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In the Clinic®

Atrial Fibrillation

New options for managing atrial fibrillation have become available since December 2010, when In the Clinic last considered this subject. For example, the CHA_2DS_2-VASc score has become the standard for predicting thromboembolic risk. In addition, non–vitamin K–dependent oral anticoagulants have been approved for prophylaxis against thromboembolic disease, and agents to reverse these drugs are becoming available. Moreover, catheter ablation is being used more frequently to prevent recurrent atrial fibrillation, and closure of the left atrial appendage with a device can now be done for patients who are unable to receive systemic anticoagulation.

Diagnosis

Treatment

Patient Information

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Atrial fibrillation 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. This disorder is a major cause of morbidity, mortality, and health care expenditure. In the United States, 2.3 million persons have atrial fibrillation, and this number is expected to increase to 5.6 million by 2050 (1). Atrial fibrillation is associated with a 5-fold risk for stroke and is estimated to cause 15% of all strokes (2). It is also associated with a 2-fold risk for all-cause mortality, independent of comorbid conditions (3).

Diagnosis

Who is at risk for atrial fibrillation?

Atrial fibrillation occurs in fewer than 1% of persons 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 white persons than in black persons (1). The risk for atrial fibrillation increases with aging and the presence and severity of underlying heart disease, particularly congestive heart failure and valve disease. Other commonly associated conditions include sleep-disordered breathing and hypertension.

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. Chest pain and palpitations are particularly common in younger patients, whereas fatigue and shortness of breath are more often seen in elderly persons (4). However, many persons, particularly the elderly, have asymptomatic (silent) atrial fibrillation, including some with severe symptoms during other episodes of atrial fibrillation (5). Silent atrial fibrillation is often recognized during routine interrogation of pacemakers placed for bradycardia in patients with no history of atrial fibrillation (6). Symptoms are generally greatest at disease onset—when episodes are typically paroxysmal and rates are rapid (before rate-controlling drugs are prescribed)—and tend to diminish over time, especially when arrhythmia becomes persistent. Symptoms result predominantly from elevation of ventricular rate (either at rest or when exacerbated by exercise) and to a lesser degree from the irregular ventricular rate and loss of atrial contribution to cardiac output.

On physical examination, signs include a faster-than-expected heart rate, which varies greatly from patient to patient; an "irregularly irregular" time between heart sounds; 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) of a patient with atrial fibrillation. It shows that a single ECG is sufficient to diagnose atrial fibrillation, provided it is recorded during the arrhythmia. However, atrial fibrillation is often paroxysmal, so a normal result on one ECG does not rule it out. Monitoring for a longer time can be helpful when atrial fibrillation is suspected and the initial ECG is normal. In patients with daily symptoms, 24- or 48-hour continuous Holter monitoring is usually sufficient for diagnosis. New patch monitors allow 7 to 10 days

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4. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. Am Heart J. 2006;152:1097-103. [PMID: 17161061]
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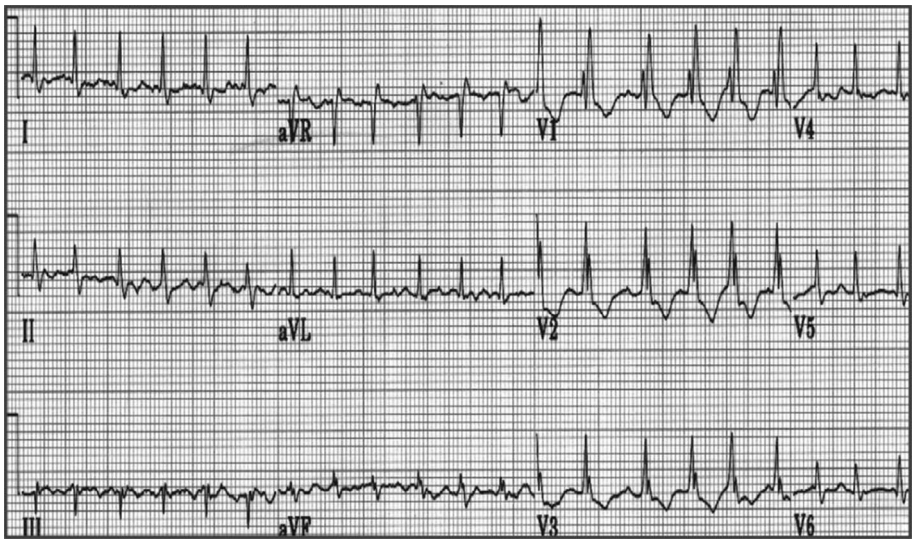
Figure 1. **Electrocardiogram showing atrial fibrillation with rapid ventricular rate.**



of continuous monitoring without attached leads and are a good alternative to traditional Holter monitors (7). 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 miss atrial fibrillation in patients with very infrequent episodes. Therefore, confirming the diagnosis in some patients with nonspecific symptoms and long periods between episodes can take years.

Implanted pacemakers and implantable cardioverter-defibrillators with atrial leads identify and record both symptomatic and asymptomatic atrial fibrillation. Subcutaneous implanted monitors are also increasingly used to identify atrial fibrillation, particularly in patients with cryptogenic stroke in whom identification of atrial fibrillation will result in initiation of anticoagulation (8).

What is the role of history and physical examination?

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, including pulmonary disease, hyperthyroidism, use of adrenergic drugs (such as those used to treat pulmonary disease) or other stimulants, and use of alcohol. Other risk factors include diabetes, obesity, and sleep-disordered breathing. A family history might identify first-degree relatives with atrial fibrillation, which may have therapeutic implications in the future.

What other electrocardiographic arrhythmias can be confused with atrial fibrillation?

Other arrhythmias that are commonly confused with atrial fibrillation include sinus rhythm with frequent premature atrial contractions, atrial flutter, and atrial tachycardia. The key electrocardiographic findings of atrial fibrillation are the absence of P waves

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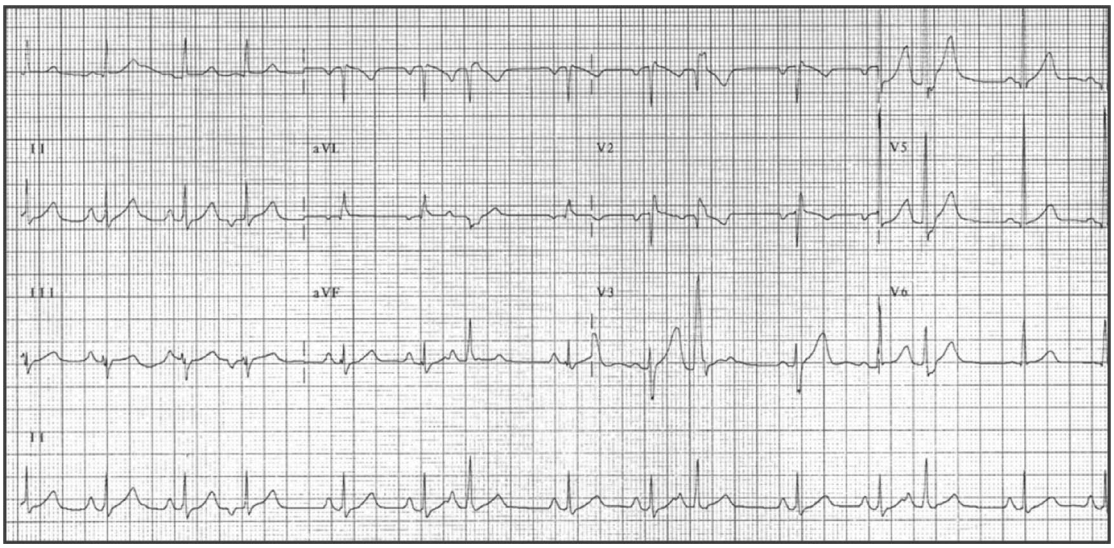
Figure 2. **Electrocardiogram showing sinus rhythm with frequent premature atrial contractions.**



and the presence of an irregular ventricular rhythm without a recurring pattern. When an irregular rhythm is present but the diagnosis of atrial fibrillation is uncertain, clinicians should examine long recordings from multiple leads to look 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 atrial fibrillation, but the presence of P waves and other features identifies sinus rhythm with frequent premature atrial contractions. The QRS is wide with the premature beat because of aberrant conduction. **Figure 3** is an ECG of another irregular rhythm that might be attributed to atrial fibrillation, 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 classification of atrial fibrillation is a subject of debate, the most accepted convention categorizes atrial fibrillation as paroxysmal, persistent, long-standing persistent, or permanent (8) (see the Box). In paroxysmal atrial fibrillation, episodes terminate without intervention in less than 7 days (often within 24 hours). Persistent atrial fibrillation lasts longer than 7 days or requires an intervention, such as cardioversion, to restore sinus rhythm. Long-standing persistent atrial fibrillation is continuous atrial fibrillation lasting longer than 12 months. Permanent atrial fibrillation means that the arrhythmia is continuous, and interventions to restore sinus rhythm have either failed or not been attempted. Categories can change over time, so clinicians should classify patients according to the current or most common pattern.

These distinctions are useful because they may predict the response to therapy. For example, patients may be less likely to respond to antiarrhythmic drug therapy or nonpharmacologic therapy as the pattern progresses from paroxysmal to persistent to permanent. Patients in all categories should be assessed for the need for anticoagulation independent of the frequency or duration of atrial fibrillation episodes.

10. Naito M, David D, Michelson EL, Schaffenburg M, Dreifus LS. The hemodynamic consequences of cardiac arrhythmias: evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm and atrial fibrillation in a canine model. Am Heart J. 1983;106:284-91. [PMID: 6869209]
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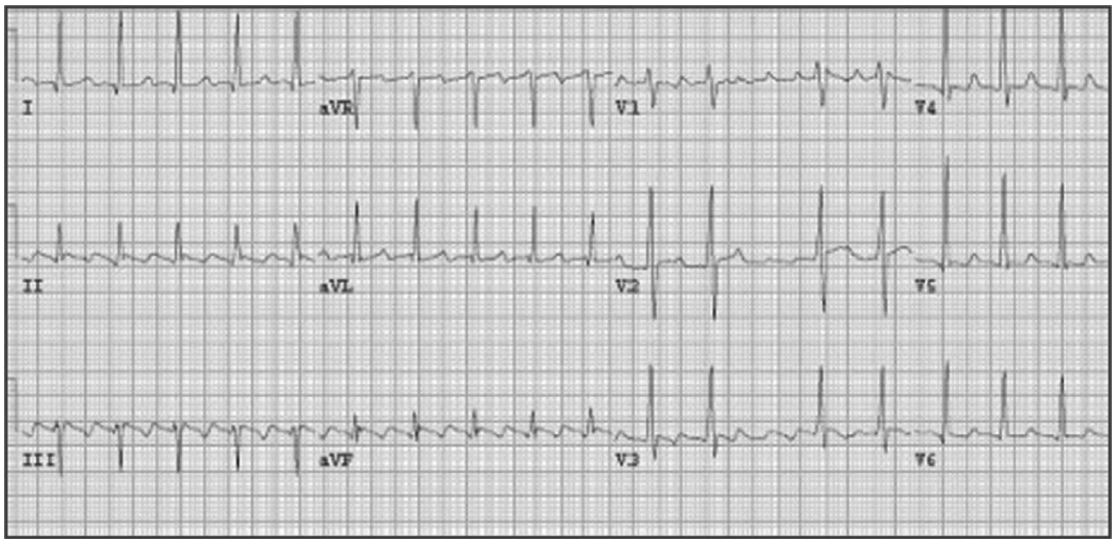
Figure 3. **Atrial flutter.**



Classic "saw-tooth" flutter waves are seen in all 12 leads, and the ventricular response is mostly regular. (There is a transient change from 2:1 to 4:1 atrioventricular conduction following the 12th QRS complex.)

What laboratory studies should clinicians obtain in patients newly diagnosed with atrial fibrillation?

When patients are initially diagnosed with atrial fibrillation, clinicians should measure serum electrolytes and thyroid-stimulating hormone levels to identify possible causes. They should also perform blood tests of renal and hepatic function to guide selection of drug therapy and check the stool for occult blood before starting anticoagulation. Transthoracic echocardiography (TTE) helps reveal underlying structural heart disease that may not otherwise be recognized and can identify tachycardia-induced cardiomyopathy, which may occur when atrial fibrillation has been present for an extended period. It is also indicated to rule out atrial clot when transthoracic images are inadequate or cardioversion is planned in a patient who has received anticoagulation for less than 3 weeks. In patients with appropriate clinical indications, additional tests may be warranted for pulmonary embolism, acute myocardial infarction, or acute heart failure.

What underlying conditions should clinicians look for?

Eighty percent of patients with atrial fibrillation have structural heart disease, particularly hypertension but also coronary artery disease, valvular heart disease, or cardiomyopathy. Atrial fibrosis occurs frequently with structural heart disease and is considered central to the arrhythmia's pathogenesis (9). The commonly used term "nonvalvular" atrial fibrillation was originally meant to refer to atrial fibrillation in the absence of rheumatic heart disease but has now been generalized to atrial fibrillation in the absence of other forms of valve disease.

Some acute illnesses are associated with atrial fibrillation, 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. The likelihood of recurrence in postsurgical patients and the best methods to screen for re-

Classification of Atrial Fibrillation

Paroxysmal: Episodes spontaneously terminate in 7 d

Persistent: Episodes last >7 d and require intervention to restore sinus rhythm

Long-standing persistent: Continuous atrial fibrillation lasting >12 mo

Permanent: Interventions to restore sinus rhythm have either failed or have not been attempted

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currence remain undefined. Obesity and sleep apnea are also associated with increased incidence.

Atrial fibrillation can occur in persons with no predisposing conditions. These patients are typically men aged 40 to 50 years. Symptoms often occur at night, at rest, after 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 atrial fibrillation 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 are asymptomatic. An ECG during episodes is 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 patch continuous monitor may be helpful. The initial assessment should include laboratory tests for electrolytes, thyroid-stimulating hormone, and renal function to rule out underlying disorders or contraindications to therapies. An echocardiogram should be done to look for structural heart disease.

CLINICAL BOTTOM LINE

Treatment

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

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

Although atrial fibrillation is not always symptomatic, when present the symptoms can be disabling. They are usually caused by inappropriately rapid ventricular rates or the irregularity of the ventricular response (10). 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, or hypertrophic obstructive cardiomyopathy.

Stroke is the most common form of clinically detectable arterial thromboembolism associated with atrial fibrillation. In patients with nonvalvular atrial fibrillation, the average annual risk for arterial thromboembolism, including stroke, is 5%; the risk is particularly high in patients older than 75 years and those with a history of stroke or transient ischemic attack (8). Left atrial thrombi, mostly arising from the left atrial appendage, are believed to cause most strokes in patients with atrial fibrillation (9).

Treating the tachycardia of atrial fibrillation is important because tachycardia can lead to cardiomyopathy (11).

When should clinicians consider immediate cardioversion?

Prompt cardioversion should be considered for new-onset atrial fibrillation when arrhythmia has been present for less than 48

15. Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA): Clinical Trials.gov identifier: NCT0091150.
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hours. One common example is a hospitalized patient on cardiac monitoring. Most patients with atrial fibrillation 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 atrial fibrillation and Wolff-Parkinson-White syndrome can have extremely rapid atrioventricular conduction mediated by the accessory pathway, which can be life-threatening and requires urgent cardioversion.

Which patients should clinicians consider hospitalizing?

Although atrial fibrillation is usually managed in an outpatient setting, clinicians should consider hospitalizing patients with atrial fibrillation when management requires close monitoring for safety (see the Box).

Should clinicians attempt rate control or rhythm control?

Traditionally, most clinicians have preferred rhythm control to rate control, but high-quality clinical trials now show that compared with rate control, rhythm control generally does not improve mortality, frequency of stroke or hospitalization, or quality of life (12–14). Rate control is easier and prevents exposure to the potential adverse effects of antiarrhythmic agents. However, rhythm control may be useful in selected patients with severe symptoms (before or after failure of rate control) and in younger patients without structural heart disease.

The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial included 4060 patients with atrial fibrillation 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 (12).

A subsequent trial extended these observations to patients with severe heart failure by randomly assigning 1376 patients to rate control or rhythm control. Patients had atrial fibrillation, left ventricular ejection fraction of 0.35 or less, and heart failure symptoms. At 37 months, 25% of patients in the rate-control group died of cardiovascular disease compared with 27% in 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 (14).

In addition, these trials did not include catheter ablation, surgical ablation, or other nonpharmacologic approaches to the maintenance of sinus rhythm. Ongoing trials are addressing this issue (15).

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 atrial fibrillation, even if rhythm control is ultimately the goal. Although criteria for rate control vary with patient age, the traditional target has been 60 to 80 beats per minute at rest and 90 to 115 beats per minute during moderate exercise. However, a study comparing a strategy of lenient rate con-

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 patient is unable to be monitored in an outpatient setting)
- For acute anticoagulation if risk for stroke is very high
- Need for telemetry monitoring during initiation of certain drugs
- Procedures, such as cardiac catheterization, electrophysiologic studies, and catheter or surgical ablation and placement of pacemakers or implantable defibrillators

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trol (resting heart rate ≤110 beats/min) with a strategy of strict rate control (≤80 beats/min) found no advantage to the stricter strategy (16). Recommended first-line therapy to decrease atrioventricular nodal conduction includes β-blockers and nondihydropyridine calcium-channel antagonists.

Digitalis and amiodarone slow conduction through the atrioventricular node but are not recommended as first-line monotherapy for rate control (9). 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. It does have the advantage of rate slowing without the potential for lowering blood pressure. Amiodarone is occasionally used to reduce ventricular response if other agents have failed, but this practice is difficult to justify because of the drug's associated toxicities (17, 18).

What strategies should clinicians consider for rhythm control?

Rhythm control is no longer the preferred strategy for most patients with atrial fibrillation. However, the trials comparing rate and rhythm control have not included younger patients or those with highly symptomatic atrial fibrillation. Therefore, it is reasonable to consider rhythm control in these patients. Also, experienced clinicians often prefer rhythm control for the first episode of symptomatic atrial fibrillation 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. In these patients, the conversion rate with antiarrhythmic drugs is significantly 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 atrial fibrillation lasting longer than 48 hours. In addition, serum potassium, serum magnesium, and ionized calcium levels should be greater than 4.0, 1.0, and 0.5 mg/dL, respectively. In most cases, cardioversion should be performed in a hospital setting to permit adequate monitoring of rate control and potential adverse effects, such as bradycardia and the proarrhythmic effects of antiarrhythmic drugs (9).

Antiarrhythmic drugs other than amiodarone generally have equal 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 (19). 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, disopyramide, and procainamide, are used infrequently because of noncardiac side effects and a concern for proarrhythmia. Drugs that block potassium chan-

Table 1. **Drug Therapy for Rate and Rhythm Control in Atrial Fibrillation**

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Side Effects*	*Notes*
Rate-controlling agents					
β-Blockers					
Metoprolol	Selective β-1-adrenergic-receptor blocking agent	5 mg IV every 5 min, up to 15 mg; 50–100 mg PO twice daily	Convenient IV administration in NPO patients, rapid onset of action, dependable AV nodal blockade	Bradycardia, hypotension, heart block, bronchospasm (less frequently than nonselective β-blockers), worsening of CHF	
Propranolol	Nonselective β-adrenergic-receptor blocking agent	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	Inexpensive, commonly available	Bradycardia, hypotension, heart block, bronchospasm, worsening of CHF	
Esmolol	Short-acting IV β-1 selective adrenergic receptor blocking agent	0.05–0.2 mg/kg per min, IV	Short-acting, titratable on or off with very rapid half-life	Bradycardia, hypotension, heart block, bronchospasm (less frequent)	Occasionally inconsistent effect in high-catecholamine states
Pindolol	Nonelective β-adrenergic-receptor blocking agent with intrinsic sympathomimetic activity	2.5–20 mg PO 2 to 3 times daily	Less bradycardia, less bronchospasm	Bradycardia, hypotension, heart block	Less propensity for heart block than other β-blockers
Atenolol	Selective β-1-adrenergic-receptor blocking agent	5 mg IV over 5 min, repeat in 10 min; 25–100 mg PO once daily	Does not cross blood-brain barrier; fewer CNS side effects	Bradycardia, hypotension, heart block	
Nadolol	Nonselective β-adrenergic-receptor blocking agent	20–120 mg once daily	Lower incidence of crossing of blood-brain barrier; fewer CNS side effects	Bradycardia, hypotension, heart block	Oral form only
Calcium-channel blockers					
Verapamil	Calcium-channel blocking agent	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	Consistent AV nodal blockade	Hypotension, heart block, direct myocardial depression	Do not use in the Wolff–Parkinson–White syndrome
Diltiazem	Calcium-channel blocking agent	0.25–0.35 mg/kg IV followed by 5–15 mg/h; 120–360 mg PO daily as slow release	Consistent AV nodal blockade	Hypotension, heart block, less myocardial depression	Do not use in the Wolff–Parkinson–White syndrome

Continued on following page

Table 1–Continued

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Side Effects*	*Notes*
Cardiac glycoside: Digoxin	Na+-K+ pump inhibitor; increases intracellular calcium	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	Particularly useful for rate control in CHF	Heart block; digoxin-associated arrhythmias (see Diagnosis section)	Do not use a loading dose. First-line therapy only in patients with decreased LV systolic function. Dosage adjustment required in renal impairment. Not useful for rate control with exercise. Not useful for conversion of AF or atrial flutter to NSR
Antiarrhythmic agents					
Class Ia					
Procainamide	Prolongs conduction and slows repolarization by blocking inward Na+ flux	1–2 g every 12 h (shorter-acting oral preparations are no longer available)	Convenient IV dosing available with maintenance infusion, and conversion to PO tablets. Very effective at converting AF to NSR	Hypotension common (slow rate of infusion), negative inotropic agent, nausea, vomiting, lupus-like syndrome, QT prolongation, proarrhythmia	Not commonly recommended because of frequent side effects. Need to follow drug levels and QT interval for toxicity, adjust dose in patients with renal insufficiency, and avoid in patients with more-than-mild renal function impairment. Not for use in patients with severe LV dysfunction
Quinidine gluconate	Prolongs conduction and slows repolarization; blocks fast inward Na+ channel	324–648 mg PO every 8–12 h	Relatively effective in converting AF to NSR but may take several days to achieve NSR because of PO dosing	Proarrhythmia, nausea, vomiting, diarrhea, QT prolongation	Not commonly recommended because of frequent side effects. Follow drug levels and QT interval for toxicity. Adjust dose in patients with renal insufficiency. Oral agent only
Disopyramide	Similar electrophysiologic properties to procainamide and quinidine	150 mg PO every 6–8 h, or 150–300 mg twice a day	Can be useful in patients with hypertension and normal LV function. Is useful in patients with hypertrophic obstructive cardiomyopathy	QT prolongation (not PR or QRS), torsade de pointes, heart block	Rarely used in current era of antiarrhythmic therapy. Oral agent only, negative inotropic properties. Potent anticholinergic properties can cause urine retention or exacerbation of narrow angle glaucoma
Class Ic					
Flecainide	Blocks Na+ channels (and fast Na+ current)	50–150 mg PO every 12 h. Also, single loading doses of 300 mg are efficacious in conversion of recent-onset AF	Efficacy in paroxysmal AF with structurally normal hearts	Atrial flutter or atrial tachycardia with rapid ventricular response. VT and VF in diseased hearts	Not for use in patients with structurally abnormal hearts
Propafenone	Blocks myocardial Na+ channels	225–400 mg PO every 8 h. Also, single loading doses of 600 mg are efficacious in conversion of recent-onset AF	Efficacy in paroxysmal and sustained AF	Atrial flutter or atrial tachycardia with rapid ventricular response	Antiarrhythmic and weak calcium-channel and β-blocking properties. Not for use in patients with structurally abnormal hearts

Continued on following page

Table 1–Continued

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Side Effects*	*Notes*
Class III					
Ibutilide	Prolongs action potential duration (and atrial and ventricular refractoriness) by blocking rapid component of delayed rectifier potassium current	1 mg IV over 10 min. May be repeated once if necessary	Efficacy in acute and rapid conversion of AF to NSR	Polymorphic VT (torsade de pointes) occurred in 8.3% of patients in a clinical trial (most with LV dysfunction), QT prolongation	In some centers, only used in the electrophysiology laboratory. May also be used to facilitate unsuccessful direct-current cardioversion. IV form only
Amiodarone	Blocks Na+ channels (affinity for inactivated channels). Block calcium channels. Noncompetitive α- and β-receptor inhibitor	5–7 mg/kg IV up to 1500 mg per 24 h; 400–800 mg PO daily, for 3–4 wk, followed by 100–400 mg PO daily	Safest agent for use in patients with structural heart disease. Good efficacy in maintaining NSR chronically	Bradycardia, QT prolongation, hyperthyroidism, lung toxicity, argyria (blue discoloration of skin) with chronic use	Can be used in the Wolff–Parkinson–White syndrome. β-blocking properties
Sotalol	Nonselective β-1 and β-2 blocking agent. Prolongs action potential duration	80–240 mg PO every 12 h	Helpful for rate control because of β-blocking properties	Fatigue, depression, bradycardia, torsade de pointes, CHF	β-blocking properties, but some negative inotropic activity. Lethal arrhythmias possible. Adjust dose in patients with renal insufficiency. Initiate on telemetry
Dofetilide	Blocks rapid component of the delayed rectifier potassium current ($I_{K\gamma}$), prolonging refractoriness without slowing conduction	500 μg twice daily	Able to be used for conversion to and maintenance of NSR. Well-tolerated	QT prolongation, torsade de pointes (2%–4% risk). Greatest risk in patients with baseline prolonged QT, patients with hypokalemia, patients taking other repolarization-prolonging agents, and after conversion to NSR	Must be strictly dosed according to renal function, body size, and age. Contraindicated in patients with creatinine clearance <20 mL/min. Risk–benefit ratio determination in progress per larger clinical experience. No known significant drug interactions. Initiate on telemetry
Dronedarone	Blocks Na+ channels (affinity for inactivated channels). Blocks calcium channels. Noncompetitive α- and β-receptor inhibitor	400 μg twice daily	Modest efficacy. Shown to reduce hospitalizations and cardiovascular mortality in patients with nonpermanent AF	Gastrointestinal intolerance	Contraindicated in patients with permanent AF or decompensated CHF

AF = atrial fibrillation; AV = arteriovenous; CHF = congestive heart failure; CNS = central nervous system; IV = intravenous; LV = left ventricular; NPO = not by mouth; NSR = normal sinus rhythm; PO = by mouth; VF = ventricular fibrillation; VT = ventricular tachycardia.

nels (class III effects), such as sotalol and dofetilide, can prolong the QT interval and cause torsade de pointes.

Amiodarone can cause permanent liver and lung toxicity that is dose- and duration-dependent (17, 18). Liver toxicity causes 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 show a broad range of findings, including segmental or diffuse infiltrates. Other side effects include thyroid dysfunction (hypothyroidism or hyperthyroidism), sun sensitivity, and tremors (18).

Dronedarone is a multichannel blocking drug similar in structure to amiodarone but without iodine and with less antiarrhythmic efficacy. A study of 4300 patients demonstrated its safety in patients who had atrial fibrillation without advanced heart failure (20). As a result, dronedarone is approved by the U.S. Food and Drug Administration (FDA) to reduce hospitalizations in patients with atrial fibrillation but is contraindicated for decompensated congestive heart failure. Another trial in patients with permanent atrial fibrillation found increased mortality associated with dronedarone compared with placebo, and thus it is also contraindicated in this group (21).

When should clinicians use antiarrhythmic drugs to prevent recurrence?

Antiarrhythmic drugs have only modest effects compared with placebo in prolonging the time to recurrence of atrial fibrillation (17) (**Table 1**). Therefore, such 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 a mean follow-up of 16 months, recurrence of atrial fibrillation was 35% for amiodarone compared with 63% for sotalol or propafenone (22).

When is anticoagulation indicated?

Patients with paroxysmal, persistent, and permanent atrial fibrillation have the same indications for anticoagulation. Anticoagulation is indicated when the risk for thromboembolism exceeds that for serious anticoagulation-associated bleeding (9).

Because of the delicate balance between risk and benefit, investigators have developed guides to indicate which patients warrant anticoagulation. The most popular of these is the CHA_2DS_2-VASc (Cardiac Failure, Hypertension, Age 65-74 and ≥75 [Doubled], Diabetes, and Stroke [Doubled], Vascular disease [includes myocardial infarction, aortic plaque and peripheral vascular disease]) score (9,23,24) (**Table 2**). **Table 3** presents recommendations for using the score to choose therapy. Current guidelines recommend anticoagulation for all patients with documented atrial fibrillation (symptomatic or asymptomatic) and 2 or more of the CHA_2DS_2-VASc risk factors. Anticoagulation is considered reasonable but not mandatory when 1 risk factor is present (9).

A 2007 meta-analysis of 28 044 patients with atrial fibrillation in 29 clinical trials reported that, compared with control patients, patients receiving adjusted-dose warfarin (6 trials; n = 2900) had 64% (95% CI, 49% to 74%) fewer strokes and patients receiving antiplatelet agents (8 trials; n = 4876) had 22% (CI, 6% to 35%) fewer strokes. Warfarin was superior to antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials; n = 12 963 participants), and both therapies were associated with a beneficial tradeoff between strokes and major extracranial hemorrhage (25).

What anticoagulation regimens should clinicians use?

Warfarin is the traditional choice for anticoagulation in patients with atrial fibrillation, and the dose should be adjusted to an international normalized ratio (INR) of 2.0 to 3.0. The dose for most patients with prosthetic heart valves should be adjusted to an INR of 2.5 to 3.5. Aspirin 325 mg/d is often used as an alternative to warfarin under the following circumstances: contraindication/allergy to warfarin or to the non–vitamin K–dependent oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban; no previous stroke or transient ischemic attack; age 65 years or younger; and no hypertension, diabetes, or heart failure (9, 26–29). The data supporting aspirin as thromboembolic prophylaxis for atrial fibrillation are very weak and exist only for full-dose therapy. Aspirin plus clopidogrel prevents more strokes than aspirin alone, but this combination is not as effective as warfarin and has an equivalent bleeding risk (30).

Table 2. **CHA_2DS_2 VASc Score**

Characteristic	*Points*
Congestive heart failure	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/transient ischemic attack	2
Vascular disease	1
Age 65–74	1
Sex category (female sex)	1

Table 3. **Guidelines for Thromboembolic Prophylaxis According to CHA_2DS_2-VASc Score**

CHA_2DS_2-VASc Score	*Recommendation*
0	No therapy required
1	No therapy required but treatment with aspirin or an anticoagulant (warfarin, dibagatrin, rivoxaraban, apixaban, or edoxaban) is also reasonable
2 or more	Anticoagulation with warfarin, dibagatrin, rivoxaraban, apixaban, or edoxaban

Table 4. **Non–Vitamin K–Dependent Anticoagulant Medications for Atrial Fibrillation**

Variable	*Dabigatran*	*Rivaroxaban*	*Apixaban*	*Edoxaban*
Mechanism	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Dose	150 mg twice daily	20 mg once daily with food	5 mg twice daily	60 mg once daily in patients with CrCl >50 and ≤95 mL/min
Renal dose adjustment	75 mg twice daily in patients with CrCl 15–30 mL/min	15 mg once daily in patients with CrCl 15–50 mL/min	2.5 mg twice daily in patients with ≥ 2 of: age >80 y, ≤60 kg, creatinine ≥1.5 mg/dL	30 mg once daily in patients with CrCl 15–50 mL/min
Contraindications	CrCl <15 mL/min Mechanical heart valve	CrCl <15 mL/min Mechanical heart valve	CrCl <15 mL/min Mechanical heart valve	CrCl >95 mL/min Mechanical heart valve

CrCl = creatinine clearance.

In patients at lower risk for thromboembolism, the clinician can start warfarin without a loading dose or concurrent heparin, but patients at higher risk should be hospitalized and given unfractionated heparin while waiting to achieve target levels for oral anticoagulation. Non–vitamin K–dependent oral anticoagulants can be started and achieve therapeutic anticoagulation within hours. Data on use of low-molecular-weight heparin in this setting are limited.

Before cardioversion, warfarin should be used to achieve an INR of 2.0 to 3.0 for at least 3 to 4 consecutive weeks in patients with atrial fibrillation of undetermined duration or atrial fibrillation lasting more than 48 hours. Warfarin should be continued for at least 4 weeks after cardioversion. When non–vitamin K–dependent oral anticoagulants are used instead of warfarin, they also are given for 3 to 4 weeks before anticoagulation. Adherence to these agents is more difficult to assess because blood tests are not needed to assess anticoagulation, so patients need to be educated about not missing doses.

An alternative approach is to perform transesophageal echocardiography. If a left atrial clot is not present and anticoagulation has been started, the patient can be cardioverted. It is critical that therapeutic anticoagulation be present at the time of cardioversion and continue uninterrupted for at least 4 weeks (9). Patients with thrombus in the left atrial appendage must receive anticoagulation for 4 weeks before cardioversion regardless of the duration of atrial fibrillation, 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, necessitating frequent INR monitoring and dosage adjustments. These limitations have led to more frequent use of the non–vitamin K–dependent oral anticoagulants.

All 4 non–vitamin K–dependent anticoagulants have been approved as noninferior alternatives to warfarin for prevention of thromboembolism in patients with atrial fibrillation who do not have a mechanical heart valve (26–29) (**Table 4**). These drugs have the advantage of not requiring recurrent blood tests to assess INR and minimal potential for drug–drug interaction. They also are not influenced by diet, act rapidly, and are cleared to varying degrees through the kidneys with guidelines for renal dose adjustment.

An important advantage of the non–vitamin K–dependent oral anticoagulants is their significantly lower risk for intracranial hemorrhage than warfarin. The reason for this beneficial property has yet to be identified. The non–vitamin K–dependent oral anticoagulants are contraindicated in patients with mechanical heart valves (31), but they can be used in patients with native valve disease, except for mitral stenosis (26–29).

Because onset and clearance of non–vitamin K–dependent oral anticoagulants are more rapid than those of warfarin, management is easier when anticoagulation is temporarily discontinued. However, when the anticoagulant effect of warfarin needs to be reversed urgently or immediately, vitamin K, fresh frozen plasma, and prothrombin complex concentrates are available. Antidotes for the non–vitamin K–dependent oral anticoagulants have been developed. Idarucizumab is a humanized antibody fragment that is approved for reversing life-threatening bleeding associated with the direct thrombin inhibitor, dabigatran (32). Andexanet-α is a modified recombinant derivative of factor Xa that acts as a decoy receptor to reverse the effects of rivaroxaban, apixaban, and

edoxaban and is currently under FDA review (33).

When should clinicians consider nondrug therapies?

Nondrug therapies for atrial fibrillation are usually considered after failure of drug therapy. These include catheter ablation of the atrioventricular node followed by permanent pacing, catheter or surgical ablation of parts of the atrium where atrial fibrillation begins, and occluding the left atrial appendage for stroke prevention.

Atrioventricular node 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 nondihydropyridine calcium-channel blockers and β-blockers. Ablation is highly effective for control of excessive tachycardia but requires pacemaker insertion and can lead to progressive left ventricular dysfunction. Pacing therapy without AV node ablation has little effect on the burden of atrial fibrillation but may be helpful in patients with paroxysmal atrial fibrillation and symptomatic bradycardia, which is often a side effect of drug therapy.

Ablation of parts of the left atrium where fibrillation begins has been shown to be effective in preventing recurrent symptomatic atrial fibrillation in highly selected patients (9). The ideal patient has paroxysmal disease, is young and otherwise healthy, and has no structural heart disorders; however, ablation has also shown effectiveness in patients with persistent atrial fibrillation. Recent guidelines acknowledge that this therapy is reasonable for highly symptomatic patients with paroxysmal or persistent atrial fibrillation in whom an attempt at antiarrhythmic drug therapy has failed (9). It is associated with a likelihood of improving symptoms of approximately 70%, but patients may require a second procedure to achieve this level of success. Major complications occur in fewer than 1% of cases and include cardiac perforation, atrioesophageal fistula, pulmonary vein stenosis, and stroke. A minimally invasive surgical ablation (Maze procedure) is also available at specialized centers. It is important to emphasize that ablation should not be considered a cure—it is offered to reduce atrial fibrillation burden and improve symptoms and quality of life. High-quality information on long-term outcomes after the procedure is currently unavailable. A patient's decision to have ablation should not be based on the expectation of avoiding anticoagulation, and there is currently no evidence that any rhythm-control therapy is reliably associated with reduced risk for thromboembolism.

A significant percentage of strokes in patients with atrial fibrillation is believed to occur from emboli originating in the left atrial appendage. The FDA has approved the Watchman device for occlusion of the appendage when a nonpharmacologic alternative to warfarin is sought with consideration of the risks of this device compared with the bleeding risks of warfarin. Major risks include cardiac perforation and embolization of the device (34). Similarly, the atrial appendage can be ligated through a minimally invasive surgical approach; however, this approach has not been prospectively compared with systemic anticoagulation.

How should clinicians monitor patients?

Although there are few studies about what type of monitoring patients with atrial fibrillation should receive, most clinicians agree that regular follow-up is important to determine the effectiveness of therapy. For many patients, monitoring warfarin anticoagulation drives the frequency of follow-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 exercise heart rates to determine the adequacy of therapy. Patients who have not improved on rhythm-control drugs should be switched to rate-control drugs or nonpharmacologic therapy. Amiodarone requires liver and thyroid function studies every 6 months and chest radiography every year. Pulmonary function tests with assessment of DLCO are generally done at the start of therapy and only if pulmonary toxicity is suspected. Patients receiving dofetilide, sotalol, dabigatran, rivaroxaban, apixaban and edoxaban should have renal function tested at least annually to determine the need for dose adjustment.

What's new in this update?

In the Clinic last considered the management of atrial fibrillation in December 2010 (35). There have been several important changes since then. Dronedarone is now contraindicated in the setting of permanent atrial fibrillation. The CHA_2DS_2-VASc score has become the standard for predicting thromboembolic risk. The non–vitamin K–dependent oral anticoagulants have all been approved as alternatives to warfarin for thromboembolic prophylaxis, and a reversal agent for dabigatran is now available. Catheter ablation has become more widely accepted for preventing recurrent atrial fibrillation in selected patients, especially for young and otherwise-healthy persons without structural heart disease who have paroxysmal atrial fibrillation. Closure of the left atrial appendage using an atrial occlusion device is approved for patients at risk for stroke who are unable to take systemic anticoagulation.

Treatment... Atrial fibrillation treatment goals include reducing the frequency and severity of symptoms, preventing stroke, and preventing tachycardia-related cardiomyopathy. Patients who should receive anticoagulation with warfarin or the non–vitamin K–dependent oral anticoagulants should be chosen using the CHA_2DS_2-VASc score. Treatment should first focus on rate control by using β-blockers or calcium-channel antagonists, aiming for a resting rate between 60 and 110 beats per minute. Rhythm control may be attempted in patients who do not respond to rate-controling medications or have intolerable symptoms related to atrial fibrillation. Atrial fibrillation ablation and atrioventricular nodal ablation therapy may be appropriate for selected patients with highly symptomatic disease despite drug therapy. Closure of the left atrial appendage is an alternative for thromboembolic protection in patients at risk for stroke who are not good candidates for anticoagulation.

CLINICAL BOTTOM LINE

Practice Improvement

Do U.S. stakeholders consider management of patients with atrial fibrillation when evaluating the quality of care physicians deliver?

In 2016, the American College of Cardiology and the American Heart Association released updated clinical performance and quality measures for the treatment of atrial fibrillation and atrial flutter (36). The updated version kept the 3 measures in the previous version and added 21 new ones, including 6 regarding performance (3 inpatient and 3 outpatient) and 18 regarding quality (10 inpatient and 8 outpatient).

What do professional organizations recommend with regard to management of patients with atrial fibrillation?

The material presented in this review has been updated and is consistent with the 2014 guidelines from the American Heart Association, American College of Cardiology, and Heart Rhythm Society (9).

In the Clinic

Tool Kit

Atrial Fibrillation

Patient Information

https://medlineplus.gov/atrialfibrillation.html
Information from the National Institutes of Health MedlinePlus.

www.mayoclinic.org/diseases-conditions/atrial-fibrillation/home/ovc-20164923
Information useful to both patients and medical professionals from the Mayo Clinic.

www.myvirtualpaper.com/doc/aha-publications/atrial-fibrillation-your-healthiest-life/2012092701/%230#0
Interactive patient guide from the American Heart Association.

Guidelines

http://annals.org/aim/article/716992/management-newly-detected-atrial-fibrillation-clinical-practice-guideline-from-american
The American College of Physicians/American Academy of Family Physicians guidelines for the managements of newly detected atrial fibrillation.

www.onlinejacc.org/content/64/21/2246
The American College of Cardiology, American Heart Association, and Heart Rhythm Society joint 2014 guidelines for management.

Other Information

www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/AFib-Resources-For-Patients-Professionals_UCM_423786_Article.jsp#.WHOmt1MrLAU
Resources for patients and professionals from the American Heart Association.

In the Clinic

WHAT YOU SHOULD KNOW ABOUT ATRIAL FIBRILLATION

What Is Atrial Fibrillation?

Atrial fibrillation, or Afib, is when your heart beats very fast or not normally. Over time, this can damage your heart muscle. It can also cause stroke because Afib can cause blood clots to form in the heart and travel to the brain. It can come and go, or you can have it all the time. It is more common in people with heart conditions and in older people. You are at a higher risk for stroke from Afib if you:

- Are older than 65 years
- Have heart failure
- Have high blood pressure
- Have breathing difficulties when you sleep

What Are the Warning Signs?

Many people with Afib have no symptoms and do not know that they have it. When people have symptoms, they can include:

- A pounding, fluttering, or irregular feeling in the chest
- Shortness of breath
- Chest pain
- Weakness or feeling tired
- A sensation of not feeling right

How Is It Diagnosed?

Your doctor may order an electrocardiogram (ECG), a painless test that tracks your heartbeat. Your doctor may see Afib on an ECG if you have it during the test. If you have symptoms that could be Afib but your ECG is normal, your doctor may ask you to wear a monitor that tracks your heart's activity while you go about your day.

How Is It Treated?

- Afib is treated to reduce symptoms, prevent stroke, and prevent the heart from becoming too large and thick.
- Your doctor may prescribe medicines called blood thinners, or medicines that slow the heartbeat and make it more regular.
- If medicines do not work, your doctor may recommend a procedure called "ablation." Ablation is a procedure that helps to stop abnormal heart signals.

- In some cases, a pacemaker can be implanted near your heart to keep your heartbeat regular.
- Talk to your doctor about the best treatment plan for you.

Questions for My Doctor

- How long will I need to take medicines for Afib?
- What are the side effects of my medicines?
- Should I worry about other medicines I'm taking?
- Can I still do all the things I like to do?
- How can I reduce my risk of stroke?
- Can I exercise with Afib?
- When should I go to the emergency room?

Bottom Line

- Afib is when your heart beats very fast or not normally. This can cause stroke.
- Some people with Afib have no symptoms. Others can feel a pounding or fluttering in the chest, shortness of breath, dizziness, and weakness.
- Your doctor may diagnose Afib after a test called an ECG, which tracks your heartbeat. He or she may also want to monitor your heart for a longer time to see if you have Afib.
- People with Afib may need to be on medicines to prevent stroke. In some cases, your doctor may recommend having a procedure to help you feel better. Talk with your doctor about the best treatment plan for you.

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

American College of Physicians
www.acponline.org/patient_ed/cardiovascular
Medline Plus
https://medlineplus.gov/atrialfibrillation.html
Heart Rhythm Society
www.hrsonline.org/Patient-Resources/Heart-Diseases-Disorders/Atrial-Fibrillation-Afib

Patient Information

Correction: Atrial Fibrillation

A recent In the Clinic (1) contains an error regarding the administration of apixaban dosing. Table 4, Non-Vitamin K–Dependent Anticoagulation Medications for Atrial Fibrillation, incorrectly states that the apixaban dose should be 2.5 mg twice daily in patients with ≥2 of: age >80y, ≥60 kg, creatinine ≥1.5 mg/dL. However, that dose should be applied in patients with at least 2 of the following: age >80y, ≤60 kg, creatinine ≥1.5 mg/dL.

Reference

1. Zimetbaum P. In the Clinic: atrial fibrillation. Ann Intern Med. 2016;166: ITC33-48 [PMID: 28265666] doi:10.7326/AITC201703070