Atrial Fibrillation: When - and How - to Convert to Sinus Rhythm

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Your patient with atrial fibrillation (AF) is hemodynamically stable and you have successfully established rate control. Your next step is to weigh the risks and benefits of attempting to restore sinus rhythm. In up to one half of patients, AF of recent onset converts spontaneously to normal sinus rhythm within 24 hours. Thus, in some cases, the most appropriate approach may be to control the ventricular response, identify and treat comorbid conditions, initiate anticoagulation, and closely monitor the patient.

Because a clot generally requires 2 to 3 days to form, it is usually safe to delay cardioversion for the first 24 hours in a stable patient with a controlled ventricular rate. To attempt medical cardioversion during this time may confuse the issue. If cardioversion does occur, it will be unclear if this is a result of medication or whether it is spontaneous.

On the other hand, recent findings related to electrical remodeling suggest that the longer the delay before medical or electrical conversion is attempted, the lower the likelihood of acute conversion to and maintenance of sinus rhythm. [1,2] How much difference a delay of days or a few weeks makes is unknown. Pharmacologic conversion appears to be most effective when initiated within 7 days of the onset of AF. [3]

Here, we address the rationale for conversion to and maintenance of sinus rhythm and describe the antiarrhythmic agents used in medical cardioversion. In part 1 of this series (page 526), we discussed rate control and prevention of thromboembolism in patients with AF.

RATIONALE FOR CONVERSION TO SINUS RHYTHM

Symptom control. Physiologically, it seems preferable to restore sinus rhythm whenever possible. Although the condition of many patients improves with rate control, some continue to have significant symptoms. [4] Even in the absence of concomitant heart disease, patients with AF have reduced exercise capacity [5] and experience higher heart rates during exercise than those in sinus rhythm. [6] One study of patients with heart failure showed that those in whom rate control had been achieved but who had persistent AF had only marginal improvement in left ventricular ejection fraction and symptoms. In contrast, the ejection fraction improved and symptoms diminished significantly in patients in whom sinus rhythm was maintained. [7]

Atrial contribution to ventricular filling. Patients who depend more on "atrial kick" for ventricular filling may have more to gain from restoration of sinus rhythm than other patients with AF. This group includes those with underlying left ventricular (systolic) dysfunction or with unusually stiff ventricles (diastolic dysfunction from hypertension or aortic stenosis). Loss of atrial kick (which may contribute 20% to 30% to ventricular filling in such patients [8]) places these patients at increased risk for continued symptomatic heart failure even after rate control.

Reduced need for anticoagulation. Another reason to consider rhythm conversion in patients with AF is to reduce the need for anticoagulation. The latter therapy is not without risk, and it is not appropriate in certain patients, such as those at high risk for falls, those with active ulcer disease, and those who previously experienced significant hemorrhage with anticoagulation. Many physicians stop anticoagulation once sinus rhythm has been restored. However, it is not yet entirely clear whether anticoagulation should be discontinued in patients converted to sinus rhythm, because some may have other factors that continue to predispose them to embolization. [9] A significant number of these patients may have occult paroxysmal AF which, without anticoagulation, places them at greatly increased risk for stroke.

Prevention of left atrial enlargement. AF may result from, and is a risk factor for, left atrial
enlargement.\textsuperscript{10,11} AF leads to atrial dilation, which further predisposes to persistent AF and subsequent further dilation (ie, "AF begets AF\textsuperscript{8}11\textsuperscript{23}). Left atrial size affects impulse conduction properties associated with electrical remodeling, which may be reflected in a patient’s ability to undergo cardioversion successfully and maintain sinus rhythm. The larger the left atrium, the less the likelihood of successful cardioversion. Once sinus rhythm is restored, the atrium often diminishes in size.\textsuperscript{12} Besides left atrial size, other factors involved in maintenance of normal sinus rhythm include the duration of AF, left ventricular function, electrical remodeling, and specific antiarrhythmic therapy.\textsuperscript{13,14}

**PREPARATION FOR CARDIOVERSION**

**Anticoagulation.** Before cardioversion is undertaken, several issues need to be addressed. If possible, determine how long the patient has been in AF. The American College of Chest Physicians strongly recommends anticoagulation with warfarin (target INR, 2 to 3) for at least 3 weeks before elective cardioversion if AF has been present for more than 48 hours or for an unknown amount of time.\textsuperscript{3,15} Continue anticoagulation for 3 to 4 weeks after conversion to sinus rhythm. This recommendation is based on the high number of reported embolic events (up to 5.6%) after cardioversion,\textsuperscript{16} which are thought to result from dislodging of preexisting clots or formation of new clots in the stunned atrium.\textsuperscript{17} Restoration of normal atrial function may be delayed for several weeks or more after conversion to a normal electrical rhythm.

**Transesophageal echocardiography.** Specific echocardiographic factors have been identified that may correlate with an increased risk of stroke in patients with nonrheumatic chronic AF.\textsuperscript{18,19} Transesophageal echocardiography (TEE) may be used to identify these factors, which include:

- Left atrial clot.
- Large atrial size (or depressed atrial appendage function).
- Complex aortic plaque.
- Spontaneous echocardiographic contrast.

However, the absence of these factors does not eliminate the risk of embolization after cardioversion.\textsuperscript{20} Therefore, although TEE before cardioversion is not routinely recommended, it may clearly be helpful in selected cases.

**PHARMACOLOGIC CARDIOVERSION**

Whether to initially attempt cardioversion pharmacologically (and with which agent) or electrically depends on the individual patient.\textsuperscript{21} Typically, pharmacologic cardioversion is tried first, followed by electrical cardioversion if it fails. This approach is reasonable in many cases because medical therapy is less invasive. Furthermore, the probability of success with electrical cardioversion is increased when the patient is already taking an antiarrhythmic agent.\textsuperscript{22} The initial choice of an antiarrhythmic must be individualized. In general, long-term efficacy is relatively similar among the various agents, with a reported range for maintaining sinus rhythm of 50% to 70% after 1 year and 40% to 50% after 3 years.\textsuperscript{19,23} Table 1 lists factors to consider in selecting an antiarrhythmic.
It is difficult to compare the conversion rates of the various pharmacologic agents because a number of variables affect the ultimate success rate. These include left atrial size, left ventricular function, length of time the patient has been in AF, the presence of concomitant cardiovascular disease, and electrophysiologic milieu. Even placebo has documented short-term conversion rates as high as 48%. Conversely, AF tends to recur in many patients regardless of the drug used. The efficacy of treatment is best judged by reduction in the rate of recurrence or severity and duration of AF episodes, rather than elimination of AF.

Several classes of pharmacologic agents have shown good rates of conversion and maintenance of sinus rhythm, with broad ranges reported for each drug depending on study conditions. Certain clinical situations may make one agent initially preferable to another. A listing of agents used to maintain sinus rhythm, with suggested dosages and adverse events, is provided in Table 2.

The class IA agents (disopyramide, procainamide, and quinidine); class IC agents (flecainide and propafenone); and class III agents (amiodarone, dofetilide, ibutilide, and sotalol) are all effective to varying degrees in restoring or maintaining sinus rhythm.

<table>
<thead>
<tr>
<th>Drug class and drug</th>
<th>Daily dose</th>
<th>Potentially adverse effects</th>
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<tbody>
<tr>
<td>Class IA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>400 - 750 mg</td>
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<tr>
<td>Class IC</td>
<td></td>
<td></td>
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<tr>
<td>Flecainide</td>
<td></td>
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<tr>
<td>Propafenone</td>
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<tr>
<td>Class III</td>
<td></td>
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</tr>
<tr>
<td>Amiodarone</td>
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<tr>
<td>Dofetilide</td>
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<td>Ibutilide</td>
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<td>Sotalol</td>
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Class III
Amiodarone†

100 - 400 mg
Drugs and dosages determined by consensus based on published studies.

†A loading dose of 600 mg/d is usually given for 1 month or 1000 mg/d for 1 week.
Class IA agents. Historically, these agents were the most commonly prescribed antiarrhythmics for AF. Oral quinidine is effective at both restoring and maintaining sinus rhythm. In one meta-analysis, quinidine demonstrated a mean efficiency of 41% in maintaining sinus rhythm after a median time of 1 year.28 In another study, the 24-hour conversion rate with combined quinidine and digoxin was 47%.29 Intravenous procainamide was also shown to be effective in older, uncontrolled studies, in which conversion rates were as high as 58%.30

Class IA agents have been associated with a number of serious side effects. A meta-analysis of randomized controlled trials showed that long-term treatment of AF with quinidine was associated with a 3-fold increase in mortality in the ensuing 1 to 2 years.31 Other significant risks associated with quinidine include organ toxicity and proarrhythmia (including sudden death). Moreover, the efficacy of this agent decreases with time.32

The principal side effects associated with short-term use of procainamide include hypotension and QRS and QT prolongation, which may predispose to torsades de pointes.33 Long-term use of procainamide is also limited because of the almost inevitable development of drug-induced systemic lupus erythematosus, nausea, and neutropenia.26

Disopyramide has a unique vagolytic effect in addition to its class IA properties. This may make it a preferred agent for a patient with AF that results from increased vagal tone (such as AF in a well-conditioned athlete or nocturnal AF).26

Class IC agents. When used appropriately, propafenone and flecainide appear to be the most effective drugs for acute conversion of AF to sinus rhythm. Success rates of up to 78% with flecainide and 72% with propafenone have been reported after a single oral dose (usually twice the maintenance oral dose); conversion is achieved in 8 to 12 hours.34

Although generally well tolerated, these drugs should not be used in patients with structural heart disease because of the high risk of potentially lethal proarrhythmia in this setting. This recommendation reflects the results of the Cardiac Arrhythmia Suppression Trial (CAST), in which the risk of death significantly increased when flecainide and encainide were used to treat ventricular arrhythmias in patients with coronary disease.35 CAST specifically implicated flecainide and encainide, but these warnings are generally applied to all IC agents. Although these restrictions limit the broader use of class IC agents, they can be considered first-line therapy for patients with true lone AF or those with hypertension and minimal left ventricular hypertrophy.26 Another consideration is that arrhythmia often recurs in the form of atrial flutter with a slow atrial rate of 180 to 220 beats per minute. Concomitant use of an atrioventricular (AV) nodal blocking agent to prevent the possibility of 1:1 AV conduction is recommended.36

Class III agents. Although their effects vary, these agents appear to work by prolonging the QT interval. With the exception of ibutilide, they are generally less useful for acute conversion of AF and are used more commonly to maintain sinus rhythm. Ibutilide has been reported effective in approximately 30% of cases for acute conversion of AF to sinus rhythm.37 The drug works rapidly (usually within 60 to 90 minutes); about half of patients in whom ibutilide is effective convert to sinus rhythm within the first 10 minutes.37

Sotalol is unique in that it also possesses significant nonselective β-blocking activities. This may make it an antiarrhythmic of choice for patients with coronary artery disease who have normal left ventricular function.26

Unlike most other antiarrhythmics, amiodarone and the newest approved class III agent, dofetilide, appear relatively safe for patients with significant systolic heart failure.38-41 Amiodarone was also shown to be effective even in some patients with large left atrial size (60 mm or more) and previous poor response to other agents.42 Amiodarone is associated with a lower incidence of torsades de pointes than other class III agents but carries the risk of significant organ toxicity (such as pulmonary fibrosis, liver function abnormalities, and thyroid dysfunction) as well as ocular disturbances, skin discoloration, and adverse drug interactions (most notably with warfarin and digoxin).43

Dofetilide has been associated with a significantly decreased number of hospitalizations for heart failure exacerbation with concomitant AF.39 This agent appears to be associated with a lower
incidence of organ toxicity but more frequent occurrence of torsades de pointes (0.8% overall, 3.39% in patients with left ventricular dysfunction); consequently, the manufacturer has restricted the availability of dofetilide to prescribers who have participated in a special educational program.\textsuperscript{44} Unfortunately, class III agents are associated with substantial risk. Because they prolong the QT interval, there is a significant likelihood of proarrhythmia if excessive QT prolongation occurs.\textsuperscript{45} Be sure patients are not taking other drugs that prolong the QT interval. Hypokalemia, hypomagnesemia, and hypocalcemia, which can also affect repolarization, must be avoided as well.\textsuperscript{46}

REFRACTORY AF
If AF is refractory to pharmacologic or electrical cardioversion, consider referral for surgical therapy. Options include pacing, AV nodal ablation, and circumferential pulmonary vein ablation. Future management for certain patients may include potentially curative ablation therapy of atrial reentry currents.

References:

21. Reiffel JA. Selecting an antiarrhythmic agent for atrial fibrillation should be a patient-specific, data-driven decision. Am J Cardiol. 1998;82:72N-81N.