

## Drug therapy for termination of atrial fibrillation and maintenance of sinus rhythm

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Antiarrhythmic drug therapy to maintain sinus rhythm has not been demonstrated in randomized clinical trials to improve prognosis or prevent thromboembolic complications in patients with atrial fibrillation (AF). Therefore, drug therapy to restore and maintain sinus rhythm should be limited to those patients who have a greater symptomatic burden of AF. Patients with AF may be completely unaware of their arrhythmia or may present with palpitations, poor exercise tolerance or symptoms of congestive heart failure. In general, younger patients with paroxysmal arrhythmia and patients with decreased left ventricular compliance tend to be more symptomatic. The present article outlines the mechanisms of action of antiarrhythmic drugs in AF. Drugs that are recommended and frequently used to convert AF and maintain sinus rhythm are reviewed, and the toxicity of antiarrhythmic drug toxicity is discussed.

**Key Words:** *Antiarrhythmic agents; Arrhythmia; Atrial fibrillation; Cardioversion; Drugs*

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### RECOMMENDATIONS

#### Conversion of atrial fibrillation

##### Class I

- 1) Electrical or pharmacological conversion should be considered in patients with atrial fibrillation (AF) who are hemodynamically stable (level of evidence C).
- 2) Immediate conversion to sinus rhythm is recommended in patients with AF who are hemodynamically unstable. Electrical cardioversion is more effective and is preferred over pharmacological conversion in these patients (level of evidence C).

##### Class IIA

- 1) Rate control with anticoagulation therapy alone is acceptable while awaiting spontaneous conversion in patients with AF of less than 48 h duration (level of evidence B).
- 2) Pharmacological agents may be used to accelerate conversion of AF in patients with AF of less than 48 h duration (level of evidence B). See Table 1 for drug recommendations.
- 3) Antiarrhythmic drugs may be used to pretreat patients before electrical cardioversion (to decrease early recurrence of AF and to enhance cardioversion efficacy) (level of evidence B).

#### La pharmacothérapie de la suppression de la fibrillation auriculaire et du maintien du rythme sinusal

Les antiarythmiques utilisés pour maintenir le rythme sinusal n'ont pas montré, dans des essais cliniques menés avec hasardisation, leur efficacité à améliorer le pronostic ou à prévenir les complications thromboemboliques chez les patient atteints de fibrillation auriculaire (FA). La pharmacothérapie visant à rétablir et à maintenir le rythme sinusal devrait donc être limitée aux patients qui manifestent le plus de symptômes. Dans certains cas, la FA peut être complètement asymptomatique, tandis que, dans d'autres, elle peut causer des palpitations, une faible tolérance à l'effort et même des symptômes d'insuffisance cardiaque. En général, les jeunes qui présentent de l'arythmie paroxystique et les patients qui ont une diminution de la compliance ventriculaire gauche ont tendance à présenter davantage de symptômes. Le présent article donne un aperçu des mécanismes d'action des antiarythmiques utilisés dans le traitement de la FA. Nous passerons en revue les médicaments recommandés et souvent prescrits pour réduire la FA et maintenir le rythme sinusal et nous traiterons également de la toxicité des antiarythmiques.

##### Class IIB

- 1) Blockade of the angiotensin-renin system may be considered in combination with amiodarone before electrical cardioversion to decrease the recurrence rate of AF (level of evidence B).

#### Maintenance of sinus rhythm in patients with AF

##### Class I

- 1) Oral antiarrhythmic drugs may be used in patients with recurrent AF in whom long-term maintenance of sinus rhythm is desired and in whom a reversible cause of AF is not identified (level of evidence B).
- 2) The choice of an antiarrhythmic drug should be based on the safety profile of the different agents, taking into account the clinical characteristics of the patient (level of evidence B). Recommendations regarding specific agents are listed in Table 2.

##### Class IIA

- 1) In patients without risk factors for proarrhythmia, antiarrhythmic drugs may be initiated as outpatients (level of evidence B).
- 2) In patients with structural heart disease (including those with left ventricular [LV] dysfunction) amiodarone may be initiated as outpatients (level of evidence B).

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**TABLE 1**  
**Recommended drugs for the conversion of atrial fibrillation**

Class I	Ibutilide (level of evidence A) Flecainide (level of evidence A) Procainamide (level of evidence B) Propafenone (level of evidence A)
Class IIA	Chronic oral amiodarone (level of evidence B)
Class III	Sotalol (level of evidence B)

3) An atrioventricular (AV) nodal blocking agent is recommended in patients treated with a class IC antiarrhythmic drug (level of evidence B).

**Class IIB**

1) Patients treated with sotalol or dofetilide should be reassessed if QTc exceeds 480 ms (level of evidence C).

**Class III**

1) Sotalol should not be used for rate control alone in patients with permanent AF (level of evidence C).

**INTRODUCTION**

Antiarrhythmic drug therapy to maintain sinus rhythm has not been demonstrated in randomized clinical trials to improve prognosis or prevent thromboembolic complications in patients with AF. Therefore, drug therapy to restore and maintain sinus rhythm should be limited to those patients who have a greater symptomatic burden of AF. Patients with AF may be completely unaware of their arrhythmia or may present with palpitations, poor exercise tolerance or symptoms of congestive heart failure. In general, younger patients with paroxysmal arrhythmia and patients with decreased LV compliance tend to be more symptomatic. Uncommonly, uncontrolled AF with a rapid ventricular response rate may cause LV dysfunction, which is reversible after rhythm reversion or control of the ventricular response.

**MECHANISMS OF ACTION OF ANTIARRHYTHMIC DRUGS IN AF**

AF is due to the coexistence of multiple reentrant atrial wavelets which are often initiated by arrhythmogenic foci located within the pulmonary veins (1-3). During AF, electrical remodelling of atrial myocytes occurs as a defense mechanism against excessive calcium overloading. This results in a shortened atrial action potential duration and refractory period, thus favouring reentry (4,5). In addition, underlying heart disease, renin-angiotensin system activation and persistent arrhythmia may lead to atrial structural changes also favouring intra-atrial reentry (6).

The primary action of class I drugs is blockade of sodium channels and, therefore, slowing of atrial conduction, especially at pivot points of reentrant circuits (7). In addition, these drugs suppress automaticity and increase atrial refractory periods at faster rates (8). As a result, these drugs increase the size of functional reentrant circuits and increase the probability that a circulating wavelet encounters refractory tissue, thus extinguishing itself (9,10).

**TABLE 2**  
**Chronic antiarrhythmic drug selection**

Patients with structurally normal hearts	
First choices	Propafenone Flecainide Sotalol*
Second choice	Amiodarone
Alternative choices	Disopyramide Dofetilide†
Patients with structurally abnormal hearts	
Coronary artery disease with normal ventricular function	
First choice	Sotalol*
Second choice	Amiodarone
Additional choices	Dofetilide† Propafenone
Left ventricular dysfunction (with or without congestive heart failure)	
First choice	Amiodarone
Second choice	Dofetilide†
Hypertension with left ventricular hypertrophy	
First choices	Sotalol* Amiodarone Propafenone Flecainide

\*Contraindicated in women older than 65 years of age taking diuretics;  
†Dofetilide is available in Canada through Health Canada's special access program

Class III drugs such as dofetilide and sotalol prolong atrial action potential and the refractory period by blocking repolarizing potassium currents (11). These effects may prevent premature atrial complexes from initiating AF (12) and may cause conversion of AF by prolonging refractoriness sufficiently without affecting conduction velocity.

Amiodarone has multiple effects including slowing of atrial conduction (as described for class I drugs) and classic class III properties. Unlike other antiarrhythmic drugs, amiodarone may reverse the electrophysiological and biochemical remodeling associated with AF (13).

**DRUG CONVERSION OF AF**

Drug therapy may be used for conversion in patients with hemodynamically stable AF in whom long-term maintenance of sinus rhythm is desired. Therapy to control the ventricular rate response to AF should be initiated before or simultaneously with therapy to convert the arrhythmia.

Before attempting drug conversion, patients should be adequately anticoagulated to prevent postconversion thromboembolic complications (see Connolly and Gillis, pages 71B-73B). Because thromboembolism is associated with the return of mechanical atrial contraction after conversion, the risk of thromboembolic complications after cardioversion is similar whether conversion is achieved electrically or with drugs.

**DRUG EFFICACY FOR AF CONVERSION**

Recent-onset AF (less than 48 h duration) terminates spontaneously in approximately 50% of cases. Commonly used drugs for rate control (digoxin, calcium channel blockers and

**TABLE 3**  
**Frequently used drugs to convert atrial fibrillation**

Drug	Dose	Efficacy	Risks	Cost (dose)*
Class IA				
Procainamide	15 mg/kg to 17 mg/kg iv	++	5% hypotension	\$6.28 (1 g)
Class IC				
Propafenone	600 mg orally	+++	Hypotension, 1:1 flutter	\$1.74 (600 mg)
Flecainide	300 mg to 400 mg orally	+++	Hypotension, 1:1 flutter	\$3.09 (300 g)
Class III				
Amiodarone combined iv and oral loading (1.0 g iv for 24 h and 400 mg bid for one week)		+	Hypotension, phlebitis, gastrointestinal	\$78.00 (1 g iv)
Ibutilide	1 mg to 2 mg iv	++	2% to 3% TdP	\$262.50 (1 mg)

\*Based on actual costs in one Canadian hospital pharmacy, iv Intravenously; TdP Torsade de pointes

beta-blockers) are no better than placebo for AF conversion. The decision to await spontaneous conversion (while actively controlling rate) versus pursuing pharmacological or electrical conversion depends on the duration of AF and the symptomatic status of the patient. In general, pharmacological conversion will accelerate AF conversion.

If AF persists beyond 48 h, spontaneous termination is less common and active therapy is recommended. Drug conversion, although less effective than electrical cardioversion, avoids the need for general anaesthesia and may reduce the early recurrence of AF (30% to 40% of patients electrically cardioverted).

Table 3 summarizes the reported efficacy of antiarrhythmic drugs to convert AF. The details of individual trials may be found in the references listed or in systematic reviews of the subject (14).

Many trials include patients with atrial flutter. Because the conversion rate for atrial flutter is greater for sotalol and ibutilide, the reported efficacy rates for AF are probably overestimated. Trials also excluded patients with known sick sinus syndrome and intraventricular conduction delays. As a result, the incidence of bradycardia complicating drug conversion may be underestimated and antiarrhythmic drugs must be used with caution.

Several clinical trials have shown that the duration of AF is the main determinant of the efficacy of antiarrhythmic drugs in converting AF. Only 20% to 30% of patients with AF lasting more than 48 h will convert with currently available oral or intravenous antiarrhythmic agents.

### CLASS I DRUGS

Oral quinidine has been used for many years for AF conversion (15-22). Its use has been largely abandoned because of a high incidence of gastrointestinal side effects and a risk of torsade de pointes ventricular arrhythmia (particularly after AF conversion). Procainamide continues to be used in a large number of centres and is more effective than placebo (23-25). Comparative studies have shown it to be inferior to ibutilide and flecainide (26-29).

Class IC agents such as flecainide and propafenone terminate recent onset AF in 50% to 80% of patients (15-17,30-44). Most studies have used single oral doses and have excluded patients with LV dysfunction and intraventricular conduction abnormalities. Conversion rates increase up to 24 h after administration. In general these drugs were well tolerated.

### CLASS III DRUGS

Studies (20,21,45-47) of sotalol for conversion of AF suggest a conversion rate of 20% to 30%. In comparative trials (47), it has been found to be inferior to quinidine and ibutilide and no more efficacious than placebo. As a result, sotalol is not recommended for acute conversion of AF. Ibutilide is a newer intravenous class III medication that converts AF to sinus rhythm in 30% to 50% of cases (26,27,45,48). It has been demonstrated to be superior to procainamide and sotalol in comparative studies. Its main limitation is the occurrence of torsade de pointes ventricular arrhythmia in 2% to 3% of patients.

Studies (18,19,49-61) of amiodarone to convert AF have had variable results. It has moderate efficacy (30% to 40%) in patients with persistent AF when treated with prolonged oral loading regimens (three to four weeks) (49,55,56). However, intravenous amiodarone has been shown to be of limited value in some but not all acute conversion studies (51-53,57-59,61). For this reason, it should not be used routinely for conversion of AF.

### DRUG PRETREATMENT BEFORE ELECTRICAL CARADIOVERSION

The majority of recurrences of AF occur within one month of electrical cardioversion and frequently occur within the first hour after conversion (62).

Antiarrhythmic drugs may be useful as pretreatment before electrical cardioversion to increase the success rate of the procedure and to prevent early recurrences of AF (63). Conflicting data exist concerning the utility of calcium channel blockers to prevent early recurrences of AF after electrical cardioversion and, for this reason, it cannot be recommended at this time (64-66). Two randomly assigned studies (67,68) have shown that blockade of the renin-angiotensin system improves the proportion of amiodarone-treated patients remaining in sinus rhythm after electrical cardioversion. This approach is promising but needs further confirmatory studies.

### DRUG THERAPY FOR MAINTENANCE OF SINUS RHYTHM

This section is summarized in Table 4. In the absence of a reversible cause, AF is usually recurrent. Placebo-controlled trials have shown that the one-year recurrence rate of AF in the absence of an antiarrhythmic drug is approximately 75%. Antiarrhythmic drug therapy is usually necessary to decrease the number of episodes in patients with paroxysmal AF and to prevent recurrence in patients with persistent AF.

**TABLE 4**  
Drugs frequently used to maintain sinus rhythm

Drug	Dosage (mg/day)	Efficacy (%)*	Cost per month (dose) <sup>†</sup>
Class IA			
Disopyramide	400–750	50	\$54 (250 mg bid)
Class IC			
Propafenone	450–900	50	\$59 (150 mg tid)
Flecainide	100–300	50	\$73 (100 mg bid)
Class III			
Sotalol	80–320	50	\$74 (80 mg tid)
Amiodarone	100–400	70	\$53 (200 mg daily)
Dofetilide <sup>‡</sup>	0.5–1	60–70	–

\*Efficacy is defined by the absence of atrial fibrillation one year after initiating therapy; <sup>†</sup>As provided by a commercial pharmacy in Montreal, Quebec; <sup>‡</sup>Dofetilide is available in Canada through Health Canada's special access program. bid Twice daily; tid Three times daily

The dosages, efficacy and side effects of different antiarrhythmic drugs are summarized in Tables 4 and 5 (69-83). Of the presently available oral antiarrhythmic drugs, amiodarone has been demonstrated in comparative studies to be more efficacious than other drugs (75,76). However, it also has significant noncardiac side effects limiting its widespread use as an agent of first choice. Other agents have the potential for significant proarrhythmia when given to patients with underlying heart disease (69,77,78). As a result, the choice of a chronic antiarrhythmic drug in an individual patient is usually guided by the safety profile of the drug with respect to the clinical characteristics of the patient (Table 2).

Patients without underlying heart disease can be treated initially with sotalol, propafenone or flecainide. These drugs, while less effective than amiodarone, have fewer side effects in this population. While no clear advantages are apparent among sotalol, propafenone or flecainide, individual patients may respond more favourably to one agent over another. For example, patients in whom physical activity frequently precipitates AF may respond better to a pure beta-blocker or sotalol. Occasionally, patients who experience AF during intense vagal reactions may respond to disopyramide. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (81), in which serial drug selection and cardioversion was performed as needed, sinus rhythm was maintained in 82% and 73% of patients after one and three years, respectively.

The overall goal of antiarrhythmic drug therapy is to suppress symptoms due to AF. Patients may have occasional breakthrough arrhythmia without excessive symptoms. In these patients, therapy should not be considered a failure and should be continued. If significant arrhythmia does recur, dose increases or an alternative agent should be considered. Throughout the clinical course of an individual patient, the relevance of antiarrhythmic drug therapy should be reassessed. In some patients, AF will recur with minimal symptoms due to adequate rate control. In others, the arrhythmia will recur despite multiple drug trials. Leaving the patient in permanent AF with adequate rate control and anticoagulation is an appropriate therapy at this stage. If the patient remains too symptomatic, then a non-pharmacological form of therapy should be considered.

**TABLE 5**  
Toxicity of antiarrhythmic drugs

Drug	Side effects
Class IA	
Disopyramide	Congestive heart failure Torsade de pointes Dry mouth, blurred vision, urinary retention Bradycardia
Class IC (propafenone and flecainide)	
	Congestive heart failure Ventricular tachycardia Bradycardia Atrial proarrhythmia (1:1 flutter)
Class III	
Sotalol	Bradycardia Torsade de pointes Beta-blocker side effects
Amiodarone	Photosensitivity Bradycardia Gastrointestinal upset Thyroid dysfunction Phlebitis Hepatic toxicity Neuropathy Pulmonary toxicity Torsade de pointes (rare)
Dofetilide*	Torsade de pointes

\*Available in Canada through Health Canada's special access program

## ANTIARRHYTHMIC DRUG TOXICITY

This section is summarized in Table 5. All antiarrhythmic drugs have potentially serious side effects, which may limit therapy. Class IA and class III drugs may cause torsade de pointes ventricular arrhythmia in 1% to 3% of cases (this arrhythmia rarely occurs with amiodarone). Risk factors for torsade de pointes include hypokalemia, hypomagnesemia, a prolonged baseline QT interval, being female, LV dysfunction and renal failure (in the case of sotalol and dofetilide) (82,83). To minimize the risk of torsade de pointes, serum potassium, magnesium and renal function should be measured periodically. Periodic electrocardiograms should be performed and the antiarrhythmic drug should be reassessed if excessive QT prolongation occurs (QT greater than 480 ms). Patients taking a class IA or class III drug should avoid other medications which may prolong the QT interval. These include domperidone, erythromycin, clarithromycin and some antipsychotic medications. Complete lists are available at <<http://www.torsades.org>>.

All drugs may aggravate bradycardia due to coexisting sinus node dysfunction or AV block. Drug discontinuation or implantation of a permanent pacemaker may become necessary in these patients.

Atrial flutter frequently coexists in these patients or can occur because of antiarrhythmic drug transformation of AF. This occurs most frequently with class IC drugs. Because these drugs slow atrial conduction, the atrial rate is often much slower than that observed with classic atrial flutter, thus allowing the possibility of 1:1 AV conduction (82). To prevent this complication, a negative dromotropic drug (digoxin, beta-blocker, diltiazem or verapamil) is recommended as adjunctive therapy when class IC drugs are used.

Class I drugs may exacerbate congestive heart failure and, therefore, should not be administered to patients with LV dysfunction. They may also provoke ventricular arrhythmias in these patients and are associated with an increased risk of sudden death (77,78,82). Class I drugs are also proarrhythmic during experimental episodes of acute myocardial ischemia. As a result, they should be used with caution in patients with stable coronary artery disease, even in those with normal LV function.

Amiodarone may aggravate bradycardia and rarely causes torsade de pointes (when it occurs it is usually in association with severe bradycardia). In general, noncardiac toxicity (as listed in Table 5) limits its use. To minimize these effects, patients should use adequate sun protection when outdoors. Clinical history, hepatic enzymes and thyroid function should be monitored periodically. Patients should be questioned for new pulmonary symptoms and, if present, further pulmonary evaluation is indicated to exclude possible pulmonary toxicity.

### INPATIENT VERSUS OUTPATIENT INITIATION OF ANTIARRHYTHMIC DRUG THERAPY

Patients with no underlying heart disease have a low risk of proarrhythmia. As a result, antiarrhythmic drug initiation can be generally started as an outpatient if sinus node dysfunction or AV conduction disturbances are not present. Special caution should be taken in patients currently in AF because underlying sinus node function may be unknown. Dofetilide has specific dosing and labelling requirements necessitating inpatient

initiation in all patients. Sotalol may be initiated as an outpatient in an individual without risk factors for torsade de pointes.

Patients with underlying heart disease have a higher risk of proarrhythmia. Drugs should be initiated inpatient with electrocardiogram monitoring if a drug other than amiodarone is used. Amiodarone has been shown to be safe even when given as an outpatient in patients with LV dysfunction. Inpatient initiation should be considered if underlying conduction abnormalities are present.

### CONCOMITANT MEDICAL THERAPY IN PATIENTS WITH AF

Appropriate treatment of coexisting cardiovascular conditions is important, especially hypertension and LV dysfunction. For example, in the AFFIRM study (81), hypertension was the predominant cardiovascular condition in 50% of patients and was prevalent in 70% of patients. Several lines of evidence suggest that blockade of the angiotensin-renin system may have salutary effects in patients with AF. Angiotensin-converting enzyme (ACE) inhibition attenuates electrical (84) and structural (85) remodelling in experimental models of AF. Clinical data (86,87) suggest that treatment with an ACE inhibitor reduces the incidence of recurrent AF in patients with LV dysfunction. In addition, as mentioned earlier, pretreatment with angiotensin receptor blockers or an ACE inhibitor reduces the occurrence of AF after electrical cardioversion in amiodarone-treated patients (67,68).

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