Purpose: To review current management approaches for rate and rhythm control in atrial fibrillation (AF) and to describe potential pharmacologic strategies for the future.

Epidemiology: More than 2 million people in the United States have AF and the prevalence is as high as 10% in those over 80 years of age. Stroke risk is increased about 5-fold in those with AF.

Review Summary: Atrial fibrillation is common, especially in the elderly, and is associated with significant morbidity and mortality. In particular, the risks of cardioembolic stroke and heart failure are elevated in those with AF. The goals of therapy in AF are to reduce the risk of stroke, AF recurrences, and heart failure. In addition to anticoagulation with aspirin or warfarin, the main options for rate control include calcium channel blockers, β-blockers, digoxin, and atrioventricular node ablation. Maintaining sinus rhythm to reduce symptoms, stroke risk, and progression of adverse atrial remodeling is the other main strategy for AF therapy.

Type of Available Evidence: Nationally recognized treatment guidelines, randomized controlled studies, retrospective analyses, systematic reviews/meta-analyses.

Grade of Available Evidence: Good (guideline-documented agents used in rate and rhythm control); fair (studies exploring effects of statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in AF).

Conclusion: Patients with AF have several pharmacologic options for rate or rhythm control in AF. Researchers have recently identified new mechanisms involved in AF and studies may soon lead to new forms of combination therapy that are more effective and safer in preventing onset or recurrences of AF.


Atrial fibrillation (AF) is one of the most common and challenging conditions presenting to family practitioners, internists, and cardiologists. Although evidence-based algorithms are available to guide clinicians in the diagnosis and treatment of patients with this arrhythmia, the management task can be complex. In part, subtle symptomatology, variability of patient presentations, and potential for associations with other diseases may pose a diagnostic challenge. In addition, response to many antiarrhythmic drugs is highly variable and unpredictable in terms of efficacy, tolerability, and safety. After a discussion of the epidemiology, clinical implications, and management strategies for AF, this review aims to update clinicians on several studies that offer insight into the pathophysiology of AF—including the roles of inflammation, sex, and genetic susceptibility. [Editor’s Note: Nonpharmacologic options for AF management will be explored in a follow-up article, to appear in an upcoming issue of JHASM.]
DEFINITIONS

Atrial fibrillation is a common type of supraventricular tachyarrhythmia that involves continuous electrical activity spreading across the atria, causing the atria to fibrillate at rates of 300 to 600 beats per minute (bpm). This disorganized atrial activity is captured on the electrocardiogram (ECG) as rapid waves of varying size and shape in place of classic P waves. The ventricular rhythm in this setting often is characterized as “irregularly irregular,” with the exact response determined by the status of the atroventricular (AV) node, vagal and sympathetic tone, and drugs.16

The accepted terminology for AF classifies the disease by its pattern of presentation into paroxysmal AF, which is a self-terminating AF; persistent AF, which is a sustained AF that requires electric or pharmacologic cardioversion to restore sinus rhythm; and permanent AF, which indicates a complete inability to maintain sinus rhythm.1 The self-terminating episodes generally last fewer than 7 days and most fewer than 24 hours in duration. Both the paroxysmal and persistent AF varieties often are recurrent. Whereas these categories are used every day by electrophysiologists, most clinicians recognize that their patients often straddle categories—for example, alternating between paroxysmal and persistent—and therefore may find other descriptors more germane. For example, AF directly precipitated by conditions such as surgery, myocarditis, or hyperthyroidism are sometimes called secondary AF; the term “lone AF” is used to describe a presentation in a patient with no underlying structural heart disease, and nonvalvular AF indicates an absence of valve disease.

EPISEDEMOLOGY

More than 2 million individuals in the United States have AF.14 The overall prevalence of about 0.4% increases dramatically with age to about 2% at ages 60 to 69, to 4.6% at ages 70 to 79, and to 9% or 10% in those 80 years or older.15,16 About 1 in 4 individuals over the age of 40 will experience AF.9 As the US population ages over the next several decades, and as more of these older individuals will be long-term survivors of myocardial infarctions and heart failure, the overall AF prevalence is expected to increase to more than 5 million.7

This rising prevalence is of concern because of the significant morbidity, mortality, and costs associated with AF. In particular, and notwithstanding more widespread use of prophylaxis with anticoagulants, about 1 of every 6 stroke patients in the United States is found to have AF.9 Overall, AF increases stroke risk about 5-fold.10,11 In terms of overall mortality, the relative risks for death in men and women with AF are 1.5 and 1.9, respectively,12 and AF remains a strong predictor of mortality in conditions such as hypertrophic cardiomyopathy.13 As the leading cause of hospitalization for arrhythmias in the United States14 and as a major contributor to strokes, chronic heart failure, and complications following open-heart surgery and diminished quality of life, AF also results in high economic costs.15

PRESENTATION AND ASSOCIATED CONDITIONS

Many patients with AF have no symptoms and are completely unaware of an abnormal heart rhythm. In fact, recent data gleaned from pacemaker and implanted defibrillator interrogated data indicate that surprisingly high percentages of patients with paroxysmal AF or even with no history of AF have frequent asymptomatic episodes of fibrillation16-19; similarly, many patients presenting with stroke are found to have asymptomatic AF.

When they do occur, the most commonly reported symptoms of AF include palpitations—a disturbing awareness of the rapid and irregular heartbeat—and classic indications of hemodynamic compromise such as chest pain, dyspnea, fatigue, or lightheadedness.1 Even in patients who are minimally symptomatic, however, sustained AF may lead to signs of heart failure or cardiomyopathy.

Framingham data from the 1970s to the 2000s indicate that patients with different cardiac conditions have different rates of AF prevalence. These AF rates include, for example: 10% to 40% in heart failure, 20% in rheumatic heart disease, 1% to 2% in coronary artery disease, 5% to 10% in hypertension, 2% to 3% in thyrotoxicosis, and 5% to 40% in postoperative aortocoronary artery bypass surgery.20-22 (Note that it is mainly those bypass patients who are using periopera-
ative β-blockers or amiodarone who have the lower rates of AF. Conversely, patients with AF have relatively high rates of hypertension (56%), coronary artery disease (19%), valve disease (18%), thyroid disease (11%), sinus node dysfunction (11%), dilated cardiomyopathy (10%), and alcohol abuse (8%).

The association of AF with heart failure deserves special mention. Substudy analysis of several large trials now confirms that AF prevalence increases in parallel with worsening New York Heart Association functional class (Figure 1), from less than 5% in Class I to 25% to 50% in Class III-IV.23 The prevalence of AF is especially high in older patients and in women with heart failure, whereas it may be lower in African Americans.24

This tight association of AF with heart failure may reflect an underlying pathophysiologic connection in certain patients whereby increasing atrial pressure leads to atrial stretch and subsequent fibrosis. This substrate may result in altered electrophysiologic properties and subsequent fibrillation. Conversely, heart failure due to AF usually is caused by uncontrolled ventricular rate. Whatever the possible mechanisms linking AF and heart failure, it is clear that patients with heart failure as well as those requiring hemodialysis25 have elevated mortality risk if they also have AF.26 Though the impact of restoration of normal sinus rhythm in the setting of heart failure or chronic renal insufficiency is unclear, recent evidence suggests that heart failure medications such as angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) may actually diminish overall mortality in part by preserving normal sinus rhythm.

**EMERGING RISK FACTORS AND THERAPEUTIC TARGETS**

Recent studies continue to shed light on possible new associations of AF with disease states or risk factors. Based on preliminary evidence and the related therapeutic implications, systemic inflammation is one of the most exciting areas of active investigation. The Cardiovascular Health Study evaluated the relationship of AF with C-reactive protein (CRP), a blood marker of inflammation, in 5806 subjects who were followed for 7 years.27 These researchers found that higher CRP levels (measured using ultrasensitive enzyme-linked immunosorbent assay) were strongly associated with the presence of AF; for example, AF prevalence was 3.7% in those in the lowest CRP quartile (<0.97 mg/L) compared with 7.4% in those in the fourth CRP quartile (>3.41 mg/L) (P = .002). They also found that baseline CRP predicted the future development of AF as well as the rate of AF-free survival (Figure 2).

Other large prospective studies have now confirmed that high levels of CRP independently predict the likelihood of AF.27 Related investigations also have shown that CRP levels are higher in those with persistent AF versus those with paroxysmal AF28,29; CRP levels are higher in those with symptomatic AF versus those with asymptomatic AF;27 and increased CRP levels predict failure of cardioversion to restore cardiac rhythm29,30 as well as a reduced ability to maintain sinus rhythm after successful cardioversion.31,32 Although the cause of elevated CRP levels in AF patients is unknown, the underlying mechanism may involve inflammation-based atrial remodeling. The implications of this line of research have already been pursued in studies evaluating the efficacy of anti-inflammatory agents such as aspirin and statins in treating AF, and preliminary results are discussed in the following section.

Several studies have now defined the nature of AF risk in women. Although the prevalence of AF is higher in men, the overall risk of mortality associated with AF may be higher in women.33 In general, women with heart failure have almost double the risk of associated AF, and women with AF also tend to be more symptomatic with lower quality of life and higher ventricular rates, stroke risk, and proarrhythmic risk (ie, while taking antiarrhythmic drugs).34 One study of sex effects in therapy for persistent AF showed that 192 women responded much better to rate control than to rhythm control (P < .0001) (Figure 3).35 This contrasted with the results in 330 men who had similar responses to either rhythm or rate control (P < .4). Only 35% of the women randomized to rhythm control were actually in normal sinus rhythm at the end of the study and the rate of adverse effects with antiarrhythmic agents (including palpitations and the need for pacemakers as a result of bradycardia) was higher in women than in
men. These women also suffered from higher rates of heart failure and stroke. A large study, the Anticoagulation and Risk Factors in AF Trial (ATRIA, N=13,559) also recently documented that women have a 60% greater relative risk of stroke; the incidence of stroke was much higher in women (3.5%/year) than in men (1.8%/year).

Recent studies have highlighted other risk factors and associations in AF. For example, one study involving over 2000 individuals showed that the 4-year risk of developing AF increased according to the number of risk factors (which included hypertension, diabetes mellitus, overt coronary heart disease, and parental AF) that had been documented in the parents. Sleep apnea and higher body mass indexes also have been associated with increased risk of AF.

### Pharmacologic Management of Atrial Fibrillation

#### Goals and Guidelines

After the diagnosis of AF is confirmed with the hist-

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**Table 1. Antithrombotic Therapy in Patients With Atrial Fibrillation: ACC/AHA/ESC Recommendations Based on Risk Stratification**

<table>
<thead>
<tr>
<th>Patient Features</th>
<th>Antithrombotic Therapy</th>
<th>Class Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than 60 years – No heart disease (lone AF)</td>
<td>Aspirin (325 mg per day) or no therapy</td>
<td>I</td>
</tr>
<tr>
<td>Age less than 60 years – Heart disease but no risk factors</td>
<td>Aspirin (325 mg per day)</td>
<td>I</td>
</tr>
<tr>
<td>Age greater than or equal to 60 years – No risk factors</td>
<td>Aspirin (325 mg per day)</td>
<td>I</td>
</tr>
<tr>
<td>Age greater than or equal to 60 years – with diabetes mellitus or CAD</td>
<td>Oral anticoagulation (INR 2 to 3)</td>
<td>I</td>
</tr>
<tr>
<td>Age greater than or equal to 75 years – especially women</td>
<td>Oral anticoagulation (INR approx. equal to 2)</td>
<td>I</td>
</tr>
<tr>
<td>HF</td>
<td>Oral anticoagulation (INR 2 to 3)</td>
<td>I</td>
</tr>
<tr>
<td>LV ejection fraction less than or equal to 0.35</td>
<td>Oral anticoagulation (INR 2 to 3)</td>
<td>I</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Oral anticoagulation (INR 2 to 3)</td>
<td>I</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Oral anticoagulation (INR 2 to 3)</td>
<td>I</td>
</tr>
<tr>
<td>Rheumatic heart disease (mitral stenosis)</td>
<td>Oral anticoagulation (INR 2.5 to 3.5 or higher may be appropriate)</td>
<td>I</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td>Oral anticoagulation (INR 2.5 to 3.5 or higher may be appropriate)</td>
<td>I</td>
</tr>
<tr>
<td>Prior thromboembolism</td>
<td>Oral anticoagulation (INR 2.5 to 3.5 or higher may be appropriate)</td>
<td>I</td>
</tr>
<tr>
<td>Persistent atrial thrombus on TEE</td>
<td>Oral anticoagulation (INR 2.5 to 3.5 or higher may be appropriate)</td>
<td>I</td>
</tr>
</tbody>
</table>

*Risk factors for thromboembolism: HF, LV ejection fraction less than 0.35, and history of hypertension.

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; AF = atrial fibrillation; CAD = coronary artery disease; HF = heart failure; INR = international normalized ratio; LV = left ventricular; TEE = transesophageal echocardiography.

An antithrombotic agent should be based on the patient’s absolute risks of stroke and bleeding and on the relative risks and benefits for a particular patient (Table get international normalized ratio 2.0-3.0).38 Intermediate or higher risk might receive warfarin (enteric-coated aspirin 325 mg daily, whereas those at lower risk can be treated with aspirin or warfarin may be the only therapy indicated.37 Despite meta-analyses and guideline summaries showing that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (risk reduction of 61%; 95% confidence interval, 47%-71% vs placebo),1,2 there is a persistent chronic underuse and improper dosing of warfarin in clinical practice. Whereas a discussion of antithrombotic therapy and monitoring is beyond the scope of this article, clinicians are encouraged to administer oral anticoagulation or aspirin to most patients with AF to prevent thromboembolism. In many cases, patients with long AF are advised to initiate aspirin therapy. The selection of the antithrombotic agent should be based on the patient’s absolute risks of stroke and bleeding and on the relative risks and benefits for a particular patient (Table 1).1 In recent years, the patient risk of stroke as indicated by age and comorbid conditions has been used to guide anticoagulant selection; for example, those deemed at low stroke risk (0.5%/year) may receive enteric-coated aspirin 325 mg daily, whereas those at intermediate or higher risk might receive warfarin (target international normalized ratio 2.0-3.0).18

Cardioversion

In some patients with AF, rapid restoration of normal sinus rhythm with either electrical cardioversion or antiarrhythmic drugs may be necessary. In particular, immediate electrical cardioversion is recommended in patients with paroxysmal AF and a rapid ventricular response who have ECG evidence of acute myocardial infarction or symptomatic hypotension, angina, or heart failure that does not respond promptly to pharmacologic measures.1 Cardioversion also may be required to prevent ventricular fibrillation in certain patients with Wolff-Parkinson-White syndrome or to relieve hemodynamic instability.1 More generally, pharmacologic cardioversion also is considered in AF as a strategy to reduce the chance of atrial remodeling and scarring, which set the stage for increasingly frequent AF episodes.

Pharmacologic cardioversion is most effective when initiated within 7 days after AF onset.1 The agents with the strongest recommendations for first-line use in this setting when the ejection fraction is normal include flecainide (oral 200 to 300 mg; intravenous [IV] at 1.5 to 3.0 mg per kg over 10 to 20 minutes), ibutilide (IV at 1 mg over 10 minutes, repeating 1 mg when necessary), and propafenone (oral 450 to 600 mg; IV at 1.5 to 2.0 mg per kg over 10 to 20 minutes).1 (Note that these dosages listed in the American College of Cardiology/American Heart Association [ACC/AHA] guidelines may differ from those recommended by the manufacturers.) In patients with persistent AF, success rates are about 65% to 90% with electrical cardioversion19 but the relapse rates without concomitant antiarrhythmic therapy are high.1 Because of the risk of torsades de pointes, pharmacologic cardioversion with the agents mentioned above is often performed on an inpatient basis.1,2 In addition, care must be taken to identify patients with structural heart disease defined as a low left ventricular ejection fraction, left ventricular hypertrophy, or coronary artery disease. Patients with structural heart disease are limited to specific antiarrhythmic agents only.

Rate and Rhythm Control for Long-term Management

Longer-term management of the arrhythmia involves a choice between rate and rhythm control strategies. Control of the ventricular rate often is prioritized in order to reduce symptoms and tachycardia-induced cardiomyopathy. In part, this bias toward rate control also reflects the reality that the alternative (antiarrhythmic drugs) is only about 60% effective in the long-term and also carries risks of proarrhythmic effects and other side effects.

The main options for rate control are calcium channel blockers (CCBs), β-blockers, digoxin, and AV node ablation with required pacemaker implantation. Negative chronotropic therapy is aimed mainly at depressing conduction across the AV node and achieving a ventricular rate between 60 to 80 bpm at rest and between 90 to 115 bpm during moderate exercise.1 Table 2 provides details on dosing and side effects of the main drug options for blocking AV nodal conduction.1 A meta-analysis of 54 trials indicates that the nondihydropyridine CCBs such as verapamil or diltiazem and β-blockers such as atenolol and metoprolol can control ventricular rates at rest and with exercise; these agents are superior to digoxin for rate control in those patients who do not have contraindications to...
these therapies.\textsuperscript{2} In patients with congestive heart failure or low left ventricular ejection fractions, CCBs are not recommended given the risk of worsening cardiac contractility and further decompensation.

Pharmacologic rate control requires careful dose titration. Some patients develop symptomatic bradycardia. The suspected etiology of the AF may impact this risk of bradycardia and can guide treatment choices. For example, in the rare vagally mediated AF, the ventricular rate usually increases to no more than 120 bpm in conjunction with pauses or slowing of the sinus rate, eating, or during sleep. For those patients who complain of getting palpitations at night, drugs such as \( \beta \)-blockers or digoxin may actually aggravate the AF by slowing the heart rate. Confirmation with a Holter monitor may be needed before initiating treatment, which may include atrial pacing. By contrast, the more common adrenergically mediated AF typically is seen in the morning hours and in relation to effort, stress, cardiac surgery, thyrotoxicosis, or dilated cardiomyopathy; in these patients, \( \beta \)-blockers and AV node blockers are still prime treatment options along with all the other pharmacologic and nonpharmacologic choices.

If rate control is ineffective in preventing symptoms and if the ablation/pacemaker option is not desirable for any reason in a particular patient, then rhythm control may be instituted with antiarrhythmic drugs or nonpharmacologic means such as multisite atrial pacing or ablation techniques. In some cases, restoring the lost AV synchrony will diminish the symptoms. Achieving rhythm control also may limit the atrial remodeling and altered electrophysiologic state that contributes to even more AF—the mechanism behind the mantra of “atrial fib begets atrial fib”—and also to the stroke risks associated with AF. Thus, even if the rhythm control drugs are effective in controlling symptoms in “only” 60% of patients, they still have a place in therapy. In many individual patients, even a partial reduction of the arrhythmia burden may be deemed a partial success.\textsuperscript{3} Analysis of randomized clinical trials with antiarrhythmic agents shows strong evidence for the efficacy of amiodarone, propafenone, and sotalol and moderate evidence for flecainide.\textsuperscript{4} There have been few direct comparative trials.

### Table 2. Rate Control With Oral Agents: ACC/AHA/ESC Recommendations for Patients With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Loading Dose</th>
<th>Onset</th>
<th>Usual Maintenance Dose\textsuperscript{1}</th>
<th>Major Side Effects</th>
<th>Class Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>0.25 mg PO each 2 h; up to 1.5 mg</td>
<td>2 h</td>
<td>0.125 to 0.375 mg daily</td>
<td>Digitalis toxicity, heart block, bradycardia</td>
<td>I</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>NA</td>
<td>2 to 4 h</td>
<td>120 to 360 mg daily in divided doses; slow release available</td>
<td>Hypotension, heart block, HF</td>
<td>I</td>
</tr>
<tr>
<td>Metoprolol\textsuperscript{\dagger}</td>
<td>NA</td>
<td>4 to 6 h</td>
<td>25 to 100 mg BID</td>
<td>Hypotension, heart block, asthma, HF</td>
<td>I</td>
</tr>
<tr>
<td>Propranolol\textsuperscript{\dagger}</td>
<td>NA</td>
<td>60 to 90 min</td>
<td>80 to 240 mg daily in divided doses</td>
<td>Hypotension, heart block, bradycardia, asthma, HF</td>
<td>I</td>
</tr>
<tr>
<td>Verapamil</td>
<td>NA</td>
<td>1 to 2 h</td>
<td>120 to 360 mg daily in divided doses; slow release available</td>
<td>Hypotension, heart block, digoxin interaction, HF</td>
<td>I</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>800 mg daily for 1 wk; 600 mg daily for 1 wk; 400 mg daily for 4 to 6 wk</td>
<td>1 to 3 wk</td>
<td>200 mg daily</td>
<td>Pulmonary toxicity, skin discoloration, hypothyroidism, corneal deposits, optic neuropathy, warfarin interaction, proarrhythmia</td>
<td>IIB</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; PO = by mouth; HF = heart failure; NA = not applicable; BID = twice a day.

*Drugs are listed alphabetically within each class of recommendation.

\textsuperscript{1}Recomended maintenance dosages are the usual ones necessary, but higher doses may be appropriate in some patients.

\textsuperscript{\dagger}The table includes representative members of the type of beta-blocker drugs, but other similar agents could be used for this indication in appropriate doses.

As shown in Figure 4, the choice of the antiarrhythmic agent currently is driven less by efficacy than by safety considerations and the presence or absence of underlying heart disease. Table 3 outlines the dosing and potential adverse effects with these agents. Particular note should be taken of the organ toxicity seen with amiodarone and the proarrhythmic state known as torsades de pointes that occurs with many agents. A drug that is initially safe might become proarrhythmic when the patient develops coronary artery disease or heart failure.

As indicated in Figure 4, those patients who cannot tolerate and/or cannot be adequately controlled with antiarrhythmic or rate control therapy can be considered for nonpharmacologic therapies such as radiofrequency catheter ablation or surgical Cox-maze procedures.

**Comparing Rate vs Rhythm Strategies**

Recent studies have described the efficacy of rhythm and rate control both in reducing symptoms and in decreasing mortality in AF. The largest of these was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, which enrolled 4060 elderly patients (mean 69.7 years) with AF >6 hours in the prior 6 months and a high risk of stroke or death (eg, 70% had hypertension, 65% had left atrial enlargement, 38% had coronary artery disease, and 24% had heart failure). These patients were randomized to rate or rhythm control and followed for a mean of 3.5 years. Overall, AFFIRM found that neither strategy conferred a survival advantage over the alternative (Figure 5). These results match those from 3 other smaller trials comparing rate and rhythm control strategies: the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study, the Strategies of Treatment of Atrial Fibrillation (STAF) study, and the Fibrillation (RACE) study, the Cardioversion for Persistent Atrial Rate Control versus Electrical

Overall, AFFIRM found that neither rate control nor rhythm control conferred a survival advantage over the alternative (Figure 5). These results match those from 3 other smaller trials comparing rate and rhythm control strategies: the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study, the Strategies of Treatment of Atrial Fibrillation (STAF) study, and the

**Table 3. Sinus Rhythm Control with Oral Agents: ACC/AHA/ESC Recommendations for Patients With Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone‡</td>
<td>100 to 400 mg</td>
<td>Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsade de pointes (rare), hepatic toxicity, thyroid dysfunction</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>400 to 750 mg</td>
<td>Torsade de pointes, HF, glaucoma, urinary retention, dry mouth</td>
</tr>
<tr>
<td>Dofetilide§</td>
<td>500 to 1000 mcg</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td>Flecainide</td>
<td>200 to 300 mg</td>
<td>Ventricular tachycardia, congestive HF, enhanced AV nodal conduction (conversion to atrial flutter)</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>1000 to 4000 mg</td>
<td>Torsade de pointes, lupus-like syndrome, GI symptoms</td>
</tr>
<tr>
<td>Propafenone</td>
<td>450 to 900 mg</td>
<td>Ventricular tachycardia, congestive HF, enhanced AV nodal conduction (conversion to atrial flutter)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>600 to 1500 mg</td>
<td>Torsade de pointes, GI upset, enhanced AV nodal conduction</td>
</tr>
<tr>
<td>Sotalol§</td>
<td>240 to 320 mg</td>
<td>Torsade de pointes, congestive HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; GI = gastrointestinal; AV = atrioventricular; HF = heart failure.

*The drugs and doses given here have been determined by consensus based on published studies.
†Drugs are listed alphabetically.
‡Dose should be adjusted for renal function and QT-interval response during in-hospital phase.
§A loading dose of 600 mg/day is usually given for 1 month or 1000 mg/day over 1 week.

**Figure 4. ACC/AHA/ESC Guideline for Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm in Patients With Recurrent Paroxysmal or Persistent Atrial Fibrillation**
Pharmacological Intervention in Atrial Fibrillation (PIAF) study. A recent meta-analysis on the same topic also concluded that ventricular rate control in combination with anticoagulation was at least equivalent to rhythm control in appropriate patients. Although these studies suggest no special benefit of rhythm control in patients at high risk of recurrence and adverse outcomes, it should be pointed out that rhythm control in these trials was imperfect, with a high proportion of patients actually not maintained in sinus rhythm. Because most study endpoints occur during AF, the full mortality benefit of true rhythm control remains in question and the decision between rate and rhythm is still mainly guided, as described above, by symptoms and associated conditions.

Whereas AFFIRM has shortcomings, it also provides a solid perspective on practical treatment issues and, for example, reminds clinicians of the importance of keeping high-risk patients on warfarin even if they have maintained sinus rhythm for several weeks or months. In AFFIRM anticoagulated patients in the rhythm control group actually had slightly lower rates of ischemic strokes than those in the rate control group. But in those patients not taking warfarin, the stroke risk in the rhythm control group was almost double that in the rate control group. The bottom-line message here is that warfarin therapy in higher-risk AF patients needs to be maintained for life.

**POTENTIAL NEW MANAGEMENT STRATEGIES: ACE-Is, ARBs, AND STATINS**

The renin-angiotensin-aldosterone system may play a role as a mediator of atrial structural and electrical remodeling in AF. Several studies have now tested this hypothesis by measuring the impact of ACE-Is or ARBs on AF frequency and outcomes. One of the first such studies was a retrospective analysis of 374 patients in the Studies of Left Ventricular Dysfunction (SOLVD) who had heart failure but not baseline AF or atrial flutter. When the charts and ECGs of these patients were reviewed, 10 (5.4%) of the patients in the enalapril group had AF during the follow-up period (mean 2.9 years) compared with 45 (24%) in the placebo group ($P < .0001$) (Figure 6). The anti-AF impact of the ACE-I was greatest in patients with no overt heart failure, implying a benefit in terms of atrial stabilization of earlier treatment.

In another recent study, an ARB was evaluated for its impact on sinus rhythm maintenance after conversion from persistent AF (>7 days). Of the 75 patients...
randomized to amiodarone, 85% had recurrent AF during the following 2 months; in the 79 patients receiving both amiodarone and irbesartan, the recurrence rate was significantly lower at 63% (P = .008). Follow-up over a longer period also showed that patients treated with the ARB had a greater probability of remaining free of AF (79.5% versus 55.9%, P = .007). Recently, a study of amiodarone used with either an ARB or a CCB in 250 hypertensive patients with a history of recent paroxysmal AF showed a 1-year rate of ECG-documented AF of 13% in the ARB group versus 39% in the CCB group; the blood pressure reduction was similar in these groups.47

Do these apparent effects of ACE-Is and ARBs on new and recurrent AF have any real clinical benefit in terms of patient morbidity and mortality? This question was recently considered as part of the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. First, in 8851 patients with hypertension but without ECG-verified AF, the occurrence of new-onset AF was tracked for a mean of 4.8 years.48 New-onset AF was seen in 150 patients randomized to losartan versus 221 to a β-blocker (P < .001). These patients with new-onset AF had 2-, 3-, and 5-fold increased rates, respectively, of cardiovascular events, stroke, and hospitalization for heart failure. Thus, although previous studies had shown that ACE-Is and ARBs independently decreased the incidence of stroke, this LIFE study was the first to show that both new-onset AF and subsequent stroke were significantly reduced by an ARB compared with a β-blocker, despite similar blood pressure reductions.

In the smaller subset (N=342) of LIFE patients who entered the trial with both AF and left ventricular hypertrophy, 36 of those randomized to losartan and 67 of those randomized to the β-blocker had 1 of the primary endpoints (death, stroke, myocardial infarction) (hazard ratio 0.58, P = .009).51 Losartan-based treatment was most effective in terms of reducing cardiovascular mortality and stroke (Figure 7). Again, these LIFE results were independent of blood pressure reduction and indicate that an ARB can reduce the risks of new-onset and recurrent AF and that the prevalence of uncontrolled AF impacts the level of cardiac morbidity and mortality in patients with hypertension and left ventricular hypertrophy.

The mechanisms of ACE-I and ARB action in AF are unknown but may involve regression of hypertrophy or a reversal of atrial remodeling or fibrosis.46-48,52 Though the use of these agents in preventing AF appears promising, further study is required.53

As mentioned earlier, the level of CRP has been shown to be elevated in patients with AF.26,27 Statins are known to have anti-inflammatory effects, to lower CRP levels, and also to reduce the incidence of stroke.54 Although it is premature to recommend CRP testing as a screen for stroke risk and/or statin therapy,55 several investigators have studied the ability of statins to change the incidence and impact of AF. In one of the first of these provocative studies, the association between statin use and the risk of developing AF was examined in 449 patients with chronic stable coronary artery disease.56 Over a 5-year period, 52 patients (12%) developed AF. In the 59% of patients who used statins over the 5-year study period, the risk of developing AF was significantly reduced (odds ratio 0.48) (Figure 8). This protection against AF was seen even after adjustment for age, hypertension, cholesterol levels, and sex. Subsequent studies seem to confirm that lowering of CRP with statins is associated with a reduction in various types of primary or secondary AF.29,57,58

Figure 7. Angiotensin II Receptor Blocker Reduced Mortality (Versus β-Blocker) in Patients With Hypertension, Left Ventricular Dysfunction, and Atrial Fibrillation*

*Data from the Losartan Intervention For End Point Reduction in Hypertension (LIFE) Study (N =342, with 1472 patient-years of follow-up; intention to treat analysis).
CV = cardiovascular; CVA = cardiovascular accident; MI = myocardial infarction.
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Figure 8. Statin Prevented Atrial Fibrillation Onset in Patients With Coronary Artery Disease

![Graph showing the probability of AF-free survival over follow-up years for Statin users and Non-users.]

AF = atrial fibrillation.
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CONCLUSION

Studies show the promise of novel strategies for diminishing the incidence and impact of AF in years to come. As these new strategies aimed at the renin-angiotensin-aldosterone system and inflammation are refined and as we come to understand their mechanisms, clinicians may soon have new reasons and evidence to employ combination therapy earlier in certain patients at risk of developing AF. The old debate of rate versus rhythm control in AF may need to be opened up to new approaches. If these new approaches can be validated in large controlled trials, our patients will benefit.

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