Selecting an Antiarrhythmic Agent for Atrial Fibrillation Should Be a Patient-Specific, Data-Driven Decision

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Selecting an antiarrhythmic agent for atrial fibrillation (AF) should be a patient-specific decision. When possible, it should be based on sound rationale and available clinical data. This article details many of the thought processes that must go into this decision process and offers some suggested algorithmic starting points based on these considerations. With a patient's first episode of AF, termination is appropriate, but antiarrhythmic therapy should usually be withheld in order to assess the recurrence pattern. However, if severe hemodynamic or ischemic intolerance would make recurrence a serious risk, or if an early symptomatic recurrence is highly likely, antiarrhythmic therapy would be appropriate. Acute AF may terminate spontaneously or may be terminated iatrogenically. The latter may be achieved by direct current or pharmacologic approaches. The risks, benefits, and optimum utility of these approaches are addressed in the article. Infrequent recurrences may be treated with cardioversion; frequent or severely symptomatic episodes are best treated with attempts at suppression with chronic antiarrhythmic drug administration. Since the therapeutic efficacy of maintaining sinus rhythm is similar for the currently available agents, the drug selection process should be based in large part on safety and convenience considerations. The factors underlying this selection process and one suggested algorithm for drug choice are provided in this article.
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When a patient with atrial fibrillation (AF) is encountered, a series of issues must be addressed (Table I). Among the more prominent are: Is there a reversible cause? Is the patient at high risk for embolic or other adverse consequences? How long has the patient been in AF? Is the patient symptomatic? Does the patient require therapy? Is there underlying structural heart disease (SHD)? Which therapeutic approaches and agents are most appropriate to consider?[1–4]

Although maintaining sinus rhythm might theoretically be the approach of choice for all AF patients in hopes of not only reducing symptoms but also prolonging life and/or reducing thromboemboli formation, survival and embolic benefits have not yet been proven—as is discussed elsewhere in this supplement.[5,6] Consequently, the most definitive current reason for maintaining sinus rhythm is symptom relief or, more specifically, to reduce symptoms associated with AF that persist despite adequate ventricular rate control.

The pursuit of sinus rhythm involves consideration of several issues. Is the AF episode the patient's first or a recurrence? Is the AF paroxysmal or now persistent? If paroxysmal, how frequent and protracted, and what symptoms have been provoked? What agent(s) should be considered for therapy? How should they be administered? What response will be considered as efficacy? It is these latter questions specifically associated with the pursuit of sinus rhythm that this article will address.

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ISOLATED VERSUS RECURRENT AF FREQUENCY AND DURATION

When a patient is encountered during his/her first episode of AF, its natural history is uncertain. It may terminate spontaneously or iatrogenically, but the certainty or frequency of recurrence is unknown. Since long-term antiarrhythmic drug (AAD) therapy would not seem appropriate for the patient without recurrent AF, it has been my practice not to initiate AAD treatment routinely following the patient's first episode. Rather, I prefer to determine the recurrence pattern. Exceptions to this policy include the patient whose presenting symptoms were hemodynamically or ischemically severe and probably not just rate related; the patient whose demographics suggest a high likelihood of recurrence (such as huge atria, sinus node dysfunction, advanced underlying SHD); and/or the patient in whom rate-controlling drugs are felt to be contraindicated or likely to be ineffective (Figures 1 and 2). In such patients, who are encountered relatively infrequently, the risks and inconveniences of chronic AAD therapy should be deemed less than the risks from a recurrence.

When a recurrence occurs, paroxysmal AF can be deemed to be present. But not all paroxysmal AF is alike, and its therapy should be tailored to the patient (Figures 1, 2, and 3). Episodes of AF for 2 minutes twice a year or for 2 hours twice a day are both paroxysmal AF, but their impact on quality of life, if symptomatic, would be quite different. Infrequent, brief paroxysmal AF may require no AAD therapy. For infrequent but protracted and symptomatic paroxysmal AF, rapid cardioversion of each event and/or attempt at AAD prophylaxis may be considered. For many patients, intermittent direct current (DC) or pharmacologic cardioversion may prove to be less of

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TABLE I Important Clinical Issues to Address When a Patient with Atrial Fibrillation (AF) Is First Encountered

- Is there a reversible cause?
- Is the patient at high, low, or intermediate risk for an adverse consequence?
- How long has the AF episode been ongoing?
- Is the patient symptomatic, and are the symptoms predominantly rate related or not?
- Does the patient require therapy? If so: for rate control? for rhythm control?
- Is there underlying structural heart disease?
- What is the age and activity pattern of the patient?
- Which therapeutic approaches and agents are most appropriate to consider?

a clinical burden than chronic suppressive daily therapy. Ibutilide[7,8] has been approved by the US Food and Drug Administration (FDA) specifically for this purpose; and although propafenone and flecainide are not indicated by the FDA for pharmacologic cardioversion of recent onset paroxysmal AF, single oral doses of propafenone (600 mg) or flecainide (300 mg) have been used[2,9–15] to facilitate paroxysmal AF termination and/or to prevent immediate recurrence (Table II). If and when episodes become so frequent or prolonged that the patient prefers chronic suppressive therapy, the approach can be altered.

Importantly, there may be differences to consider when deciding between DC cardioversion and AAD administration.[2] Some of these (Table II) relate to expected efficacy and safety issues. AF episodes >1 month's duration are less likely to be successfully terminated pharmacologically than shorter episodes. It is also likely that episodes converted early will be less likely to result in early appearance of persistent or chronic AF, as the electrical and mechanical remodeling of the atria that occurs with development of AF[16,17] will have less time to become established. The concept of early termination as one means of reducing protracted AF is further explored in Figure 3. In addition to the above, pharmacologic termination should be associated with a lower incidence of immediate postconversion resumption of AF since the antiarrhythmic properties of the drug that facilitated termination (prolonged refractoriness and/or conduction impairment to inhibit reentry) will continue while plasma concentrations of the drug decline. This contrasts with the immediacy and brevity of DC shock. Thus, early conversion by AAD therapy cannot be separated from a simultaneous effect on prevention of immediate recurrence.

THERAPEUTIC EFFICACY: DEFINITION

For patients with recurrent AF and no reversible underlying disorder, recurrences remain likely despite AAD therapy. In almost all series of AAD trials for AF, approximately 50% of patients will have a recurrence during a follow-up of 6–36 months.[18–49] Thus, efficacy cannot be realistically defined as the complete absence of any AF. Rather its frequency and duration and the quality of associated symptoms should be used to define efficacy (Table III). Changing persistent AF requiring in-hospital cardioversion to self-terminating paroxysmal AF or reducing frequent or protracted

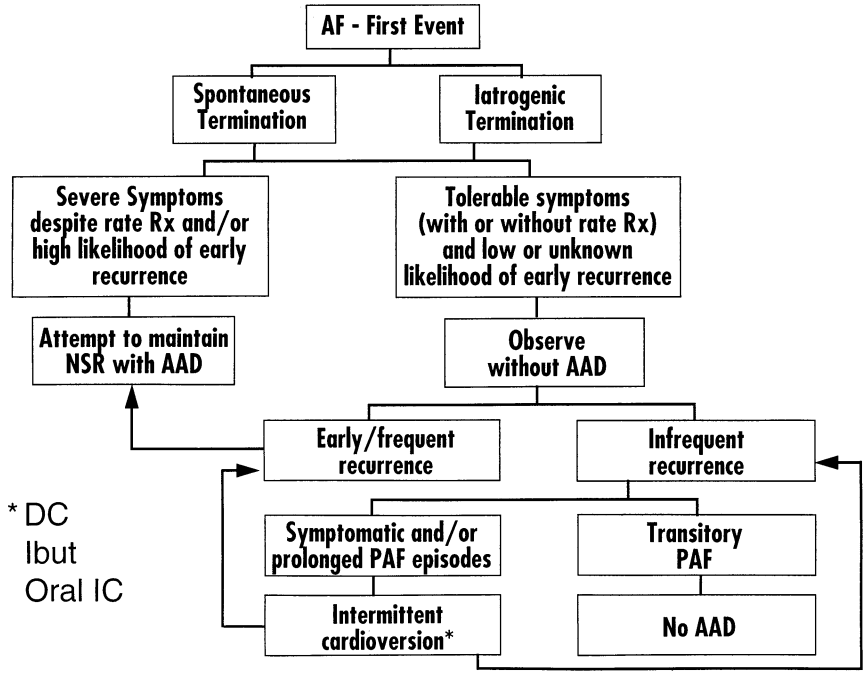

FIGURE 1. A suggested approach to the first episode of atrial fibrillation (AF). See text for discussion. AAD = antiarrhythmic drug; DC = direct current cardioversion; Ibut = ibutilide; NSR = normal sinus rhythm; PAF = paroxysmal AF; Oral IC = oral conversion therapy with a class IC agent; Rx = treatment.

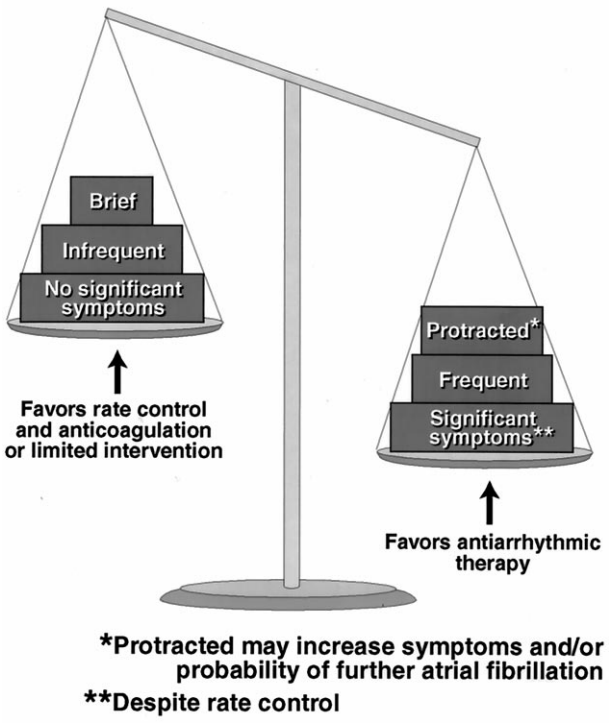

FIGURE 2. A schematic of a scale showing those features that would favor antiarrhythmic drug therapy to limit the duration of an atrial fibrillation (AF) episode or reduce recurrent events. Any of the features on the right side would favor intervention, especially significant symptoms despite rate control. Frequent events, even if less severe, may prompt some patients to seek relief. Protracted episodes are likely to increase the probability of symptoms or possibly to increase the risk of further AF due to tachycardia atrial remodeling. A combination of symptoms, frequency, and/or prolonged duration will virtually always lead to antiarrhythmic intervention. In contrast, the features on the left side would favor rate control plus anticoagulation or limited intervention since the risk–benefit balance, cost, and possibly nuisance symptoms associated with daily antiarrhythmic therapy may not favor intervention.

paroxysmal AF to infrequent and/or brief episodes should usually be considered an adequate response by both the realistic physician and patient. Thus, quality of life becomes the factor defining the therapeutic approach to be used.

ANTIARRHYTHMIC DRUG SELECTION FOR THE MAINTENANCE OF SINUS RHYTHM

When a therapeutic strategy of attempting to maintain normal sinus rhythm has been chosen—in contrast to chronic rate control plus anticoagulation or to intermittent acute cardioversion without chronic suppressive therapy—a drug selection process must then be activated. Such a process must reflect considerations of the various clinically important features each potential drug possesses. In general, these include expected efficacy, pharmacokinetic and pharmacodynamic properties and interactions, and untoward events (Table IV). (In a minority of patients treatment may also or alternatively involve ablational or pacing techniques. These are discussed elsewhere in this supplement.)

TABLE II Important Considerations Regarding Factors that Favor Selection Method for Cardioversion or Enhancement of Termination

Factors favoring DC cardioversion
- Hemodynamic/ischemic urgency, and patient is NPO
- AF duration is >1 month
- Low likelihood of immediate recurrence
- Increased risk for antiarrhythmic drug proarrhythmia
  - —QT_c ≥460 ms
  - —Active ischemia
  - —Advanced structural heart disease
  - —Hypokalemia or hypomagnesemia
  - —Marked bradycardia
- Currently on an antiarrhythmic drug
- Sinus node/conduction system disease that precludes antiarrhythmic drug administration without a pacemaker

Factors favoring ibutilide
- AF duration <30 days
- Absence of torsade de pointes markers
  - —QT_c normal
  - —Potassium and magnesium concentrations normal
  - —Absence of bradycardia
  - —No marked ventricular hypertrophy or LV failure
  - —Others
- Not on an antiarrhythmic drug
- Favorable cost (compared with DC cardioversion)
- Fresh chest wound
- Urgent, but patient is not NPO

Factors favoring oral (e.g., class IC agent) single-dose method (see text)
- AF duration <5 days
- Absence of His-Purkinje disease
- Absence of sinus node dysfunction
- Absence of structural heart disease
- Absence of active ischemia
- Absence of hemodynamic urgency
- Reasonable possibility of immediate AF recurrence without drug
- Low cost
- Likelihood of infrequent AF recurrence

AF = atrial fibrillation; DC = direct current; LV = left ventricular; NPO = nothing by mouth.

EFFICACY FOR AF PREVENTION

For an antiarrhythmic agent to be effective therapy for AF, it must interact beneficially with the electrophysiologic mechanisms generating and/or maintaining the AF. Accordingly, AADs may prevent AF by a variety of mechanisms. These are identified in Table V. Since AF may be initiated and/or maintained by different mechanisms in different patients, it should be immediately obvious that no single AAD should or could be uniformly effective. Thus, the selection of an AAD for the prevention of recurrent AF must involve a consideration of the electrophysiologic and autonomic properties possessed by the drug, the probable contributory factors to AF in the patient (which may be impossible to clarify beyond the assumption of reentry in most patients but which may be revealed by careful historical and/or electrocardiographic review in some), the proarrhythmic potential associated with the patient's underlying SHD, and the potential specific adverse effects identified for the individual drug being considered. Even then, these considerations are only a guide to drug prescription or avoidance, with much of the therapy still remaining empiric.

In theory and in practice, any drug that prolongs

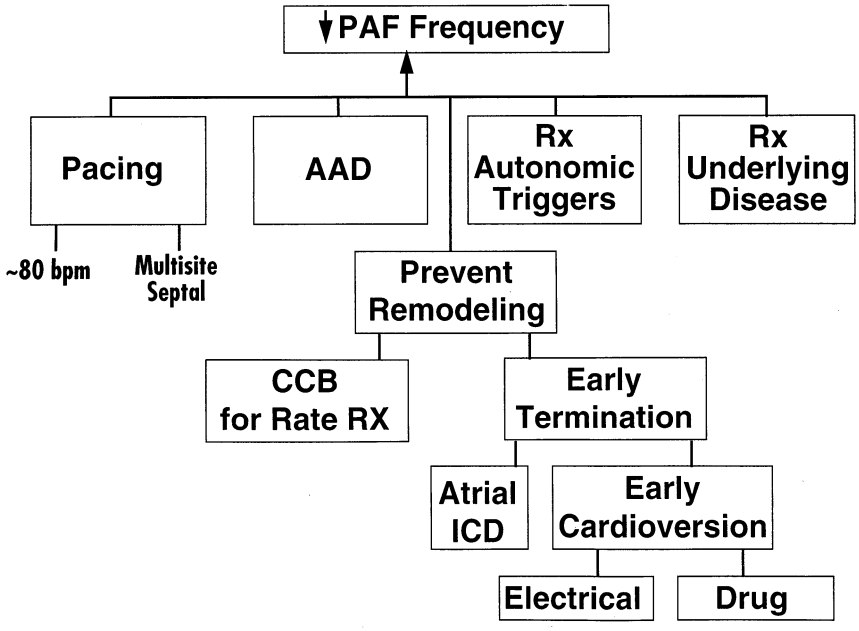

FIGURE 3. Possible approaches to decrease the frequency of paroxysmal atrial fibrillation (PAF). See text for discussion. AAD = antiarrhythmic drug; CCB = calcium channel blocker; ICD = implantable cardioverter defibrillator; Multisite = simultaneous multisite atrial pacing; Rx = treat; RX = treatment; Septal = atrial septal pacing.

refractoriness in the atria, whether by sodium channel inhibition or impairment of repolarization processes, may be effective in most AF circumstances. Dose limitations, however, may preclude uniformly achieving the electrophysiologic alterations necessary for efficacy. In patients who appear to have a parasympathetic contribution to the development of AF (as with nocturnal, postprandial, or bending-associated onset), a regimen that possesses anticholinergic properties may be particularly useful (e.g., disopyramide), whereas vagomimetic drugs (e.g., digitalis) may be profibrillatory. Although the literature does not contain prospective series contrasting drugs with different autonomic profiles in such patients, my own experience suggests that nocturnal paroxysmal AF can be totally or substantially limited by the pre-bedtime administration of either propantheline bromide (without an associated AAD) or controlled-release disopyramide without a repeat dose in the morning. Similarly, there are some patients whose paroxysmal AF appears to have a sympathetic trigger (e.g., stress or exercise induction) or caffeine sensitivity where a regimen including β blockade or verapamil can increase antiarrhythmic efficacy. In those patients in whom AF can be shown to be repeatedly precipitated by an atrial automatic rhythm, the efficacy balance among AADs should shift toward class I agents and away from class III, as the latter have no significant effect on automatic depolarizing currents.

For most patients, however, the selection of an AAD remains empiric. It should therefore not be surprising to learn that the literature suggests similar rates of efficacy among all the currently available AADs.[18–49] The class IA and IC agents, sotalol, and amiodarone have each been shown to have efficacy for prevention of AF that is greater than that of placebo. Although the specific efficacy rates vary among series, it is likely that the differences in absolute efficacy rates largely reflect interseries differences among patients (e.g., underlying heart disease, AF setting, AF duration, prior drug resistance, β-blocker prevention of catecholamine drug reversal, etc). Support for this assumption comes from the various drug comparison trials that have been published,[18,19,24–26,28,29,32,35,38–41,43,44] in which the efficacy rates between or among the drugs being compared have usually been similar. Table VI shows data from some representative series. Although some physicians believe that amiodarone may be slightly more effective than other agents, this has not been uniformly demonstrated to be the case and, even if possibly true, it is not clearly so by an order of magnitude.

Accordingly, if efficacy in controlling AF is similar among AADs, for most patients the drug selection process should be guided by safety considerations.[3] This is particularly true for such arrhythmias as AF, where recurrences are rarely life threatening and hence neither should be therapy.

SAFETY CONSIDERATIONS IN AAD SELECTION FOR AF

Though nuisance symptoms (e.g., loose stools, anorexia, constipation, metallic taste, photosensitivity, altered skin pigment, and the like) and dosing regimens are important considerations in AAD selection, the major safety considerations should include events that could be lethal. These may be grouped as organ toxic or proarrhythmic. Additional important features, as may relate to individual patients, are negative inotropic potential and bradyarrhythmic (nodal suppres-

sion, conduction block) potential. The latter clearly come into play in patients with underlying sinus bradycardia/advanced conduction disease, where drug administration may necessitate permanent pacemaker implantation before starting a class I or III AAD (in the setting of sinus node dysfunction) or a class I drug (in patients with bundle branch block), or where underlying congestive symptoms or severely depressed ventricular function may preclude use of a negatively inotropic drug, regardless of its other merits.

TABLE III Efficacy Considerations in Atrial Fibrillation (AF)

- Recurrences are likely in the absence of a correctable underlying disorder
- Total prevention with antiarrhythmic drug therapy is unlikely
- Realistic goals are the conversion of
  - Frequent recurrences to infrequent
  - Protracted episodes to brief
  - Significant symptoms to acceptable
- Since AF is rarely life-threatening, therapeutic safety should take precedence over total AF suppression

TABLE IV Important Clinical Features of Antiarrhythmic Drugs Used for Prevention of Atrial Fibrillation

- Safety
  - Minimizing organ toxic risk
  - Minimizing proarrhythmic risk
- Other morbidity
  - Minimizing bradycardic risk
  - Minimizing negative inotropic risk
  - Minimizing nuisance symptoms
- Dosing convenience
- Interactions
  - Drug–drug
  - Drug–device
- Cost
  - Of drug
  - Of follow-up
- Efficacy

TABLE V Mechanisms Underlying Antiarrhythmic Efficacy for Prevention of Atrial Fibrillation (AF)

- Suppression of initiating ectopy
- Suppression of tachyarrhythmias that may degenerate into AF
- Suppression of retrograde accessory pathway conduction or intrabypass tract reentry
- Prevent conditions (refractoriness/conduction delay balance) necessary to maintain intra-atrial reentrant wavelets
- Prevent autonomic alterations that can facilitate conditions favorable for intra-atrial reentrant wavelets

ORGAN TOXICITY

Organ toxicity, to be distinguished from more benign nuisance effects, may be defined as noncardiac, end-organ effects that have the potential for lethal outcome. Lupus erythematosus, agranulocytosis, thrombocytopenia, and pulmonary fibrosis typify this concern. Although drugs that most commonly produce such conditions do so only in the minority of exposed patients and can usually be discontinued prior to a fatality by careful follow-up, unfortunate outcomes do occur. Thus, as a general rule, the AADs with the lowest potential for an organ-toxic event should be considered as first-line therapy, when possible. In this respect, among the agents that are now available and are used most commonly for AF, propafenone, flecainide, sotalol, and disopyramide would be considered as safest, whereas quinidine, procainamide, and amiodarone should be considered as carrying organ toxicity risk.[3] Package insert guidelines provide details about the hematologic, hepatic, thyroid, and pulmonary follow-up necessary for the ongoing surveillance of patients taking these agents. Even with low-dose amiodarone, the risk of pulmonary fibrosis (some cases with fatal outcome despite scheduled follow-up) has been shown in the recent prospectively performed Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) study,[50] European Myocardial Infarct Amiodarone Trial (EMIAT),[51] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[52] to average approximately 1.5–2.0%/year.

PROARRHYTHMIA

Proarrhythmia may be defined, for purposes of this discussion, as the production of any new arrhythmia during the treatment of a preexisting one. For practical purposes, however, what clinicans are most concerned about is the production of a hemodynamically destabilizing or lethal ventricular tachyarrhythmia by a drug that is being used to treat the more benign arrhythmia, AF. Certainly, ventricular fibrillation, rapid polymorphic ventricular tachycardia, such as torsade de pointes, or sustained monomorphic ventricular tachycardia would all be relevant examples. Importantly, when considering the production of proarrhythmia, several interacting conditions come into play, and unlike organ toxicity, the risk is not identified simply by drug features alone. Most importantly, there is contributing interplay among the actions of a drug, the presence, type, severity, and course of any underlying SHD present,[53,54] the dosing regimen, and other exogenous factors such as heart rate, electrolyte concentrations, and gender. The mechanisms of the interplay between SHD and AAD proarrhythmia have recently been reviewed elsewhere.[53,54] However, it is important to stress at least the following:

(1) The definition of SHD for purposes of AAD administration should be based on the presence of a condition that could increase the proarrhythmic potential of an AAD.[53] Mitral stenosis with normal ventricular function, for example, would not be SHD under this definition.

(2) The presence of ischemia and/or regional conduction impairment appears to facilitate the potential for fatal proarrhythmia with class I drugs in the form of ventricular tachycardia or fibrillation.[53] In the Cardiac Arrhythmia Suppression Trial (CAST),[55] mortality was increased in postinfarction patients given class IC drugs in the absence of preexisting sustained ventricular tachyarrhythmias. In sustained ventricular tachycardia patients, difficult-to-terminate, very wide QRS ventricular tachycardia with class IC drugs has been recognized since their introduction more than a

TABLE VI Representative Comparative Drug Trials

Investigator	Type of AF	Drugs	No. of Patients	% Maintenance of NSR (mo)	p Value
Juul-Moller et al.[19]	Persistent	Sot	98	52 (6)	NS
		Quin	85	48 (6)	
Lloyd et al.[24]	Persistent	Quin	28	67 (6)	NS
		Diso	29	45 (6)	
Zehender et al.[25]	Persistent	Quin	11	90 (3)	NS
		Amio	12	92 (3)	
Reimold et al.[29]	Persistent	Propaf	50	30 (12)	NS
		Sot	50	37 (12)	
Szyszka et al.[35]	Postoperative	Quin	78	43 (12)	NS
		Amio	56	40 (12)	
		Propaf	43	38 (12)	
Chimienti et al.[38]	Paroxysmal	Flec	97	77 (12)	NS
		Propaf	103	75 (12)	
Aliot et al.[39]	Paroxysmal	Flec	48	77 (12)	NS
		Propaf	49	76 (12)	
Naccarelli et al.[40]	Paroxysmal	Flec	122	71 (9)	<0.007
		Quin	117	55 (9)	
Bellandi et al.[41]	Paroxysmal	Propaf	102	55 (12)	<0.005
		Sot	106	70 (12)	
Richiardi et al.[43]	Paroxysmal	Propaf	102	45 (12)	N/A
		Quin	102	30 (12)	
Lee et al.[44]	Paroxysmal	Propaf	48	87 (3)	<0.01
		Quin	48	46 (3)	

Amio = amiodarone; Diso = disopyramide; Flec = flecainide; N/A = not available; NS = not significant; Propaf = propafenone; Quin = quinidine; Sot = *d,l*-sotalol.

decade and a half ago. In contrast, when used for supraventricular tachyarrhythmias in the absence of SHD, these same class IC agents do not produce any excess mortality.[56,57] In fact, it is the remarkably low incidence of sustained ventricular proarrhythmia that was among the reasons the FDA approved propafenone and flecainide for the therapy of symptomatic paroxysmal AF unassociated with SHD. Life-threatening ventricular proarrhythmia occurs in only a fraction of a percent of such patients given class IC agents. Post–myocardial infarction (MI) studies other than CAST suggest that risk exists in SHD for other class I drugs as well.[58]

(3) Torsade de pointes may occur with class IA or III agents—though rather infrequently with amiodarone as compared with the class IA drugs, sotalol, dofetilide, and others. Although SHD, including ventricular hypertrophy, dilation, and ischemia, appears to increase the risk of torsade de pointes and ventricular fibrillation with these agents,[54] torsade de pointes

TABLE VII Proposed Algorithm for Selecting an Initial Drug for Maintenance of Sinus Rhythm

No structural heart disease
- If history suggests parasympathetic trigger: disopyramide
- If history suggests sympathetic trigger: β blocker, sotalol, or possibly verapamil
- No definitive autonomic trigger
  - — Propafenone or flecainide (see text)
  - — (More data need to become available about dofetilide before determining whether it should also be considered here)
  - — Consider sotalol if patient compliance requires monotherapy

Hypertension (with/without mild–moderate LV hypertrophy)
- If no ischemia and normal LVEF: propafenone or flecainide (propafenone is preferred by our group)

Ischemic heart disease
- If normal or reasonable LV function: sotalol (see text)
- If reduced LV function (with LVEF >25%) but NYHA CHF class 0–II: sotalol, amiodarone, or dofetilide (when available, plus a β blocker) (see text)
- If severe LV dysfunction or advanced congestive symptoms: amiodarone (or possibly dofetilide) (see text)

Non-ischemic dilated cardiomyopathy

Amiodarone (based upon the GESICA[63] and CHF-STAT[64] survival data; sotalol or dofetilide if amiodarone intolerance

Other
- Individualize choice based upon anticipated proarrhythmic risks while attempting to minimize organ toxicity
- Ventricular hypertrophy/stretch may increase risk of torsade de pointes
- Fibrosis/poor cell contact/inflammation/infiltration may increase reentrant proarrhythmic risk

CHF = congestive heart failure; CHF–STAT = Congestive Heart Failue–Survival Trial of Antiarrhythmic Therapy; GESICA = Grupo de Estudio de la Sobrevida en la Insufficiencia Cardiaca en Argentina; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

TABLE VIII Features of Individual Patients that Affect Antiarrhythmic Drug Selection Beyond the Basic Algorithmic*Approach

- Prior drug history
- Absolute/relative contraindications
- Nuisance symptoms, dosing, and cost considerations
- Anticipated stability of underlying heart disease
- Potential for drug interactions with other therapies
- Utility of non-antiarrhythmic actions of an antiarrhythmic drug
- Gender

* See Table VII.

can be produced by these drugs in patients without SHD. In patients with supraventricular tachyarrhythmias and no major risk markers, such as those enrolled in clinical drug trials, the torsade de pointes incidence appears to be in the 1–3% range. It will be higher in the presence of the above structural alterations, bradycardia, and in women, and therefore, in clinical practice. Recognizing that most episodes of torsade de pointes are self-terminating and may not even be long enough to produce symptoms, the actual risk of fatality is lower than the observed incidence of torsade de pointes. Yet it is not zero; and in the structurally normal heart, because torsade de pointes may cause both syncope and ventricular fibrillation, non-torsade de pointes–producing agents, such as the class IC drugs, are preferred by some as the first-line agents. Moreover, because drug-related torsade de pointes is usually bradycardic or pause related, it may be more apt to be seen if drug-induced bradycardia is also present and/or following AF termination rather than during the faster rates present with AF. Although amiodarone carries a very low proarrhythmia risk in the structurally normal heart, as do the class IC drugs, its organ toxicity profile makes it less attractive as an initial agent compared with the class IC alternatives.

(4) In the presence of SHD, such as postinfarction or ventricular failure, where use of class I drugs can carry a significant mortality risk,[53] at least some of the class III agents appear reasonable to consider. Although *d*-sotalol, a "pure" potassium channel blocker, was associated with increased mortality in the postinfarction Survival with Oral *d*-Sotalol (SWORD) trial,[59] this was not true in the subgroup with ventricular ectopy but left ventricular ejection fraction <30% and remote infarction, where mortality was similar to placebo. The assumption is that antiarrhythmic benefit from decreasing lethal ventricular arrhythmias with *d*-sotalol in the low–ejection fraction patients offset its proarrhythmic risk. However, in other post-MI subgroups who were at lower risk for a spontaneous fatal arrhythmia, *d*-sotalol–induced proarrhythmia resulted in excess mortality. Neutral mortality risk (versus placebo) similar to the SWORD low–ejection fraction group has also been seen with dofetilide in patients with ejection fractions <35% in the Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial[60] (despite a torsade de pointes incidence of 3–4%), and with amiodarone in post-MI patients with either left ventricular ejection fractions <40% or frequent/complex ventricular ectopy in the European Myocardial

	SHD	Primary Focus	Rate Rx	AAD for Prevention	Preferred A'coag	Other Considerations that May Alter Therapy
PAF	+	Variable	Variable	Variable	Warfarin	• Frequency • Definable Onset of Symptoms • Accessory Pathway • Brady-Tachy Syndrome • "Focal" Atrial Fibrillation
	–	Variable	CCB/BB	IC	Age Variable	
Persistent AF	+	Prevent	Variable	Variable	Warfarin	
	–	Prevent	CCB/BB	IC	Age Variable	
Chronic AF	+	Rate Rx	Variable	N/A	Warfarin	• N/A
	–	Rate Rx	CCB/BB	N/A	Age Variable	

FIGURE 4. Atrial fibrillation (AF): a multifaceted arrhythmia with multifaceted therapy. This figure is a tabular format approach to major therapeutic issues in AF. It indicates that approaches need to vary according to the AF presentation, the presence (type and severity) of underlying structural heart disease, the age of the patient, and the presence of several important modifiers—including preexcitation, associated sinus node dysfunction or vagotonia, the probability of a focal source for AF initiation, the frequency of the arrhythmia, and the patient's ability to identify accurately the onset of each episode. The antiarrhythmic drug selection process, therefore, is but one of several patient-specific decisions to be made by the treating physician. AAD = antiarrhythmic drug(s); A'coag = anticoagulation; BB = β blockers; CCB = calcium channel blockers; IC = class IC antiarrhythmics; N/A = not applicable; PAF = paroxysmal AF; Rx = therapy; SHD = structural heart disease.

Infarction Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).[51,52] Perhaps because of its β-blocking actions in addition to its class III effects, *d,l*-sotalol has also been associated with lack of mortality risk in post-MI patients, as was shown by Julian et al.[61] Consequently, in the patient with ischemic heart disease, where symptomatic AF demands therapy, *d,l*-sotalol, amiodarone, and dofetilide, when it becomes available, are probably the agents one would choose. Based on organ toxicity potential and proarrhythmic profile, sotalol or dofetilide (the latter given with a β blocker) may be best in the absence of overt heart failure,[62] whereas dofetilide or amiodarone may be best in patients with congestive failure, where proarrhythmia with other agents is generally increased. When failure is severe, amiodarone should be chosen, as its proarrhythmic rate will be lowest and disease prognosis ameliorates long-term organ toxicity concerns.

CONCLUSION: A STARTING-POINT ALGORITHM FOR INDIVIDUALIZED PATIENT DRUG SELECTION FOR AF PREVENTION

The above issues taken together have led our group to suggest an algorithmic approach (Table VII) for the initial selection of an AAD for the maintenance of normal sinus rhythm in patients with AF.[3] Others have suggested similar algorithms. It is my hope that knowledge of our approach and its rationale will be helpful to the readers of this supplement when they encounter AF patients in their own practices. Although we recognize that an algorithm is only a starting point and that many individual patient considerations (Table VIII) might modify its application, an algorithm provides at least an initial guide that focuses on the important organ toxicity and proarrhythmic considerations that must be overriding.[65] For AF, the concept of an algorithmic approach is also applicable to other aspects of its therapy (Figure 4). Clearly, however, neither our algorithm nor any other is inviolate. As clinical trials are completed and new data become available, such algorithms, which are data driven, will continue to evolve.

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DATA DRIVEN DECISIONS—PICKING THE CORRECT AGENT: DISCUSSION LED BY JAMES A. REIFFEL, MD

Augustus O. Grant, MD (Durham, NC): How do you decide when a given recurrence is early, and when to treat because the recurrences of atrial fibrillation (AF) are random events? As a corollary, how many events do you need to document before you have a good estimate as to how frequent the recurrence is going to be?

James A. Reiffel (New York, NY): That's a difficult question. I often let the patient make the decision as to what is too frequent and when to treat, remembering that what I'm trying to do is improve the patient's quality of life. I will usually tell them, here's the list of drugs we might choose from. Here are the potential effects. You tell me when you want to be exposed to those effects or live with your AF.

Steven Winters, MD (Morristown, NJ): Is the atrial stunning and post-conversion embolic risk different with electrical conversion than it is with drug conversion?

Dr. Reiffel: To the best of my knowledge the answer is no. I think the atrial stunning is related to the fibrillation. If it were related to the cardioversion, then we should anticoagulate every patient we convert in the electrophysiologic lab for any arrhythmia. We should have our chronic defibrillator patients anticoagulated.

Richard Page, MD (Dallas, TX): How does the duration of the AF affect your decision to use electrical versus pharmacological cardioversion?

Dr. Reiffel: I think if the AF is >1 month, that favors electrical conversion over drug conversion. The efficacy of drug conversion falls with the duration of AF. For the ibutilide data, the 35–40% efficacy rate tends to hold pretty flat for 3 weeks and after about 1 month it's $<10\%$.

Charles Webb, MD (Detroit, MI): I have several questions regarding anticoagulation, such as: how

long has the patient been in AF, when is the next episode going to be, when you see their next episode how long will they be in it, and do you stop the anticoagulation that you started after the first event, assuming they're in a high-risk group?

Dr. Reiffel: My own philosophy is that the patient who cannot tell me accurately, to my conviction, when he or she goes into AF is suspect, and I would leave them chronically anticoagulated. I have most of my paroxysmal AF patients on chronic warfarin.

Steven Kutalek, MD (Philadelphia, PA): I think once you make a decision to initiate warfarin because they've had AF, you can't discriminate by patients who know and those who don't know that they're going to have a recurrence once sinus rhythm has been restored. One issue is the patient who has a contraindication to anticoagulation, and there's a desire to restore sinus rhythm in the hope that anticoagulation can be discontinued. I would argue there are no data to say you can stop anticoagulation. I don't see any recommendation that we could make to do that.

Dr. Reiffel: I agree.

Koonlawee Nademanee, MD (Los Angeles, CA): Most of us believe that if AF extends beyond 48 hours, the risk of emboli is high and that necessitates anticoagulation for at least 3 weeks before cardioversion. Because of the stunned atrium, function doesn't return to normal immediately, hence anticoagulation is continued for $\geq$4 weeks after conversion.

Brian Olshansky, MD (Maywood, IL): You indicated there were really 2 reasons to treat AF: to decrease symptoms and occasionally to prevent death. I think there's another reason: the necessity to follow up with the doctor, how frequently you have to see a doctor, the cost effectiveness of the therapies and the fact that in reality it doesn't take 3 weeks to anticoagulate a patient before you cardiovert them. I had one patient that a referring doctor was seeing for 5 months before he got a correct international normalized ratio.

Dr. Reiffel: That's valid—it is all part of the quality-of-life issue.

Dr. Grant: If you choose to use ibutilide, you've got to be prepared to cardiovert the patient, so the fact that they're not NPO doesn't make them any more desirable, in my mind.

Dr. Reiffel: I agree with you, except that you'll only have to electrically convert (and possibly sedate) 2% rather than 100%.

Mark Carlson, MD (Cleveland, OH): Do you think it may be appropriate to give a drug to improve the efficacy of the cardioversion itself?

Dr. Reiffel: Yes, in 2 respects. First, there are some drugs that lower defibrillation thresholds in the atrium, and they tend to be the class III drugs; ibutilide, for example. If you're using pharmacotherapy to augment electrical effects, a nice combination is ibutilide and then direct current (DC) cardioversion. Second is for the patient who has infrequent episodes but some of them in the past have occurred immediately following DC cardioversion. Hence, they may be given a drug, cardioverted, and kept on a drug for up to a month to prevent the immediate recurrence. Hopefully, with remodeling during normal sinus rhythm, the drug is then stopped and then they're okay.

Dr. Sager: I guess one of the other issues that could be put into this equation is that the class IC drugs can be started as outpatient therapy. All of the dofetilide investigations were based on a 3-day hospital admission. What about sotalol—inpatient or outpatient?

Dr. Reiffel: In DIAMOND, dofetilide (started with inpatients) had a 3.3% incidence of torsades, as I remember, which is about the same as has been reported in some of the abstracts for the supraventricular tachycardias. That's the major reason for inpatient monitored observation.

The incidence of torsades with sotalol in the normal heart is extremely low. In the supreventricular arrhythmia database (not just the normal hearts) it was about 1.7%. I will selectively start sotalol on an outpatient basis, but I insist that they go slow on the dose and use a transtelephonic monitor, to monitor the QT interval. The one thing about sotalol is the torsades doesn't tend to be idiosyncratic; it's QT related. Also, I will not do it if any torsade risk marker is present, e.g., undue bradycardia, low K^+ or Mg^+, LVH, or the like.

Kevin Ferrick, MD (Bronx, NY): What is nonstructural heart disease? Is a physical examination, electrocardiography and echocardiography, enough or do you include a treadmill, Holter, etc.?

Dr. Reiffel:I think all patients need a history and physical targeted toward heart disease, an electrocardiogram, and an echocardiogram. If they have risk markers for coronary disease (age included), I exercise them too. Of note, if an exercise test is done, I look not only to exclude ischemia, but I also assess QT interval behavior.