In the Clinic

Atrial Fibrillation

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CME Objective: To review current evidence for the diagnosis and treatment of atrial fibrillation.

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Atrial fibrillation (AF) is the most common, clinically significant cardiac arrhythmia. It occurs when a diffuse and chaotic pattern of electrical activity in the atria suppresses or replaces the normal sinus mechanism, leading to deterioration of mechanical function. Atrial fibrillation is a major cause of morbidity, mortality, and health care expenditures; prevalence in the United States is 2.3 million cases and is estimated to increase to 5.6 million by the year 2050 (1). Atrial fibrillation is associated with a 5-fold increased risk for stroke and is estimated to cause 15% of all strokes (2). Independent of coexisting diseases, the presence of AF confers a 2-fold increased risk for all-cause mortality (3).

### Diagnosis

#### Who is at risk for atrial fibrillation?
Atrial fibrillation occurs in less than 1% of individuals aged 60 to 65 years, but in 8% to 10% of those older than 80 years. Prevalence is higher in men than in women and higher in whites than in blacks (1). The risk for AF increases with the presence and severity of underlying heart failure and valvular disease.

#### What symptoms and signs should cause clinicians to suspect atrial fibrillation?
Some patients have prominent symptoms, including palpitations, shortness of breath, exercise intolerance, chest pain, and malaise. However, many patients, particularly the elderly, have asymptomatic (silent) AF, including some patients who have severe symptoms during other AF episodes (4). Symptoms are generally greatest at disease onset—when episodes are typically paroxysmal—and tend to diminish over time, especially when the arrhythmia becomes persistent. Symptoms result from elevation of ventricular rate (either at rest or exaggerated by exercise), irregular ventricular rate, and loss of atrial contribution to cardiac output.

On physical examination, signs of AF include a faster-than-expected heart rate, which varies greatly from patient to patient, an “irregularly irregular” time between heart sounds on auscultation, and peripheral pulses that vary irregularly in both rate and amplitude.

#### Is a single electrocardiogram sufficient to diagnose or exclude atrial fibrillation?
Figure 1 is an electrocardiogram (ECG) showing AF, and it indicates that a single ECG is sufficient to diagnose AF provided it is recorded during the arrhythmia. However, AF is often paroxysmal, so a single ECG showing normal rhythm does not exclude the diagnosis. Monitoring for a longer time can be helpful when AF is suspected and the initial ECG is normal. In patients with daily symptoms, 24- or 48-hour continuous Holter monitoring is usually sufficient to make the diagnosis. In patients with less-frequent symptoms, monitoring during longer periods with electrocardiographic loop recorders may be necessary. However, even monitoring for periods as long as a month can be nondiagnostic in patients with very infrequent episodes. In addition, because patients must turn loop recorders on after symptoms begin, these recorders are not helpful in detecting asymptomatic arrhythmias or arrhythmia-associated nonspecific symptoms that the patient may not recognize as being related to AF. It may take years to confirm the diagnosis of AF in some patients because they have nonspecific symptoms and long periods between episodes.

Some newer devices avoid these problems. New types of event monitors detect irregular ventricular rhythms and automatically start recording regardless of symptoms.

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In addition, implanted pacemakers and implantable defibrillator–cardioverters with atrial leads identify and record both symptomatic and asymptomatic AF. Other new devices continuously record heart rhythms for as long as a month and wirelessly transmit data to a central monitoring station, where automated systems interpret cardiac rhythms and report diagnoses in real time (4a).

What is the role of history and physical examination in patients with atrial fibrillation?

History and physical examination help determine the duration of symptoms and identify potential underlying causes. Clinicians should seek historical and physical evidence of hypertension, heart failure, cardiac surgery, murmurs indicative of stenotic or regurgitant valvular disease, and other indications of structural heart disease. In addition, clinicians should look for signs and symptoms of noncardiac causes of AF, including pulmonary disease, hyperthyroidism, use of adrenergic drugs (such as those used to treat pulmonary disease) or other stimulants, and use of alcohol. A family history might identify first-degree relatives with AF, which may someday have therapeutic implications.

What other electrocardiographic arrhythmias can be confused with atrial fibrillation?

Other arrhythmias that are commonly confused with AF include sinus rhythm with frequent premature atrial contractions, atrial flutter, and atrial tachycardia. The key electrocardiographic findings of AF are the absence of P waves and the presence of an irregular ventricular rhythm without a recurring pattern. When an irregular rhythm is present but the diagnosis of AF is uncertain, clinicians should examine long recordings from multiple leads looking for partially obscured P waves in deformed T waves and ST segments.

Figure 2 is an ECG of an irregular rhythm that might be attributed to AF, but the presence of P waves and other features identify sinus rhythm with frequent premature atrial contractions. Figure 3 is an ECG of another irregular rhythm that might be attributed to AF, but the presence of “saw-tooth” P waves and a ventricular response that varies from 2:1 atrioventricular conduction to 4:1 atrioventricular conduction identifies atrial flutter.

How should clinicians classify atrial fibrillation?

Although knowledgeable observers disagree on the answer to this question, the most accepted convention categorizes AF as paroxysmal, persistent, or permanent (5) (Box 1). “Paroxysmal” AF means that episodes terminate without intervention in fewer than 7 days (often within 24 hours). “Persistent” AF means that episodes last longer than 7 days or require an intervention, such as cardioversion, to restore sinus rhythm. “Permanent” AF means that the arrhythmia is continuous, and interventions to restore sinus rhythm have either failed or not been attempted. The same patient may be classified into different categories at different times, so clinicians should classify patients according to the current pattern or most common pattern.

These distinctions are useful because they predict responses to therapy. For example, patients are less likely to respond to
antiarrhythmic drug therapy as the pattern goes from paroxysmal to persistent to permanent. Patients in all 3 categories, however, require anticoagulation.

**What laboratory studies should clinicians obtain in patients newly diagnosed with atrial fibrillation?** When patients initially present with AF, clinicians should measure serum electrolytes and thyroid-stimulating hormone to identify possible causes. They should measure blood tests for renal and hepatic function to guide the selection of drug therapy and check a stool Hemoccult test before starting anticoagulation. Transthoracic echocardiography helps determine the patient’s potential responsiveness to antiarrhythmic therapy by measuring left atrial size and assessing for valvular heart disease, pericardial disease, and left ventricular hypertrophy. A transesophageal echocardiogram to exclude atrial clot is indicated when transthoracic images are inadequate or cardioversion is planned in a patient who has been therapeutically anticoagulated for less than 3 weeks. In patients with appropriate clinical indications, additional tests may be appropriate to evaluate the patient for pulmonary embolism, acute myocardial infarction, or acute heart failure.

**What underlying conditions should clinicians look for in patients with atrial fibrillation?** Eighty percent of patients with AF have structural heart disease, particularly hypertensive heart disease but also coronary artery disease, valvular heart disease, or cardiomyopathy. Atrial fibrosis occurs frequently with structural heart disease, and many people consider atrial fibrosis central to the arrhythmia’s pathogenesis. “Lone” AF refers to AF in the absence of heart disease. Some experts believe that the diagnosis of lone AF should be restricted to patients younger than 60 years of age because it is difficult to exclude structural heart disease in older patients (6).

Some acute illnesses are associated with AF, including acute myocardial infarction, pulmonary embolism, and thyrotoxicosis. Atrial fibrillation occurs in approximately 40% of patients after cardiac or thoracic surgery, but it may also occur after other types of major surgery or during a severe illness. Obesity and sleep apnea are associated with an increased incidence of AF.

Atrial fibrillation also occurs in people who have no predisposing conditions. These patients are typically men 40 to 50 years of age, and symptoms often occur at night, at rest, following vigorous exercise, or with alcohol use. The mechanisms are unclear but may involve increases in circulating catecholamines, changes in myocardial conduction times and refractory periods, and increases in vagal tone. Other forms of AF without known underlying conditions occur during waking hours and are preceded by emotional stress or exercise.

### Diagnosis...

Atrial fibrillation is the most common clinically significant cardiac arrhythmia, and its prevalence increases with advancing age. Typical symptoms include palpitations, shortness of breath, and exercise intolerance. However, some patients report only general malaise, and many patients are asymptomatic. Electrocardiogram recordings during episodes are the only way to confirm the diagnosis. If the diagnosis is suspected and the ECG is normal, longer monitoring with a loop recorder or a Holter monitor can be helpful. The initial assessment should include laboratory tests for electrolytes, thyroid-stimulating hormone, and renal and hepatic function to rule out underlying disorders or contraindications to therapies. An echocardiogram should be done to look for structural heart disease.

### CLINICAL BOTTOM LINE

**Classification of Atrial Fibrillation**

- **Paroxysmal:** Episodes spontaneously terminate within 7 days
- **Persistent:** Episodes last >7 days and require intervention to restore sinus rhythm
- **Permanent:** Interventions to restore sinus rhythm have either failed or have not been attempted

Situations in Which Patients with Atrial Fibrillation May Require Hospitalization

- Uncertain or unstable underlying arrhythmia
- Acute myocardial infarction, altered mental status, decompensated heart failure, or hypotension
- Intolerable symptoms despite hemodynamic stability
- Elective cardioversion (if monitored outpatient setting is not available)
- Acute anticoagulation if very-high risk for stroke
- Telemetry monitoring during initiation of certain drugs
- Procedures such as cardiac catheterization, electrophysiological studies, pacemakers, implantable defibrillators, or catheter or surgical ablation

Treatment

What are the complications of atrial fibrillation, and how can therapy decrease the risk for these events?

There are 3 reasons to treat AF: to reduce symptoms, to prevent thromboembolism, and to prevent cardiomyopathy.

Although AF is not always symptomatic, the symptoms can be disabling. Symptoms are usually caused by inappropriately rapid ventricular rates or the irregularity of the ventricular response (7). The loss of atrial contribution to ventricular filling (“atrial kick”) is well tolerated by most patients except those with ventricular hypertrophy from long-standing hypertension, aortic stenosis, and hypertrophic obstructive cardiomyopathy.

Stroke is the most common form of arterial thromboembolism during AF. In patients with nonvalvular AF, the average annual risk for arterial thromboembolism, including stroke, is 5%, and the risk is higher in patients older than age 75 years (8). The risk is related to specific features of AF as well as other risk factors for thromboembolism (9). Left atrial thrombi cause 75% of strokes in patients with AF (10).

It is important to treat the tachycardia of AF because it can lead to cardiomyopathy if left untreated (11).

When should clinicians consider immediate cardioversion in patients with atrial fibrillation?

Prompt cardioversion should be considered for new-onset AF when the duration of the arrhythmia is less than 48 hours. One example is a hospitalized patient on cardiac monitoring. Most patients with AF do not require immediate cardioversion, but it can obviate the need for anticoagulation and may be appropriate in selected patients with decompensated heart failure, severe angina or acute infarction, hypotension, or high risk for acute stroke. Patients with AF and the Wolf-Parkinson-White syndrome can have extremely rapid atrioventricular conduction mediated by the accessory pathway, which can be a potentially life-threatening condition and require urgent cardioversion.

Which patients with atrial fibrillation should clinicians consider hospitalizing?

Although AF is usually managed in an outpatient setting, clinicians should consider hospitalizing patients with AF when management requires close monitoring for safety (12) (Box 2).

Should clinicians attempt rate control or rhythm control?

Traditionally, most clinicians have preferred rhythm control to rate control, but recent, high-quality clinical trials have shown that rhythm control generally does not improve mortality, stroke, hospitalization, or quality of life compared with rate control (13, 14). Rate control is easier to accomplish and prevents exposure to the potential adverse effects of antiarrhythmic agents. On the other hand, rhythm control may be useful in selected patients with severe symptoms (before or after failure of rate control) or in younger patients without structural heart disease.

The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial included 4060 patients with AF who had at least 1 risk factor for stroke. The mean age was 69 years, and structural heart disease, aside from hypertension, was unusual. All-cause mortality at 5 years was 25.9% in the rate-control group and 26.7% in the rhythm-control group (P = 0.080). Patients with apparently successful rhythm control still needed anticoagulation because of persistent stroke risk, and patients who were able to maintain sinus rhythm had a survival advantage that was almost balanced by the disadvantage imposed by antiarrhythmic drug therapy (15).
A more recent trial extended these observations to patients with severe heart failure by randomly assigning 1376 patients with AF, left ventricular ejection fraction of ≤35%, and heart failure symptoms to rate control versus rhythm control. At 37 months, death from cardiovascular disease occurred in 25% of the rate-control group and in 27% of the rhythm-control group (P = 0.6). There was no improvement in all-cause mortality, stroke, heart failure, or need for hospitalization in the rhythm-control group (16).

What strategies should clinicians consider for rate control in patients with rapid atrial fibrillation?

Clinicians should consider drug therapy to control ventricular rate in all patients with AF, even if rhythm control is eventually done. Although criteria for rate control vary with patient age, the traditional target has been heart rates of 60 to 80 beats per minute at rest and between 90 to 115 beats per minute during moderate exercise (17). However, a recent study comparing a strategy of lenient rate-control (resting heart rate ≤110 beats per minute) with a strategy of strict rate control (≤80 beats per minute), found no advantage to the stricter rate control strategy (18). Recommended first-line therapy to decrease atrioventricular nodal conduction includes β-blockers and nondihydropyridine calcium-channel antagonists (Table 1). A recently approved antiarrhythmic medication, dronedarone, has also been shown to be safe and modestly effective for rate control of AF (19).

Digitalis and amiodarone block the atrioventricular node but are not recommended as first-line monotherapy for rate control (17). Digitalis does not reduce the tachycardia that occurs with exercise, and it is unlikely to control rate in patients with heart failure and high sympathetic activity. Amiodarone is occasionally used to reduce ventricular response if other agents have failed, but this practice is difficult to justify because of the associated toxicities (20).

What strategies should clinicians consider for rhythm control in patients with atrial fibrillation?

Rhythm control is no longer the preferred strategy in most patients with AF. The trials comparing rate control with rhythm control, however, have not included younger patients or those with highly symptomatic AF. Therefore, it is reasonable to consider rhythm control in these patients. Also, experienced clinicians often prefer rhythm control for the first episode of symptomatic AF in younger patients because many maintain sinus rhythm without antiarrhythmic drug treatment after cardioversion.

Patients can be converted to normal sinus rhythm with direct electrical current or with drugs. Electrical cardioversion is indicated when the patient is hemodynamically unstable. When the patient is hemodynamically stable, the conversion rate with antiarrhythmic drugs is lower than that with electrical direct current but does not require deep sedation or general anesthesia and may facilitate the choice of antiarrhythmic drug therapy to prevent recurrence.

Patients should receive therapy to achieve both rate control and adequate anticoagulation before elective direct current or pharmacologic cardioversion of AF more than 48 hours in duration. In addition, the serum potassium level should be greater than 4.0 mmol/L, serum magnesium level should be greater than 1.0 mmol/L, and ionized calcium levels should be greater than 0.5 mmol/L. In most cases, cardioversion should be performed in a monitored hospital setting to permit adequate assessment of the degree of rate control, bradycardia, proarrhythmic effects of antiarrhythmic agents, and other adverse effects (21).

Antiarrhythmic drugs other than amiodarone generally have equal...
**Table 1. Drug Therapy for Rate and Rhythm Control in Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Benefits</th>
<th>Side Effects</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Rate-Controlling Agents</strong></td>
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<td><strong>ß-Blockers</strong></td>
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<td>Metoprolol</td>
<td>Selective ß₁-adrenergic– receptor blocking agent</td>
<td>5 mg IV every 5 min, up to 15 mg 50–100 mg PO twice daily</td>
<td>Convenient IV administration in NPO patients, rapid onset of action, dependable AV nodal blockade</td>
<td>Bradycardia, hypotension, heart block, bronchospasm (less frequently than nonselective ß-blockers), worsening of CHF</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Nonsel ective ß-adrenergic– receptor blocking agent</td>
<td>1–8 mg IV (1 mg every 2 min). 10–120 mg PO 3 times daily; long-acting preparation: 80–320 mg PO once daily.</td>
<td>Short-acting, titratable on or off with very rapid half-life</td>
<td>Bradycardia, hypotension, heart block, bronchospasm (less frequent)</td>
<td>Bradycardia, hypotension, heart block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Short-acting IV ß₁ selective adrenergic receptor-blocking agent</td>
<td>0.05–0.2 mg/kg per min IV</td>
<td>Short-acting, titratable on or off with very rapid half-life</td>
<td>Bradycardia, hypotension, heart block, bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>Nonsel ective ß-adrenergic– receptor blocking agent</td>
<td>2.5–20 mg PO 2–3 times daily</td>
<td>Less bradycardia, less bronchospasm</td>
<td>Bradycardia, hypotension, heart block</td>
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<tr>
<td>Atenolol</td>
<td>Selective ß₁-adrenergic– receptor blocking agent</td>
<td>5 mg IV over 5 min, repeat in 10 min. 25–100 mg PO once daily</td>
<td>Does not cross blood–brain barrier, fewer CNS side effects</td>
<td>Bradycardia, hypotension, heart block</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>Nonsel ective ß-adrenergic– receptor blocking agent</td>
<td>20–120 mg once daily</td>
<td>Lower incidence of crossing blood–brain barrier, fewer CNS side effects</td>
<td>Bradycardia, hypotension, heart block</td>
<td>Oral form only</td>
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<tr>
<td><strong>Calcium-channel blockers</strong></td>
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<tr>
<td>Verapamil</td>
<td>Calcium-channel blocking agent</td>
<td>5–20 mg in 5-mg increments IV every 30 min, or 0.005 mg/kg per min infusion. 120–360 mg PO daily, in divided doses or in the slow-release form.</td>
<td>Consistent AV nodal blockade</td>
<td>Hypotension, heart block, direct myocardial depression</td>
<td>Do not use in the Wolff–Parkinson–White syndrome</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Calcium-channel blocking agent</td>
<td>0.25–0.35 mg/kg IV followed by 5–15 mg/h. 120–360 mg PO daily as slow release</td>
<td>Consistent AV nodal blockade</td>
<td>Hypotension, heart block, less myocardial depression</td>
<td>Do not use in the Wolff–Parkinson–White syndrome</td>
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<tr>
<td><strong>Cardiac glycoside</strong></td>
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<tr>
<td>Digoxin</td>
<td>Na+/K+ pump inhibitor, increases intracellular calcium</td>
<td>0.75–1.5 mg PO or IV in 3–4 divided doses over 12–24 h. Maintenance dose: 0.125 mg PO or IV to 0.5 mg daily</td>
<td>Particularly useful for rate control in CHF</td>
<td>Heart block, digoxin-associated arrhythmias; dosage adjustment required in renal impairment</td>
<td>First-line therapy only in patients with decreased left-ventricular systolic function. Not useful for rate control with exercise. Not useful for conversion of AF or aflutter to NSR.</td>
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<td><strong>Antiarrhythmic agents</strong></td>
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<tr>
<td>Class Ia</td>
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<tr>
<td>Procainamide</td>
<td>Prolongs conduction and slows repolarization by blocking inward Na+ flux</td>
<td>1–2 g q 12 h (shorter-acting oral preparations are no longer available)</td>
<td>Convenient IV dosing available with maintenance infusion, and conversion to PO tablets, very effective at converting AF to NSR</td>
<td>Not recommended because of frequent side effects, including hypotension, nausea, vomiting, lupus-like syndrome, QT prolongation, and arrhythmia</td>
<td>Need to follow drug levels and QT interval for toxicity, adjust dose in patients with renal insufficiency. Not for use in patients with severe LV dysfunction.</td>
</tr>
<tr>
<td>Quinidine gluconate</td>
<td>Prolongs conduction and slows repolarization. Blocks fast inward Na+ channel</td>
<td>324–648 mg PO every 8–12 h</td>
<td>Relatively effective in converting AF to NSR but may take several days to achieve NSR because of PO dosing</td>
<td>Proarrhythmia, nausea, vomiting, diarrhea, QT prolongation</td>
<td>Not recommended because of frequent side effects. Follow drug levels and QT interval for toxicity. Adjust dose in patients with renal insufficiency. Oral agent only.</td>
</tr>
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</table>

(continued on next page)
efficacy, so susceptibility to side effects should guide the choice among them (Table 1). Drugs that block cardiac sodium channels (class I effect), such as flecainide and propafenone, are useful in patients without coronary heart disease or advanced left ventricular dysfunction. They should not be used in patients with significant structural heart disease because they have been associated with increased mortality in these patients (22). Their side effects are due to unwanted sodium-channel blockade in other organ systems, such as the gastrointestinal tract (resulting in anorexia or esophageal reflux) and the central nervous system. Other class I drugs, such as quinidine and procainamide,

Table 1 (continued). Drug Therapy for Rate and Rhythm Control in Atrial Fibrillation

<table>
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<tr>
<td>Class Ia</td>
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<tr>
<td>Disopyramide</td>
<td>Similar electrophysiologic properties to procainamide and quinidine</td>
<td>150 mg PO every 6–8 h, or 150–300 mg twice a day</td>
<td>Can be useful in patients with hypertension and normal LV function</td>
<td>QT prolongation (not PR or QRS), torsades de pointes, heart block</td>
<td>Rarely used in current era of antiarrhythmic therapy. Oral agent only, negative inotropic properties.</td>
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<tr>
<td>Class Ic</td>
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<tr>
<td>Flecainide</td>
<td>Blocks Na+ channels (and fast Na+ current)</td>
<td>2 mg/kg, IV, 50–150 mg PO every 12 h, 2 mg/kg, IV, 150–300 mg PO every 8 h</td>
<td>Efficacy in paroxysmal AF with structurally normal hearts</td>
<td>Aflutter or atrial tachycardia with rapid ventricular response but not with acute single loading doses, VF and VF in diseased hearts</td>
<td>Not for use in patients with structurally abnormal hearts</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Blocks myocardial Na+ channels</td>
<td>2 mg/kg, IV, 150–300 mg PO every 8 h, or 1 mg IV over 10 min.</td>
<td>Efficacy in paroxysmal and sustained AF</td>
<td>Aflutter or atrial tachycardia with rapid ventricular response, but not with acute single loading doses.</td>
<td>Antiarrhythmic and weak calcium channel and ß-blocking properties. Not for use with structural heart disease.</td>
</tr>
<tr>
<td>Class III</td>
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<tr>
<td>Ibutilide</td>
<td>Prolongs action potential duration (and atrial and ventricular refractoriness) by blocking rapid component of delayed rectifier potassium current</td>
<td>1 mg IV over 10 min. May be repeated once if necessary.</td>
<td>Efficacy in acute and rapid conversion of AF to NSR</td>
<td>Polymorphic VT (torsades de pointes) occurred in 8.3% of patients in a clinical trial (most with LV dysfunction), QT prolongation</td>
<td>In some centers, only used in the electrophysiology laboratory. May also be used to facilitate unsuccessful direct-current rectifier potassium cardioversion. Can be used in the Wolff–Parkinson–White syndrome.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Blocks Na+ channels (affinity for inactivated channels), Noncompetitive ß- and ß-receptor inhibitor.</td>
<td>5–7 mg/kg IV up to 1500 mg per 24 h, or 400–800 mg PO daily, for 3–4 wk, followed by 100–400 mg PO daily</td>
<td>Safest agent for use in patients with structural heart disease, good efficacy in maintaining NSR chronically</td>
<td>Bradycardia, QT prolongation, hyperthyroidism, lung toxicity, argyria (blue discoloration of skin) with chronic use</td>
<td>Antiarrhythmic and weak calcium channel and ß-blocking properties. Not for use with structural heart disease.</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Nonselective ß- and ß-blocking agent, prolongs action potential duration</td>
<td>80–240 mg PO every 12 h</td>
<td>Similar efficacy to quinidine, but fewer adverse effects. Better rate control because of ß-blocking properties.</td>
<td>Fatigue, depression, bradycardia, torsades de pointes, CHF</td>
<td>B-blocking properties, but some positive inotropic activity. Lethal arrhythmias possible. Adjust dose in patients with renal insufficiency. Initiate on telemetry. Must be strictly dosed according to renal function, body size, and age. Contra-indicated in patients with creatinine clearance &lt;20 ml/min. Initiate on telemetry.</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Blocks rapid component of the delayed rectifier potassium current (IR), prolonging refractoriness without slowing conduction</td>
<td>500 μg twice daily</td>
<td>More effective than quinidine in conversion to and maintenance of NSR</td>
<td>QT prolongation, torsades de pointes (2%–4% risk).</td>
<td>Antiarrhythmic and weak calcium channel and ß-blocking properties. Not for use with structural heart disease.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Similar to amiodarone—blocks sodium, potassium, and calcium channels</td>
<td>400 mg twice daily</td>
<td>Well-tolerated and safe</td>
<td>Gastrointestinal intolerance</td>
<td>Antiarrhythmic and weak calcium channel and ß-blocking properties. Not for use with structural heart disease.</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; CNS = central nervous system; IV = intraventricular; LV = left ventricular; NPO = nil per os; NSR = normal sinus rhythm; PO = orally; VF = ventricular fibrillation; VT = ventricular tachycardia.

are used infrequently because of noncardiac side effects and a concern for proarrhythmia. Drugs that block potassium channels and thus have class III effects, such as sotalol and dofetilide, can prolong the QT interval and cause torsades de pointes.

Amiodarone can be used in patients with advanced structural heart disease. However, amiodarone can cause permanent liver and lung toxicity that is dose- and duration-dependent (23). Hepatic toxicity is characterized by hepatitis that can progress to cirrhosis. Pulmonary toxicity can develop within 6 weeks or after years of therapy and most often manifests as cough and dyspnea. Pulmonary imaging can demonstrate a broad range of findings, including segmental or diffuse infiltrates. Other side effects include thyroid dysfunction (hypothyroidism, hyperthyroidism), sun sensitivity, and ocular symptoms.

Dronedarone is a multichannel blocking drug similar in structure to amiodarone but without iodine. A study of 4300 patients demonstrated its safety in patients with AF who did not have advanced heart failure (24). As a result, dronedarone is approved by the U.S. Food and Drug Administration (FDA) to reduce hospitalizations in patients with AF but is contraindicated for decompensated heart failure (24). As a result, dronedarone is approved by the U.S. Food and Drug Administration (FDA) to reduce hospitalizations in patients with AF but is contraindicated for decompensated heart failure (24).

When should clinicians use antiarrhythmic drugs to prevent the recurrence of atrial fibrillation?
Antiarhythmic drugs have only modest effects compared with placebo in prolonging the time to recurrence of AF (25) (Table 1). Therefore, antiarrhythmic drug therapy is generally considered effective if it reduces the frequency of episodes and symptoms.

The Canadian Trial of Atrial Fibrillation randomly assigned 403 patients to amiodarone, sotalol, or propafenone and found that after mean follow-up of 16 months, recurrence of AF was 35% for amiodarone therapy compared with 63% for sotalol or propafenone therapy (26).

Some nonantiarrhythmic drugs, such as angiotensin-converting enzyme inhibitors and statins, reduce the incidence of AF in patients with heart failure, presumably because of their antithrombotic effects (27).

When is anticoagulation indicated for patients with atrial fibrillation?
Patients with paroxysmal, persistent, and permanent AF have the same indications for anticoagulation. Anticoagulation is indicated when the risk for thromboembolism exceeds that for anticoagulation-associated bleeding (8, 17). For example, a patient older than 65 years with AF and no other risk factors has a risk for thromboembolism of about 1%, which approximates the risk for major bleeding on warfarin when the international normalized ratio (INR) is between 2.0 and 3.0 (28-30).

Because of the delicate balance between risk and benefit, investigators have developed guidelines to indicate which patients with AF warrant anticoagulation therapy. The most popular of these guidelines is the CHADS, (Cardiac Failure, Hypertension, Âge, Diabetes, and Stroke [Doubled]) score (31, 32), which is discussed in Table 2, and Table 3 presents recommendations for therapy based on this score. Clinicians should consider long-term anticoagulation in patients who are at high risk for recurrent AF or have asymptomatic AF, intracardiac thrombus, or known risk factors for thromboembolism, which include age 275 years, recent heart failure, left ventricular dysfunction, diabetes mellitus, hypertension, and previous thromboembolism. Many clinicians use a cutoff of 65 rather than 75 years to initiate warfarin
therapy when the patient also has coronary artery disease.

A 2007 meta-analysis of 28,044 patients with AF in 29 clinical trials reported that, compared with control patients, patients on adjusted-dose warfarin (6 trials, 2900 participants) had 64% (95% CI, 49% to 74%) fewer strokes and patients on antiplatelet agents (8 trials, 4876 participants) had 22% (CI, 6% to 35%) fewer strokes. Warfarin was superior to antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12,963 participants), and both therapies were associated with a beneficial tradeoff between strokes and major extracranial hemorrhages (33).

Some recent data indicate that current incidences of stroke and bleeding are lower because of improved therapy for hypertension (34), and other recent data indicate that the incidence of major bleeding remains high in the elderly (35). As a result, some experts advise alternative therapy for anticoagulation (36), but consensus recommendations for anticoagulation in patients with AF have not changed. Also, although genetic tests can identify variants in some of the enzymes that control warfarin metabolism (37), most experts do not recommend using these genetic tests until clinical trials determine whether the information they provide can improve patient outcomes from better warfarin dosing.

**What anticoagulation regimens should clinicians use in patients with atrial fibrillation?**

Warfarin is the first choice for anticoagulation in patients with AF, and the dose should be adjusted to an INR of 2.0 to 3.0. Most patients with prosthetic valves should have the warfarin dose adjusted to an INR of 2.5 to 3.5. Aspirin 325 mg/d can be used as an alternative to warfarin in the following circumstances: contraindication/allergy to warfarin; no previous stroke or transient ischemic attack; ≤75 years of age; and no hypertension, diabetes, or heart failure (38). Aspirin plus clopidogrel prevents more strokes than aspirin alone (39), but this combination is not as effective as warfarin and has a bleeding risk equivalent to that of warfarin (40).

In patients at lower risk for thromboembolism, the clinician can start warfarin without a loading dose or concurrent heparin, but patients at higher risk for thromboembolism should be hospitalized and given

---

**Table 2. Stroke Risk in Patients with Nonvalvular Atrial Fibrillation Not Treated with Anticoagulation According to CHADS2 Index**

<table>
<thead>
<tr>
<th>CHADS2 Risk Criteria</th>
<th>Score</th>
<th>Adjusted Stroke Rate (%/y)† (95% CI)</th>
<th>CHADS, Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past stroke or TIA</td>
<td>2</td>
<td>1.9 (1.2 to 2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>1</td>
<td>2.8 (2.0 to 3.8)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>4.0 (3.1 to 5.1)</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>5.9 (4.6 to 7.3)</td>
<td>3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>8.5 (6.3 to 11.1)</td>
<td>4</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
<td>12.5 (8.2 to 17.5)</td>
<td>5</td>
</tr>
<tr>
<td>120</td>
<td></td>
<td>18.2 (10.5 to 27.4)</td>
<td>6</td>
</tr>
</tbody>
</table>

CHADS2 = Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); TIA = transient ischemic attack.

* Reproduced from reference 5 with permission from the American Heart Association.
† The adjusted stroke rate was derived from multivariate analysis assuming no aspirin use.

Data from from references 30 and 31.

**Table 3. Antithrombotic Therapy for Patients with Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>Aspirin, 81–325 mg daily</td>
</tr>
<tr>
<td>1 moderate risk factor</td>
<td>Aspirin, 81–325 mg daily or warfarin (INR, 2.0–3.0, target 2.5)</td>
</tr>
<tr>
<td>Any high risk factor or more than 1 moderate risk factor</td>
<td>Warfarin (INR, 2.0–3.0, target 2.5)*</td>
</tr>
</tbody>
</table>

### Less-Validated or Weaker Moderate Risk Factors

<table>
<thead>
<tr>
<th>High Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke, TIA, or embolism</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Prosthetic heart valve†</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; LV = left ventricular; TIA = transient ischemic attack.

* Reproduced from reference 5 with permission from the American Heart Association.
† If mechanical valve, target INR >2.5.
unfractionated heparin while waiting to achieve target levels for oral anticoagulation. Data on use of low-molecular-weight heparin in this setting are limited.

Warfarin should be used to achieve an INR of 2.0 to 3.0 for at least 3 to 4 consecutive weeks before cardioversion and at least 4 weeks after cardioversion in patients with AF of undetermined duration or AF lasting more than 48 hours. An alternative approach is to perform a transesophageal echocardiogram, and if clot is not present, anticoagulate with heparin for 48 hours before cardioversion followed by 4 weeks of warfarin anticoagulation (40). Patients with thrombus in the left atrial appendage must be anticoagulated for 4 weeks before cardioversion regardless of the duration of AF, and most clinicians repeat the transesophageal echocardiogram before cardioversion to confirm that the thrombus has resolved.

Warfarin has a narrow therapeutic window, and its metabolism is affected by many drug and dietary interactions, requiring frequent INR monitoring and dosage adjustments. These limitations have prompted a search for alternative anticoagulants.

One clinical trial of dabigatran, a direct thrombin inhibitor, compared 2 doses (110 mg and 150 mg twice daily) of dabigatran with warfarin in patients who had nonvalvular AF. The lower dose of dabigatran was as effective as warfarin in preventing strokes, and it was associated with fewer bleeding complications than warfarin. The higher dose of dabigatran was more effective than warfarin in preventing strokes and caused an equivalent number of bleeding events (41).

The FDA has approved dabigatran at 150 mg twice daily for prevention of stroke and systemic embolism in persons with AF and creatinine clearance greater than 30 mL/min. However, the FDA approval does not allow a superiority claim over warfarin.

When should clinicians consider nondrug therapies for patients with atrial fibrillation?

Clinicians should consider nondrug therapy only after failure of drug therapy. Nondrug therapies include use of a catheter or surgery to ablate the atrioventricular node followed by permanent pacing, catheter or surgical ablation of parts of the atrium where AF begins, and occluding the left atrial appendage for stroke prevention.

Atrioventricular nodal catheter ablation is used when pharmacologic rate control cannot be achieved, usually because of intolerance to medications. This situation is most common in elderly patients or patients with advanced heart failure or obstructive pulmonary disease, which limits the use of β-blockers. Atrioventricular nodal ablation is highly effective (42) but requires pacemaker insertion and can lead to progressive left ventricular dysfunction. Pacing therapy without atrioventricular nodal ablation has little effect on the burden of AF but may be helpful in patients with paroxysmal AF and symptomatic bradycardia, which is often a side effect of drug therapy.

Ablation of parts of the atrium where AF begins has been shown to be effective in preventing recurrent symptomatic AF in highly selected patients (43). The ideal patient is a young, otherwise healthy person without structural heart disease who has paroxysmal AF. Recent guideline statements have acknowledged that it may be reasonable to provide this therapy for highly symptomatic patients with paroxysmal AF in whom an attempt at antiarrhythmic drug therapy has failed. This relatively aggressive approach may prevent progressive AF-related morbidity (e.g., residual risk for stroke, medication side effects), but long-term benefit on mortality has not been demonstrated. The effect of
In the Clinic

last considered the
What’s New in This Update?

about what type of monitoring is

Although there are few studies

they can be recommended (45).

How should clinicians monitor patients with atrial fibrillation?

Although there are few studies about what type of monitoring is

appropriate for patients with AF, most clinicians agree that patients should

have regular follow-up to determine the effectiveness of therapy. For many

patients, monitoring warfarin anticoagulation drives the frequency of fol-

low-up. During these visits clinicians should also ask about palpitations,

easy fatigability, and dyspnea on exertion to determine whether symptoms

are adequately controlled. In addition, they should measure resting and exer-

cise heart rates to determine the adequacy of therapy. Patients who have

not improved on rhythm-control drugs should be switched to rate-control

drugs. Except for amiodarone, which requires liver and thyroid function

studies every 6 months and chest radiography every year, routine tests

drug side effects are not necessary.

Treatment... Atrial fibrillation treatment goals include reducing the frequency and

severity of symptoms, preventing stroke, and preventing tachycardia-related car-

diomyopathy. Selection of patients for anticoagulation with aspirin or warfarin

should be based on the CHADS2 score. Focus treatment first on rate control by us-

ing beta-blockers or calcium-channel antagonists aiming for a resting rate be-

tween 60 and 110 beats per minute. Rhythm control may be reasonable in pa-

tients who do not respond to rate control. Atrial ablation and atrioventricular

nodal ablation therapy may be appropriate for selected patients with highly

symptomatic AF despite drug therapy.

What’s New in This Update?

In the Clinic last considered the management of AF in 2008 (46).

Since then, several important changes have occurred. In the rate-control strategy for the drug

treatment of AF, the upper target for heart rate at rest has increased from 80 to 110 beats per minute

(18). Dronedrone, a new antirhythmic drug similar to amio-

darone in effectiveness but with fewer side effects, has become available for the management of

patients with AF, primarily in the rhythm-control strategy (19, 24).

Although genetic tests can identify variants in some of the en-

zymes that control warfarin metabolism (37), most experts do not

recommend using these genetic tests until clinical trials determine

whether the information they provide improves patient outcomes.

Dabigatran is a new anticoagulant that in early trials appears to be as

effective as warfarin for preventing thromboembolism but has

fewer adverse effects (41). The FDA has recently approved it for

prevention of stroke and systemic embolism in patients with AF.

Catheter ablation of parts of the atrium where AF begins has be-

come more widely accepted for

preventing recurrent AF in select-
ed patients, especially for young

and otherwise healthy persons

without structural heart disease

who have paroxysmal AF (43, 44).

CLINICAL BOTTOM LINE

40. ACTIVE Writing Group of the ACTIVE Investigators. Clopi-

dogrel plus aspirin versus oral anticoagulation for atrial fibr-

illation in the Atrial fibrillation Clopidogrel Trial with Inver-

sartan for prevention of Vascular Events (ACTIVE I): a ran-


(PMID: 16763758)

41. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steer-

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gatran versus war-

farin in patients with atrial fibrillation. N


Epub 2009 Aug 30.

(PMID: 19717840)

42. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clini-

ical outcomes after ablation and pacing therapy for atrial fib-

rillation: a meta-


(PMID: 10715260)

43. Packer DL, Asir-

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apy of atrial fibrilla-

tion. J Cardiovasc

Electrophysiol. 2003;14:S296-309.

(PMID: 15005218)

44. Crandall MA, Bradley DJ, Packer DL, Asir-

vatham SJ. Contem-

porary management of atrial fibrillation: update on anticoag-

ulation and invasive management strate-

ges. Mayo Clinic


(PMID: 19567719)

45. Cruz-Gonzalez I, Yan \( B \), Lam YY. Left atrial appendage exclu-

sion: state-of-the-art. Catheter Cardiovasc

Inter. 2011;72:806-

13. (PMID: 20888009)
In the Clinic

Atrial Fibrillation

PIER Modules
www.pier.acponline.org
Access the PIER module on atrial fibrillation for updated, evidence-based information designed for rapid access at the point of care.

Quality Measures
pier.acponline.org/qualitym/prv.html
Access the PIER Quality Measure Tool, which links newly developed quality measures issued by the Ambulatory Quality Alliance and the Physician Quality Improvement QA Alliance and CMS’s Physician Quality Reporting Initiative program to administrative criteria for each measure and provides clinical guidance to help implement the measures and improve quality of care.

Patient Information
www.annals.int therapeutic tools
Download copies of the Patient Information sheet that appears on the following page for duplication and distribution to your patients.

Anticoagulation Flow Sheet
Download a copy of a flow sheet to help manage patients on warfarin.

Guidelines
www.americanheart.org/downloadable/heart/222_ja20017993p_1.pdf
Access the American Heart Association, American College of Cardiology, and European Society of Cardiology joint 2006 guidelines for the management of patients with atrial fibrillation.
www.annals.org/cgi/reprint/139/12/1009.pdf
Access the American College of Physicians/American Academy of Family Physicians 2003 guidelines for the management of newly detected atrial fibrillation.
www.nice.org.uk/Guidance/CG36
Access 2010 guidelines for the management of atrial fibrillation from the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology.

Do U.S. stakeholders consider management of patients with atrial fibrillation when evaluating the quality of care physicians deliver?
The Centers for Medicare & Medicaid Services has issued specifications for 74 measures that make up the 2008 Physician Quality Reporting Initiative, although none of them directly measure the quality of AF therapy. However, one of the stroke measures examines the percentage of patients 18 years of age or older with a diagnosis of ischemic stroke or transient ischemic attack and documented paroxysmal, persistent, or permanent AF who were prescribed an anticoagulant at discharge.

What do professional organizations recommend with regard to the management of patients with AF?
In 2003, the American College of Physicians and the American Academy of Family Physicians released a guideline on AF management (47). The material presented in this review has been updated and is consistent with the 2006 guidelines from the American Heart Association and American College of Cardiology (17) and the 2010 guidelines by the European Society of Cardiology (48).
THINGS YOU SHOULD KNOW ABOUT ATRIAL FIBRILLATION

What is atrial fibrillation?

- Atrial fibrillation is an irregular and sometimes very fast heart beat. Atrial fibrillation can come and go or be constant. It is more common in people with heart conditions and in older people than in younger people.

Atrial fibrillation can lead to 3 bad health outcomes:

- Symptoms can make a person unable to do their usual activities.
- Over the long term, a very fast heartbeat can damage heart muscle.
- Atrial fibrillation can cause stroke when blood clots form in the heart and travel to the brain.

How would I know if I have atrial fibrillation?

- Many people with atrial fibrillation have no symptoms and don’t know that they have it.
- When people have symptoms, they include palpitations (pounding in the chest), shortness of breath, or tiredness.
- Your doctor may see atrial fibrillation on an electrocardiogram (ECG) if an episode occurs during the test.
- If you have symptoms that could be atrial fibrillation but your ECG is normal, your doctor may send you for a test that records your heartbeat while you go about your usual activities.
- If you have atrial fibrillation, your doctor may do an echocardiogram to look for heart problems. Echocardiograms use sound waves to take pictures of the heart.

What is the treatment?

- Many patients with atrial fibrillation need to be on drugs to prevent stroke. Some people need only aspirin. Others need to take the blood thinner warfarin.
- Treatment usually includes drugs to slow the heart down or make it more regular.
- Less often, more aggressive treatment with catheters, surgery, or a pacemaker is needed.
- Atrial fibrillation treatment can have dangerous side effects. It is important to follow instructions and see your doctor regularly.

For More Information

www.nlm.nih.gov/medlineplus/tutorials/atrialfibrillation/htm/_no_50_no_0.htm
MedlinePlus

www.hrspatients.org/patients/heart_disorders/atrial_fibrillation/default.asp
Heart Rhythm Society

circ.ahajournals.org/cgi/content/full/117/20/e340
American Heart Association
1. An 88-year-old man is evaluated for follow-up of persistent atrial fibrillation with a rapid ventricular response diagnosed several months ago. His initial diagnosis was made during evaluation before cataract surgery. He underwent transesophageal echocardiography-guided cardioversion after diagnosis, but the atrial fibrillation recurred within 2 weeks. He has been managed with warfarin, digoxin, and verapamil. He was initially prescribed atenolol, but discontinued it because of side effects of fatigue and impaired concentration and memory. He is entirely asymptomatic despite an inadequately controlled ventricular rate. He also has hypertension treated with valsartan. He states that he generally is averse to taking more medications.

On physical examination, his blood pressure is 140/80 mm Hg, and his pulse is 147/min. Cardiac auscultation reveals an irregularly irregular rhythm and a grade 2/6 holosystolic murmur. Estimated central venous pressure is 6 cm H₂O. The lungs are clear to auscultation and there is no edema. Serum thyroid-stimulating hormone level is normal.

Which of the following is the most appropriate management for this patient?
A. Add amiodarone
B. Add digoxin
C. 24-hour ambulatory monitoring
D. Implanted loop recorder

2. A 42-year-old man is evaluated for recurrent, highly symptomatic paroxysmal atrial fibrillation. He was initially diagnosed 6 months ago. His evaluation revealed no underlying cause and his resting electrocardiogram and echocardiogram were normal. Despite treatment with metoprolol, episodes occur 3 to 4 times daily and last from a few minutes to several hours. During events, he feels drained and unable to concentrate, with a sensation of an irregular heartbeat. He experiences dyspnea on exertion and lightheadedness, but denies chest discomfort and syncope. Episodes are triggered by activity, caffeine, and alcohol (both of which he discontinued upon diagnosis). He takes no medications other than the metoprolol.

On physical examination, blood pressure is 130/60 mm Hg and pulse is 70/min and regular. S₁ and S₂ are normal, and there is no murmur or extra heart sounds. Estimated central venous pressure is 5 cm H₂O, and the lungs are clear. There is no edema. The remainder of the physical examination is normal.

Which of the following is the most appropriate management for this patient?
A. Add amiodarone
B. Add digoxin
C. Change hydrochlorothiazide to furosemide
D. Increase metoprolol dosage

3. A 60-year-old woman is evaluated for follow-up after hospitalization 2 weeks ago for pulmonary edema and volume overload that readily resolved with intravenous diuretics. She is currently feeling well without edema or shortness of breath. A stress echocardiogram done in the hospital was negative for ischemia and showed an ejection fraction of 60% and no significant valvular abnormalities. She has a history of hypertension, hyperlipidemia, and chronic atrial fibrillation. She takes metoprolol (75 mg twice daily), hydrochlorothiazide, warfarin, aspirin, and pravastatin.

On physical examination, she is afebrile. Blood pressure is 150/90 mm Hg and pulse is 50/min. Jugular veins are not distended, and the lungs are clear. Cardiac examination shows an irregularly irregular rhythm with variable intensity of the S₁ with no murmurs. There is no edema.

Which of the following is the most appropriate adjustment to her treatment?
A. Add candesartan
B. Add digoxin
C. Change hydrochlorothiazide to furosemide
D. Increase metoprolol dosage

4. A 77-year-old woman is admitted to the hospital for intermittent dizziness over the past few days. She does not have chest discomfort, dyspnea, palpitations, syncope, orthopnea, or edema. She underwent coronary artery bypass graft surgery 6 years ago after myocardial infarction. She has hypertension, hyperlipidemia, and paroxysmal atrial fibrillation with a history of rapid ventricular response. Over the past several years, she has “slowed down” and has had problems with memory, which she attributes to aging. Medications are metoprolol, hydrochlorothiazide, pravastatin, lisinopril, aspirin, and warfarin.

On physical examination, her blood pressure is 137/88 mm Hg and her pulse is 52/min. Estimated central venous pressure is 7 cm H₂O. The point of maximum impulse is felt in the fifth intercostal space and at the midcostal line. Cardiac auscultation reveals bradycardia with regular S₁ and S₂, as well as an S₃. A grade 2/6 early systolic murmur is heard at the left upper sternal border. The lungs are clear to auscultation. Edema is not present.

On telemetry, she has sinus bradycardia with rates between 40/min and 50/min, with two symptomatic sinus pauses of 3 to 5 seconds each.

Which of the following is the most appropriate management for this patient?
A. Add amiodarone
B. Discontinue metoprolol
C. Echocardiography
D. Pacemaker implantation

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.