Guidelines for Potassium Channel Blocker Use

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KEYWORDS

• Atrial fibrillation • Atrial flutter • Potassium channel blockers • Practice guidelines
• Ventricular arrhythmias

KEY POINTS

- The choice of antiarrhythmic drug is based on the efficacy and safety profile and influenced by the presence or absence of structural heart disease.
- Because of its adverse side-effect profile, amiodarone is recommended for the management of atrial fibrillation only when other agents have failed or are contraindicated.
- Antiarrhythmic drugs do not improve survival in those with ventricular arrhythmias or at risk of sudden cardiac arrest.
- For treatment of symptomatic ventricular arrhythmias in the setting of coronary artery disease or cardiomyopathy, amiodarone is generally the preferred agent, although sotalol may be considered in patients with mild ventricular dysfunction.

INTRODUCTION

This article summarizes recommendations for the clinical use of antiarrhythmic drugs for the treatment and prevention of atrial and ventricular arrhythmias based on the current guideline and consensus documents. By the nature and process of guideline/consensus document development, the role of the novel potassium channel blockers that are currently under clinical investigation, some of which are discussed in earlier articles, have not yet been determined. It is also important to emphasize that many of the antiarrhythmic drugs currently available for clinical use have effects on multiple ion channels, including potassium ion channels, which contribute to their efficacy.

ATRIAL FIBRILLATION/ATRIAL FLUTTER

Guidelines for the management of atrial fibrillation (AF) and atrial flutter have recently been updated by the Canadian Cardiovascular Society,[1–3] the European Society of Cardiology[4,5] and the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS).[6] Randomized clinical trials have failed to show a superiority of a rhythm control strategy compared with a heart rate control strategy on survival or stroke prevention.[7–9] Accordingly, the choice of a rhythm control strategy should be individualized based on the severity of symptoms, the impact on patients' quality of life, the desire to improve clinical outcomes, as well as patient preferences.[1–6] Choices of antiarrhythmic drug therapy are based on the presence or absence of significant structural heart disease and a history of congestive heart failure as well as the safety and efficacy profile of the drugs.

PHARMACOLOGIC CARDIOVERSION OF RECENT-ONSET ATRIAL FIBRILLATION

The choice of antiarrhythmic drugs for pharmacologic cardioversion of recent-onset AF are shown

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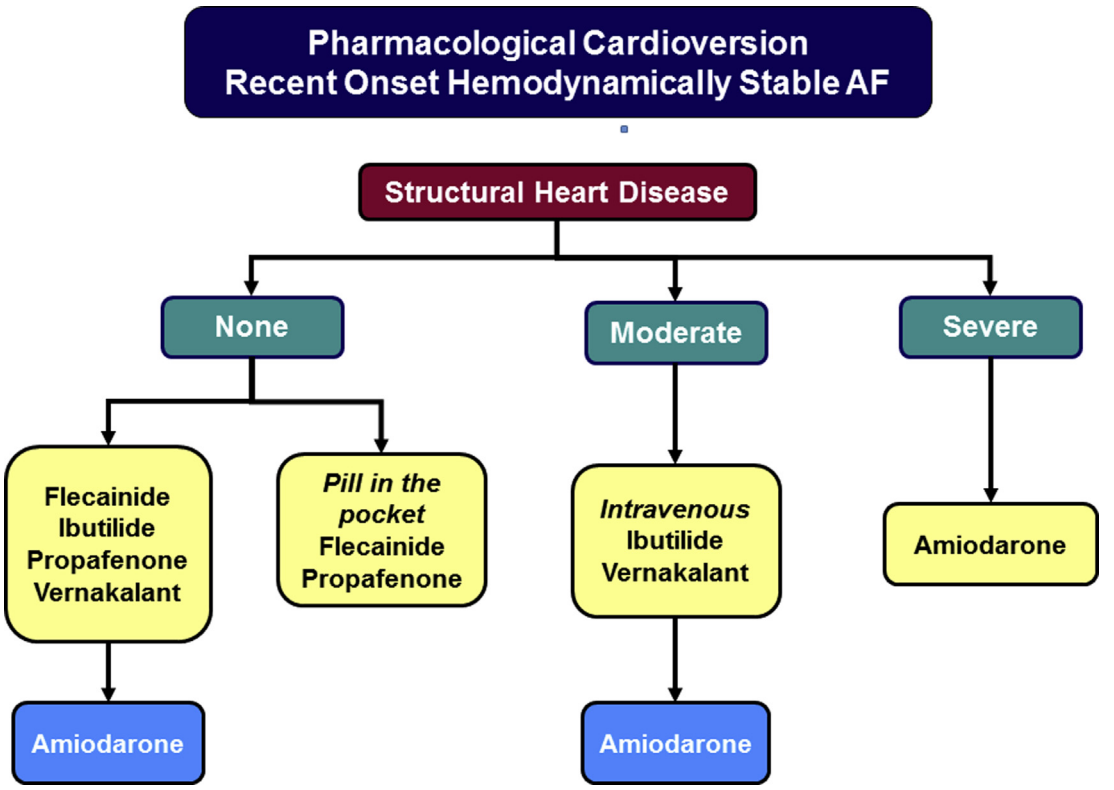

Fig. 1. Drug choices for pharmacologic conversion of recent-onset AF are based on the presence or absence and severity of structural heart disease.

in Fig. 1 and Table 1. The ACC/AHA/HRS' guidelines recommend the use of flecainide, dofetilide, propafenone, or intravenous ibutilide for cardioversion of AF or atrial flutter if contraindications for the selected drug are absent.[6] It is also recommended that dofetilide therapy should be initiated in hospital under continuous electrocardiogram (ECG) monitoring because of the risk of marked QT interval prolongation. The European Society of Cardiology's guidelines recommend

Table 1
Drugs for pharmacologic cardioversion of atrial fibrillation

Intravenous Drugs	Dose
Flecainide	2 mg/kg
Ibutilide	1 mg over 10 min may repeat once (0.001 mg/kg if weight <60 kg)
Propafenone	2 mg/kg
Amiodarone[a]	150 mg over 10 min then 1 mg/min × 6 h then 0.5 mg/min for 18 h or switch to oral dose
Vernakalant	3 mg/kg over 10 min; 2 mg/kg after 10 min if AF persists
Oral Drugs	**Dose**
Amiodarone	400–800 mg in divided doses to a total of 10 g then 100–200 mg/d
Flecainide	200–300 mg single dose
Propafenone	450–600 mg single dose
Dofetilide	125–500 mg bid based on creatinine clearance and QT interval

[a] Amiodarone is less effective for early termination of AF.

the initial choice of intravenous flecainide, propafenone, ibutilide, or vernakalant for pharmacologic cardioversion of recent-onset AF in the setting of no or minimal structural heart disease, the use of intravenous ibutilide or vernakalant in the presence of moderately severe structural heart disease, and the use intravenous amiodarone in the setting of severe structural heart disease.[5] Intravenous flecainide, propafenone, and vernakalant are not available in North America.

Practical tips

- The risk of torsade de pointes ventricular tachycardia following administration of ibutilide can be reduced by pretreatment with magnesium sulfate administered intravenously.
- When compared over 6 hours, intravenous amiodarone is not as effective as intravenous flecainide, ibutilide, propafenone, or vernakalant for termination of AF.
- All guidelines indicate that flecainide or propafenone may be considered as a pill in the pocket approach in the absence of significant structural heart disease if observed to be safe in a monitored setting.
- Adding a rapidly acting beta-blocker or calcium channel blocker in conjunction with flecainide or propafenone may be considered for prevention of atrial flutter with 1:1 atrioventricular conduction particularly if this approach has been demonstrated to be safe in a monitored setting.

In current clinical practice, a trial of longer-term antiarrhythmic drug therapy (2–4 weeks) chosen based on clinical factors for pharmacologic cardioversion is frequently considered before a planned electrical cardioversion if AF persists.[1,6]

MAINTENANCE OF SINUS RHYTHM

The choices of antiarrhythmic drugs for a rhythm control strategy are summarized in **Fig. 2** and **Table 2**. Antiarrhythmic drug choices are guided by the presence or absence of structural heart disease as well as their safety profile. The European Society of Cardiology's guidelines consider the presence of left ventricular hypertrophy as a contraindication for the use of flecainide, propafenone, or sotalol,[5] whereas the current Canadian guidelines do not.[1] The decision to eliminate left ventricular hypertrophy as a discriminating factor for some antiarrhythmic drug choices was based on a lack of compelling clinical evidence of harm in this setting.[1,10] The American guidelines do not recommend the use of dofetilide, flecainide, propafenone, or sotalol in the presence of severe left ventricular hypertrophy defined as a wall thickness greater than 1.5 cm.[6]

The recommendation of dronedarone, dofetilide, flecainide, propafenone, or sotalol as first-line choices for treatment of AF in the absence of significant structural heart disease is based on their side-effect profile compared with amiodarone. Over the long-term, these drugs individually have a modest efficacy for suppression of AF compared with amiodarone (30%–50% at 1 year vs 60%–70% at 1 year for amiodarone).[1] However, the higher incidence of significant adverse effects associated with amiodarone use has led to this hierarchical recommendation that its use be considered when other drugs have failed or are contraindicated.[1,5,6]

Dronedarone is the only drug reported to reduce hospitalizations and improve survival as reported in the ATHENA trial (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/Atrial Flutter).[11] However, dronedarone has been reported to increase mortality in patients with recently decompensated heart failure[12] and in patients with permanent AF and significant cardiovascular risk factors.[13] Consequently, the updated AF guidelines recommend that dronedarone is contraindicated in patients with a history of heart failure or in patients in permanent AF.[2,5,6] Sotalol may be used with caution in patients with a mild reduction in systolic function.[1,6] Dofetilide has been reported to be safe in the setting of systolic dysfunction, but it must be initiated in hospital under continuous ECG monitoring for detection of significant QT interval prolongation and detection of torsade de pointes ventricular tachycardia.[6] Dofetilide is not included in the Canadian or European guidelines, as it has not been approved by regulatory agencies. Amiodarone remains the only agent recommended for use in patients with severe left ventricular systolic dysfunction.[1–6]

Practical tips

- Flecainide and propafenone are contraindicated in the setting of coronary artery disease and prior myocardial infarction.
- Class IC drugs should be combined with atrioventricular nodal blocking drugs.
- These drugs are contraindicated in the setting of long QT syndrome.

- Other drugs that prolong the QT interval should be avoided or used with caution.
- Sotalol and dofetilide should be used with caution in patients at risk for QT interval prolongation, for example, women and patients on diuretics.
- Dronedarone should be used with caution in combination with digoxin.
- Dronedarone should not be used in permanent AF.
- Dronedarone should be avoided in patients with a history of heart failure.

Despite the widespread dissemination of these guidelines, survey data from multiple geographies identify nonadherence to the current guidelines.[14,15] Amiodarone is often prescribed as first-line therapy for patients with minimal structural heart disease. Furthermore, in as many as 20% of patients, the prescription of class IC antiarrhythmic drugs did not conform to the guidelines.

TREATMENT OF VENTRICULAR ARRHYTHMIAS AND PREVENTION OF SUDDEN CARDIAC DEATH

Recommendations on the management of ventricular arrhythmias and prevention of sudden cardiac death have recently been published.[16,17] In randomized clinical trials, the currently available membrane active antiarrhythmic drugs have not been shown to improve survival.[16–22] Indeed class IC antiarrhythmic drugs have been shown to be harmful in patients with ventricular premature beats following a myocardial infarction,[18] and d-sotalol increased mortality in patients with left ventricular dysfunction following myocardial infarction.[21] Clinical trials have demonstrated the superiority of implantable cardioverter defibrillators (ICD) compared with antiarrhythmic drug therapy in primary and secondary prevention trials.[23–28] Thus, the role of antiarrhythmic therapy is primarily adjunctive and limited to specific situations. The choice of antiarrhythmic drug therapy is frequently limited to amiodarone because of the presence of severely depressed left ventricular dysfunction and the known proarrhythmic effects

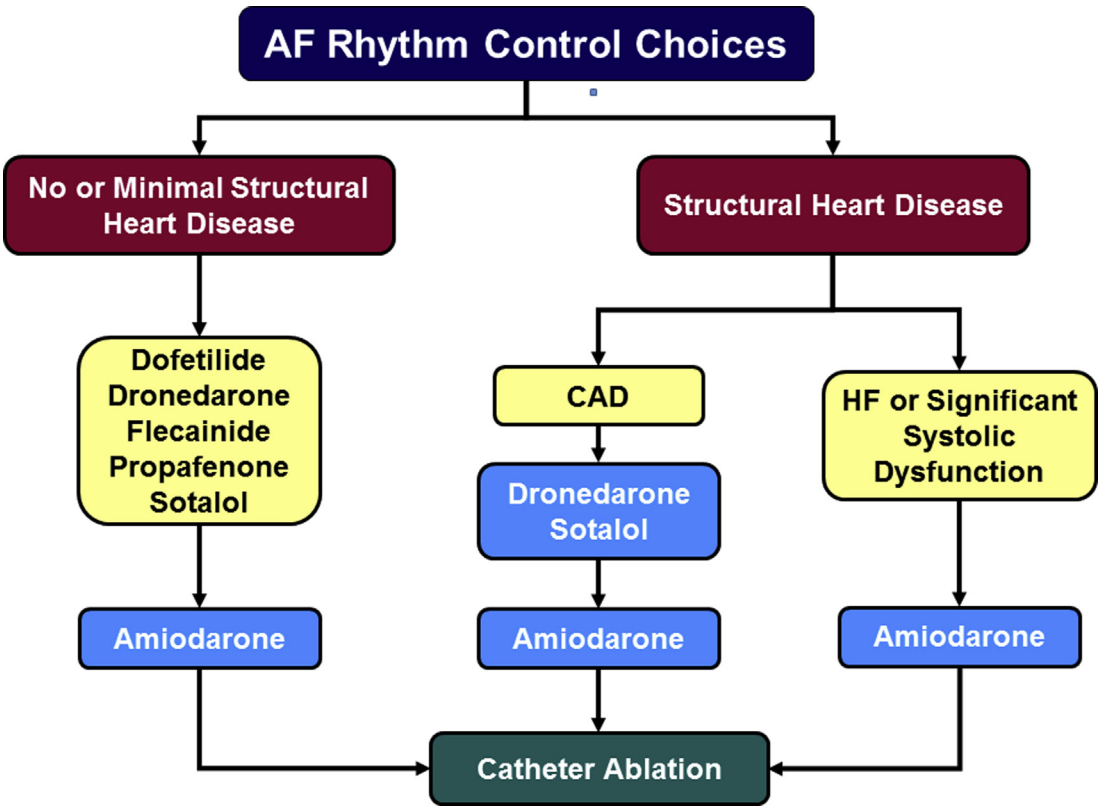

Fig. 2. Drug choices for maintenance of sinus rhythm are based on drug safety profile and presence of structural heart disease. CAD, coronary artery disease; HF, heart failure.

Table 2
Antiarrhythmic drugs for rhythm control

Class	Drug	Dosage	Efficacy	Adverse Effects
IC	Flecainide	50–200 mg bid	30%–50% at 1 y	Bradycardia Rapid ventricular response to AF or atrial flutter (1:1 conduction) Ventricular proarrhythmia
	Propafenone	150–300 mg tid	30%–50% at 1 y	Abnormal taste Bradycardia Rapid ventricular response to AF or atrial flutter (1:1 conduction) Ventricular proarrhythmia
III	Amiodarone	100–200 mg once daily (after 10 g loading)	60%–70% at 1 y	Bradycardia GI upset Hepatic toxicity Neuropathy, tremor Photosensitivity Thyroid dysfunction Pulmonary toxicity Torsades de pointes (rare)
	Dronedarone	400 mg bid	40% at 1 y	Bradycardia GI upset
	Sotalol	40–160 mg bid	30%–50%	Torsades de pointes Bradycardia Beta-blocker side effects

Abbreviations: AV, atrioventricular; CAD, coronary artery disease; EF, ejection fraction; GI, gastrointestinal; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

of other class I or class III antiarrhythmic drugs in this setting.

Sotalol and amiodarone have been used to suppress atrial and ventricular arrhythmias in the ICD population with the aim of reducing shock therapy.[29,30] However, sotalol should not be used in the setting of severe left ventricular dysfunction.

Practical tips

- Amiodarone is recommended for the treatment of polymorphic ventricular tachycardia in the setting of acute coronary syndromes.
- Amiodarone may be considered for the treatment of symptomatic ventricular arrhythmias following myocardial infarction or in the setting of left ventricular dysfunction, but it has no impact on survival.
- Class IC drugs are contraindicated for the treatment of ventricular arrhythmias following myocardial infarction and in patients with left ventricular dysfunction.
- Amiodarone or catheter ablation is recommended for ICD patients to prevent recurrent shocks due to sustained ventricular arrhythmias.
- Sotalol is useful for prevention of shocks in ICD patients with mild to moderate left ventricular dysfunction.

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