Management of Atrial Fibrillation
Case Study and Commentary, Paul R. Sutton, MD, PhD, and Jane Y. Yeh, MD

INSTRUCTIONS
The following article, “Management of Atrial Fibrillation,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 648.

OBJECTIVES
After participating in the continuing education activity, primary care physicians should be able to:
1. Understand the indications for urgent cardioversion in patients with atrial fibrillation
2. Be familiar with the classes of agents commonly used for rate control and how to optimize rate control
3. Understand how to choose an appropriate antiarrhythmic agent according to a patient’s comorbidities
4. Understand how to assess stroke risk and choose appropriate antithrombotic therapy
5. Understand how to identify patients at high risk for bleeding complications and how to reduce bleeding risk in patients on chronic anticoagulation

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality. AF increases in prevalence with increasing age. It is rare in persons younger than 50 years of age but occurs in approximately 1% of persons aged 60 years, approximately 5% of persons between the ages of 70 and 75 years, and in more than 10% of persons older than 80 years [1–3]. AF is a major risk factor for thromboembolic stroke, increasing the risk of stroke 5-fold compared with persons without AF. Approximately 1 in 6 ischemic strokes are associated with AF [4]. Symptomatic AF may also impair functional status, reduce quality of life, and decrease survival [5–7].

The increasing prevalence of AF with age has important implications in the aging U.S. population. Currently, there are an estimated 2.3 million persons in the United States with AF. This number is projected to increase to more than 3 million by the year 2020 and to more than 5 million by the year 2050 [3]. Furthermore, the proportion of patients with AF who are 80 years or older is expected to increase to more than 50% by the year 2050 [3].

Much is known about the risk for stroke associated with AF. Warfarin and to a lesser extent aspirin reduce the risk of stroke. Rate control may be accomplished with β blockers, calcium channel blockers, or digitalis. Restoration of sinus rhythm may be accomplished by pharmacologic or electrical means. Controversy remains regarding optimal therapies for individual patients. Furthermore, treatment of patients with AF is associated with significant side effects, notably an increased hemorrhagic risk. Optimal management of anticoagulation and reduction of hemorrhagic risk are important considerations in the treatment of patients with AF.

CASE STUDY 1
Initial Presentation
A 75-year-old man presents to his primary care physician with a complaint of heart palpitations that have been present for 10 days. The patient reports that he feels his “heart racing” with moderate exertion. This sensation is accompanied by a feeling of mild dyspnea.

- What are important elements in the evaluation of patients with AF?

Clinical Workup
The history should detail the frequency and severity of symptoms, precipitants, and comorbidities (particularly cardiovascular and pulmonary). It is also important to ask about prescription and nonprescription medications that may be proarrhythmic or may interact with medications used in the treatment of AF. AF may be associated with acute illness, including surgery (eg, AF is very common following coronary artery bypass grafting), pericarditis, myocarditis, myocardial infarction, pulmonary embolus or other pulmonary disease, hyperthyroidism, fever, or alcohol intake. AF may occur in the absence of any heart disease (ie, “lone atrial fibrillation”) but most commonly occurs in the setting of some underlying heart disease, usually hypertension, ischemic heart disease, or

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congestive heart failure [8]. Lone AF is more common in the outpatient setting, where the incidence approached 30% in one series [9]. Other, less common predisposing conditions include valvular heart disease, pulmonary disease, and hyperthyroidism [10]. Specific triggers such as excessive alcohol intake, sympathomimetic ingestion (caffeine, adrenergic decongestants, cocaine, amphetamines), stress, or inadequate sleep should be sought. It is reasonable to treat any underlying disease that may contribute to AF, as successful treatment of the underlying condition may eliminate AF.

Physical examination findings consistent with AF include an irregularly irregular heart rhythm, a first heart sound that varies in intensity according to the length of the pause between consecutive beats, and an apical-radial pulse deficit. An apical-radial pulse deficit occurs when rapidly successive ventricular contractions that are heard or palpated at the ventricular apex produce a stroke volume insufficient to manifest a palpable radial pulse due to shortened diastolic time. The physical examination should also focus on the presence of signs of congestive heart failure (ie, third heart sound, elevated jugular venous pressure, or pulmonary crackles). Among laboratory tests, thyroid-stimulating hormone is generally tested to rule out occult thyroid disease.

An electrocardiogram (ECG) is necessary to document AF. A chest radiograph is usually performed to assess for signs of congestion, evidence of enlargement of the cardiac silhouette, and evidence of underlying pulmonary disease. Transthoracic echocardiography is recommended for all patients with newly diagnosed AF to evaluate atrial and ventricular dimensions and left ventricular (LV) wall thickness and function and to exclude valvular or pericardial disease [11]. Trans-thoracic echocardiography should not be used to detect left atrial thrombus. A Holter or event monitor may be used to diagnose AF in the setting of suspected AF not captured on a static ECG. Stress testing of some form is recommended if ischemic heart disease is suspected.

History

The patient reports that the palpitations lasted for several hours on the day prior to presentation and then recurred while he was getting dressed this morning. He reports several similar, self-limited, episodes over the past 3 or 4 months. He denies chest pain or orthopnea. He denies tremor or changes in his skin, bowel habits, or tolerance of ambient temperatures. His past medical history is notable for hypertension, generally well controlled with lisinopril, and type 2 diabetes mellitus, also well controlled on glyburide. His only other medications are acetaminophen for chronic degenerative joint disease of both knees and a daily aspirin. He does not drink coffee, smoke, or use any illicit drugs. He drinks 1 or 2 glasses of wine with dinner most evenings. He walks 30 to 60 minutes daily.

Physical Examination and ECG

On physical examination, the patient’s heart rate is noted to be in the 120s with an irregularly irregular rhythm. Blood pressure is 148/92 mm Hg. There are no palpable thyroid masses. The patient’s chest is clear to auscultation and percussion. He has no jugular venous distension or bruits. Cardiac examination is notable for an irregularly irregular tachycardia and an early systolic murmur at the left upper sternal border without radiation. The intensity of the first heart sound varies with the heart rate. He has no peripheral edema. Neurologic examination is unremarkable except for a mildly antalgic gait. An ECG reveals AF with a ventricular response rate of 128 bpm and no evidence of LV hypertrophy, prior infarct, or active ischemia.

- How are the arrhythmia patterns of AF characterized?
- What are the potential clinical sequelae of AF?

The patient presented with 10 days of AF symptoms. He had palpitations and dyspnea with moderate exertion, suggestive of a rapid ventricular response. His history is notable for several similar episodes over the past 3 or 4 months. There is no single set of definitions that is widely accepted to describe the variety of patterns of AF. We will use the classification scheme recommended by the recent American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) consensus committee [11]. First detected AF represents an initial presentation of AF that generally lasts less than 1 day but may last as many as 7 days. Recurrent AF describes patients with 2 or more discrete episodes of AF. Recurrent AF may be paroxysmal, if the arrhythmia spontaneously terminates, and persistent, if the AF episodes last more than 7 days. Permanent AF is a durable, consistent arrhythmia. This patient has recurrent persistent AF. The use of this simple descriptive classification scheme makes it easier to classify patients and compare studies of various therapeutic modalities.

AF results from chaotic electrical activity and rapid, mechanically disorganized atrial contractions. The atrioventricular node (AV node) is bombarded with irregular electrical activity that produces irregular ventricular contractions. Ventricular rates are determined by the intrinsic electrical properties of the AV node and conduction system, medications, and autonomic tone; ventricular rates may be very rapid in otherwise healthy, active patients with AF. Rapid ventricular response frequently causes palpitations, reduced exercise tolerance, and, in some cases, congestive heart failure due to systolic or diastolic dysfunction. Long-standing AF may result in cardiomyopathy. Increased myocardial
demand associated with tachycardia may result in ischemia. Finally, the absence of coordinated atrial mechanical activity results in relative stasis of intra-atrial blood flow and is thrombogenic. Systemic embolization of atrial embolus is an important cause of ischemic stroke.

• What are the initial clinical considerations in a patient with AF?

Clinical issues in patients with AF may be divided into 4 categories: (1) assessment of clinical stability, (2) treatment to attain rate control, (3) restoration of sinus rhythm, and (4) reduction of stroke risk. Adequate rate control and/or restoration of sinus rhythm are usually necessary to treat symptoms of AF.

• What are the indications for urgent cardioversion?

Assessment of Need for Urgent Cardioversion

In all patients presenting with AF it is appropriate to consider whether indications exist for urgent cardioversion to restore sinus rhythm. Current Advanced Cardiac Life Support guidelines [12] recommend cardioversion for patients with evidence of coronary ischemia, hemodynamic instability, or hypoperfusion suspected to be due to AF and rapid ventricular response. Subsets of patients that are likely to develop life-threatening complications of AF include those with significant ischemic heart disease, congestive heart failure, mitral valve stenosis, hypertrophic cardiomyopathy, or pulmonary hypertension. Restoration of sinus rhythm results in (1) slowing of the ventricular rate leading to reduced myocardial oxygen demand and increased diastolic filling time, and (2) restoration of the atrial contribution to ventricular filling during diastole (perhaps 15% to 20% of normal cardiac preload).

Cardioversion may be accomplished with direct current (DC) cardioversion or with short-acting antiarrhythmic therapies, such as ibutilide. Electrical cardioversion requires the application of 100 to 360 Joules (J) DC synchronized with ventricular electrical depolarization. DC cardioversion is rapid and initially very effective. Electrical cardioversion succeeds in restoring sinus rhythm in 70% to 90% of patients [13,14]. Higher energies are generally more successful than lower energies, and some experts recommend beginning at 300 J or higher [11]. DC cardioversion is more effective than pharmacologic cardioversion at restoring sinus rhythm in patients who have been in AF for less than 1 year. Patients receive conscious sedation or anesthesia prior to cardioversion and need to be closely observed by telemetry.

A variety of medications are effective for pharmacologic cardioversion, including amiodarone, dofetilide, flecaïnide, propafenone, quinidine, and ibutilide [11]. Pharmacologic cardioversion is most effective in patients who have been in AF for less than 1 week [11,15]. Ibutilide confers a risk of prolongation of the QT interval and torsade de pointes for approximately 4 hours after cardioversion, so patients should be carefully monitored and their potassium and magnesium levels should be maintained in a normal range. The risk of embolism in patients not prophylactically anticoagulated prior to cardioversion is 1% to 7% [16,17]; as a result, urgent cardioversion should be reserved for those patients who are hemodynamically unstable as a result of AF and cannot be adequately managed in the short-term by rate control alone. In all other patients, it is appropriate to treat initially with agents to achieve adequate ventricular rate control prior to consideration of cardioversion.

• What are recommended approaches to ventricular rate control?

Establishment of Ventricular Rate Control

Adequate control of ventricular rate is important to reduce symptoms of AF. It is usually necessary to treat with rate-controlling agents prior to cardioversion, when AF recurs following cardioversion, and when cardioversion is not attempted. Several classes of medications are commonly used for rate control: nondihydropyridine calcium channel blockers (diltiazem and verapamil), β blockers, and cardiac glycosides (eg, digoxin). These agents may be used intravenously to rapidly reduce the ventricular response rate in AF or may be given orally for chronic rate control. Table 1 lists available routes of administration, typical dosages, and major side effects for representative medications.

Ventricular response rates are principally governed by the rate of atrial impulses, refractoriness of the AV node, and autonomic tone. The AV node is more responsive to increases in sympathetic tone than vagotonic (parasympathetic) influences. As a result, digoxin and other cardiac glycosides that act via an indirect vagotonic mechanism are generally less effective in controlling heart rates during exercise or disease states when sympathetic tone is high. For this reason, digoxin is now less commonly used as initial and sole therapy for ventricular rate control in AF. Diltiazem and β blockers such as metoprolol or atenolol are now most commonly prescribed for chronic rate control. The medication dose is adjusted to provide adequate control during rest and exertion, usually in the range of 60 to 80 bpm at rest and 90 to 115 bpm with moderate exertion [18]. Assessment of adequate rate control is sometimes accomplished with Holter monitor or
exercise testing [11]. Combinations of medications are sometimes required; in general, combinations of digoxin and β blockers are more effective than digoxin and diltiazem [19]. Some precautions must be remembered when initiating rate control therapy. Diltiazem, verapamil, and β blockers may potentiate high-degree heart block, particularly in patients with sick sinus syndrome or other conduction abnormalities. Nondihydropyridine calcium channel blockers and β blockers are also negative inotropes and should be initiated with caution in patients with decreased LV ejection fraction (LVEF). Digoxin and cautious introduction of a β blocker are recommended in the setting of reduced LVEF. Patients should be evaluated for ECG evidence of pre-excitation syndromes, such as Wolff-Parkinson-White (WPW) syndrome, prior to initiation of rate control therapy. Patients with WPW may develop accelerated conduction via accessory pathways when treated with digoxin or calcium channel blockers, resulting in very rapid ventricular rhythms that have the potential to degenerate to ventricular fibrillation and death. β Blockers are unlikely to be effective for rate control in patients with WPW. In hemodynamically stable patients with WPW and AF, antiarrhythmics that affect both atrial and ventricular excitation are used, such as amiodarone, procainamide, disopyramide, ibutilide, or quinidine. Amiodarone offers superior rate control in patients with pre-excitation and AF because of its β blocker properties. Urgent DC cardioversion is recommended in patients who are hemodynamically unstable.

### Initial Treatment

The patient’s chest radiograph is normal. Echocardiography reveals no valvular abnormalities and demonstrates normal LV function. The physician recommends that the patient abstain completely from alcohol use and explains that rate control with pharmacologic therapy offers a simple and effective means of controlling his symptoms. In view of the patient’s active lifestyle, diltiazem or β blockers are

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### Table 1. Pharmacologic Agents for Heart Rate Control in Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose</th>
<th>Onset</th>
<th>Maintenance Dose</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg over 2 min</td>
<td>2–7 min</td>
<td>5–15 mg/hr</td>
<td>Hypotension, heart block, heart failure</td>
</tr>
<tr>
<td>Esmolol*</td>
<td>0.5 mg/kg over 1 min</td>
<td>5 min</td>
<td>0.05–0.2 mg/kg/min</td>
<td>Hypotension, heart block, bradycardia, bronchospasm, heart failure</td>
</tr>
<tr>
<td>Metoprolol*</td>
<td>2.5–5 mg bolus over 2 min; up to 3 doses</td>
<td>5 min</td>
<td>Not applicable</td>
<td>Hypotension, heart block, bradycardia, bronchospasm, heart failure</td>
</tr>
<tr>
<td>Propranolol*</td>
<td>0.15 mg/kg</td>
<td>5 min</td>
<td>Not applicable</td>
<td>Hypotension, heart block, bradycardia, bronchospasm, heart failure</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.075–0.15 mg/kg over 2 min</td>
<td>3–5 min</td>
<td>Not applicable</td>
<td>Hypotension, heart block, heart failure</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg every 2 hr, up to 1.5 mg</td>
<td>2 hr</td>
<td>0.125–0.25 mg daily</td>
<td>Digitalis toxicity, heart block, bradycardia</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Not applicable</td>
<td>2–4 hr</td>
<td>120–360 mg</td>
<td>Hypotension, heart block, heart failure</td>
</tr>
<tr>
<td>Metoprolol*</td>
<td>Not applicable</td>
<td>4–6 hr</td>
<td>25–100 mg twice daily</td>
<td>Hypotension, heart block, bradycardia, bronchospasm, heart failure</td>
</tr>
<tr>
<td>Propranolol*</td>
<td>Not applicable</td>
<td>60–90 min</td>
<td>80–240 mg daily in divided doses</td>
<td>Hypotension, heart block, bradycardia, bronchospasm, heart failure</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Not applicable</td>
<td>1–2 hr</td>
<td>120–360 mg daily</td>
<td>Hypotension, heart block, heart failure, digoxin interaction</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg every 2 hr, up to 1.5 mg</td>
<td>2 hr</td>
<td>0.125–0.375 mg daily</td>
<td>Digitalis toxicity, heart block, bradycardia</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>800 mg daily for 1 week</td>
<td>1–3 weeks</td>
<td>200 mg daily</td>
<td>Pulmonary toxicity, skin discoloration, thyroid disorders, corneal deposits, optic neuropathy, warfarin interaction, proarrhythmia</td>
</tr>
<tr>
<td></td>
<td>600 mg daily for 1 week</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>400 mg daily for 4–6 weeks</td>
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</table>


*The table includes representative β blocker drugs, but other similar agents could be used for this indication in appropriate doses.*
reasonable choices. He initiates treatment with long-acting diltiazem, which results in effective rate control and significant amelioration of symptoms. The physician also presents to the patient the option of elective cardioversion.

- Do patients benefit from restoration of sinus rhythm?

Restoration of Sinus Rhythm

It remains uncertain whether patients without an urgent or emergent indication for cardioversion benefit from restoration of sinus rhythm. Potential benefits include (1) decreased risk of thromboembolic complications, (2) mitigation of symptoms due to AF, (3) decreased myocardial oxygen demand, and (4) optimized cardiac output. Chronic AF also leads to myocardial fibrosis that contributes to the persistence of atrial fibrillation and may lead to cardiomyopathy [20]. While it has been hypothesized that restoration of sinus rhythm may confer quality of life and/or survival benefit in patients with AF, little direct evidence for or against this hypothesis currently exists. Cardioversion is nonetheless frequently performed on patients with AF, particularly those with symptoms due to AF.

Available studies provide little conclusive evidence for or against strategies of cardioversion versus medical therapy (rate control and anticoagulation). The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial randomized 252 patients to rate control (with diltiazem) versus rhythm control (using amiodarone) [21]. In 1 year of follow-up, amiodarone was successful in restoring sinus rhythm in 23% of patients, and patients in the amiodarone group were able to walk farther in a standardized 6-minute walking test. There was no difference between the 2 groups in self-reported quality of life. There were significantly more hospitalizations in the amiodarone group (69% versus 24%); two thirds of the hospitalizations in the amiodarone group were for drug-related adverse events [21]. These results suggest that antiarrhythmic therapy alone is modestly successful in restoring sinus rhythm and comes at the significant cost of increased hospitalizations and drug-related side effects. A second recent study suggests that short-term quality of life may be improved in a subset of patients with symptomatic AF treated with antiarrhythmic therapy who do not develop subsequent recurrence of AF [22]—that is, restoration of sinus rhythm in patients who have symptomatic AF results in an improvement in symptoms. There is currently little evidence that restoration of sinus rhythm prevents the development of heart failure in patients with AF [23]. In contrast, restoration of sinus rhythm significantly increases LV function in patients with AF and already established LV systolic dysfunction [24].

An important randomized trial comparing the strategies of cardioversion versus optimal medical therapy (rate control and anticoagulation) for AF is underway (AFFIRM) [25,26]. Total mortality is the primary outcome for this study involving more than 4000 mostly elderly patients with AF. Important secondary outcomes include a combined endpoint (total mortality and disabling stroke), functional status, quality of life, cost effectiveness, and bleeding complications. Preliminary results of the AFFIRM trial were discussed at the 2002 ACC annual meeting. After 3.5 years of follow-up, there were no significant differences in total mortality, stroke, or quality of life between groups randomized to rate versus rhythm control. These results, if confirmed, suggest that rate control and anticoagulation are very reasonable first-line therapies for AF.

- What are current recommendations regarding restoration of sinus rhythm?

In the absence of firm outcomes data, expert panels recommend cardioversion (electrical or pharmacologic) in patients with AF when symptoms are unacceptable [11]. This is a class I recommendation (‘general agreement that the procedure or treatment is useful and effective’) based on the lowest strength of data (expert consensus) in the recent ACC/AHA/ESC practice guideline [11]. Decisions to cardiovert should be strongly influenced by patient preference and are impacted by duration of AF, stroke risk, and comorbidities that may influence the desirability of restoring sinus rhythm [27]. There is little consensus regarding the optimal initial therapy for cardioversion. Options include an initial attempt at electrical cardioversion or cardioversion with a short-acting agent such as ibutilide, pharmacologic cardioversion with an appropriately chosen long-acting antiarrhythmic therapy, or electrical cardioversion after initiating an antiarrhythmic medication [11,28,29]. Electrical cardioversion after initiation of antiarrhythmic medication reduces the risk of recurrent AF, but exposes patients to potentially unnecessary side effects of antiarrhythmic medications. Recurrent AF after electrical cardioversion may be treated with repeated electrical cardioversion with the addition of antiarrhythmic therapy versus acceptance of AF with rate control and anticoagulation as appropriate.

- What is the approach to prophylactic anticoagulation in patients undergoing cardioversion?

Anticoagulation for 3 to 4 weeks prior to cardioversion and 4 weeks afterwards is recommended in order to reduce the risk of cardioversion-associated thromboembolism. The risk
of thromboembolism is 1% to 7% without prophylactic anti-coagulation and 0.3% to 0.7% with anticoagulation [30,31]. There has been recent interest in a strategy of anticoagulation and cardioversion directed by transesophageal echocardiography (TEE). While transthoracic echo is unable to reliably detect thrombus in the left atrial appendage, TEE is estimated to have a sensitivity of 97% for the detection of left atrial thrombus [32]. It is reasonable to proceed to electrical cardioversion if TEE is negative for left atrial thrombus. According to one recent multicenter trial, the incidence of embolic events was not statistically different between patients randomized to standard anticoagulation followed by electrical cardioversion if TEE is negative for left atrial thrombus. According to a recent multicenter trial, the incidence of embolic events was not statistically different between patients randomized to standard anticoagulation followed by electrical cardioversion versus TEE-directed electrical cardioversion [33]. Hemorrhagic complications (mostly minor) were less common in the TEE group, and the time to cardioversion was substantially shorter (3 days versus 30 days for the standard care group) [33]. There was no difference between the 2 groups in maintenance of sinus rhythm, functional status, or mortality at 8 weeks. A second study suggests that maintenance of sinus rhythm may be more likely following early TEE-directed cardioversion [34].

Patients with onset of initial AF episode less than 48 hours prior to cardioversion are unlikely to have developed left atrial thrombus and are therefore at low risk for embolic complications (0.8%) and may be cardioverted without prior anticoagulation [35]. It is important to note, however, that it is often difficult to reliably define the onset of AF (and therefore thromboembolic risk with cardioversion). Despite restoration of normal sinus rhythm on ECG, mechanically disorganized atrial function and embolic risk may persist for some time following cardioversion [36,37]. Therefore, anticoagulation is recommended for 4 weeks following successful cardioversion. In summary, prophylactic anticoagulation prior to cardioversion or TEE-directed cardioversion are both reasonable approaches. It is not clear at this point whether one strategy is preferable and for which subsets of patients. The potentially very short interval between TEE and cardioversion makes this a theoretically attractive strategy in patients with particularly bothersome AF symptoms.

- What agents are used for maintenance of sinus rhythm following cardioversion?

**Maintenance of Sinus Rhythm**

AF recurs frequently following cardioversion. In a recent study of 394 patients with AF who were successfully cardioverted, approximately half of patients developed recurrent AF by 6 months [38]. Another group reported successful cardioversion in 86% of patients with AF, but recurrence of AF in 39% by 1 month, and 85% recurrence by 1 year [39]. Antiarrhythmic therapy improves maintenance of sinus rhythm; 50% to 70% of patients treated with low-dose amiodarone (200 to 300 mg/day) remained in sinus rhythm after 3 years of follow-up [40,41]. Although low-dose amiodarone is well-tolerated over the short term, 22% of patients discontinued amiodarone therapy after 3 years of follow-up due to side effects, most commonly skin discoloration, pulmonary fibrosis, and thyroid toxicity [40]. It is important to recall that amiodarone interferes with the protein binding of warfarin, resulting in higher international normalized ratios (INRs). The dose of warfarin must be decreased approximately 50% when amiodarone is initiated. Sotalol is less effective than amiodarone for maintenance of sinus rhythm, but may be better tolerated [42]. Class I antiarrhythmic agents such as quinidine, procainamide, disopyramide, flecaïnide, and propafenone, are effective in preventing recurrences of AF, but confer an increased risk of arrhythmia. Class I antiarrhythmics are contraindicated in patients with structural heart disease [11]. The recurrence of AF following antiarrhythmic therapy does not necessarily indicate failure; therapy with antiarrhythmics may be considered successful if the frequency, duration, and symptoms of AF are reduced. Figure 1 outlines a recommended approach for choice of antiarrhythmic therapy for maintenance of sinus rhythm based on the presence or absence of structural heart disease and other factors [11]. Table 2 lists commonly used medications for the maintenance of sinus rhythm.

- What nonpharmacologic treatments for AF are available?

A variety of nonpharmacologic therapies for AF exist. Surgical or radiofrequency catheter ablation of atrial tissues has been successfully used to control AF in selected patients. Radiofrequency catheter ablation of the AV node followed by ventricular pacing is associated with increased exercise tolerance and quality of life [43]. This is generally reserved for patients with permanent AF who have inadequate ventricular rate control despite maximum medical therapy or in those with intolerable side effects secondary to medications for rate control. Pacing is also effective for suppression of AF and maintenance of ventricular rates in patients with sick sinus syndrome. Atrial- or dual-chamber pacemakers are associated with lower mortality and reduced risk of thromboembolic events and chronic AF compared with single-chamber ventricular pacemakers [44,45]. Suppression of AF by atrial pacing may be effective in selected patients but remains of uncertain clinical value [11]. Internal atrial defibrillators have been developed and are effective at restoring
sinus rhythm in patients refractory to antiarrhythmic therapy [46]. The defibrillatory shock generated by these units is uncomfortable, however, potentially limiting patient acceptance. The so-called “Maze” procedure, consisting of isolating atrial tissue by surgical means or with radiofrequency catheter ablation, is also an effective treatment for selected patients with refractory AF [47–50]. Appropriate patient selection for these procedures remains uncertain, although they would be reasonable in a subset of patients with refractory AF despite maximal medical therapy who require cardiac surgery for another indication [51].

Figure 1. Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Choose antiarrhythmic medications by following the arrows according to the presence or absence of the specified comorbidities. First-line medications are listed in the box immediately below a given comorbidity (eg, sotalol in patients with CAD). Second-line agents are listed in the next box down. Within a given box, drugs are listed alphabetically and not in order of suggested use. CAD = coronary artery disease; HF = heart failure; LVH = left ventricular hypertrophy. (Reprinted from Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences [Committee to develop guidelines for the management of patients with atrial fibrillation] developed in collaboration with the North American Society of Pacing and Electrophysiology. Eur Heart J 2001;22:1852–923, with permission from Elsevier Science.) *For adrenergic atrial fibrillation, β blockers or sotalol are the initial drugs of choice. †Consider nonpharmacologic options to maintain sinus rhythm if drug failure occurs.

- What can be done to reduce the risk of stroke in patients with AF who do not undergo cardioversion or in whom cardioversion is unsuccessful?

Reduction of Stroke Risk
AF is a major risk factor for ischemic stroke; approximately 1 in 6 ischemic strokes occur in patients with AF [52]. The average risk of stroke in patients with nonvalvular AF is 5% per year, more than 2 to 7 times the risk in patients without
AF [11, 53]. Patients with rheumatic valvular disease have a 14-fold increased risk of AF and a 17-fold increased risk of stroke compared with healthy age- and sex-matched controls [54]. There are abundant data demonstrating that antithrombotic therapy with warfarin or aspirin reduces the risk of stroke in patients with AF. Analysis of the 5 major randomized controlled trials in patients with AF demonstrates that warfarin reduces the relative risk of stroke (both ischemic and hemorrhagic) by 68% (95% confidence interval [CI], 47% to 71%) compared with placebo (Figure 2) [55].

Warfarin offers equivalent protection against disabling and nondisabling strokes, and for both primary and secondary prevention. Aspirin offers considerably less protection against stroke. The estimated relative reduction in risk of stroke is 19% (95% CI, 2% to 34%) (Figure 2) [55]. Aspirin therapy is not statistically better than placebo for the prevention of stroke in patients with AF and a prior history of stroke [55]. Low-dose warfarin plus aspirin is no better than aspirin alone in reducing stroke risk and is associated with a higher risk of bleeding than adjusted-dose warfarin [56, 57]. Warfarin confers a higher risk of bleeding complication than aspirin alone; greater protection against stroke comes at the price of greater bleeding risk. In general, warfarin is recommended for those patients with higher absolute risk for stroke (and thus greater absolute benefit from anticoagulation), while aspirin is a reasonable choice for patients with AF who are at lower absolute risk.

- How does one determine which patients should receive anticoagulation therapy?

Patient selection for warfarin remains a controversial and unsettled issue. While warfarin clearly reduces the risk for stroke in patients with AF, 3 important caveats bear mentioning. The longest of the trials of warfarin in AF lasted only 2.2 years, while the need for antithrombotic therapy for patients with AF typically lasts much longer. Second, trials excluded patients felt to be at a very high bleeding risk, such as patients with liver disease, active alcohol abuse, or persons with a history of falls; it is uncertain how to balance benefit versus risk for a considerable proportion of patients in a typical outpatient clinic. Third, patients with certain comorbidities have not been well studied but are nonetheless recommended to receive warfarin or equivalent anticoagulation. Patients with AF and hypertrophic cardiomyopathy or valvular disease (eg, rheumatic heart disease) are at extremely high risk of thromboembolic complications, and anticoagulation is recommended [11]. Although controversial, a recent guideline also recommended anticoagulation for patients with AF and thyrotoxicosis [11].

Multivariate analysis of AF trials reveal several factors that independently increase the risk of stroke among
patients with AF: previous stroke or transient ischemic attack (TIA), diabetes mellitus, history of hypertension, ischemic heart disease, congestive heart failure, and increasing age [55,58–61]. Among echocardiographic features, left atrial size or calcification of the mitral annulus have been associated with stroke risk in some trials, but only LV systolic dysfunction has been consistently identified as a risk factor for stroke in patients with AF [62]. Patients without any of these risk factors (patients with “lone AF”) have a very low risk of stroke, only 1.3% over 15 years of follow-up [63]. On the other hand, elderly patients with a history of prior stroke and other risk factors have a stroke risk in excess of 10% per year without antithrombotic therapy. Given the known risks of chronic anticoagulation, risk-stratification schema have been proposed to identify patient subsets that would benefit from warfarin therapy (Table 3). In general, these schemes identify patients over the age of 65 years or with any of the known clinical risk factors as having an intermediate-to-high risk of stroke. Patients in these risk groups benefit, on average, from warfarin therapy.

The recently published CHADS2 score provides a simple tool to more precisely estimate annual stroke risk [64]. The CHADS2 score is calculated by adding 1 point for the presence of each of 4 risk factors for stroke (Congestive heart failure, Hypertension, Age ≥ 75 years, or Diabetes) and 2 points for a history of Stroke or TIA. The resulting score accurately predicts stroke risk per 100 patient-years in the absence of antithrombotic therapy (Table 4). Although there remains significant uncertainty regarding the appropriate threshold for treatment with chronic anticoagulation versus aspirin therapy in patients with AF, a recently published guideline suggests that patients with an annual stroke risk of less than 2% (corresponding to a CHADS2 score of 0 or 1) do not benefit significantly from warfarin compared with aspirin, while...

Figure 2. Efficacy of antithrombotic therapy for prevention of total strokes (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation. (A) Warfarin compared with placebo. (B) Aspirin compared with placebo. The bars show estimated risk reduction (%) with 95% confidence interval. AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation Study; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; SPAF = Stroke Prevention in Atrial Fibrillation Study; SPINAF = Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study; EAF = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; LASAF = Low-dose Aspirin, Stroke, and Atrial Fibrillation; UK-TIA = United Kingdom Transient Ischaemic Attack Study. (Adapted from Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–7; and Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences [Committee to develop guidelines for the management of patients with atrial fibrillation] developed in collaboration with the North American Society of Pacing and Electrophysiology. Eur Heart J 2001;22:1852–923, with permission from Elsevier Science.)
those with an annual stroke risk of 6% or higher (corresponding to a CHADS2 score of 3 or higher) clearly benefit from anticoagulation [11]. More than 100 patients with an annual risk of stroke of 2% would need to be treated with warfarin for 1 year to prevent 1 stroke compared with treatment with aspirin (number needed to treat [NNT] = 100) [65].

The recommended target intensity of anticoagulation results from balancing the competing risks of stroke reduction versus hemorrhage. Hemorrhagic risk increases as a function of patient age and intensity of anticoagulation [66–68]. The risk of ischemic stroke increases below an INR of 1.6, while the incidence of hemorrhagic complications increases above an INR of 3.5 to 4.0 (Figure 3) [67,69]. The risk of intracranial bleeding essentially doubles for every 0.5 increase in the INR [67]. (Please see Case Study 2 for more details regarding the assessment and reduction of hemorrhagic risk.)

A target INR of 2.5 is recommended for primary and secondary prevention of stroke in most patients with AF [11]. Treatment with this goal in mind will assist most patients in

---

**Table 3. Published Risk-Stratification Schemes for Primary Prevention of Thromboembolism in Patients with Nonvalvular Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Source</th>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation Investigators [55]</td>
<td>Age ≥ 65 yr</td>
<td>Did not distinguish high-risk from intermediate-risk patients</td>
<td>Age &lt; 65 yr</td>
</tr>
<tr>
<td></td>
<td>History of hypertension</td>
<td></td>
<td>No high-risk features</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American College of Chest Physicians [2]</td>
<td>Age &gt; 75 yr</td>
<td>Age 65-75 yr</td>
<td>Age &lt; 65 yr</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Coronary artery disease</td>
<td>No risk factors</td>
</tr>
<tr>
<td></td>
<td>History of hypertension</td>
<td>Thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular dysfunction*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than 1 intermediate risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke Prevention in Atrial Fibrillation [62]</td>
<td>Women &gt; 75 yr</td>
<td>History of hypertension</td>
<td>No high-risk features</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure &gt; 160 mm Hg</td>
<td></td>
<td>No history of hypertension</td>
</tr>
<tr>
<td></td>
<td>Left ventricular dysfunction*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Patients with atrial fibrillation and prior thromboembolism are at high risk of stroke, and anticoagulation is indicated for secondary prevention in such cases. (Adapted from Pearce LA, Hart RG, Halperin JL. Assessment of three schemes for stratifying stroke risk in patients with nonvalvular atrial fibrillation. Am J Med 2000;109:45–51, with permission from Excerpta Medica Inc.)

*Left ventricular dysfunction refers to moderate to severe wall motion abnormality assessed globally by 2-dimensional echocardiography, reduced ejection fraction, fractional shortening less than 0.25 by M-mode echocardiography, or clinical heart failure.

**Table 4. National Registry of Atrial Fibrillation CHADS2 Score for Predicting Stroke Risk in Nonvalvular Atrial Fibrillation**

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Adjusted Stroke Rate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2–3.0)</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0–3.8)</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1–5.1)</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6–7.3)</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3–11.1)</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2–17.5)</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5–27.4)</td>
</tr>
</tbody>
</table>

Note: CHADS is an acronym for the risk factors for stroke in patients with atrial fibrillation (congestive heart failure, hypertension, age, diabetes, and stroke). The CHADS2 Score is calculated by adding 1 point for each of 4 conditions (recent congestive heart failure, hypertension, age ≥ 75 years, or diabetes mellitus) and adding 2 points for having had a prior stroke or transient ischemic attack. CI = confidence interval. (Adapted with permission from Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–70.)

*The adjusted stroke rate is the expected stroke rate per 100 patient-years, assuming that aspirin was not taken. Aspirin reduces the risk of stroke by approximately 20%.

For patients with an annual stroke risk of 6% or more, the corresponding NNT is 25 or fewer patients treated with warfarin compared with aspirin to prevent 1 stroke. For patients with 2% to 6% stroke risk where benefit of anticoagulation is roughly equivalent to the hemorrhagic risk, careful discussion and patient preferences are of paramount importance. It remains to be seen whether laboratory markers of inflammation, platelet activation, or hemostasis will allow patients in this risk category to be further risk stratified. Most patients with AF are elderly and have comorbidities that confer substantial stroke risk; therefore, most patients with AF should be considered candidates for warfarin therapy.

- **What is the recommended target intensity of anticoagulation in patients with AF?**
achieving a safe and effective range of INRs between 2.0 and 3.0. Because of an increased risk of major bleeding in the elderly, an expert panel recently recommended anticoagulation to a target INR of 2.0 (range 1.6 to 2.5) as primary prevention for patients older than 75 years of age [11]. Patients with a history of stroke should be anticoagulated to the more aggressive target of 2.5 (range 2.0 to 3.0) regardless of age. INRs should be checked at least weekly during initiation of therapy and every 4 to 6 weeks once stable. Warfarin may be safely and effectively initiated in outpatients [70]. Patients should be treated with warfarin 5 mg daily for 4 days and their INR should be checked on the fifth day. Weekly warfarin requirements to maintain an INR of 2.5 can be reliably estimated based on the INR following 4 days of standard treatment (see Table 5) [70].

It is generally safe to hold anticoagulation for a period of several days prior to surgery in patients anticoagulated for AF [71]. Because the stroke risk measured over a period of several days is low, even for patients at 10% or greater annual risk of stroke, anticoagulation may be safely held for 4 days prior to elective surgery, allowing the INR to decline to 1.5 or less, then may be restarted at the usual dose on the night following surgery. Resumption of anticoagulation would be appropriately further delayed in patients with spinal or neurosurgery. This strategy minimizes hemorrhagic and stroke risk, and usually avoids the necessity of hospitalizing patients for treatment with unfractionated heparin. If patients are felt to be at very high risk for stroke, they may be treated with intravenous unfractionated heparin or subcutaneous low-molecular heparin [11], although there are little data for the use of low-molecular-weight heparin in patients with AF.

**Elective Cardioversion and Follow-up**

The patient and his physician decide to try elective cardioversion to restore sinus rhythm. The patient is anticoagulated with warfarin to a target INR of 2.5, and he undergoes DC cardioversion 1 month after presentation. He develops recurrent AF 1 month after cardioversion. His diliazem is discontinued, and he is placed on sotalol for rate control and as an antiarrhythmic (sotalol has significant β blocker activity). Other reasonable choices would have been propafenone, flecainide, or amiodarone in this patient without significant structural heart disease (Figure 1). Repeat cardioversion successfully restores sinus rhythm, and he remains in sinus rhythm 6 months after cardioversion. His warfarin therapy is discontinued 4 weeks after the second cardioversion. He remains on sotalol.

**CASE STUDY 2**

**Initial Presentation**

A 78-year-old man with a history of AF presents to the emergency department with an abrasion on the right side of his face and a large periorbital ecchymosis after a fall.
The patient reports a mechanical fall while walking without his front-wheeled walker. He struck his head on a dresser as he fell. He reports no loss of consciousness. He reports no alterations in his vision. He denies chest pain or palpitations prior to the fall. He has a history of paroxysmal AF diagnosed several years earlier and is being treated with amiodarone for maintenance of sinus rhythm, digoxin for rate control, and aspirin. His past medical history is otherwise notable for life-threatening bipolar affective disorder, hypertension, hypercholesterolemia, and parkinsonism. His medications include amiodarone, valproic acid, paroxetine, simvastatin, and carbidopa/levodopa. He has not previously been anticoagulated because of the risk of falls.

**Physical Examination**

On physical examination, he is an elderly man with a large periorbital ecchymosis. He is afebrile and has a blood pressure of 140/80 and a heart rate of 83 bpm that is irregularly irregular. He has tenderness over the right zygoma, but no bony abnormalities are noted. He has full movement of his extraocular muscles and his pupils are equal, round, and reactive. His chest is clear to auscultation and percussion. His cardiovascular examination is notable for brisk carotid upstroke without bruits and a normal jugular venous pulsation. He has an irregularly irregular rhythm. He has no murmurs or third heart sound. He does not have edema. Neurologically, he is alert and oriented. His gait is narrow-based with a low amplitude arm swing. He has some increase in muscular tone in his right upper and lower extremities, but no tremor. A noncontrast head CT scan shows no blood or mass effect. The head CT scan shows evidence of 2 old lacunar strokes in the basal ganglia.

### Table 5. Predicted Weekly Warfarin Maintenance Dose Based on the INR on Day 5 after 5 mg/day of Warfarin

<table>
<thead>
<tr>
<th>INR on Day 5</th>
<th>Mg/Week</th>
<th>INR on Day 5</th>
<th>Mg/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>71</td>
<td>1.1</td>
<td>57</td>
</tr>
<tr>
<td>1.2</td>
<td>48</td>
<td>1.3</td>
<td>43</td>
</tr>
<tr>
<td>1.4</td>
<td>39</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>1.6</td>
<td>33</td>
<td>1.7</td>
<td>31</td>
</tr>
<tr>
<td>1.8</td>
<td>29</td>
<td>1.9</td>
<td>27</td>
</tr>
<tr>
<td>2.0</td>
<td>26</td>
<td>2.1</td>
<td>24</td>
</tr>
<tr>
<td>2.2</td>
<td>23</td>
<td>2.3</td>
<td>22</td>
</tr>
<tr>
<td>2.4</td>
<td>21</td>
<td>2.5</td>
<td>20</td>
</tr>
<tr>
<td>2.6</td>
<td>19</td>
<td>2.7</td>
<td>18</td>
</tr>
</tbody>
</table>

INR = international normalized ratio. (Reprinted from Pengo V, Biasiolo A, Pegoraro C. A simple scheme to initiate oral anticoagulant treatment in outpatients with nonrheumatic atrial fibrillation. Am J Cardiol 2001; 88:1214–6, with permission from Excerpta Medica Inc.)

### History

The patient reports a mechanical fall while walking without his front-wheeled walker. He struck his head on a dresser as he fell. He reports no loss of consciousness. He reports no alterations in his vision. He denies chest pain or palpitations prior to the fall. He has a history of paroxysmal AF diagnosed several years earlier and is being treated with amiodarone for maintenance of sinus rhythm, digoxin for rate control, and aspirin. His past medical history is otherwise notable for life-threatening bipolar affective disorder, hypertension, hypercholesterolemia, and parkinsonism. His medications include amiodarone, valproic acid, paroxetine, simvastatin, and carbidopa/levodopa. He has not previously been anticoagulated because of the risk of falls.

### Bleeding Risk

Chronic anticoagulation with warfarin is associated with several risks, principally hemorrhage and drug interactions. The risk of bleeding complications reduces the net benefit conferred by chronic anticoagulation and contributes to physician reluctance to prescribe warfarin [75,76]. The elderly, who are among the group at highest risk for stroke and therefore receive the greatest benefit from warfarin therapy, may be at the greatest risk of bleeding complications. Analysis of complications from the large trials of anticoagulation for AF demonstrate that the average annual risk of major hemorrhage (defined as intracranial hemorrhage, bleeding sufficient to cause hospitalization, or hemorrhage

Paroxysmal AF refers to AF that is episodic, typically lasts less than 72 hours, and is self-limited. The risk of stroke and the efficacy of antithrombotic therapy in patients with paroxysmal AF have not been well defined. While patients with paroxysmal AF represent approximately 40% of patients with AF seen in outpatient practice, they represent only a small fraction of patients in the major AF trials [72]. The risk of stroke in paroxysmal AF was similar to that in continuous AF in the 2 trials that included patients with paroxysmal AF [73,74]. Accordingly, recommendations regarding antithrombotic therapy do not distinguish between patients with paroxysmal and other types of AF [11].

This patient who was found to be in AF following a fall despite treatment with amiodarone is certainly at risk for recurrent falls due to parkinsonism and centrally acting medications. On the other hand, his age, hypertension, and radiographic evidence of prior strokes places him in an extremely high risk for stroke. According to the CHADS2 score, his risk of stroke is 8.5% per year (95% CI, 6.3% to 11.1%).

### How can one determine the risk for bleeding in a patient who would benefit from anticoagulation?
Because of a small number of patients with a history of gastrointestinal bleeding and a history of stroke, these 2 risk factors are treated together.


Bleeding complications are more common among the very old (patients older than 80 years of age) [68]. The SPAF investigators reported an annual major hemorrhage risk of 4.2% among patients 75 years of age or older, with intracranial hemorrhage occurring at a rate of 1.8% per year [66]. Bleeding risk is likely higher in general practice than among patients enrolled in AF trials, although studies have conflicted on this point [78,79].

Landeefeld and colleagues devised an index that reliably predicts bleeding risk [79,80]. The Outpatient Bleeding Risk Index identifies 4 easily ascertainable clinical features that predict subsequent bleeding risk: (1) age 65 years or older, (2) history of stroke, (3) history of gastrointestinal bleed, and (4) 1 of 4 specific comorbidities (recent myocardial infarction, hematocrit < 30%, serum creatinine > 1.5 mg/dL, or diabetes mellitus). Patients without any of these risk factors had a cumulative incidence of major bleeding of 2% to 3% at 12 months; patients at intermediate risk with 1 or 2 risk factors had a risk of 5% to 12% at 12 months; and patients at high risk with 3 or 4 risk factors had a cumulative risk of major hemorrhage of 23% to 48% at 12 months [79]. Bleeding risk in the presence and absence of risk factors is shown in Table 6. Much of the risk attributable to warfarin occurs during the first 3 months of treatment, when risk of excessive anticoagulation is highest [81].

There is understandable reluctance to prescribe warfarin to patients at high risk for falls. Surprisingly little is known about the risk posed by falls for patients on chronic anticoagulation. A recent decision analysis estimated that the risk of subdural hematoma is increased 40% among chronically anticoagulated patients who fall compared with patients who do not fall, although this estimate is based on observational data and subject to a number of important assumptions [53]. Interestingly, this decision analysis suggested that fall risk had virtually no influence on deciding on optimal therapy for AF, despite the increased risk of intracranial bleeding and residual neurological deficit [53]. According to their analysis, the risk of subdural hematoma would have to be at least 65-fold higher for patients receiving warfarin before no treatment would be favored over warfarin for elderly patients with AF; preferred treatment choices were also insensitive to wide variations in fall risk [53]. While this decision analysis is subject to a number of potential criticisms, its major conclusion is that reduction of stroke risk (and the attendant disability of stroke) trumps most other concerns in decisions regarding warfarin therapy for patients with AF who are at high risk for stroke. Studies of patient preferences are congruent with this latter assertion. While physicians may be reluctant to prescribe warfarin to patients with increased bleeding or falls risk, patients strongly prefer to avoid disability due to stroke, even at the cost of increased risk of intracranial bleeding [82–84].

Table 6. Outpatient Warfarin Therapy in Patients with Specific Combinations of Risk Factors: Estimated Probabilities and Observed Frequencies of Major Bleeding at 3 and 12 Months*

<table>
<thead>
<tr>
<th>History of GI Bleed or Stroke*</th>
<th>Comorbid Conditions†</th>
<th>Estimated Probability of Major Bleeding (95% CI)</th>
<th>[Observed frequency of major bleeding, %]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age &lt; 65 years</td>
<td>3 months</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>0.01 (0.005–0.02)</td>
<td>0.02 (0.01–0.05)</td>
</tr>
<tr>
<td>Absent</td>
<td>Present</td>
<td>0.04 (0.01–0.05)</td>
<td>0.07 (0.03–0.11)</td>
</tr>
<tr>
<td>Present</td>
<td>Absent</td>
<td>0.05 (0.03–0.14)</td>
<td>0.09 (0.04–0.14)</td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
<td>0.08 (0.03–0.14)</td>
<td>0.19 (0.07–0.29)</td>
</tr>
</tbody>
</table>

Note: Estimated probabilities of major bleeding are derived from a proportional hazards model in a derivation cohort (n = 556) [4]. The observed frequency of major bleeding is based on 820 patients combined from the derivation and validation cohorts [5]. CI = confidence interval; GI = gastrointestinal. (Reprinted from Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998;105:91–9, with permission from Excerpta Medica Inc.)

*Because of a small number of patients with a history of gastrointestinal bleeding and a history of stroke, these 2 risk factors are treated together.
†The 4 specific comorbid conditions are recent myocardial infarction, renal insufficiency, severe anemia, or diabetes mellitus.
Strategies to Reduce Risk of Bleeding

Two studies have identified a number of potentially modifiable factors related to major bleeding complications or excessive anticoagulation (INR > 6.0) (Table 7) [81,85]. Not surprisingly, patients with greatly variable INRs during follow-up are more likely to have bleeding complications [81]. Additionally, a number of medications and complementary medicines can potentiate the action of warfarin or otherwise increase bleeding risk. Directly addressing these potentially modifiable factors or increasing patient monitoring when these factors are present may reduce bleeding risk.

The introduction of point-of-care instruments capable of measuring capillary whole blood prothrombin time has significantly improved outpatient monitoring of patients chronically taking warfarin. These instruments have been used in a variety of ways to reduce bleeding risk. There is considerable observational data that suggest that anticoagulation clinics staffed by physicians, pharmacists, physician-extenders, and/or nurses reduce bleeding risk [86,87]. Advantages include consistent, algorithm-based adjustment of INRs, provision of a centralized point-of-contact for anticoagulation-related questions and concerns, and dedicated staff with experience in chronic anticoagulation. Patients may also monitor their INRs at home and either report the results to an anticoagulation clinic (self-monitoring) or self-adjust their warfarin levels according to predetermined nomograms (self-management). Self-management of INRs has been shown to improve therapeutic control in a randomized controlled trial of patients on short-term anticoagulation for deep venous thrombosis following hospital discharge; there was no increased risk of bleeding complications [88]. More patients in the self-management group were in the target INR range compared with usual care in a dedicated anticoagulation clinic [88]. Two additional randomized controlled trials have shown that patient self-management results in effective and safe anticoagulation with high patient-rated satisfaction, compared with usual care by primary care physicians [89,90]. In these studies, self-management was supported by structured patient education and a dedicated anticoagulation clinic available for patient questions or concerns. The study of Beyth and colleagues enrolled primarily elderly inpatients with increased bleeding risk at the time anticoagulation was initiated [90]. Importantly, this study found that major bleeding events were significantly reduced in the self-management group; at 6 months, the cumulative risk of bleeding was 12% in the usual care group compared with 5.6% in the self-management group (P < 0.05) [90]. This 50% reduction corresponds to a NTN of approximately 15 patients for 6 months to prevent 1 major bleeding event in this group of patients at increased risk of bleeding complications. Self-management of chronic anticoagulation with warfarin has been recommended as one of 11 most highly rated practices to improve patient safety in a recently published Agency for Healthcare Research and Quality report [91,92].

Table 7. Potentially Modifiable Factors Associated with an Increased Risk for Major Bleeding Complications or Excessive Anticoagulation (INR > 6.0).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent initiation of warfarin therapy (within 3 months)</td>
<td></td>
</tr>
<tr>
<td>Highly variable INRs</td>
<td></td>
</tr>
<tr>
<td>More than 2.5 g of acetaminophen within the prior week (more acetaminophen is associated with greater risk)</td>
<td></td>
</tr>
<tr>
<td>Recently started a drug that potentiates warfarin</td>
<td></td>
</tr>
<tr>
<td>Advanced cancer</td>
<td></td>
</tr>
<tr>
<td>Decreased oral intake</td>
<td></td>
</tr>
<tr>
<td>Acute diarrheal illness</td>
<td></td>
</tr>
</tbody>
</table>

INR = international normalized ratio.

- How can bleeding risk be reduced?

Initiation of Warfarin Therapy and Follow-up

After a prolonged discussion of the risks and benefits of warfarin therapy, the patient and his physician elect to initiate warfarin therapy with a target INR of 2.5. Aspirin is discontinued as it offers uncertain cardiovascular benefit in patients on warfarin and substantially increases the risk of gastrointestinal and intracranial bleeding [93]. The patient is provided educational training while in the hospital and instructed on warfarin self-monitoring at discharge. He elects to continue follow-up with the dedicated anticoagulation clinic affiliated with the hospital. Given the patient’s history of life-threatening bipolar affective disorder and profound reluctance to make any changes to his psychotropic medications, his physician felt that his risk of falls could best be reduced by encouraging him to use his front-wheeled walker and providing physical therapy follow-up, including a home safety evaluation. The patient enters a verbal contract to use his front-wheeled walker whenever he leaves his home. He has been subsequently followed for more than 2 years without incident.

Financial disclosures: None.

Author contributions: conception and design, PRS, JYY; analysis and interpretation of data, PRS, JYY; drafting of the article, PRS, JYY; critical revision of the article for important intellectual content, PRS, JYY; final approval of the article, PRS, JYY; statistical expertise, PRS;
References

the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.


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EVALUATION FORM: Management of Atrial Fibrillation

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Part 1. Please respond to each statement. 

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was provided with new information pertinent to my practice.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I reaffirmed a specific skill or knowledge.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This article will help with clinical decision making.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant clinical outcomes are addressed.</td>
<td></td>
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<tr>
<td>The case is communicated in a manner that kept my interest.</td>
<td></td>
<td></td>
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<tr>
<td>The case presentation is realistic and effective.</td>
<td></td>
<td></td>
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<tr>
<td>I could easily interpret the tables and figures.</td>
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</tr>
<tr>
<td>My attitude about this topic changed in some way.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional comments: ______________________________________________________________________________________
__________________________________________________________________________________________________________

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .  

- see no need to change my practice.
- will seek more information before modifying my practice.
- intend to change the following aspect(s) of my practice: (Briefly describe)__________________________________________________________________________________________
__________________________________________________________________________________________________________


Signature: ___________________________ Date: ___________________________

Part 4. Identifying information: Please PRINT legibly or type the following:

Name: _______________________________ Fax number ___________________________
Address: ___________________________ Telephone number _______________________
_________________________________________ Social Security number: ___________________________
(Required and confidential)

Medical specialty: ___________________________

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