toxicities of such therapy. If drug therapy fails to achieve a meaningful improvement in patient QOL, then alternatives to the strategy of pharmacologic rhythm control should be considered, including catheter ablation of AF or rate control alone.

Practical tip. When pursuing a rhythm-control strategy for AF, there needs to be a reasonable expectation of maintenance of sinus rhythm.

RECOMMENDATION

We recommend the optimal treatment of precipitating or reversible predisposing conditions of AF prior to attempts to restore or maintain sinus rhythm (Strong Recommendation, Low-Quality Evidence).

We recommend a rhythm-control strategy for patients with AF or AFL who remain symptomatic with rate-control therapy or in whom rate-control therapy is unlikely to control symptoms (Strong Recommendation, Moderate-Quality Evidence).

We recommend that the goal of rhythm-control therapy should be improvement in patient symptoms and clinical outcomes, and not necessarily the elimination of all AF (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of the addition of class I or class III antiarrhythmic drugs to rate-control therapy.

Mechanism of action of antiarrhythmic drugs

The mechanisms underlying AF are complex, likely differing among patients and even within individual patients as a function of the evolution of their cardiac condition.[28] It has been hypothesized that AF is initiated by arrhythmogenic foci, often originating in the pulmonary veins.[29] However, AF is maintained by multiple small reentrant wavelets, sometimes described as "rotors."[30] Formation and persistence of these wavelets is favoured by a shortened atrial refractory period and action potential duration, which occur during AF.[31] The primary action of many antiarrhythmic medications is to lengthen refractory periods by prolonging action potential duration, to inhibit the formation of wavelets responsible for AF maintenance,[32] or to reduce the phase-0 sodium current to destabilize AF-maintaining rotors.[33-35]

Table 3. Antiarrhythmic drugs for rhythm control

Class	Drug	Dosage	Efficacy at 1 Year	Toxicity	Comments
I	Flecainide	50-150 mg twice/d	30%-50%	Ventricular tachycardia Bradycardia Rapid ventricular response to AF or atrial flutter (1:1 conduction)	Contraindicated in patients with CAD or LV dysfunction Should be combined with an AV nodal blocking agent
	Propafenone	150-300 mg 3 times/d	30%-50%	Ventricular tachycardia Bradycardia Rapid ventricular response to AF or atrial flutter (1:1 conduction) Abnormal taste	Contraindicated in patients with CAD or LV dysfunction Should be combined with an AV nodal blocking agent
III	Amiodarone	100-200 mg OD (after 10 g loading)	60%-70%	Photosensitivity Bradycardia GI upset Thyroid dysfunction Hepatic toxicity Neuropathy, tremor Pulmonary toxicity Torsades de pointes (rare)	Low risk of proarrhythmia in a wide range of populations Limited by systemic side effects Most side effects are dose and duration related Very effective for rate control
	Dronedarone	400 mg twice/d	40%	GI upset Bradycardia	Only antiarrhythmic shown to reduce hospitalizations and cardiovascular mortality in ATHENA trial May increase mortality in patients with recently decompensated heart failure, EF <35% (ANDROMEDA trial) Effective rate-control agent New drug – limited experience outside trials
	Sotalol	40-160 mg twice/d	30%-50%	Torsades de pointes Bradycardia Beta-blocker side effects	Should be avoided in patients at high risk of torsades de pointes VT - especially women aged >65 y taking diuretics or those with renal insufficiency QT interval should be monitored 1 wk after starting Use cautiously when EF <40% Heart rhythm specialists may use with lower EFs if patient has ICD

ANDROMEDA, Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease; ATHENA, A Placebo-Controlled Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 Mg Bid for the Prevention of Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Flutter; AV, atrioventricular; CAD, coronary artery disease; EF, ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; VT, ventricular tachycardia.

Class I drugs, such as flecainide and propafenone, block sodium channels.[35] This slows atrial conduction, lengthens atrial refractoriness, and suppresses automaticity.[36] By destabilizing AF-maintaining rotors, this class of drugs can prevent the persistence of AF.[33-35] Class III drugs such as sotalol or dofetilide block potassium channels and thus prolong action potential duration.[37] With sufficient action potential prolongation, class III drugs prevent AF recurrence.

Drugs such as amiodarone and dronedarone have multiple effects, including both class I and class III mechanisms of action.[38] Both drugs also have noncompetitive beta-blocking and calcium channel blocking effects. Thus, both not only are capable of maintaining sinus rhythm but can be effective rate-control agents as well.[23,39]

Antiarrhythmic drug therapy to maintain sinus rhythm

In the absence of an antiarrhythmic drug, the recurrence rate of AF is about 75% over 1 year.[8] Thus, recurrences are very likely once the AF process starts. If a decision is made to pursue a long-term strategy of rhythm control, patients will often require maintenance oral antiarrhythmic drug therapy. While antiarrhythmic drugs will not completely eliminate AF, they can substantially reduce AF burden and improve QOL. Reduction of AF burden by itself without demonstration of alleviated symptoms or reduced morbidity is insufficient to recommend the routine use of class I or class III antiarrhythmic drugs. Ideally, such therapy should also reduce other, more quantitative outcomes such as hospitalization or even mortality, but to date, only limited data exist to support the notion that rhythm-control therapy can accomplish such goals.[39-41]

The dosages, efficacy, side effects, and some practical tips about the various antiarrhythmic drugs are summarized in Table 3. The choice of drugs to use depends on an individual patient's profile and the presence or absence of underlying structural heart disease, as summarized in Figures 4 and 5. Of all the currently available antiarrhythmic drugs, amiodarone has been demonstrated to have the highest efficacy in reducing AF burden.[42,43] Unfortunately, it also has numerous important noncardiac side effects, which prevent it from being used as an agent of first choice.[44] Other antiarrhythmic drugs are less efficacious but have fewer side effects compared with amiodarone.[42] These drugs still carry some risk however, particularly in patients with underlying heart disease.[45] Thus, the choice of which antiarrhythmic agent to use long-term should be guided by evidence-based outcomes (where available) and the safety and efficacy profile of each agent in the context of the specific clinical profile of the patient (see Table 3 and Figs. 4 and 5).

In patients with normal ventricular function, the first-choice antiarrhythmic drug can be either dronedarone, flecai-

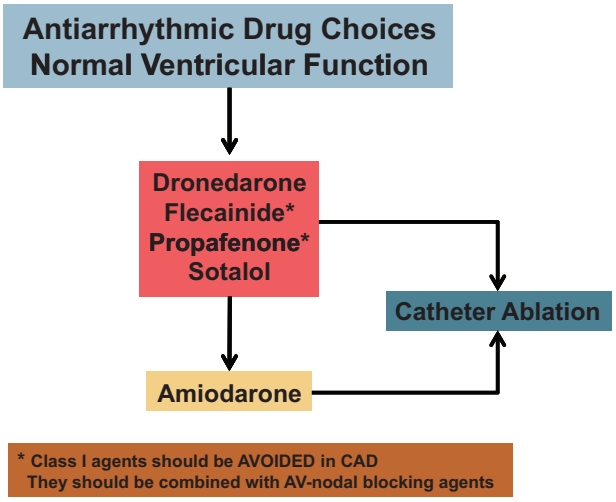

Figure 4. Antiarrhythmic drug choices for prevention of atrial fibrillation in patients without structural heart disease. Antiarrhythmic drugs are presented in alphabetical order. Given the side effect profile of amiodarone, its use is generally reserved for occasions when other drug choices have been demonstrated to be ineffective, contraindicated, or not well-tolerated. CAD, coronary artery disease; AV, atrioventricular.

nide, propafenone, or sotalol. These drugs are less effective (with respect to reducing the number and duration of recurrences) than amiodarone[42,43] but also have fewer side effects. Flecainide, propafenone, sotalol, and dronedarone likely have similar efficacy in maintaining sinus rhythm, based on their efficacies.[39,42,43,46-48] However, direct comparisons of these drugs for suppression of AF have not been made. Propafenone and flecainide must be combined with an AV nodal blocking agent in order to avoid paradoxically increasing the ventricular rate during AF or AFL (see below).[45] Furthermore, a specific effort (eg, stress test) should be made to exclude ischemic heart disease in those >50 years of age or anyone with symptoms suggestive of ischemic heart disease, or Framingham high-risk patients when propafenone and flecainide drugs are to be used. Sotalol carries a higher risk of torsades de pointes, particularly in women or those with renal insufficiency.[48-50] Dronedarone has a structure similar to amiodarone, although dronedarone is known to be less effective in maintaining sinus rhythm.[51,52]

Dronedarone is generally well-tolerated, with a relatively low incidence of side effects or proarrhythmia. In the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 Mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Flutter) trial, dronedarone was shown to reduce hospitalization and cardiovascular mortality in AF patients.[39] The panel chose not to make a specific recommendation that dronedarone should be the first antiarrhythmic drug considered for prevention of AF since dronedarone's efficacy for maintenance of sinus rhythm is comparable to other modestly effective rhythm-control agents (flecainide, propafenone, and sotalol). Also, dronedarone has been shown to be harmful in patients with decompensated heart failure (see below).[53] It is possible that the rate-control effects of dronedarone contributed to the reduction in hospitalizations for AF reported in ATHENA.

In patients with abnormal ventricular function but left ventricular ejection fraction >35%, dronedarone, sotalol, and amiodarone are all reasonable choices (Fig. 5). However, in patients with left ventricular ejection fraction <35%, amiodarone, is the only drug usually recommended because of its low risk of proarrhythmia in heart failure.[4,54] Sotalol or dronedarone could be considered for treatment of AF in dronedarone patients with a left ventricular ejection fraction <35% and in the absence of symptoms of severe heart failure, particularly if they have an implantable cardioverter defibrillator. There is an increased risk of proarrhythmia in heart failure patients taking sotalol,[45] likely because of downregulation of potassium currents and loss of repolarization reserve with heart failure.[55] However, sotalol is used selectively by heart rhythm specialists in patients protected by an implantable defibrillator. The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial found that dronedarone may increase the risk of mortality in recently decompensated heart failure patients in recently decompensated individuals (New York Heart Association classes III and IV) who were hospitalized.[53]

Although the American College of Cardiology, American Heart Association, and European Society of Cardiology 2006 AF guidelines do not recommend the use of propafenone, flecainide, or sotalol in the setting of hypertension and documented left ventricular hypertrophy,[8] the writing group felt that the scientific data supporting this recommendation is weak. Certainly, concern about the use of these drugs due to increased risk of proarrhythmia is warranted if abnormalities of repolarization are noted in the ECG. However, in this setting the choice of antiarrhythmic drug should be individualized on the basis of the patient profile and consideration of the risks and benefits of each drug.[8]

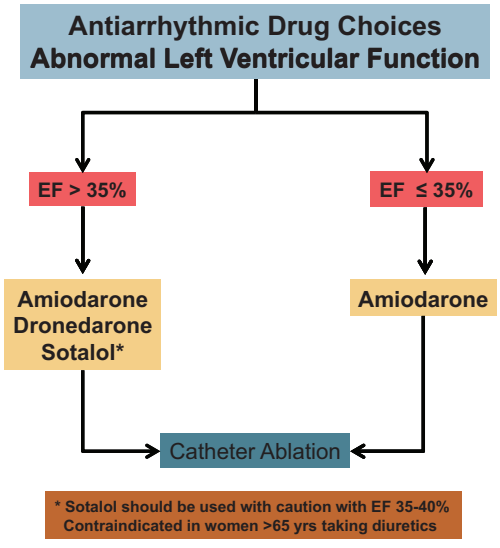

Figure 5. Antiarrhythmic drug choices for prevention of AF in patients with depressed left ventricular systolic function. Dronedarone is contraindicated in patients with acutely decompensated heart failure. Sotalol may be used with caution in selected patients with mild to moderate reduction in left ventricular ejection fraction. EF, ejection fraction.

As previously discussed, the goal of antiarrhythmic drug therapy should be reduction (not necessarily elimination) of AF burden with concomitant improvement in QOL. If a patient has occasional breakthroughs of AF, but few symptoms, therapy may be considered successful. Antiarrhythmic drug therapy should be reassessed periodically based on both efficacy and side effects. If patients fail to respond to or cannot tolerate a particular drug, an alternative drug may be tried after an appropriate washout period. If a patient fails multiple medications, then alternatives to consider include catheter ablation of AF to maintain sinus rhythm (SR) or abandonment of rhythm control in favour of rate control alone (Fig. 1).

RECOMMENDATION

We recommend use of maintenance oral antiarrhythmic therapy as first-line therapy for patients with recurrent AF in whom long-term rhythm control is desired (see Figs. 4 and 5) (Strong Recommendation, Moderate-Quality Evidence).

We recommend that oral antiarrhythmic drug therapy should be avoided in patients with AF or AFL and advanced sinus or AV nodal disease unless the patient has a pacemaker or implantable defibrillator (Strong Recommendation, Low-Quality Evidence).

We recommend that an AV blocking agent should be used in patients with AF or AFL being treated with a class I antiarrhythmic drug (eg, propafenone or flecainide) in the absence of advanced AV node disease (Strong Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of class I and class III antiarrhythmic drugs compared with rate-control therapy.

Risks of antiarrhythmic drug therapy

Risks of the various antiarrhythmic drugs are listed in Table 3. All antiarrhythmic drugs carry the potential of proarrhythmia, so that treatment of AF or AFL may increase the risk of other, more malignant arrhythmias (often ventricular in origin).[45] The class I agents (flecainide and propafenone) can increase the risk of ventricular arrhythmias in patients with coronary artery disease or left ventricular dysfunction, so these agents should be avoided in these populations.[56,57] Class I agents slow the atrial rate in AF by slowing conduction in reentrant rotors or wavelets. The ventricular response to AF is determined by complex interactions between the rate and pattern of activation of the proximal AV node from the atrium on one hand and the refractory properties of the AV node on the other. Because of the decremental conduction properties of AV nodal tissue (involving Ca^{2+}-current–dependent action potentials and zones of poor cell-to-cell coupling), atrial impulses that fail to conduct through the AV node leave the node partially refractory to the next impulse, a phenomenon called *concealed conduction*. Paradoxically, a slowing in atrial rate can therefore cause an increased ventricular response due to a reduction in the number of concealed activations in the AV node. In the most extreme cases with very slow organized atrial activation, conversion of AF to AFL and subsequent 1:1 conduction of AFL can ensue, causing a very high ventricular rate and risk of ventricular tachyarrhythmia.

Practical tip. Class I agents should be combined with an AV nodal blocking agent (beta-blocker, verapamil, diltiazem, or digoxin) to avoid this risk.

Certain class III agents, such as sotalol, lengthen the QT interval and carry a risk of torsades de pointes polymorphic ventricular tachycardia (VT) (1%-3%). Any additional risk factor that prolongs the QT interval increases the likelihood of torsades de pointes VT. This includes female sex, left ventricular dysfunction, significant left ventricular hypertrophy, bradycardia, or hypokalemia or hypomagnesemia (often resulting from diuretic use). By reducing net repolarizing current,[45,55,58] these factors can individually or collectively reduce "repolarization reserve" and increase the risk of drug-induced torsades de pointes. Advanced age reduces the efficiency of drug-eliminating systems (renal function, biotransforming capacity), as well as the volume of distribution for many drugs, and is therefore also a risk factor for drug-induced torsades de pointes. Since sotalol is cleared via the kidneys, any renal dysfunction also increases the proarrhythmic risk. Periodic ECG monitoring of the QT interval should be performed and the drug should be reassessed if the QT is longer than 500 ms or the QTc exceeds 480 ms. Other drugs that increase the QT interval (erythromycin, clarithromycin, antipsychotics) should be avoided by a patient while on sotalol (a full list is available at www.torsades.org).

Amiodarone and dronedarone both carry a low risk of proarrhythmia because of their multiple class effects. Dronedarone is generally safe and well-tolerated. In patients with decompensated heart failure, however, it has been shown to increase mortality (Table 3).[53] Amiodarone rarely causes torsades de pointes VT, but has numerous noncardiac toxicities.[44] Patients should avoid direct sun exposure to avoid photosensitivity. A clinical exam, with careful history to elicit symptoms of toxicity (eg, sleep disturbance, tremor, gait instability, constipation), and pulmonary assessment should be performed periodically to check for toxicity. Hepatic enzymes and thyrotropin should be measured every 6 months in all patients on amiodarone, regardless of symptoms.

Bradycardia can be exacerbated by any antiarrhythmic agent, whether because of sinus node or AV node dysfunction. If bradycardia results in symptoms, the drug should be discontinued, or consideration should be given to implantation of a permanent pacemaker.

Generally, class I or class III antiarrhythmic drugs may be initiated as an outpatient, in spite of the risk of proarrhythmia. Particularly in patients with no underlying heart disease, the risk of proarrhythmia is quite low. If a conduction disturbance (such as sinus or AV node dysfunction) is present or if a patient has risk factors for torsades de pointes VT or significant underlying heart disease, then consideration should be given to drug initiation in hospital. Amiodarone is the only medication that has been shown to be safe when initiated as an outpatient in patients with heart failure and left ventricular dysfunction.[4,5]

Intermittent Antiarrhythmic Drug Therapy ("Pill in the Pocket")

Some patients with symptomatic AF have relatively long-lasting episodes (eg, >4 hours) but with long intercurrent periods of sinus rhythm between episodes (eg, <2-6/y). In these patients, a strategy of daily maintenance antiarrhythmic drug therapy may be unnecessary. An alternative possibility is to prescribe oral antiarrhythmic drugs that can be taken at the time of an episode for acute termination of AF. Clinical trial data have shown this "pill in the pocket" strategy to be both safe and effective.[59] The drugs most commonly used for this purpose are class I agents given as a single dose at the onset of AF. Flecainide is given as a single or cumulative 200 to 300-mg dose, and propafenone is given as a single 450 to 600-mg dose. Both these agents have a 50% to 80% efficacy in acutely terminating AF. Some physicians also prescribe a rapidly acting beta-blocker (eg, metoprolol 50 to 100 mg), to be taken at the same time as the class I antiarrhythmic agent in order to minimize the risk of accelerating the ventricular response. In patients taking daily medication, an additional dose of the drug can be used in this manner.

Practical tip. Because of the risk of 1:1 AV conduction of AFL or the risk of bradycardia, an initial trial of this strategy may be performed in a monitored setting to verify safety and efficacy of this approach in a given patient. Combination with a rapidly acting beta-blocker or calcium blocker is recommended (for patients not already on AV nodal blocking medication or known significant AV nodal dysfunction), particularly in patients in whom this approach has been verified in a monitored setting or in patients with little risk of bradycardia or hypotension associated with this therapy.

Patients should ensure their drugs have not expired if the time between episodes is very long.

RECOMMENDATION

We recommend intermittent antiarrhythmic drug therapy ("pill in the pocket") in symptomatic patients with infrequent, longer-lasting episodes of AF or AFL as an alternative to daily antiarrhythmic therapy (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the results of clinical studies demonstrating the efficacy and safety of intermittent antiarrhythmic drug therapy in selected patients.

Cardioversion as part of the rhythm-control strategy

Maintenance antiarrhythmic drug therapy can be very effective at preventing AF recurrences. However, these drugs, given at maintenance doses, are unlikely to convert patients to sinus rhythm if AF is already present. Longer durations of AF (>48 hours) are particularly less likely to convert to sinus rhythm in response to antiarrhythmic drugs. Thus, patients in AF for whom rhythm control is desired should be considered for electrical cardioversion prior to initiation of maintenance antiarrhythmic therapy. Pharmacologic cardioversion is much less effective than electrical cardioversion. If the patient has never had an attempt at restoration of sinus rhythm, it may be appropriate to observe the patient postcardioversion without antiarrhythmic therapy.

Pretreatment with antiarrhythmic drugs for 1 to 4 weeks prior to cardioversion can improve the acute efficacy of cardioversion and reduce the chance of early recurrence of AF postcardioversion, particularly in patients with prior recurrence postcardioversion.[60-62]

Cardioversion may need to be repeated if antiarrhythmic drug therapy is changed because of recurrent persistent AF. Even when a patient is doing well on maintenance antiarrhythmic therapy, occasional recurrences of persistent AF can occur and may require a change in the antiarrhythmic drug regimen. In such patients, intermittent cardioversion to restore sinus rhythm may be an integral part of the long-term rhythm-control strategy.

RECOMMENDATION

We recommend electrical or pharmacologic cardioversion for restoration of sinus rhythm in patients with AF or AFL who are selected for rhythm-control therapy and are unlikely to convert spontaneously (Strong Recommendation, Low-Quality Evidence).

We recommend pretreatment with antiarrhythmic drugs prior to electrical cardioversion in patients who have had AF recurrence postcardioversion without antiarrhythmic drug pretreatment (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the decision of individual patients to pursue a rhythm-control strategy for improvement in QOL and functional capacity.

Drug conversion of AF

Acute restoration of sinus rhythm from recent onset AF is most commonly performed using electrical cardioversion. Drug conversion may, however, be an effective alternative. While less effective than the electrical method, pharmacologic conversion avoids the need for general anaesthesia and may reduce the risk of early recurrence of AF. Oral antiarrhythmic agents such as flecainide and propafenone may be given as single doses (see discussion of "pill in the pocket," above).[59] Ibutilide is an intravenous class III medication that is typically given as a single dose of 1 mg, which may be repeated once. It is superior to intravenous procainamide, but its use is limited by a 2% to 3% risk of torsades de pointes VT.[63,64] Ibutilide is more effective for AFL than for AF. The risk of torsades de pointes VT associated with ibutilide can be reduced by pretreatment with 1 to 2 g magnesium sulphate administered intravenously.[65] Intravenous procainamide can also be used as a single dose of 15 to 17 mg/kg over 20 to 30 minutes but is associated with a 5% risk of hypotension and is less effective than ibutilide.[63,64] Intravenous and oral amiodarone are not effective for acute conversion (conversion in <6-8 hours) of AF and therefore should not be used routinely for this purpose.[66,67]

Need for anticoagulation

When considering either electrical or pharmacologic cardioversion of AF, patients should be adequately anticoagulated to prevent postconversion thromboembolic complications.[2,8,68] The risk of thromboembolism is the same whether conversion is achieved electrically or with drugs.[2-8] Although oral antiarrhythmic drug therapy given in maintenance doses is less likely to acutely convert AF to sinus rhythm,

Table 4. Randomized trials of pacing modes and impact on AF occurrence

	Danish[80] AAI vs VVI	CTOPP[81]	Extended[82] CTOPP	MOST[83]	Danish[87] AAI vs DDD
Number	225	2568	2568	2050	177
Age (y)	71 ± 17	73 ± 10	73 ± 10	74 (67-80)	74 ± 9
Pacing indication	SND	All pacemaker patients	All pacemaker patients	SND	SND
Follow-up (y)	5.5	3.1	6.4	2.7	2.9
Pacing modes	AAI vs VVI	AAI/R or DDD/R vs VVI/R	AAI/R or DDD/R vs VVI/R	DDDR vs VVIR	AAI vs DDDR-s vs DDDR-l
AF occurrence (%/y)	4.1 vs 6.6	5.3 vs 6.3	4.5 vs 5.7	7.9 vs 10.0	2.4 vs 8.3 vs 6.2
Risk reduction (%)	46	18	20	21	73
P value	.012	.05	.009	.008	.02

AF, atrial fibrillation; AAI, atrial pacing; AAAIR, atrial rate adaptive pacing; CTOPP, Canadian Trial of Physiologic Pacing; DDDR, dual chamber rate adaptive pacing; DDDR-l, long atrioventricular delay; DDDR-s, short atrioventricular delay; SND, sinus node disease; VVI, ventricular pacing; VVIR, ventricular rate adaptive pacing.

one should consider appropriate anticoagulation prior to starting any antiarrhythmic drug therapy in patients who are in persistent AF. This applies even to patients who have low risk of stroke and may not require long-term systemic anticoagulation.[2,68]

Although the objective of the rhythm-control strategy is to reduce the burden of AF, there is no evidence that AF reduction reduces the risk of stroke or systemic embolism.[68] Many patients may have ongoing episodes of asymptomatic AF despite elimination of symptomatic episodes.[69] In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, the risk of stroke was the same in both groups for most of the trial, but in the fifth year, a nonsignificant trend toward increased risk of stroke was observed in patients assigned to rhythm control. In both arms of the AFFIRM trial, many of the strokes occurred after anticoagulation was stopped or when the international normalized ratio was subtherapeutic, which happened more often in the rhythm-control arm because of inappropriate withdrawal of oral anticoagulation with restoration of sinus rhythm, one of the presumed advantages of rhythm control in that era.[68] Thus, patients should continue on appropriate anticoagulation or antiplatelet therapy or a combination, according to their individual embolic risk as determined by the $CHADS_2$ score.[2]

Nonpharmacologic therapy for rhythm control

If antiarrhythmic drug therapy is ineffective at reducing symptoms or not well-tolerated, consideration of AF ablation may be desirable.[11] If AF ablation is a serious option, the patient should be referred to an arrhythmia expert for further discussion.

RECOMMENDATION

We recommend radiofrequency ablation of AF in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm-control strategy remains desired (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL with the small but measurable risk of serious complication with catheter ablation.

Novel therapeutic targets

Experimental research into the substrates that initiate and maintain AF have identified some molecular targets upstream of the electrophysiologic parameters important for AF which might provide novel therapeutic targets for therapy of AF.[9,70,71] Candidates for upstream therapy include statins (3 hydroxy-3-methyl-glutaryl-CoA reductase inhibitors), drugs that suppress the renin-angiotensin-aldosterone system, and omega-3 fatty acids. Statins may prevent adverse atrial electrical remodelling associated with AF by anti-inflammatory antioxidant, anti-proliferatory, or antiapoptotic effects.[70-74] Blockers of the renin angiotensin system may prevent myocyte hypertrophy, apoptosis, and intercellular fibrosis, as well as exerting indirect effects on atrial myocyte electrophysiology.[70,75] Clinical studies have reported that statin therapy may prevent AF, particularly in patients following cardiac surgery.[76] However, a consistent benefit has not been observed in all patient groups evaluated.[77] Drugs which inhibit the renin angiotensin system have been reported to be effective for primary and secondary prevention of AF, with the greatest benefit observed in patients with left ventricular hypertrophy and/or heart failure.[78] However, valsartan did not prevent AF recurrence in the largest randomized prospective trial to date, testing the hypothesis that angiotensin receptor blockade might be an effective therapy for AF.[79] At present, studies are underway evaluating the role of omega-3 fatty acids for prevention of AF.[71,73,74] The evidence to date, however theoretically appealing, does not support specific recommendations directed at upstream molecular targets as part of the management strategy for AF.

Prevention of AF in the pacemaker population

A number of prospective, randomized clinical trials have reported that atrial- or dual-chamber pacing reduces the risk of paroxysmal and permanent AF in patients with symptomatic bradycardia as the primary indication for cardiac pacing.[80-84] The data from these trials are summarized in Table 4. In contrast, the United Kingdom Pacing and Cardiovascular Events Trial Investigators did not observe a benefit of dual-chamber pacing over ventricular for prevention of AF in patients with AV block as the indication for pacing.[85] Thus, these data suggest that the primary benefit of dual-chamber pacing for reducing the risk of AF is observed in patients with sinus node disease and intact AV node conduction.

The Mode Selection Trial Investigators reported that patients who were more frequently paced in the ventricle were more likely to develop AF.[86] The risk of developing AF increased approximately 1% for each 1% increase in ventricular pacing. Nielsen et al[87] also reported that patients with sick sinus syndrome randomized to atrial rate adaptive pacing pacing were less likely to develop AF during follow-up (7.4%) compared with patients randomized to dual-chamber rate adaptive pacing with a short (≤150 ms) or long (300 ms) AV intervals (23.3% and 17.5%, respectively). There are no data to

suggest that atrial overdrive pacing substantially reduces AF.[88] Recently, algorithms designed to minimize ventricular pacing have been shown to reduce the risk of persistent AF following pacemaker implantation in patients with sinus node disease.[89]

RECOMMENDATION

We suggest that patients requiring pacing for the treatment of symptomatic bradycardia secondary to sinus node dysfunction, atrial or dual-chamber pacing be generally used for the prevention of AF (Conditional Recommendation, High-Quality Evidence).

We suggest that, in patients with intact AV conduction, pacemakers be programmed to minimize ventricular pacing for prevention of AF (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations recognize a potential benefit of atrial or dual-chamber pacing programmed to minimize ventricular pacing to reduce the probability of AF development following pacemaker implantation.

Management of AF: Chronic Disease Management Principles

Chronic disease management principles dictate that the primary care physician is central to coordination of patient care. Ideally, support for the primary care physician should facilitate delivery of care, with specialty clinics providing care to more complex cases and tertiary care specialists reserved for the most challenging cases. To facilitate management of AF patients, specialty clinics have been formed in some regions, and others are in planning stages.[90] Participation of the referring physicians is essential to the success of AF clinics, in which nurse clinicians or nurse practitioners play a key role in patient education and reassurance about both AF and the treatment plan. Direct contact with an AF physician specialist may not be required in all cases. In some instances, recommendations about urgent intervention to control the ventricular rate and initiate anticoagulation to prevent stroke are provided by the AF physician specialist, with reassessment at a later date. Some data suggest that patient education and continuity of care provided by AF clinics may reduce emergency room visits.[90]

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