The treatment of atrial fibrillation includes anticoagulation, rate control, and rhythm control. New US guidelines for the management of atrial fibrillation have recently been published. 1

ANTICOAGULATION

Atrial fibrillation increases the risk of thromboembolic stroke. Anticoagulant therapy reduces this risk, but it can cause intracranial and other serious bleeding. The risk of bleeding must be weighed against the benefit of thromboembolic risk reduction.

A new scoring system, the CHA2DS2-VASc score, has been designed to aid in this assessment for patients with non-valvular atrial fibrillation. An algorithm from the recent US guidelines recommends oral anticoagulant treatment for patients who have a CHA2DS2-VASc score ≥2. For patients with a CHA2DS2-VASc score of 0, who have a very low risk of thromboemboli, it would be reasonable to omit antithrombotic therapy. For patients with a CHA2DS2-VASc score of 1, the US guidelines recommend no antithrombotic therapy or use of either aspirin or an oral anticoagulant, but evidence supporting use of aspirin for this indication is limited. European guidelines recommend use of an oral anticoagulant for patients with a CHA2DS2-VASc score of 1, except for women with no other risk factor, for whom no antithrombotic therapy is recommended. 2

Patients with atrial fibrillation associated with a mechanical valve, a bioprosthetic valve, prior mitral valve repair, or mitral stenosis should take warfarin.

WARFARIN — When anticoagulation is indicated, the benefits of long-term warfarin therapy in preventing ischemic stroke in patients with atrial fibrillation outweigh the risk of major bleeding.

Dosing — The main drawback of warfarin has been the need for close monitoring and dosage adjustment to keep the international normalized ratio (INR) between 2 and 3. The usual starting dosage range is 2-5 mg once daily, varying with the weight and age of the patient. Algorithms are available at www.warfarindosing.org.

Drug Interactions — Maintaining the INR in the desired range is made more difficult by warfarin’s numerous interactions with food and with other drugs (see Table 2). In patients with atrial fibrillation, the most important of these is with amiodarone, which decreases the warfarin dose requirement by one-third to one-half. Another interaction is with the widely used analgesic acetaminophen;
occasional use of acetaminophen generally has little or no effect on the INR in patients on chronic warfarin therapy, but in some patients even a few grams of acetaminophen can cause a dramatic increase in INR. Patients on chronic warfarin therapy who take more than 2 g/day of acetaminophen for more than a few days should be monitored closely for INR changes.

**NEWER ORAL ANTICOAGULANTS** — In patients with nonvalvular atrial fibrillation, dabigatran etexilate, rivaroxaban, and apixaban all appear to be at least as effective as warfarin in preventing stroke, and in clinical trials all caused less intracranial bleeding than warfarin.\(^5\) Patients with atrial fibrillation associated with a mechanical valve, a bioprosthetic valve, prior mitral valve repair, or mitral stenosis should take warfarin. The three new oral anticoagulants do not require routine INR-type monitoring, have no dietary restrictions, and may have fewer interactions with other drugs compared to warfarin, but they have no established method for determining the extent of anticoagulation, have no specific antidote to reverse their anticoagulant effect, and are not recommended for use in patients with end-stage kidney disease.

**DABIGATRAN** — The oral direct thrombin inhibitor dabigatran etexilate is FDA-approved for prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation.\(^5\)

**Bleeding Risk** — Because of multiple spontaneous reports of severe, sometimes fatal, bleeding with dabigatran, the FDA conducted a post-marketing study in >134,000 Medicare patients ≥65 years old which found that the risks of intracranial bleeding and ischemic and thromboembolic stroke were lower with dabigatran than with warfarin, but the risk of major gastrointestinal bleeding was higher with dabigatran.\(^7,8\)

**Drug Interactions** — Dabigatran etexilate is a substrate of the efflux transporter P-glycoprotein (P-gp). Co-administration with P-gp inducers such as rifampin reduces serum concentrations of dabigatran and may decrease its effectiveness. P-gp inhibitors such as amiodarone may increase serum concentrations of dabigatran.\(^9\)

**Reversibility** — Unlike warfarin, which can be reversed by vitamin K, there is no specific antidote for dabigatran-induced bleeding. Its anticoagulant effect is not reversible except by hemodialysis.

**RIVAROXABAN** — The factor Xa inhibitor rivaroxaban is also FDA-approved for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.\(^10\) It should not be used in patients with moderate or severe hepatic impairment.

**Reversibility** — Due to the high percentage of drug bound to protein in plasma, rivaroxaban is not expected to be dialyzable. Preliminary studies suggest that its anticoagulant effect may be reversed by prothrombin complex concentrate.\(^11\)

**Drug Interactions** — Rivaroxaban is a substrate of CYP3A4 and P-gp. Co-administration of drugs that inhibit CYP3A4 and P-gp may increase serum concentrations of rivaroxaban, leading to an increased risk of bleeding. Co-administration of drugs that are inhibitors of P-gp and strong inhibitors of CYP3A4, such as ketoconazole, are contraindicated. Co-administration of P-gp inducers and strong inhibitors of CYP3A4, such as rifampin, should also be avoided.\(^9\)

**APIXABAN** — The factor Xa inhibitor apixaban is the third new oral anticoagulant to be approved by the FDA for use in patients with nonvalvular atrial fibrillation. In clinical trials, apixaban was the only one of the new oral anticoagulants to cause less overall bleeding than warfarin, but the trials were conducted in somewhat different populations and used slightly different definitions of major bleeding.\(^12\) Apixaban should not be used in patients with severe hepatic impairment.

**Reversibility** — There is no established antidote to reverse the anticoagulant effect of apixaban, which persists for about 24 hours after the last dose, and the drug is not dialyzable. Preliminary studies suggest that it may be reversible with prothrombin complex concentrate.\(^11\)

**Drug Interactions** — Apixaban is a substrate of CYP3A4 and P-gp. The dose should be reduced to 2.5 mg twice daily if it is used concurrently with drugs that inhibit both CYP3A4 and P-gp, such as itraconazole, ritonavir,
or clarithromycin. Coadministration of drugs that induce both CYP3A4 and P-gp, such as rifampin, should be avoided.

**RATE CONTROL**

Ventricular rate control is now widely used as first-line therapy for management of chronic atrial fibrillation. Antiarrhythmic drugs have not been shown to be more effective in preventing serious complications and have considerable toxicity. Lenient rate control (resting heart rate ≤110 beats per minute), particularly in patients with a structurally normal heart and no heart failure, is easier to achieve and appears to be as effective as strict rate control (resting heart rate <80 beats per minute). The drugs most commonly used for rate control in atrial fibrillation are listed in Table 4.

**BETA-ADRENERGIC BLOCKERS** — A beta-blocker such as propranolol, metoprolol, or esmolol given intravenously can acutely control the ventricular rate in atrial fibrillation or flutter. Oral beta-blockers are used for long-term rate control. Beta-blockers are preferred over calcium channel blockers for patients with coronary disease or systolic dysfunction. They should be used cautiously in patients with decompensated heart failure.

**CALCIUM CHANNEL BLOCKERS** — Verapamil and diltiazem prolong AV nodal refractoriness and are effective in slowing the ventricular rate in atrial fibrillation or flutter. Their IV use can be complicated by hypotension or bradycardia in patients with underlying heart disease, especially with concurrent use of other cardiodepressant drugs such as beta-blockers. Verapamil and diltiazem may be preferred over beta-blockers for long-term use in patients with chronic obstructive pulmonary disease or asthma. They should not be used in patients with decompensated heart failure or Wolff-Parkinson-White syndrome.

Unlike verapamil and diltiazem, dihydropyridine calcium channel blockers (all the other calcium channel blockers available in the US) generally have no rate-controlling activity.

**AMIODARONE** — More often used as a rhythm control agent, IV amiodarone has been used for ventricular rate control in some critically ill patients, and oral amiodarone has been used when other treatments have failed to control heart rate.

**DIGOXIN** — Generally used as an adjunctive agent, digoxin can help control ventricular response in atrial fibrillation or flutter, but other drugs are more effective. Digoxin, like verapamil and diltiazem,
has many interactions with other drugs (see Table 6). Dronedarone, a non-iodinated analog of amiodarone, has been less effective than amiodarone and has been associated with severe adverse effects, including increased mortality in patients with persistent atrial fibrillation. 15

Propafenone and flecainide are generally reserved for patients with structurally normal hearts; they should only be used with a beta-blocker, verapamil, or diltiazem. Sotalol, a non-selective beta-blocker, is better tolerated than quinidine or some other older drugs now seldom used for this indication, but it increases the QT interval and can cause torsades de pointes; it should be avoided in patients with baseline QT prolongation and in those receiving other drugs should not be used in patients with Wolff-Parkinson-White syndrome.

RHYTHM CONTROL

The treatment of choice for urgent conversion of atrial fibrillation is DC cardioversion. Antiarrhythmic drugs, particularly amiodarone, can be used to restore and maintain normal sinus rhythm.

DRUG THERAPY – The antiarrhythmic drugs most commonly used now to prevent episodes of paroxysmal atrial fibrillation and to maintain sinus rhythm after cardioversion are listed in Table 5.

Amiodarone is the most effective antiarrhythmic drug for maintenance of sinus rhythm, but it can cause multiple adverse effects, some severe, and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Oral Formulations</th>
<th>Usual Adult Dosage</th>
<th>Some Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol (Brevibloc, and generics)</td>
<td>–</td>
<td>IV: 500 mcg/kg bolus over 1 min, then 50-300 mcg/kg/min; titrate to desired effect</td>
<td>Heart block, hypotension, bradycardia, bronchospasm, pain at infusion site</td>
</tr>
<tr>
<td>Metoprolol (Lopressor, Toprol XL, and generics)</td>
<td>50, 100 mg tabs; 25, 50, 100, 200 mg ER tabs</td>
<td>PO: 25-400 mg once/d or bid2</td>
<td>Heart block, hypotension, bradycardia, bronchospasm, depression</td>
</tr>
<tr>
<td>Propranolol (Inderal LA, and others)</td>
<td>10, 20, 40, 60, 80 mg tabs; 60, 80, 120, 160 mg ER caps</td>
<td>PO: 10-40 mg tid or qid2</td>
<td>Heart block, hypotension, bradycardia, bronchospasm, depression</td>
</tr>
<tr>
<td>Atenolol (Tenormin, and generics)</td>
<td>25, 50, 100 mg tabs</td>
<td>PO: 25-100 mg once/d</td>
<td>Bradycardia, depression, worsening of peripheral arterial insufficiency</td>
</tr>
<tr>
<td>Bisoprolol (Zebeta, and generics)</td>
<td>5, 10 mg tabs</td>
<td>PO: 2.5-10 mg once/d</td>
<td>Bradycardia, depression, worsening of peripheral arterial insufficiency</td>
</tr>
<tr>
<td>Carvedilol (Coreg, and generics; Coreg CR)</td>
<td>3.125, 6.25, 12.5, 25 mg tabs; 10, 20, 40, 80 mg ER caps</td>
<td>PO: 3.125-25 mg bid</td>
<td>Similar to other beta-adrenergic blockers, but more orthostatic hypotension</td>
</tr>
<tr>
<td>Nadolol (Corgard, and generics)</td>
<td>20, 40, 80 mg tabs</td>
<td>PO: 10-240 mg once/d</td>
<td>Bradycardia, depression, worsening of peripheral arterial insufficiency</td>
</tr>
<tr>
<td>Diltiazem (Cardizem LA, and others)</td>
<td>30, 60, 90, 120 mg tabs; 120, 180, 240, 300, 360, 420 mg ER caps</td>
<td>PO: 120-360 mg once/d or divided tid or qid2</td>
<td>Heart block, hypotension, heart failure, bradycardia, edema</td>
</tr>
<tr>
<td>Verapamil (Calan, Calan SR, and others)</td>
<td>40, 80, 120 mg tabs; 120, 180, 240 mg ER tabs or caps</td>
<td>PO: 120-480 mg once/d or divided tid or qid2</td>
<td>Heart block, hypotension, heart failure, bradycardia, dizziness, headache, fatigue, edema, nausea, constipation</td>
</tr>
<tr>
<td>Amiodarone (Cordarone, and others)</td>
<td>100, 200 mg tabs2</td>
<td>PO: 100-200 mg once/d</td>
<td>Arrhythmias, nausea, vomiting, abnormal vision, abdominal pain, skin discoloration, taste disturbances</td>
</tr>
<tr>
<td>Digoxin (Lanoxin, and others)</td>
<td>0.125, 0.25 mg tabs</td>
<td>PO: 0.125-0.25 mg once/d</td>
<td>Bradycardia, AV block, arrhythmias, anorexia, nausea, vomiting, diarrhea, abdominal pain, headache, confusion, abnormal vision</td>
</tr>
</tbody>
</table>

ER = Extended-release
1. Dosage adjustment may be required for hepatic or renal impairment.
2. Dosage given as a range; dose and interval will vary depending on formulation used.
3. Cordarone is only available in 200-mg tablets.
that also prolong the QT interval. Disopyramide is sometimes used to maintain normal sinus rhythm in patients with vagally-induced atrial fibrillation. Dofetilide has been effective in patients with compromised left ventricular function, but it requires in-hospital dose titration and can cause torsades de pointes.

CATHETER ABLATION — Radiofrequency catheter ablation of the cardiac tissue causing an arrhythmia can restore sinus rhythm and may be superior to antiarrhythmic drugs in maintaining sinus rhythm and improving symptoms, exercise capacity, and quality of life. Complications are rare, but can be fatal.

Table 5. Some Rhythm Control Agents: Dosage and Adverse Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Oral Formulations</th>
<th>Usual Adult Dosage</th>
<th>Some Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td><strong>Cordarone, and others</strong> 100, 200 mg tabs³</td>
<td><strong>PO:</strong> 400-600 mg daily in divided doses for 2-4 weeks, then 100-200 mg q24h 150 mg over 10 min, then 1 mg/min for 6 hrs, then 0.5 mg/min for 18 hrs; after 24 hrs 0.25 mg/min IV maintenance: 0.5-1 mg/min Cardiac arrest: 300 mg IV push</td>
<td><strong>PO:</strong> Pulmonary fibrosis, bradycardia, heart block, QT prolongation and possible torsades de pointes (unusual; &lt;1%), hyper- or hypothyroidism, GI upset, alcoholic-like hepatitis, peripheral neuropathy, ataxia, tremor, dizziness, photosensitivity, blue-gray skin, corneal microdeposits, optic neuritis  IV: Hypotension, bradycardia, phlebitis at site of administration, torsades de pointes</td>
</tr>
<tr>
<td>Disopyramide</td>
<td><strong>Norpace, and generics; Norpace CR</strong> 100, 150 mg caps; 100, 150 mg ER caps</td>
<td><strong>PO:</strong> 100-400 mg q6-12h⁴</td>
<td>Anticholinergic effects (urinary retention, aggravation of glaucoma, constipation), hypotension, heart failure, ventricular tachyarrhythmias, QT prolongation and possible torsades de pointes, heart block, nausea, vomiting, diarrhea, hypoglycemia, nervousness</td>
</tr>
<tr>
<td>Dofetilide</td>
<td><strong>Tikosyn</strong> 0.125, 0.25, 0.5 mg caps PO: 0.125-0.5 mg q12h⁷</td>
<td><strong>QT prolongation and torsades de pointes</strong></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td><strong>Multaq</strong> 400 mg tabs PO: 400 mg q12h</td>
<td>Hepatotoxicity, worsening heart failure with increased mortality possible, bradycardia, diarrhea, nausea, vomiting, abdominal pain, photosensitivity, QT prolongation and possible torsades de pointes</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>50, 100, 150 mg tabs PO: 50-200 mg q12h</td>
<td>Bradycardia, heart block, new ventricular fibrillation, sustained ventricular tachycardia, rapid atrial flutter, heart failure, dizziness, blurred vision, nervousness, headache, GI upset, neutropenia, QT prolongation and possible torsades de pointes</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td><strong>Rythmol, Rythmol SR, and generics</strong> 150, 225, 300 mg tabs; 225, 325, 425 mg ER caps PO: 150-425 mg q8-12h⁶</td>
<td>Bradycardia, heart block, new ventricular fibrillation, sustained ventricular tachycardia, heart failure, dizziness, light-headedness, metallic taste, GI upset, bronchospasm, hepatic toxicity</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td><strong>Betapace, Betapace AF, and others</strong> 80, 120, 160, 240 mg tabs¹¹</td>
<td><strong>PO:</strong> 40-160 mg q12h</td>
<td>Heart block, hypotension, bronchospasm, bradycardia; higher doses are associated with increased adverse effects including QT prolongation and torsades de pointes</td>
</tr>
</tbody>
</table>

ER = Extended-release
1. For maintenance of sinus rhythm. All of these drugs require monitoring at initiation for proarrhythmias.
2. Dosage adjustment may be required for hepatic or renal impairment.
3. Should not be used in patients with cardiogenic shock or second or third degree AV block.
4. Cordarone is only available in 200-mg tablets.
5. Should not be used in patients with cardiogenic shock, pre-existing second or third degree AV block, or congenital QT prolongation.
6. Dosage given as a range; dose and interval will vary depending on formulation used.
7. Available through a restricted distribution program. Contraindicated in patients with long QT syndrome or severe renal impairment.
8. Should not be used in patients with NYHA class III or IV heart failure (HF) or permanent atrial fibrillation or in patients with decompensated HF in the past 4 weeks.
9. Should be used with a beta-blocker, verapamil, or diltiazem for cardioversion. Should not be used in patients with coronary artery disease and significant structural heart disease.
10. Should not be used in patients with bronchospasm, uncontrolled heart failure, long QT syndrome, sinus bradycardia, or second or third degree AV block.
11. Betapace AF is not available in 240-mg tablets.
CONCLUSION

Anticoagulant therapy reduces the risk of thromboembolic stroke in patients with atrial fibrillation, but it can cause intracranial and other serious bleeding. The risk of bleeding must be weighed against the benefit of thromboembolic risk reduction. Patients with nonvalvular atrial fibrillation and a CHA2DS2-VASc score ≥2 for risk of stroke should take either warfarin or one of the newer oral anticoagulants (apixaban, dabigatran, or rivaroxaban). Patients with atrial fibrillation associated with a mechanical valve, a bioprosthetic valve, prior mitral valve repair, or mitral stenosis should take warfarin.

Ventricular rate control is now widely used as first-line therapy for management of chronic atrial fibrillation. Lenient rate control (resting heart rate <110 beats/minute) may be a reasonable alternative to strict control (resting heart rate <80 beats/minute). A beta-blocker, verapamil, or diltiazem is generally used for long-term rate control. A beta-blocker is preferred for patients with coronary disease or systolic dysfunction. Verapamil or diltiazem may be preferred over beta-blockers in patients with COPD or asthma. Amiodarone may be effective when other drugs have failed to control ventricular rate.

Antiarrhythmic drugs, particularly amiodarone, can be used to restore and maintain normal sinus rhythm. The treatment of choice for urgent conversion of atrial fibrillation is DC cardioversion. Radiofrequency catheter ablation of cardiac tissue responsible for triggering or maintaining an arrhythmia can also restore sinus rhythm.
LEARNING OBJECTIVES:

Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

Upon completion of this program, the participant will be able to:

1. Explain the current approach to the management of a patient with atrial fibrillation including anticoagulation, rate control, and rhythm control strategies.
2. Discuss the pharmacologic agents available for prevention of thromboembolism in patients with atrial fibrillation and compare them based on their efficacy, dosage and administration, drug interactions, and potential adverse effects.
3. Discuss the pharmacologic agents available for rate and rhythm control in patients with atrial fibrillation and compare them based on their efficacy, dosage and administration, drug interactions, and potential adverse effects.
4. Determine the most appropriate therapy given the clinical presentation of an individual patient with atrial fibrillation.

Questions start on next page
1. A 72-year-old man with nonvalvular atrial fibrillation and a CHA₂DS₂-VASc score of 2 asks you whether or not he needs to be on anticoagulant therapy. Considering the new US guidelines, which of the following would you recommend?
   a. oral anticoagulation therapy
   b. no anticoagulation therapy
   c. aspirin
   d. none of the above

2. Which of the following oral anticoagulants is recommended for patients with atrial fibrillation associated with a mechanical valve, a bioprosthetic valve, prior mitral valve repair, or mitral stenosis?
   a. apixaban
   b. dabigatran etexilate
   c. rivaroxaban
   d. warfarin

3. A 65-year-old man with nonvalvular atrial fibrillation recently saw advertisements for apixaban and rivaroxaban and asks whether he should take one of the newer anticoagulants instead of warfarin. You could tell him that, compared to warfarin, apixaban, rivaroxaban, and dabigatran etexilate:
   a. do not require routine INR-type monitoring
   b. have fewer interactions with other drugs
   c. cause less intracranial bleeding
   d. all of the above

4. Which of the following oral anticoagulants is a direct thrombin inhibitor?
   a. warfarin
   b. dabigatran etexilate
   c. apixaban
   d. rivaroxaban

5. The drugs most commonly used for rate control in patients with atrial fibrillation include:
   a. beta-blockers
   b. verapamil
   c. diltiazem
   d. all of the above

6. Which of the following beta-blockers is not available in an oral formulation?
   a. metoprolol
   b. propranolol
   c. esmolol
   d. carvedilol

7. The treatment of choice for urgent conversion of atrial fibrillation to normal sinus rhythm is:
   a. anticoagulation
   b. catheter ablation
   c. DC cardioversion
   d. digoxin

8. Adverse effects of amiodarone include:
   a. taste disturbances
   b. skin discoloration
   c. visual disturbances
   d. all of the above

9. Which of the following rhythm control agents should not be used in patients with atrial fibrillation and significant structural heart disease?
   a. propafenone
   b. amiodarone
   c. dofetilide
   d. dronedarone

10. The most effective drug available for maintenance of sinus rhythm is:
    a. sotalol
    b. amiodarone
    c. diltiazem
    d. dronedarone

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(Correspond to questions #1-10 in Comprehensive Exam #71, available January 2015)