

## Management of Atrial Fibrillation in Patients With Structural Heart Disease

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered by clinicians. The prevalence of AF increases with age, and the elderly are the fastest growing subset of the population. It has been estimated that there will be >12 million patients with AF in the United States within the next several decades.<sup>1,2</sup>

AF may present in a wide variety of clinical conditions. The optimal management strategy for an individual patient with AF depends on the patient's underlying condition. In some patients, AF occurs in the absence of structural heart disease. Clinical trials involving only or predominantly this type of AF may not be completely applicable to those with concomitant heart disorders. Structural heart disease may influence both the approach to management (ie, rate versus rhythm control) and the treatment options available. For instance, fewer antiarrhythmic drugs are available for use in patients with heart failure (HF) as opposed to AF patients who have structurally normal hearts. In addition, some patients with structural heart disease tolerate AF poorly, and the approach to these patients will differ from those with well-tolerated, minimally symptomatic AF. In this article, we will focus on the management of AF in patients with cardiac conditions commonly associated with the dysrhythmia.

Several basic principles should be considered when management approaches are planned for any patient with AF (Table 1). First, we should acknowledge that no patient wants to be in AF or does better in AF than in native (ie, untreated), stable sinus rhythm. Therefore, restoration and maintenance of sinus rhythm should be considered for every patient. In addition, a stable rhythm, even if that rhythm is persistent AF, is often better than an unstable rhythm with frequent and abrupt changes that may be highly symptomatic. An argument in favor of stability is suggested by data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. A substudy on mechanisms of death showed that the excess mortality associated with the rhythm control strategy in AFFIRM was not due to cardiac causes but rather was attributed largely to noncardiac illnesses.<sup>3</sup> It seems possible that other critical illnesses cause changes in the underlying rhythm, which in a vicious cycle further complicate the patient's problem (Figure 1).<sup>4</sup> As shown by Miyasaka and colleagues<sup>5,6</sup> in studies from Olmstead County, Minnesota, the first episode of AF may be a time of particular

concern because hospitalizations and mortality in the first few months after the first onset of AF are higher than in other periods. These observations lead us to believe that, in most patients, symptoms should be the major determinant behind choices between rhythm and rate control approaches. Stroke is one of the more serious complications of AF. In all patients, stroke risk should be assessed, and the patient's specific disease state as well as more general risk factors including the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VASc scores need to be considered.<sup>7,8</sup> The patient's long-term prognosis must also be considered. Decisions made in an 85-year-old individual might well be inappropriate for someone in their 40s and 50s who would face years of treatment.

### Heart Failure

AF and HF have been recognized as the 2 epidemics of modern cardiovascular medicine.<sup>9</sup> Both conditions frequently coexist because HF is a major risk factor for AF. The risk of AF increases 4.5- to 5.9-fold in the presence of HF, and HF is a more powerful risk factor for AF than advanced age, valvular heart disease, hypertension, diabetes mellitus, or prior myocardial infarction.<sup>10,11</sup> AF prevalence increases as HF severity worsens. AF has been estimated to occur in 5% to 10% of patients with mild HF, 10% to 26% with moderate disease, and up to 50% with advanced HF.<sup>12–15</sup> Among acutely decompensated HF patients, 20% to 35% will be in AF at presentation.<sup>16</sup> In nearly one third, the AF will be of recent onset. Overall, patients with HF develop AF at a rate of 6% to 8% per year, and AF is present in >15% of HF patients.

Controversy exists in regard to the prognostic significance of AF in HF. Although data suggest a worse prognosis for patients with HF and AF compared with those with HF but no AF, the complexities of both conditions make it difficult to determine whether AF is an independent risk factor for mortality or rather is indicative of disease severity. In addition, much of the data on prognosis were derived from early HF trials, and treatment of both conditions has improved since these studies were conducted. However, AF may negatively affect outcomes in HF through adverse hemodynamic changes, a heightened risk of thromboemboli, and exposure of patients to the harmful effects of AF therapies (eg, antiarrhythmic drugs and anticoagulants).<sup>12–14</sup> In addition, HF facilitates atrial remodeling, which promotes

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**Table 1. Basic Principles of AF Management**

- No one wants to be in AF.
- A stable rhythm is generally better than an unstable rhythm.
- Symptoms should drive decision making.
- New-onset AF signals a high-risk period.
- Development of AF generally confers a worse prognosis in most serious diseases.
- Stroke risk must be considered.
- Safety should determine the initial antiarrhythmic drug chosen for rhythm control.
- Therapy for underlying conditions should be optimal and guideline based.

AF indicates atrial fibrillation.

the development and maintenance of AF. HF studies in patients with and without systolic dysfunction have suggested an association between baseline AF and greater long-term morbidity, mortality, and/or hospitalization for HF.<sup>17–20</sup> New-onset AF also appears to have a particularly negative impact on the prognosis of patients with HF. Ahmed and Perry<sup>21</sup> found that among 944 elderly patients hospitalized with HF, new-onset AF was associated with a higher risk of death compared with patients who never developed AF or those with permanent AF. More than 80% of patients hospitalized with HF and new AF died within 4 years of discharge as opposed to 61% to 66% mortality for those without AF or with chronic AF. Interestingly, an analysis of the Carvedilol or Metoprolol European Trial (COMET) found that new-onset but not baseline AF was associated with increased subsequent morbidity and mortality.<sup>18</sup> Thus, new-onset AF appears to indicate a period of increased risk and should prompt careful evaluation and treatment.

For patients presenting with AF and decompensated HF, 3 scenarios are commonly encountered.<sup>4</sup> Some present shortly after the onset of AF, with the AF episode itself precipitating an exacerbation of chronic HF, or, conversely, decompensated HF triggers an acute AF episode. In such patients, the likelihood of early restoration of sinus rhythm (possibly spontaneous) is high if the HF symptoms can be controlled. Another pattern is seen when patients with permanent AF that is usually well rate controlled develop progressive HF and

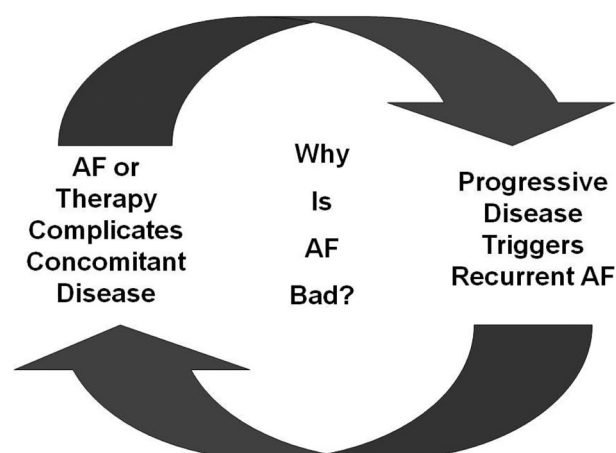
**Table 2. Key Issues to Address in the Management of Acute AF Episodes in Patients With Heart Failure**

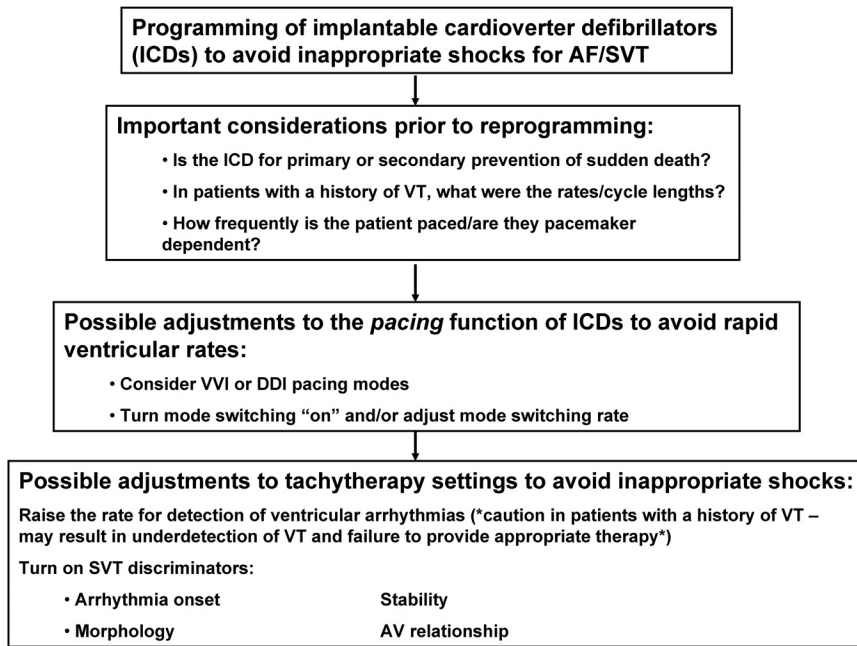
- What is the hemodynamic status of the patient?
- Does the patient have an ICD or pacemaker?
- Does the patient have preserved or reduced systolic function at baseline?
- What is the duration of the AF episode?
- Is the patient already on drugs for anticoagulation and rate or rhythm control?

AF indicates atrial fibrillation; ICD, implantable cardioverter-defibrillator.

present emergently with rapid ventricular rates due to the stress of the episode. In this group, long-term restoration of sinus rhythm will rarely be possible. Finally, some patients develop AF of which they are unaware or for which they do not seek medical attention. During the ensuing days and weeks, these patients may develop a tachycardia-induced cardiomyopathy and present with severe symptoms from acute decompensated HF.<sup>22</sup> Tachycardia-induced cardiomyopathy represents an important subset of patients with nonischemic left ventricular (LV) dysfunction because the ejection fraction (EF) often improves or normalizes with appropriate treatment. In animal models of rapid ventricular pacing, ventricular dysfunction and hemodynamic changes occur as soon as 24 hours, with continued deterioration in ventricular function for up to 3 to 5 weeks.<sup>23</sup> With cessation of pacing (ie, return to normal heart rates), positive hemodynamic changes begin by 48 hours, with recovery of LV contractile function within several weeks. Because tachycardia-induced cardiomyopathy may be difficult to diagnose acutely, practical management of patients presumed to have this condition involves guideline-based treatment of both the culprit dysrhythmia and LV dysfunction.<sup>1,24,25</sup> It is our practice to restore and attempt to maintain sinus rhythm in these patients to prevent acute exacerbations that may result in deterioration of LV function.

Similar to patients without HF, the primary tenets of AF management in HF patients include the following: (1) thromboembolic risk assessment and anticoagulation as appropriate; (2) ventricular rate control; and (3) assessment of the need for conversion to and maintenance of sinus rhythm. However, several unique issues must be considered when HF patients with AF are treated (Table 2).<sup>5</sup> Some patients have implantable cardioverter-defibrillators in place that should be programmed to minimize the risk of inappropriate shocks (Figure 2). In acute episodes, the pacing mode of pacemakers and defibrillators should be adjusted to prevent tracking of high atrial rates with subsequent rapid ventricular pacing. Because most patients with structural heart disease are on multiple medications, a careful review of the medication history is important to prevent overdosage and adverse drug interactions. In most acute situations, the hemodynamic status of the patient and severity of AF-related symptoms should drive the decision for acute restoration of sinus rhythm and management of the ventricular rate. For severely compromised patients, such as those with rate-related ischemia, hypotension, or pulmonary edema known to be due to rapid AF, immediate cardioversion may be indicated. However, among patients with AF and acute decompensated HF, imme-

**Figure 1.** Atrial fibrillation (AF) complicates concomitant disease, and underlying illnesses may exacerbate AF.



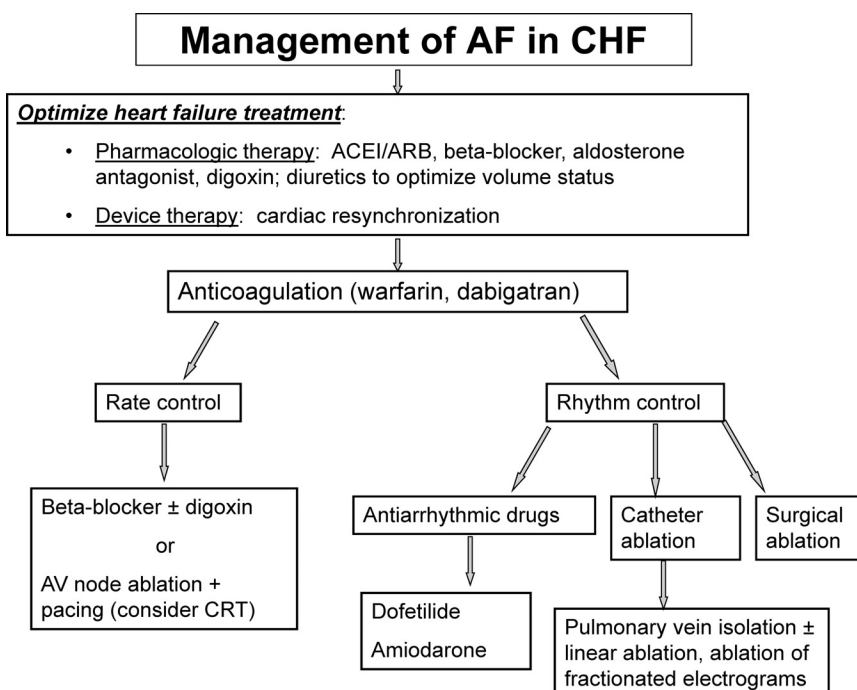
**Figure 2.** Important considerations in patients with implantable devices and atrial fibrillation (AF). SVT indicates supraventricular tachycardia; VT, ventricular tachycardia; and AV, atrioventricular.

diate cardioversion should rarely be the first step. Although cardioversion may transiently restore sinus rhythm, the recurrence rate in the still-decompensated patient will be high.<sup>26</sup> Thus, it is usually better to start with a rate control strategy until the patient's volume/hemodynamic status has improved. Importantly, concurrent optimization of HF treatments must occur for AF therapies to be most effective (Figure 3).

### Stroke Prevention

As outlined in the CHADS<sub>2</sub> index, HF and/or LVEF <35% is a risk factor for stroke in AF.<sup>1,8</sup> The American College of Cardiology/American Heart Association/European Society of

Cardiology guidelines for the management of patients with AF state that, in the presence of only 1 moderate stroke risk factor, such as HF, a daily aspirin or vitamin K antagonist (eg, warfarin) may be used for stroke prevention.<sup>1</sup> HF guidelines, however, recommend dose-adjusted warfarin in all patients with HF and a history of AF.<sup>25</sup> Because HF patients often have additional stroke risk factors, our practice is to routinely recommend systemic anticoagulation for patients with HF. A number of novel anticoagulants are under investigation and may prove effective alternatives to warfarin. The new drugs directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban).<sup>27</sup> The Randomized Evaluation of



**Figure 3.** Overview of the management of atrial fibrillation (AF) in congestive heart failure (CHF). ACEI/ARB indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AV, atrioventricular; and CRT, cardiac resynchronization therapy.

Long-Term Anticoagulation Therapy (RE-LY) study revealed dabigatran 150 mg twice daily to be superior to warfarin for stroke prevention in AF with fewer major bleeding events (with the exception of more gastrointestinal bleeding).<sup>28</sup> There was no increase in HF events among patients taking dabigatran in this study.

For patients presenting with acute episodes, the anticoagulation status must be known before any attempt to restore sinus rhythm unless the episode is definitely known to be of <48 hours' duration.<sup>1,29</sup> A patient in AF for <48 hours may generally undergo cardioversion without a requirement for prior anticoagulation.<sup>1</sup> Patients with an increased risk of stroke, however, such as those with a prior stroke or transient ischemic attack or those with a high CHADS<sub>2</sub> score, should likely receive heparin or low-molecular-weight heparin before cardioversion, with anticoagulation continued for at least 1 month. Dabigatran may be an alternative to heparin or low-molecular-weight heparin in this setting because it has a rapid onset of action and time to peak effect ( $\approx$ 2 hours).<sup>27</sup> If the AF episode has lasted >48 hours and/or the patient does not meet adequate anticoagulation criteria for cardioversion, a transesophageal echocardiogram must be performed or the patient should receive a minimum of 3 weeks of therapeutic oral anticoagulation before cardioversion.<sup>1,29</sup> Although a transesophageal echocardiogram-guided strategy circumvents the need for 3 weeks of anticoagulation before cardioversion, such patients should receive heparin, low-molecular-weight heparin, or, alternatively, dabigatran before cardioversion with continuation of oral anticoagulation for at least 1 month after cardioversion. Our practice is to continue anticoagulation indefinitely in HF patients with AF because of the high recurrence risk.

### Rate Control

Adequate control of the ventricular response to AF improves symptoms by alleviating the negative hemodynamic effects of rapid rates. LV function may improve with adequate long-term rate control, particularly if the LV dysfunction is due to persistent tachycardia.<sup>22</sup> Recent guidelines suggest a goal heart rate of 80 to 100 bpm in managing acute episodes of AF.<sup>29</sup> However, optimal heart rate control may be difficult to achieve in the setting of acutely decompensated HF, in which volume overload and hypoxemia may contribute to rapid rates. In addition, the negative inotropic effects of some rate-controlling agents may worsen HF. Thus, we believe that a realistic heart rate target is  $\leq$ 100 to 120 bpm during the early phases of treatment.<sup>4</sup>

Pharmacological options for ventricular rate control include  $\beta$ -blockers, nondihydropyridine calcium channel blockers, and digoxin. Digoxin slows the ventricular rate primarily by increasing parasympathetic tone on the atrioventricular node. However, conditions associated with high sympathetic tone, such as acute decompensated HF, may easily overcome this effect, rendering digoxin ineffective as monotherapy. Thus, additional medications are often required for adequate rate control in such situations. In addition, if the patient has already been taking digoxin, additional doses should likely be avoided because of the narrow therapeutic window of the drug. In patients who have HF with preserved systolic

function, calcium channel antagonists or  $\beta$ -blockers may be used as first-line therapy. In multiple studies of patients with HF and reduced systolic function, long-term use of  $\beta$ -blockers has been found to lessen the symptoms of HF and reduce the risk of death or HF hospitalization.<sup>30–32</sup> Our preference is therefore to use  $\beta$ -blockers for both acute and long-term rate control in such patients. Carvedilol improves LVEF with a trend toward fewer deaths and HF hospitalizations in patients with concomitant AF and HF and may therefore be the preferred  $\beta$ -blocker for patients with both conditions.<sup>33</sup> In addition, recent HF guidelines recommend against the use of calcium channel antagonists in patients with AF and systolic dysfunction.<sup>25</sup> Our approach in hospitalized patients is to initially administer both digoxin and small doses of an intravenous  $\beta$ -blocker, usually metoprolol in 2.5- or 5-mg increments, while monitoring for signs of decompensation. Ideally,  $\beta$ -blocker therapy would be initiated after the volume status is optimized or greatly improved. If tolerated, standing doses of an oral or intravenous  $\beta$ -blocker may be administered. For outpatients, we initiate therapy with a low-dose  $\beta$ -blocker (eg, carvedilol 3.125 or 6.25 mg twice daily) and follow the patients at regular intervals (often weekly) to ensure drug tolerance and rate control. The dose may then be uptitrated as tolerated. Amiodarone slows the ventricular rate and is occasionally used in combination with other rate-controlling agents if target heart rates have not been achieved or as monotherapy if other drugs are not tolerated.<sup>1</sup> Amiodarone has been shown to increase the likelihood of conversion to sinus rhythm in patients with HF and significantly reduces the ventricular rate among those who remain in AF.<sup>34</sup> The noncardiac side effects of the drug, however, prevent it from being first-line therapy. In addition, amiodarone should not be added if the patient is taking another antiarrhythmic drug that prolongs the QT interval (eg, dofetilide, sotalol), and adequate anticoagulation criteria for cardioversion must be met before administration because amiodarone increases the likelihood of conversion to sinus rhythm. Amiodarone, when used in patients taking warfarin, may increase the international normalized ratio, which should prompt careful monitoring. It is important to note that if adequate rate control and relief of volume overload can be achieved, patients may spontaneously revert back to sinus rhythm, particularly if the AF is of recent onset.

For those in whom the ventricular rate has been controlled and volume status has been optimized, the benefit of restoring sinus rhythm should be considered unless the patient has known long-standing persistent AF. In this situation, the likelihood of restoring and maintaining sinus rhythm is low, and a long-term strategy of rate control with anticoagulation would be appropriate. A rate control strategy may also be appropriate for patients with no or minimal symptoms attributable to AF. As mentioned previously,  $\beta$ -blockers are our preferred agents for rate control because of their long-term beneficial effects on morbidity and mortality among patients with impaired systolic function.<sup>30–32</sup> The combination of a  $\beta$ -blocker and digoxin may be more effective than a single agent.<sup>35,36</sup> Traditional heart rate goals for chronic management of AF have generally been 60 to 80 bpm at rest and 90 to 110 bpm during moderate exercise.<sup>1,29</sup> The Rate Control



Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II (RACE II) study, which recently challenged traditional heart rate parameters, enrolled very few patients with preexisting HF.<sup>35</sup> There was no significant difference in HF events between patients randomized to the strict (resting heart rate <80 bpm; <110 bpm with moderate exercise) or lenient (resting heart rate <110 bpm) rate control groups. Further investigation is required to define the appropriate heart rate goal for ambulatory patients with HF and AF. In the absence of additional data, we believe that a lenient approach is a reasonable starting point for most patients. Patients with refractory symptoms would then be candidates for a trial of strict rate control.

A nonpharmacological method to achieve long-term rate control is ablation of the atrioventricular junction and implantation of a permanent pacemaker. The procedure may be indicated for medically refractory AF when sinus rhythm cannot be maintained and rate control cannot be achieved. Atrioventricular junction ablation and permanent pacing have been shown to improve LV function, exercise capacity, and quality of life in patients with medically refractory AF.<sup>37</sup> Chronic right ventricular pacing, however, creates a dyssynchronous pattern of ventricular activation that may worsen HF. Thus, for patients with a baseline LVEF  $\leq$ 45% or mild to moderate HF symptoms at baseline, it is preferable to implant a biventricular pacing system at the time of atrioventricular junction ablation to avoid chronic right ventricular pacing alone.<sup>38</sup>

### Rhythm Control

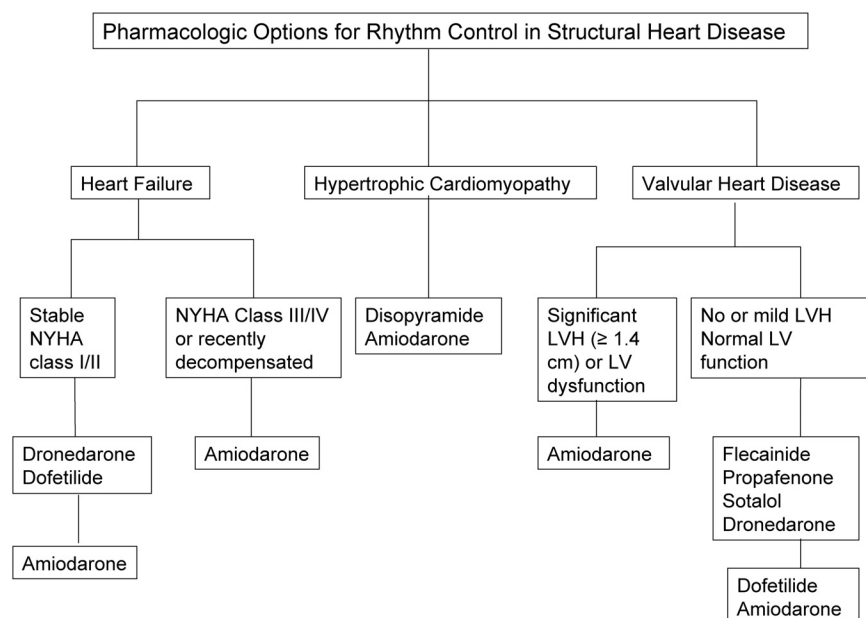
Data from prospective randomized controlled trials demonstrating a survival advantage with pharmacological maintenance of sinus rhythm in HF are lacking. The AFFIRM and RACE trials found that maintenance of sinus rhythm in mixed AF populations provided no benefit with a trend toward harm.<sup>39,40</sup> Extrapolation of these results to patients with HF must be done with caution, however, because only a small percentage of patients in both trials had reduced LVEF or HF symptoms at baseline. For instance, a subset analysis of AFFIRM found no significant improvement in mortality, hospitalization, and New York Heart Association class with rhythm control among patients with LV dysfunction, although only 339 patients had symptoms greater than or equal to New York Heart Association class II.<sup>41</sup> Some publications, however, have suggested an association between sinus rhythm and improved survival in HF patients. An analysis of the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) found that HF patients treated with amiodarone who converted to and maintained sinus rhythm had improved survival.<sup>34</sup> Maintenance of sinus rhythm in patients with an EF <35% was also associated with a significant reduction in mortality in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trials.<sup>42</sup> The mortality benefit was present in both the dofetilide and placebo groups. It is possible, however, that these observations favoring sinus rhythm may only represent a healthy responder phenomenon.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial was the first prospective randomized trial compar-

ing rate and rhythm control in HF patients.<sup>43</sup> The study randomized 1376 patients with LVEF <35%, HF symptoms, and a history of paroxysmal or persistent AF to either rhythm control (primarily amiodarone) or rate control ( $\beta$ -blockers). At a mean follow-up of 37 months, there was no significant difference in the primary outcome of death from cardiovascular causes between the rhythm and rate control groups (27% versus 25%, respectively) by intention-to-treat analysis. There was also no advantage with regard to HF hospitalization or stroke in the rhythm control group. In a subsequent on-treatment efficacy analysis of AF-CHF, neither a rhythm control strategy nor the presence of sinus rhythm was associated with improved outcomes.<sup>44</sup> The AF-CHF trial therefore appears to extend the general findings of AFFIRM to patients with HF.

In the absence of definitive data demonstrating a survival advantage with maintenance of sinus rhythm in HF patients, the decision to adopt a rhythm control approach is driven largely by symptoms. Some patients, particularly those with structural heart disease, may tolerate AF poorly (ie, develop hemodynamic instability or pulmonary edema or experience rapid heart rates that are difficult to control), and a rhythm control strategy may be preferable in such patients. Additional issues when a rhythm control strategy is considered include drug tolerance and the frequency of recurrent episodes. Those with frequent episodes of highly symptomatic AF may feel better if sinus rhythm can be maintained. We usually make at least 1 attempt to maintain sinus rhythm in any patient with more than mild symptoms associated with AF.

The primary pharmacological agents for rhythm control in patients with AF and HF are the class III antiarrhythmic drugs (Figure 4). Amiodarone has the greatest efficacy with regard to maintenance of sinus rhythm, although its widespread use is limited by noncardiac toxicities.<sup>1,29,45</sup> Although amiodarone may cause bradycardia and prolongation of the QT interval, it rarely causes ventricular proarrhythmia. It is worth noting, however, that patients with New York Heart Association class III symptoms randomized to amiodarone in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) had an increased mortality relative to placebo.<sup>46</sup> The reasons for this finding are unclear, and it has not been our practice to withhold amiodarone from such patients. The DIAMOND congestive heart failure trial found dofetilide reasonably safe and effective in HF patients.<sup>47</sup> Dofetilide was more effective than placebo in maintaining sinus rhythm with no effect on all-cause mortality but resulted in a lower combined end point of mortality and HF hospitalization. Dronedarone is another potential agent for rhythm control in AF. It is modestly effective in maintaining sinus rhythm and, when AF does occur, has ventricular rate-slowing properties. In 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 (ATHENA), which included a mixed population with paroxysmal and persistent AF, dronedarone reduced the primary end point (composite of hospitalization due to cardiovascular events and death) as well as deaths from cardiovascular causes, primarily as a result of a reduction in arrhythmic death.<sup>48</sup>



**Figure 4.** Pharmacological options for rhythm control in structural heart disease. NYHA indicates New York Heart Association; LVH, left ventricular hypertrophy; and LV, left ventricular.

Among those enrolled, 21% had a history of New York Heart Association class II or III symptoms, and 12% had LVEF <45%. Patients with HF who received dronedarone had a benefit similar to that of the entire group. The drug should not be used, however, in patients with clinically significant class II to IV or recently decompensated heart failure, nor should it be used for rate control in patients with permanent atrial fibrillation because of the increased mortality and adverse events observed in such patients in the Antiarrhythmic Trial With Dronedaron in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decreased (ANDROMEDA) and Permanent Atrial Fibrillation Outcome Study using Dronedaron on Top of Standard Therapy (PALLAS).<sup>49,49a</sup> Class Ia and Ic agents have negative inotropic properties and may increase the risk for sudden death in patients with HF because of proarrhythmic effects and should thus be avoided.<sup>1,29</sup>

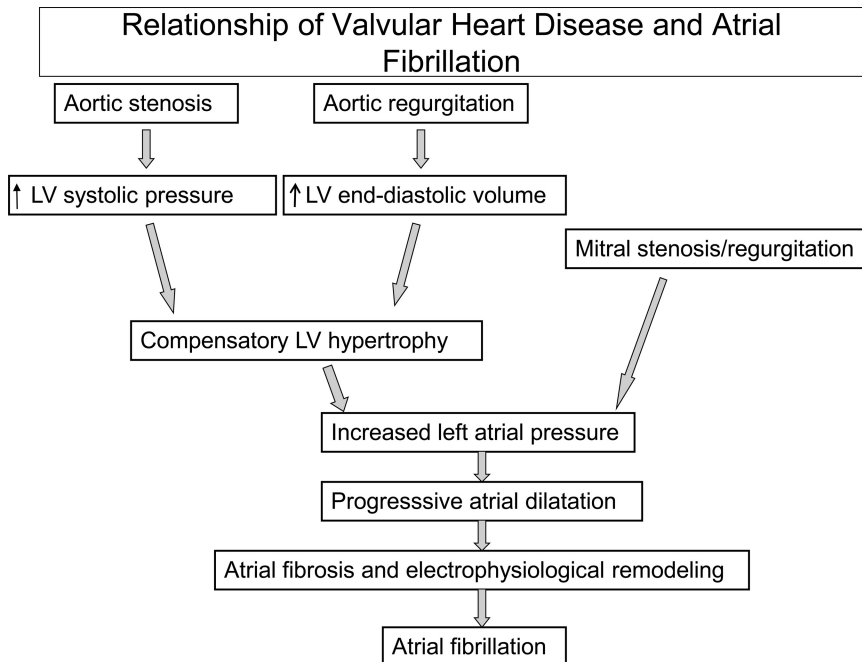
Nonpharmacological therapies, primarily catheter and surgical ablation, are also options for maintaining sinus rhythm. Catheter ablation is generally employed in patients with recurrent, symptomatic AF that is drug refractory (ie, failure of 1 or more antiarrhythmic agents).<sup>1</sup> Several studies have demonstrated a higher likelihood of maintaining sinus rhythm with catheter ablation than drug therapy.<sup>50–54</sup> These studies demonstrate an improvement in exercise capacity and quality of life as well as improvement or reversal of LV dysfunction in some cases. Pulmonary vein isolation remains the basis for all catheter ablation procedures. Further investigation is needed to determine whether additional ablation (eg, left atrial linear ablation) improves long-term efficacy in HF patients. The Comparison of Pulmonary Vein Antrum Isolation Versus AV Nodal Ablation With Biventricular Pacing for Patients With Atrial Fibrillation With Congestive Heart Failure (PABA CHF) trial compared catheter ablation with atrioventricular node ablation and biventricular pacing in 81 patients with HF and drug-refractory AF.<sup>54</sup> Ablation was superior with regard to quality of life, exercise capacity, and

improvement in LV function after 6 months of follow-up. New ablation technologies (eg, laser ablation, cold and hot balloons) remain to be studied extensively in HF patients and may yield higher success rates. In addition, minimally invasive surgical techniques are advancing and, used either alone or in combination with endocardial catheter procedures, may have a role in the management of AF patients with HF. Whether a rate or rhythm control strategy is pursued, it is imperative that the patient's stroke risk be considered and anticoagulation continued when appropriate.

### Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by unexplained LV hypertrophy and ventricular myocyte disarray.<sup>55,56</sup> HCM is caused by a number of mutations in genes usually encoding or affecting some portion of the contractile apparatus. The prevalence of HCM in the general population approximates 0.16% to 0.3%.<sup>56–58</sup> AF is common in HCM, with the arrhythmia often presenting in young adults. In a series of 480 patients followed at an HCM center, AF was seen in 22% of patients overall, with an annual new event rate of 2%.<sup>59</sup> Although myocyte disarray is not seen in the atria of patients with HCM, several characteristic features of the disease, including atrial dilatation and fibrosis, set the stage for developing AF.<sup>60</sup> Predisposing factors include elevated LV end-diastolic pressures characteristic of many patients with HCM and a variable amount of mitral regurgitation due to systolic anterior motion of the mitral valve in patients with obstruction. Symptoms from AF in patients with HCM are often severe. HCM patients with AF are at increased risk for stroke, death, and symptomatic congestive HF.<sup>59,60</sup> Rapid rates during AF may lead to hemodynamic deterioration with degeneration to ventricular fibrillation.<sup>61,62</sup> In contrast to most other conditions, AF may truly be a life-threatening arrhythmia in HCM.

Because only 1 or 2 episodes of paroxysmal AF may increase the risk of thromboembolic events, the threshold for



**Figure 5.** Relationship between valvular heart conditions and atrial fibrillation. LV indicates left ventricular.

anticoagulation should be low.<sup>63</sup> Systemic anticoagulation with warfarin is recommended indefinitely for HCM patients with paroxysmal or persistent AF.<sup>63</sup> Dabigatran and other new oral anticoagulants would be alternatives, although there are no specific data on their use in HCM.  $\beta$ -Blockers and calcium channel antagonists may be effective for controlling the heart rate in AF. Although there are no data from long-term randomized controlled trials to guide therapy,  $\beta$ -blockers are generally the initial choice to relieve symptoms in patients in sinus rhythm with LV outflow tract obstruction.<sup>56,63</sup> Verapamil also improves symptoms from outflow tract obstruction, but death has been reported in HCM patients with severe symptoms, pulmonary hypertension, and severe outflow obstruction who are given verapamil.<sup>56</sup> For these reasons, we preferentially use  $\beta$ -blockers for rate control, particularly in patients with outflow tract obstruction. Implantable cardioverter-defibrillators should be programmed to minimize the risk of shocks due to atrial arrhythmias, as in patients with HF (Figure 2).<sup>64</sup> Supraventricular arrhythmias are the most common reason for inappropriate implantable cardioverter-defibrillator discharges in these patients.<sup>64</sup>

Studies of patients with HCM have shown that chronic AF is associated with a worse prognosis (ie, greater probability of HCM-related death, functional impairment, and stroke) than paroxysmal AF.<sup>59</sup> Therefore, a rhythm control strategy is usually preferred, at least for initial management.<sup>56,63</sup> Hypertrophied myocardium is prone to the proarrhythmic effects of many antiarrhythmic drugs. Consequently, many commonly used antiarrhythmics, such as the class Ic and most class III agents, are best avoided. Amiodarone is generally regarded as the most effective antiarrhythmic drug for maintaining sinus rhythm in HCM and is the recommended agent for patients with LV wall thickness  $\geq 1.4$  cm (Figure 4).<sup>1,63</sup> However, no controlled studies demonstrating the efficacy of amiodarone in this condition are available. Disopyramide has negative inotropic effects and may be useful even in HCM patients

with sinus rhythm.<sup>65</sup> It may be worth a trial in patients with AF, particularly in young patients in whom long-term therapy with more toxic agents might not be desired. There is as yet no published experience with dronedarone in patients with HCM.

Several studies have reported on the effects of catheter ablation for AF with HCM.<sup>66–68</sup> Pulmonary vein isolation with or without additional linear lesions is the technique usually employed. Bunch et al<sup>66</sup> reported total elimination of AF in 62% of HCM patients at the 1-year time point, whereas Di Donna et al<sup>67</sup> reported only a 28% single-procedure success rate. However, the latter group eventually achieved a 67% success rate at a mean follow-up of  $29 \pm 16$  months with the use of additional ablation procedures and/or antiarrhythmic drugs.<sup>67</sup> In both series, persistent AF and increased left atrial diameter were predictors of recurrence after ablation.

### Valvular Heart Disease

AF commonly complicates valvular heart disease, particularly left-sided valvular lesions. Left atrial pressure and/or volume overload from aortic or mitral valve disease leads to structural changes in the left atrium (Figure 5). Chronic atrial stretch results in fibrotic changes that secondarily alter atrial electrophysiology and predispose to the development of atrial arrhythmias.

AF frequently complicates rheumatic mitral valve disease, developing in at least 30% to 40% over long-term follow-up in early studies of medically treated patients.<sup>69–71</sup> AF also occurs frequently in patients with mitral regurgitation regardless of the underlying valvular pathology. In patients with mitral regurgitation due to flail leaflets, AF has been observed in 18% and 48% of patients at 5- and 10-year follow-up, respectively.<sup>72</sup> With mitral regurgitation due to mitral valve prolapse, AF may develop in nearly 44% at 9 years. AF occurs more frequently in patients aged  $\geq 65$  years and with left atrial enlargement ( $\geq 50$  mm).<sup>69,72</sup> For instance, AF has been observed to occur in 75% of patients aged  $\geq 65$  years

with mitral regurgitation and atrial enlargement followed up to 10 years.<sup>72</sup> AF in aortic valve disease has been less well studied, but AF often complicates uncorrected aortic stenosis or regurgitation.

Importantly, the development of atrial arrhythmias is independently associated with an increased risk of adverse events in patients with mitral valve disease.<sup>70–72</sup> The increased mortality risk is, in large part, related to the significantly increased risk of stroke in patients with mitral valve disease who develop AF.<sup>71–74</sup> It is important to note that the CHADS<sub>2</sub> risk score was developed for patients with nonvalvular AF. Thus, for patients with valve disease, particularly rheumatic mitral valve disease, the CHADS<sub>2</sub> score does not apply. All such patients with AF, barring a contraindication, should receive systemic anticoagulation to prevent thromboembolic events.

Because of the adverse prognostic effects of AF in patients with mitral valve disease, its development affects the timing of surgery to correct these valve lesions. The American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease recommend percutaneous mitral balloon valvotomy for patients with moderate or severe mitral stenosis with new-onset AF (class IIb recommendation).<sup>75</sup> Mitral valve surgery is a class IIa recommendation for asymptomatic patients with chronic severe mitral regurgitation and preserved LV function who develop AF.<sup>75</sup>

As in other conditions, acute episodes of AF in patients with valvular heart disease should be managed according to hemodynamic stability and symptoms. There may be significant hemodynamic consequences from the development of AF resulting from the loss of atrial contribution to ventricular filling and from rapid ventricular rates shortening the diastolic filling period. Patients with obstructive valvular lesions and/or ventricular hypertrophy may be most vulnerable and potentially benefit from more aggressive strategies, including early restoration of sinus rhythm. Acute management includes anticoagulation to minimize stroke risk and pharmacological measures to control the heart rate.  $\beta$ -Blockers or nondihydropyridine calcium channel blockers are the first-line agents for rate control. Depending on the duration of AF and the hemodynamic status, cardioversion may be considered to restore sinus rhythm. It is important to continue anticoagulation for at least 1 month after cardioversion, with the decision regarding long-term anticoagulation based on the risk of recurrence.

Recurrent AF may be treated with a rate or rhythm control strategy based on the patient's symptoms. Class Ic or III antiarrhythmic agents may be used to maintain sinus rhythm in patients with valvular disease and preserved LV function (Figure 4). It is important to note that calcific, degenerative aortic stenosis has been associated with an increased risk of myocardial infarction and cardiovascular mortality.<sup>76</sup> Such patients should be screened for coronary disease before the initiation of class Ic drugs. In addition, patients with significant ventricular hypertrophy or dysfunction secondary to valvular disease are not candidates for Ic or most class III agents because of possible proarrhythmia. Amiodarone is the preferred agent if the LV wall thickness measures  $\geq 1.4$  cm.<sup>1</sup>

If antiarrhythmic drugs fail and sinus rhythm is still desired, catheter or surgical ablation may be options. Surgical Maze procedures may be considered for patients undergoing cardiac surgery to correct their valve defect(s). Modest long-term success rates have been reported after surgical Maze procedures in conjunction with mitral valve surgery.<sup>77–80</sup> Handa et al<sup>77</sup> reported that 82% of patients undergoing mitral repair with a surgical Maze procedure maintained sinus rhythm at 2 years as opposed to 53% who had a mitral repair but no Maze procedure. Patients in the Maze group also had lower rates of stroke in follow-up. Abreu Filho et al<sup>80</sup> evaluated the combination of mitral surgery and a modified Maze procedure in patients with rheumatic valve disease and permanent AF. With the use of cooled-tip radiofrequency ablation, 79% of patients receiving a modified Maze III procedure maintained sinus rhythm at 12 months compared with only 27% of the nonablation group. Predictors of persistent AF include long-standing AF before surgery ( $>1$  year) and atrial enlargement ( $>50$  mm).

### Congenital Heart Disease

Congenital heart disease constitutes the most prevalent form of major birth defects, affecting  $>1\%$  of newborns.<sup>81</sup> With improvements in diagnosis and treatment, more individuals with congenital heart disease survive childhood and live to advanced ages. Atrial arrhythmias are frequently encountered in these patients as a result of both their structural heart disease and their corrective or palliative surgical procedures. Among atrial arrhythmias, intra-atrial reentry occurs most frequently. Cavotricuspid isthmus-dependent flutter is common, as is intra-atrial reentry involving areas of slow conduction from fibrosis around atriotomy scars (particularly the right atrial lateral wall) or patches from prior cardiac surgical procedures.<sup>82–84</sup> When AF occurs in patients with congenital heart disease, it is often a late finding, and consequently it may be difficult to restore and maintain sinus rhythm.<sup>82,83</sup>

A large population-based analysis in Canada evaluated the prevalence, lifetime risk, and clinical impact of atrial arrhythmias in  $>38\,000$  individuals with congenital heart defects followed from 1983 to 2005.<sup>82</sup> The 20-year risk of developing atrial arrhythmias was 7% in a 20-year-old patient and 38% in a 50-year-old subject. Atrial arrhythmias developed in 15% of the total population of adults with congenital heart disease. More than 50% of those with severe congenital heart disease who survived past 18 years of age developed atrial arrhythmias by age 65 years. Others have reported a similar 25% to 30% prevalence of AF in adult patients with congenital heart disease.<sup>83</sup>

Atrial arrhythmias have a significant impact on morbidity and mortality and can cause significant functional decline, particularly in patients with tenuous hemodynamics or lesions that obstruct cardiac flow. In the aforementioned study, atrial arrhythmias conferred a 2.5-fold higher risk of adverse events with a near 50% increase in mortality.<sup>82</sup> Patients with congenital heart disease who developed atrial arrhythmias had a  $>50\%$  increased stroke risk and a 2- to 3-fold increased risk of HF and occurrence of cardiac interventions (eg, arrhythmia surgery, cardiac catheterization, and cardiac surgery). The heightened morbidity and mortality related to



atrial arrhythmias were detectable in the first year after development and increased with time. Defects most associated with atrial arrhythmias were, in decreasing order of prevalence, Ebstein's malformation of the tricuspid valve, transposition of the great arteries, univentricular hearts, atrial septal defect, and tetralogy of Fallot. AF is more likely among patients who have undergone surgery but who have significant residual left-sided hemodynamic defects as well as those who have never had their defects repaired.<sup>84</sup> Additional risk factors for developing atrial arrhythmias include advancing age, HF, lesion complexity, pulmonary insufficiency, and right atrial size.<sup>85</sup>

The management of patients with congenital heart disease and AF is similar to the management of AF encountered in other forms of heart disease.<sup>1,86</sup> Acute management involves anticoagulation and rate control as needed, followed by consideration of cardioversion to restore sinus rhythm. Patients with tenuous hemodynamics at baseline or those with obstructive cardiac lesions may tolerate AF poorly and warrant more aggressive therapies. Thus, an attempt at maintaining sinus rhythm may be necessary in some patients. Class III antiarrhythmic agents may protect against recurrent AF. Among 44 patients with congenital heart disease and atrial arrhythmias, sotalol completely maintained sinus rhythm in 41% and offered a partial response in 34%.<sup>87</sup> Of note, 2 patients died in the study. One experienced torsades de pointes during sotalol initiation, and a second patient died 4 months after drug initiation but 3 weeks after the last increase in drug dose. Modest success has been reported with dofetilide in 20 adult patients with congenital heart disease and refractory atrial arrhythmias.<sup>88</sup> However, only 11 patients remained on dofetilide at 1 year, and only 7 (35% of the original study group) had complete arrhythmia control. Two patients experienced torsades de pointes during initiation of therapy, and 1 had excessive QTc prolongation necessitating drug discontinuation. Thus, one must be vigilant about monitoring the QTc interval when starting or adjusting the doses of sotalol or dofetilide. Amiodarone may also be used, but the risk of noncardiac toxicities limits its routine application, particularly in young patients with an otherwise good prognosis who may require therapy for many years.

Nonpharmacological therapies for rhythm management include catheter or surgical ablation. Successful control of AF has been reported after combined right and left atrial Maze procedures, which may be considered in patients requiring cardiac surgery to correct hemodynamic issues.<sup>86</sup> No large trials have examined catheter ablation of AF in the adult congenital heart disease population. Such procedures should likely only be undertaken by operators with experience in working with patients who have complex anatomy and unusual arrhythmia substrates.

### Inherited Arrhythmia Syndromes

Lamin A/C deficiency, PRKAG2 mutations, and certain forms of the long QT syndrome (LQTS), short QT syndrome, and Brugada syndrome, among others, may be complicated by AF.<sup>89–91</sup> Lamin A/C deficiency may be responsible for up to 10% of familial dilated cardiomyopathy cases.<sup>89</sup> In the early stages of the disease, lamin A/C–deficient patients have

a characteristic ECG with low-amplitude P waves and prolonged PR interval but relatively normal QRS complex.<sup>92</sup> Most patients presenting at >30 years of age have conduction system disease and ultimately often require pacemaker placement. Patients subsequently develop AF and dilated cardiomyopathy as the disorder progresses. There are few data to guide therapy for patients with lamin A/C deficiency and AF. A high incidence of thromboembolic events has been noted in lamin A/C–deficient patients with AF (30%), and therefore anticoagulation is warranted in all such patients.<sup>93</sup> Because of the frequent development of dilated cardiomyopathy,  $\beta$ -blockers may be the best agents for heart rate control. Caution must be exercised when one uses antiarrhythmic drugs because of both conduction system disease and ventricular dysfunction. Class Ia and Ic agents are best avoided in these patients. Because many lamin A/C–deficient patients ultimately require pacemakers as a result of progressive conduction system disease, these patients may be best served by a rate control and anticoagulation strategy with biventricular pacing as needed.

Patients with PRKAG2 cardiac syndrome also frequently develop AF.<sup>90</sup> PRKAG2 cardiac syndrome results from a mutation in the  $\gamma$ -2 regulatory subunit (PRKAG2) of AMP-activated protein kinase, which plays a role in the regulation of the glucose metabolic pathway in muscle.<sup>90</sup> Patients develop ventricular preexcitation, conduction system disease, and cardiac hypertrophy. Affected patients often present with presyncope, syncope, or palpitations in late adolescence or the third decade of life. Symptoms are typically attributable to paroxysms of preexcited AF or flutter. Over time, conduction system disease may necessitate pacemaker implantation. Cardiac hypertrophy is detectable in 30% to 50% of affected patients, and chronic AF is present in >80% after age 50 years. There are no prospective data to guide therapy of AF in PRKAG2 cardiac syndrome patients. As with lamin A/C–deficient patients, it may be most prudent to ensure adequate anticoagulation for stroke prevention with the use of rate control medications as needed.

Both the long and short QT syndromes have been associated with an increased risk of AF.<sup>94–98</sup> LQTS patients have been found to have prolonged atrial action potential durations and effective refractory periods along with a predisposition for afterdepolarizations resulting in polymorphic atrial arrhythmias.<sup>94</sup> The exact prevalence of AF in LQTS is difficult to quantify, although there appears to be an increased risk of early-onset AF. Among LQTS patients followed at the Mayo Clinic, a 17.5-fold increased risk of early-onset AF (aged <50 years) compared with population-based norms has been observed.<sup>95</sup> There are no prospective trials to guide therapy of AF in LQTS patients, although drugs that prolong the QT interval should be avoided. Of note, complete suppression of AF with mexiletine has been reported in a 19-year-old patient with type 1 LQTS.<sup>96</sup> The short QT syndrome is related to gain-of-function potassium channel mutations that lead to shortened atrial and ventricular refractory periods.<sup>97,98</sup> Consequently, patients are at an increased risk of atrial and ventricular arrhythmias. A summary of 13 patients with short QT syndrome identified paroxysmal or persistent AF in 9 (70%), with the first symptomatic episode of AF occurring at

a mean age of 41 years.<sup>97</sup> In 7 of 13 (53%), AF was the first symptom of short QT syndrome. Hydroquinidine and propafenone have been effective in treating AF complicating the short QT syndrome.<sup>98</sup>

A high incidence of AF has also been identified in patients with the Brugada syndrome. A report of 115 patients with type 1, 2, and 3 Brugada ECG patterns found paroxysmal AF in 15 of 28 type 1 Brugada patients (53%) but no AF in patients with the type 2 or 3 ECG pattern.<sup>99</sup> The most important predictor of AF in Brugada syndrome was the occurrence of previous life-threatening cardiac events. Careful programming of implantable defibrillators is essential in patients with inherited arrhythmia syndromes to avoid inappropriate shocks for AF (Figure 2).

## Conclusions

A number of cardiac conditions predispose to the development of AF. A complex interaction often develops between AF and the arrhythmia substrate, and development of AF generally confers an adverse prognosis in most situations, primarily related to an increased risk of stroke. New-onset AF may signal a period of particularly increased risk and should prompt careful evaluation and treatment. Management of AF in the setting of concomitant cardiac disease primarily involves assessment of the stroke risk and anticoagulation as appropriate along with reasonable control of the ventricular response. Decisions regarding rhythm control are largely dictated by symptoms. When pursued, rhythm control should initially be attempted pharmacologically, with safety primarily determining the agent chosen. Catheter and surgical ablation are reserved as second-line therapies for patients in whom at least 1 antiarrhythmic drug has failed. Importantly, underlying diseases must be optimally managed with guideline-based therapies for AF treatments to be most effective.

## Disclosures

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