Evaluation and Management of New-Onset Atrial Fibrillation

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ABSTRACT

• **Objective:** To review the evaluation and management of new-onset atrial fibrillation (AF).
• **Methods:** Review of relevant scientific literature and clinical/professional society guidelines addressing AF.
• **Results:** AF is growing in prevalence with the aging of the population and the increasing prevalence of heart failure. The initial evaluation of patients with new-onset AF should include investigation of reversible causes and assessment of the patient’s underlying cardiac function. Key areas in the management of new-onset AF include reducing the risk of systemic thromboembolism, control of ventricular rates, and rhythm control. Maintenance of sinus rhythm with antithrombotic medications or ablation represents a treatment goal in patients who remain asymptomatic after stroke risk reduction has been addressed and attempts at adequate rate control have been made.
• **Conclusion:** AF is common and poses challenges for clinicians, but modern treatment strategies can successfully address stroke risk and effectively manage symptoms.

Atrial fibrillation is the most common arrhythmia encountered in clinical practice, affecting as many as 6 million people in the United States today [1]. It is a major risk factor for embolic stroke and is associated with increased risk of hospitalization and mortality [1]. The initial evaluation of the patient should be individualized and involves minimizing the risk of systemic thromboembolism, controlling ventricular rates, and rhythm control. In this review, we highlight evidence from clinical trials, observational data, and clinical guidelines to describe our approach to the management of new-onset atrial fibrillation.

PATHOPHYSIOLOGY AND CLASSIFICATION

Atrial fibrillation is characterized by disorganized atrial activation that leads to a deterioration of atrial mechanical function. This chaotic atrial activation, generally at atrial rates of 350 to 450 beats per minute, can lead to rapid conduction over the atrioventricular (AV) node, resulting in a fast ventricular response [2]. Disorganized and rapid atrial activity coupled with refractoriness of the AV node leads to irregularly irregular ventricular conduction. The lack of atrial systole may also result in thrombus formation with subsequent increased risk of stroke and systemic thromboembolism, particularly in patients with risk factors, such as advanced age, underlying structural heart abnormalities (eg, valvular disease or cardiomyopathy), concomitant hypertension, diabetes, or prior history of cerebrovascular events [2].

The initiation and propagation of atrial fibrillation may result from several processes. Focal atrial tachycardia triggers for atrial fibrillation initiation are most commonly found in the pulmonary veins but occur at other structures, such as the superior vena cava, ligament of Marshall, and posterior left atrial wall [3,4]. Similarly, atrial fibrillation can be initiated by atrial flutter, AV nodal reentry tachycardia, or AV reentry tachycardia and atrial tachycardias [5,6]. Regarding the maintenance of atrial fibrillation, Moe and colleagues initially proposed the multiple wavelet model in which wavelets of activation result in daughter wavelets [7,8]. Maintaining atrial fibrillation generally requires changes either in the underlying atrial structural substrate, or changes in atrial action potential duration and conduction, or both [9].

Atrial fibrillation represents the predominant pathological finding in patients with atrial fibrillation [10]. This fibrosis may be diffuse throughout the atria and involve the sinoatrial and AV nodes [11]. In addition, interstitial fibrosis replaces atrial myocytes and may lead to atrial dilation. The degree of fibrosis increases with the duration...
of atrial fibrillation, and ongoing progression of structural changes leads to a greater burden of atrial fibrillation.

Heart failure and atrial fibrillation often coexist and each may promote the development and/or the worsening of the other. One of the mechanisms by which atrial fibrillation can cause or worsen heart failure is through tachycardia-mediated cardiomyopathy, which has been shown to be reversible in canine models [12,13]. Atrial fibrillation may also lead to adverse outcomes in heart failure by increasing the risk of cerebrovascular accidents or through the associated side effects from medications or procedures used for rate or rhythm control of atrial fibrillation [14]. In the SOLVD and DIAMOND trials, atrial fibrillation was associated with increased mortality, and in the CHARM study atrial fibrillation was associated with increased mortality in patients with less severe heart failure [15,16]. However, in patients with mild to moderate heart failure in the V-HeFT I and V-HeFT II trials, cumulative mortality and heart failure hospitalization rates were not increased in patients with atrial fibrillation [17].

The classification of atrial fibrillation can help guide evaluation and treatment strategies [18]. Atrial fibrillation that is recurrent and self-terminating is defined as paroxysmal; when sustained for greater than 7 days, it is defined as persistent. Long-standing atrial fibrillation is defined as permanent atrial fibrillation. First detected atrial fibrillation may be paroxysmal, persistent, or permanent in pattern. “Lone” atrial fibrillation is said to occur in patients without other cause, whereas secondary atrial fibrillation occurs in patients with other known precipitating causes such as pericarditis or hyperthyroidism. Clearly, the current classification system is imperfect and there is significant overlap between different atrial fibrillation subtypes [19].

**PREVALENCE AND RISK FACTORS**

The prevalence of atrial fibrillation is 0.4% to 1.0% in the general population and increases with age, with a prevalence of approximately 8% in patients 80 years of age. Overall median age for patients with atrial fibrillation is 75 years [20]. The incidence of atrial fibrillation increases with age from 0.1% per year in patients under 40 years of age to as high as 1.5% in women and 2.0% per year in men greater than 80 years of age [21]. Atrial fibrillation will likely continue to represent a major cause of hospitalization as the population continues to age.

Multiple risk factors that contribute to the development of new-onset atrial fibrillation have been identified. In the Framingham cohort, identified risk factors included increasing age, structural heart disease (such as the presence of a murmur or heart failure), body mass index, hypertension, and prolonged PR interval on electrocardiogram [22]. Patients who had a greater number of risk factors had an increasing risk of developing atrial fibrillation. In the Etude en Activité Libérale sur la Fibrillation Auriculaire Study (ALFA), a total of 756 patients were followed for an average of 8.6 years. Characteristics that were more common among patients who developed atrial fibrillation included the presence of structural heart disease, including heart failure, hypertrophic cardiomyopathy, valvular heart disease, and coronary artery disease [23]. Hypertension is also an important risk factor for the development of atrial fibrillation.

**PRESENTATION**

The symptoms associated with atrial fibrillation vary widely from acute, highly symptomatic episodes to asymptomatic episodes. Patients may present with a variety of symptoms including palpitations, chest pain, fatigue, and shortness of breath. Syncope is an uncommon presentation but may represent sinus node pauses after conversion out of atrial fibrillation, rapid ventricular rates, or the presentation of other associated conditions including aortic stenosis and hypertrophic cardiomyopathy. Asymptomatic atrial fibrillation may present as heart failure, presumably related to untreated high ventricular rates. Ambulatory monitoring has shown that patients often have symptomatic and asymptomatic episodes [24], and as atrial fibrillation becomes more persistent the severity of symptoms often decreases. Finally, thromboembolism resulting in cerebrovascular accident or systemic embolism may occur and has been shown to be common in patients with asymptomatic or short episodes of atrial fibrillation [25].

**INITIAL EVALUATION**

The initial evaluation of new-onset atrial fibrillation should include a search for acute reversible causes, such as acute alcohol consumption, pericarditis, and high-catecholamine states such as those associated with surgery, hyperthyroidism, and pulmonary embolus. Treatment of hypertension may also decrease the frequency of atrial fibrillation. Atrial fibrillation may also be associated with other cardiac arrhythmias, such as atrial flutter, Wolff-Parkinson-White syndrome, and AV nodal reentry tachycardia, and treatment of the primary arrhythmia...
Atrial fibrillation may prevent further atrial fibrillation. An overview of the initial evaluation for atrial fibrillation is included in Figure 1.

The initial evaluation should include a thorough history and physical to evaluate for the common etiologies previously discussed. It is important to look for underlying heart disease, such as hypertension, heart failure, valvular disease, and atherosclerosis, as well as underlying pulmonary disease. Although less common, potential thyroid disease or underlying supraventricular tachycardias should also be investigated. Presence of symptoms should be determined. Physical examination should try to document an irregularly irregular rhythm, signs of associated cardiac disease, or other associated systemic diseases. Finally, characterization of whether atrial fibrillation is occurring in a paroxysmal, persistent or permanent pattern will help to guide treatment.

The cornerstone of diagnosis is electrocardiographic documentation of atrial fibrillation, which is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves, which results in an irregularly irregular rhythm when AV conduction is intact (Figure 2a). The QT interval can also be assessed, which may affect choice of antiarrhythmic treatment. In patients with an accessory pathway and associated Wolff-Parkinson-White Syndrome, AV conduction results in an irregularly irregular ventricular rhythm and QRS morphology due to varying degrees of conduction via the AV nodal and the accessory pathway (Figure 2b). Other associated cardiac arrhythmias may include atrial flutter (Figure 2c) or supraventricular tachycardias.

If atrial fibrillation occurs frequently, it may be recorded either through electrocardiogram or an ambulatory monitor. An electrocardiogram can also document other associated cardiac pathology including left ventricular hypertrophy, pulmonary hypertension, pre-excitation, prior myocardial infarction and evidence of AV conduction disease. Longer-duration ambulatory monitors may be necessary if atrial fibrillation is infrequent or asymptomatic [26]. These monitors may be shorter-term continuous Holter monitors (1–2 days) where the patient records a diary of symptoms, or alternatively, longer-term event monitors where the patient triggers the monitor for symptoms or a loop monitor which continuously records and documents the rhythm shortly before and after the patient recorded symptom. Auto-triggered loop monitors trigger ECG storage during symptomatic and asymptomatic episodes and have been shown to have a higher yield.
Figure 2. A: Atrial fibrillation. Note that there is no organized atrial activity and irregularly irregular ventricular rhythm. B: Pre-excited atrial fibrillation. Note that there is an irregularly irregular QRS duration and ventricular response. C: Atrial flutter.
than Holter and 30-day loop monitors [27]. Finally, implantable loop monitors can record patient-initiated and auto-triggered events for 1 to 2 years [28]. With regard to atrial fibrillation, these monitors have a role in the diagnosis of unexplained symptoms (palpitations, dyspnea) and cryptogenic stroke, and in following the efficacy of various treatments.

Several other tests should be used to characterize the cardiac pathology. A 2-dimensional Doppler echocardiogram should be performed as part of the initial evaluation in all patients with atrial fibrillation. An echocardiogram will document associated left ventricular hypertrophy, valve disease, and other ventricular systolic or diastolic dysfunction. A transesophageal echocardiogram is not needed as part of the initial evaluation but is a more sensitive test to document intracardiac thrombus formation [29,30]. A chest x-ray is mostly useful to document associated pulmonary pathology and may give some insight into the overall cardiac dimension. Blood tests to investigate renal, hepatic, and thyroid function are useful. A stress test may be useful if underlying coronary atherosclerotic disease is suspected. In selected patients, an electrophysiology study may help to detect underlying atrial flutter or supraventricular tachycardia that may serve as a trigger for atrial fibrillation.

**MANAGEMENT**

The management of atrial fibrillation varies according to the individual patient’s characteristics. The variables important to consider are

- Presence of structural heart disease
- Pattern of atrial fibrillation: paroxysmal, persistent or permanent
- Presence of comorbid conditions: hypertension, diabetes, previous stroke
- Severity of associated symptoms: asymptomatic to severe

Treatment of atrial fibrillation can be complex but revolves around 3 interdependent management considerations: controlling ventricular rates, preventing thromboembolism and rhythm control. It should be remembered that the primary 2 goals of management of atrial fibrillation are rate control and prevention of thromboembolism, which often supercede the need for rhythm control. A general outline for the initial management of newly diagnosed atrial fibrillation is shown in Figure 3.

**Rate Control**

Choice of the appropriate strategy to control ventricular rates during atrial fibrillation will depend on the acuity of the presentation and the presence of co-existing conditions such as heart failure and pre-excitation. It should be noted that ventricular rates in atrial fibrillation depend on sympathetic tone during the acute and chronic settings (sepsis, exercise). Very high ventricular rates may cause hemodynamic compromise, particularly in the setting of underlying structural heart disease.

During the acute setting, control of ventricular rates depends the degree of hemodynamic compromise. In patients who are hemodynamically unstable, which may occur in hypertrophic cardiomyopathy, aortic stenosis or pre-excited atrial fibrillation, prompt cardioversion is indicated. In patients without pre-excitation, control of ventricular rates acutely can be accomplished with IV beta-blocker (propranolol, esmolol, or metoprolol) or nondihydropyridine calcium channel antagonist (diltiazem, verapamil). In heart failure patients, amiodarone and digoxin are indicated for control of ventricular rates. Low-dose beta-blockers may be used but with careful attention to avoid worsening hemodynamic compromise. In patients with pre-excited atrial fibrillation, medications that selectively affect the AV node are contraindicated due to risk of promoting conduction exclusively over the AV accessory pathway and subsequent risk of ventricular fibrillation. Therefore, antiarrhythmic medications such as amiodarone, procainamide, or ibutilide may be used to terminate atrial fibrillation and to inhibit AV accessory pathway conduction.

In patients who are not acutely hemodynamically compromised, oral medications to control heart rate are indicated. In patients without pre-excitation, oral beta-blockers (propranolol, metprolol) and nondihydropyridine calcium channel antagonists (diltiazem, verapamil) can effectively control the rapid ventricular rate response to atrial fibrillation. With regard to the degree of ventricular rate control required, the RAte Control Efficacy in Permanent Atrial Fibrillation II trial (RATE II) compared lenient control to strict heart rate control (< 110 bpm vs < 80 bpm) and found no difference in patient outcomes between the 2 strategies [31]. Similarly, there was no association between the degree of rate control and adverse cardiac remodeling as assessed by echocardiogram in RATE II [32]. It should be noted that the RATE II trial did include a substantial propor-
tion of patients with structural heart disease, including those with decreased left ventricular function and valvular heart disease. In heart failure patients, low-dose beta-blockers, digoxin, and amiodarone are indicated for ventricular rate control. In patients with pre-excitation, ablation of the accessory pathway should be considered.

The ultimate form of ventricular rate control can be achieved with AV node ablation, which is recommended for patients with severe symptoms from atrial fibrillation or tachycardia-mediated cardiomyopathy that cannot be controlled with antiarrhythmic or rate-controlling medications [33]. Several trials have shown AV node ablation to be effective and safe in patients with medically refractory atrial fibrillation, but it should be noted that these trials were performed before ablation directed at atrial fibrillation or pulmonary vein isolation was commonly practiced. The Ablate and Pace Trial was a prospective study following 156 patients with chronic and paroxysmal atrial fibrillation that was medically refractory [34]. There was a significant improvement in quality of life measurements and an improvement in left ventricular function in those with baseline reduced systolic function. In a smaller trial of patients with chronic atrial fibrillation who had AV node ablation and pacemaker placement, there was an improvement of quality of life that was associated with a discontinuation of rate controlling medications [35]. In a recent meta-analysis, there was no improvement of quality of life indices or LV function in patients with normal LV function who underwent an ablate and pace strategy [36]. In another meta-analysis that

Figure 3. Initial management of newly diagnosed atrial fibrillation (AF). (Modified from 2011 ACC/AHA/ESC Focused Update on Atrial Fibrillation.)
comprised 21 studies with 1181 patients between 1989 and 1998, AV node ablation and pacemaker placement was associated with an improved quality of life and improved LV ejection fraction (4.4 ± 0.01%) [37].

Although AV node ablation is a technically straightforward procedure, it is associated with some serious complications that deserve mention. Overall, AV node ablation and pacemaker placement was associated with a reported overall incidence of sudden death of 2.1% (range, 0% to 11.3%) that may be associated with a lower pacing rate post AV node ablation (< 70 bpm) [37,38]. Other notable complications post-procedure include pacemaker lead failure, complications related to the need for long-term anticoagulation, and life-long pacemaker dependency. In general, AV node ablation can be performed from the right heart but does require a left-sided approach approximately 6.9% of the time [36].

Atrial fibrillation has been shown to worsen outcomes in heart failure with significant increased mortality among heart failure patients also diagnosed with atrial fibrillation in the Framingham cohort [39]. One area of controversy is whether to offer heart failure patients with atrial fibrillation biventricular pacing, as they may not receive the same benefit as those in sinus rhythm. Patients with atrial fibrillation, in general, have less biventricular pacing given that rapid AV nodal conduction may decrease the degree of biventricular pacing and increase the nonresponder rate. Guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society endorse biventricular pacing for patients with left ventricular ejection fraction less than 35% and QRS duration greater than 120 ms, but do suggest that AV node ablation may be required to increase the amount of biventricular pacing [33]. Ganesan et al reported on 6 trials comprising 768 patients with atrial fibrillation who had biventricular pacing and reported significant improvements in all-cause mortality, cardiovascular mortality, and improvement in New York Heart Association function class in patients who underwent AV node ablation [40].

Several trials have analyzed the best approach for either rate or rhythm control in heart failure. The Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure (PABA-CHF) trial assigned patients with drug-refractory, symptomatic atrial fibrillation with an ejection fraction less than 40% to either pulmonary vein isolation (PVI) (n = 41) or AV node ablation with placement of a biventricular pacemaker (n = 40) [41]. With regard to the primary composite endpoint of ejection fraction, 6-minute walk test, and Minnesota Living with Heart Failure (MLWHF) score, patients in the PVI group did better, with significant improvements in all individual components of the composite endpoint. This trial was clearly limited by the relatively small number of patients in each group. In addition, persistent atrial fibrillation patients only had ablation around the pulmonary veins (PVI), which may not be sufficient ablation in this group; however, the overall freedom from atrial fibrillation was 71% without antiarrhythmic medications. The role of ablation directly targeting atrial fibrillation in heart failure remains unclear, and the current debate often focuses on whether AV node ablation is reasonable and will increase the response to biventricular pacing.

Regarding AV node ablation in patients with normal LV function, it is reasonable to consider this strategy in patients who have failed rate-controlling medications. In heart failure patients, AV node ablation to increase the degree of biventricular pacing is also reasonable if patients have failed medical management. In both groups we assess whether rhythm control, including with PVI ablation, is a reasonable approach for the patient. In patients with severe left atrial enlargement, severely decreased left ventricular function or where the risks of a more invasive ablation for atrial fibrillation outweigh the benefits, a less invasive approach of AV node ablation may be more reasonable. Further trials are needed to validate this approach, which will be discussed below in the section on ablation for atrial fibrillation.

Anticoagulation Strategies
Embolic events in atrial fibrillation result from a complex sequence of events. Thrombus formation in atrial fibrillation usually arises from the left atrial appendage. Due to the posterior position of the left atrium, transesophageal echocardiography has a higher sensitivity and specificity for imaging the left atrial appendage (LAA) compared with transthoracic echocardiography [29]. It is generally believed that 48 hours of atrial fibrillation is required for thrombus formation; however, thrombus formation may occur sooner in the correct milieu (stasis, endothelial dysfunction and hypercoaguable state). After any type of cardioversion atrial stunning occurs, the risk of thrombus formation increases from 3 days to 3 to 4 weeks [42]. Another consideration is that up to 25% of cerebrovascular accidents in atrial fibrillation are due to other noncardiac causes, such as embolism from aortic plaques.
and intrinsic cerebrovascular disease. Patients with atrial fibrillation associated with valvular heart disease (especially mitral valvular stenosis) are at particularly high risk for thromboembolic events, and among patients with non-valvular atrial fibrillation, consistent independent risk factors for stroke in several studies include diabetes, left ventricular systolic dysfunction, increasing age, hypertension, female gender, and prior stroke or transient ischemic attack [43–47]. The CHADS2 scoring system, commonly used to assess the risk of stroke, assigns 1 point for Congestive heart failure, Hypertension, Age greater than 75 years or Diabetes mellitus, and 2 points for previous Stroke. Based on this scoring system, a score of 0 had an annualized stroke rate of 1.9%, score of 1 had a rate of 2.8%, and score of 2 a rate of 4.0% [48]. While there are several different scoring methods, the CHA2DS2-VASc scoring (Table 1) was recently refined and introduced gender, vascular disease, and a younger age (65 to 75 years) into the risk assessment [49]. Two validation studies comparing the CHA2DS2-VASc to the CHADS2 demonstrated that the CHA2DS2-VASc scoring system is better able to predict the risk of stroke and thromboembolism [50,51]. Its main strength is that it is better able to dentify truly low-risk patients compared with the CHADS2.

With regard to anticoagulation, there are several different recommendations based on the different risk scoring systems that have emerged. The AHA/ACC 2011 guidelines divide patients into high risk (previous stroke, mitral stenosis or prosthetic valves), where warfarin is recommended with goal INR 2.0 to 3.0, and low risk (female gender, age 65 to 74 years, coronary artery disease and thyrotoxicosis), where aspirin is recommended. For intermediate-risk patients (hypertension, age > 75 years, diabetes mellitus, left ventricular ejection fraction < 35%), either aspirin or warfarin with goal INR 2.0 to 3.0 is recommended based on the patient’s individual risk/benefit ratio [2]. Similarly, according to the CHADS2 scoring system, patients with a score of 2 should receive warfarin or similar oral anticoagulation, and those with a score of 0 should receive aspirin 81 to 325 mg. There has been debate about intermediate-risk patients or those with a CHADS2 of 1, since these patients have an annualized adjusted stroke rate of 2.8%. The ACC/AHA 2012 guidelines for atrial fibrillation recommend either aspirin or warfarin for these patients, while the American College of Chest Physicians suggest oral anticoagulation rather than aspirin and furthermore recommends dabigatran rather than warfarin [2,52]. The latter recommendation is derived by pooling 11 randomized trials with 6526 patients, which demonstrated a 50% decrease in the risk of stroke that was thought to outweigh the 50% increase in the risk of bleeding. The implications of anticoagulation based on the CHA2DS2-VASc score suggest that those with a score of 0 do not need any antithrombotic therapy while patients with a score of ≥ 2 should be placed on oral anticoagulation given that this patient group has an annualized thromboembolism rate of 1.6% [49,51,53,54]. The CHA2DS2-VASc score may allow for better risk stratification of patients with a CHADS2 score of 1.

There are several other important factors that deserve mention with regard to anticoagulation for atrial fibrillation. In the Stroke Prevention in Atrial Fibrillation studies, paroxysmal atrial fibrillation patients receiving aspirin had a similar risk of stroke compared to persistent atrial fibril-

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**Table 1. CHADS2, CHA2DS2-VASc, and HAS-BLED Scoring Systems**

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Points</th>
<th>CHA2DS2-VASc</th>
<th>Points</th>
<th>HAS-BLED</th>
<th>Points</th>
</tr>
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<tbody>
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<td>CHF</td>
<td>1</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Hypertension</td>
<td>1</td>
<td>Abnormal renal or liver function</td>
<td>1*</td>
</tr>
<tr>
<td>Age ≥ 75 yr</td>
<td>1</td>
<td>Age ≥ 75 yr</td>
<td>2</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Bleeding history/ predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Previous CVA or TIA</td>
<td>2</td>
<td>Stroke/TIA/ thromboembolism</td>
<td>2</td>
<td>Vascular disease†</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Female gender</td>
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*2 points for both.
†Vascular disease: Prior myocardial infarction, peripheral artery disease, or aortic plaque.
lation patients (3.2% vs 3.3%) [43]. This association between intermittent atrial fibrillation and stroke was further demonstrated in a recent trial of implantable loop monitors placed in 2580 patients, which demonstrated an association between ischemic stroke and at least 6 minutes of subclinical atrial tachycardia [25]. It also should be noted that anticoagulation guidelines are the same for patients with atrial flutter and atrial fibrillation as there appears to be a similar risk of cardiac thrombus formation [2,55].

Despite more aggressive recommendations for anticoagulation for atrial fibrillation, a minority of appropriate patients are receiving anticoagulation or are able to achieve a therapeutic INR [56]. An overestimation of bleeding risk by clinicians is an important reason why patients are not prescribed anticoagulation. There have been several recent scoring schemes designed to estimate a patient’s risk of bleeding [57,58]. The HAS-BLED score (Table 1) uses the following criteria to estimate a patient’s risk of bleeding: hypertension, abnormal renal or liver function, previous stroke, bleeding history of predisposition, labile INRs, elderly, and current drug and/or alcohol excess [57]. A HAS-BLED score ≥ 3 indicates a higher risk of bleeding. It should be noted that the HAS-BLED should not be used to withhold otherwise appropriate anticoagulation but rather indicates risk factors that can be modified and/or monitored during anticoagulation. Regarding the net benefit of anticoagulation compared with the risk of bleeding, a recent Danish analysis of > 130,000 patients showed a net clinical benefit in patients with a CHADS2 ≥ 1 and a CHA2DS2-VASc score ≥ 2 [59]. In this group at higher risk of thromboembolism, the clinical benefit was still present in patients with a HAS-BLED score ≥ 3. Therefore, the risks of anticoagulation need to be individualized and balanced against the benefits of anticoagulation in appropriate patients.

Several novel anticoagulants have recently been approved for use in nonvalvular atrial fibrillation as alternatives to warfarin. Dabigatran is a direct thrombin inhibitor that was shown to have similar rates of major hemorrhage and lower rates of stroke and systemic thromboembolism [60]. Rivaroxaban is an oral factor Xa inhibitor that has also been shown to have similar stroke and systemic embolism rates with slightly lower rates of major bleeding episodes compared with warfarin [61]. Apixaban, another oral factor Xa inhibitor, has also been demonstrated to be superior to warfarin in preventing stroke and systemic embolism as well as caused less hemorrhagic stroke [62]. Dabigatran, rivaroxaban, and apixaban are currently all approved by the Food and Drug Administration (FDA).

There are several nonpharmacological devices that are either available or will likely become available in the near future that avoid the need for chronic anticoagulation. The left atrial appendage (LAA) represents the site of thrombus formation in approximately 90% of patients with nonvalvular atrial fibrillation, and decreased blood flow velocity and stasis are common in atrial fibrillation. Therefore, elimination or closing the entrance of the LAA may substantially reduce the risk of thrombus formation. The WATCHMAN device is a nitinol self-expanding device meant to seal the LAA and is percutaneously delivered. The Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) was a noninferiority trial that randomized patients with a CHADS2 ≥ 1 to warfarin or LAA occlusion with the Watchman device [64]. The trial demonstrated a 99.9% probability of noninferiority with a significant decrease in the primary efficacy endpoint of stroke, cardiovascular death, and systemic embolism in the Watchman group. There were also a significant number of serious pericardial effusions requiring draining in the Watchman device group. This device is currently being evaluated in a second trial, the Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation vs. Long Term Warfarin Therapy (PREVAIL) trial, a randomized trial that will address some of the safety issues in the PROTECT-AF trial. Another innovative approach to LAA closure is the LARIAT suture delivery device in which a snare-like pre-tied suture loop is delivered via a percutaneous epicardial approach using an endocardial balloon catheter and wire as a marker [65,66]. There is preliminary data suggesting that this may be a safe and effective approach and an ongoing registry is following these patients. The LARIAT device is being implanted in select centers in the United States and current eligible patients are those with a CHADS2 ≥ 2 and a contraindication to oral anticoagulation. These nonpharmacological techniques to exclude the LAA will most likely become more common over time, especially for those with new-onset atrial fibrillation.

### Rhythm Control

Conversion to sinus rhythm represents the third priority in the management of atrial fibrillation after effective rate control and prevention of thromboembolism. The
primary reasons to pursue rhythm control include hemo-
dynamic compromise and bothersome symptoms associ-
ated with atrial fibrillation still present after effective rate
control. For patients with new-onset atrial fibrillation
in particular, at least 1 attempt at restoration of normal
sinus rhythm by either electrical or chemical cardiover-
sion may be reasonable.

Regardless of the means of cardioversion, risk of atrial
thromboembolism should be addressed. Patients with
atrial fibrillation of unknown duration or known to be
greater than 48 hours should receive at least 3 weeks of
anticoagulation with warfarin to a goal INR of 2.0 to 3.0
(or treatment with an alternative anticoagulation agent),
or transesophageal echocardiography prior to cardiover-
sion to exclude left atrial thrombus. For those patients
with atrial fibrillation known to be of less than 48 hours’
duration and believed to be at low risk for thrombosis,
proceeding to cardioversion may be reasonable. A higher
CHADS2 score may be useful to predict the presence of
left atrial and/or left atrial appendage thrombus. Decker et
al found no thrombi in patients with a CHADS2 score of
0 and found that heart failure in particular was associated
with a higher risk of thrombus [67]. This is in contrast
to the findings of the Assessment of Cardioversion Using
Transesophageal Echocardiography (ACUTE) trial, which
detected LAA thrombi in 10% of patients with a CHADS2
score of 0 [68]. Therefore, following the guidelines of ei-
ther anticoagulation for 3 weeks prior to cardioversion or
pre-procedural TEE is prudent [2]. After cardioversion, all
patients should receive at least 1 month of anticoagulation
due to the increased risk of thrombosis associated with atrial
stunning.

Although there is evidence to suggest that patients
in sinus rhythm have better outcomes compared with
those in atrial fibrillation [69], several large studies dem-
onstrate that strategies to maintain sinus rhythm with
antiarrhythmic medications do not reduce the risk of
mortality or hospitalization. Trials in the past pursuing
rhythm control with antiarrhythmic medications have
demonstrated no significant mortality benefit to rhythm
control [70,71]. The AFFIRM (A Comparison of Rate
Control and Rhythm Control in Patients with Atrial
Fibrillation) and RACE (Rate Control versus Electrical
Cardioversion in Persistent Atrial Fibrillation) trials are
often cited as the key trials comparing a strategy of rate
versus rhythm control with anti-arrhythmic medica-
tions in patients with newly diagnosed atrial fibrillation
and persistent atrial fibrillation, respectively [72,73].

The AFFIRM trial suggested that there may be an in-
creased mortality (although not statistically significant)
in the rhythm control arm and more hospitalizations and
adverse drug reactions in the rhythm control arm. The
RACE trial found that a rate control strategy was not
inferior to a rhythm control for the prevention of death
and other comorbidities. However, it should be noted
that patients recruited were mostly older than 65 years of
age or had other risk factors for stroke, which emphasizes
the need to consider other comorbidities when choosing
an antiarrhythmic medication. Anticoagulation was
often stopped once normal sinus rhythm was achieved
likely without adequate monitoring, which was associ-
ated with worse outcomes in the rhythm control arms
and emphasizes the need to continue anticoagulation
in these patients. In addition, these patients were not
necessarily symptomatic from their atrial fibrillation,
which represents the primary reason to pursue rhythm
control. Importantly, roughly 12% of subjects in the rate
control arm of AFFIRM crossed over to rhythm control,
primarily due to a failure of symptom control with rate
control alone in this subset of patients. Similarly, ap-
proximately 29% of patients in the rhythm control arm
crossed over to the rate control arm due to side effects
or inability to maintain normal rhythm. Therefore, the
results of the AFFIRM trial emphasize that rhythm con-
trol should be reserved for symptomatic patients given
the many side effects that accompany antiarrhythmic
medications.

Electrical Cardioversion

Electrical cardioversion synchronized to the R wave repre-
sents a safe method of cardioversion. The primary indica-
tions for electrical cardioversion include hemodynamically
unstable atrial fibrillation with or without pre-excitation
or as a method to restore sinus rhythm due to intolerable
patient symptoms. It should be noted that frequent, re-
peated electrical cardioversion is not indicated in patients
who convert quickly back to atrial fibrillation and in those
with significant drug or electrolyte abnormalities, such as
digoxin toxicity or hypokalemia. A short-term anesthetic
should be used. There are varying strategies with regard-
to picking the appropriate energy for electrical cardio-
version with some practitioners starting low and gradually
increasing while others start at a higher initial energy to
minimize the number of shocks. In general, starting with
at least 200 J for either monophasic or biphasic shock
waveforms has proven to be most effective.
Chemical Cardioversion

Antiarrhythmic medications have been shown to be effective for cardioversion of atrial fibrillation. From a practical standpoint, antiarrhythmic medications are used less commonly for conversion of atrial fibrillation given that they are less effective than electrical cardioversion. When electrical cardioversion has previously been unsuccessful, adjunctive antiarrhythmic medications may improve the success rate of electrical cardioversion. Chemical cardioversion with antiarrhythmic drugs also has the advantages of not requiring sedation and the associated required period of pre-sedation fasting. Conversion with antiarrhythmic medications is generally most successful for recent onset atrial fibrillation (< 24 hours). Before discussing these individual uses, it is worth considering each of these medications individually and circumstances when they should be considered. Table 2 lists the commonly used antiarrhythmic medications by Vaughan-Williams classification as well as associated precautions and initial doses for chemical cardioversion and maintenance of sinus rhythm.

Flecainide and propafenone are class Ic antiarrhythmic medications that are quite effective at chemical cardioversion [74,75]. These medications are generally given once for atrial fibrillation that lasts greater than 2 to 4 hours with the goal to decrease the duration of the arrhythmia. Both of these medications have been studied to cardiovert infrequent episodes of atrial fibrillation where the patient may take a higher oral dose at home in order to decrease the duration of the episode and avoid a visit to the hospital [76]. These class Ic medications may cause several side effects that are listed in Table 2. Class Ic medications should not be used in patients with structural heart disease, particularly those with abnormal ventricular function or ischemic heart disease. Conversion to atrial flutter with 1:1 AV conduction, or “1c Flutter,” causing a rapid ventricular response may also occur and, therefore, the patient may need an AV nodal blocking medication as well.

Ibutilide is used intravenously and is effective for conversion of atrial fibrillation and flutter [77,78]. It can be used in patients with structural heart disease but should be avoided in patients with depressed left ventricular function and/or heart failure. Ibutilide is a class III antiarrhythmic medication that prolongs cellular repolarization and, therefore, is related to an increased QT interval and risk of torsades de pointes. Pre-treatment with magnesium may decrease the risk of ventricular arrhythmias and the patient should be monitored for at least 4 hours after drug infusion.

Dofetilide is modestly effective for cardioversion of atrial fibrillation or flutter. In the SAFIRE-D trial, conversion was increasingly successful with higher doses (125 mcg, 6.1%; 250 mcg, 9.8%; 500 mcg, 29.9%) and increased with greater duration of treatment (24 hours, 70%; 36 hours, 91%) [79]. In general, dofetilide is used for chronic, maintenance treatment of atrial fibrillation as it requires inpatient initiation of the medication.

### Table 2. Medications Used to Chemically Cardiovert Atrial Fibrillation and Maintain Sinus Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Dose for Cardioversion</th>
<th>Daily Dose for Maintenance of Sinus Rhythm</th>
<th>Side Effects and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>200 to 300 mg</td>
<td>200 to 300 mg</td>
<td>Atrial flutter; avoid in structural heart disease</td>
</tr>
<tr>
<td>Propafenone</td>
<td>600 mg</td>
<td>400 to 900 mg</td>
<td>Hypotension, atrial flutter; avoid in structural heart disease</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg</td>
<td>NA</td>
<td>Avoid in heart failure, prolonged QT</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>125 mcg to 500 mcg</td>
<td>500 mcg to 1 g</td>
<td>Avoid with prolonged QT; dose adjust for renal dysfunction</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Oral 1.2 g/day until 10 g total</td>
<td>100 to 400 mg</td>
<td>Bradycardia, hypotension, QT prolongation; toxicities include: hepatic, thyroid, pulmonary, skin</td>
</tr>
<tr>
<td>Sotalol</td>
<td>NA</td>
<td>160 to 320 mg</td>
<td>Avoid with prolonged QT, reactive airway disease and heart failure; dose adjust for renal dysfunction</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>NA</td>
<td>800 mg</td>
<td>QT prolongation, GI side effects; avoid in heart failure, persistent AF</td>
</tr>
</tbody>
</table>
Dofetilide is also a class III anti-arrhythmic and has the same risks of torsades de pointes associated with ibutilide.

In general, amiodarone has been associated with lower efficacy for cardioversion compared to class Ic and III antiarrhythmic medications [80–82]. However, amiodarone can be given to patients with structural heart disease, is effective for ventricular rate control, and is the most effective antiarrhythmic drug for maintaining sinus rhythm over longer periods of time. As listed in Table 2, amiodarone is associated with several long-term toxicities for which long-term monitoring is required.

Vernakalant is a relatively new antiarrhythmic medication approved in the European Union for chemical cardioversion of recent-onset atrial fibrillation (duration of ≤ 7 days for nonsurgical patients and ≤ 3 days for post–cardiac surgery patients). Vernakalant is thought to act by blocking potassium channels that control early repolarization, including the ultra-rapid component of the delayed rectifier current ($I_{Kur}$). In the Atrial Arrhythmia Conversion Trials (ACT-I and ACT-III), vernakalant compared with placebo was associated conversion to sinus rhythm in approximately 51% of patients [83,84]. There were serious adverse events in both trials, including one patient with severe aortic stenosis in ACT-III who experienced hypotension and ventricular fibrillation and died. The ACT 5 was a confirmatory Phase 3 trial that was halted due to a patient who developed cardiogenic shock. This medication is not approved by the FDA due to these serious adverse effects, especially hypotension in some patients.

**Maintenance of Sinus Rhythm**

Maintenance of sinus rhythm with antiarrhythmic medications or ablation represents the next treatment goal in patients who remain symptomatic from atrial fibrillation even after stroke risk reduction has been addressed and attempts at adequate rate control have been made. The reasons to consider rhythm control as a long-term strategy include bothersome symptoms despite adequate rate control and, potentially, to improve ventricular function in selected patients with LV dysfunction believed to be due to atrial fibrillation. While it is intuitive that rhythm control may reduce cardiovascular mortality or decrease risk of stroke, it should be remembered that these endpoints have not been shown to improve with rhythm control. The Pharmacological Intervention in AF (PIAF) trial demonstrated that rate control was not inferior to rhythm control to improve symptoms and quality of life [71]. The AF Follow-up Investigation of Rhythm Management (AFFIRM) trial randomized 4060 atrial fibrillation patients at high risk of stroke and death to rhythm or rate control and demonstrated no significant difference in all-cause mortality between the treatment arms [72]. However in a post-hoc analysis of AFFIRM, the presence of sinus rhythm was associated with a significant mortality benefit, whereas the use of antiarrhythmic medications was associated with an increase in mortality [85]. These trials stress that rhythm control is indicated to control AF-related symptoms despite adequate rate control. While antiarrhythmic medications are associated with drug-related side effects and toxicities, these medications are indicated as first-line therapies for rhythm control and worth discussing before ablation.

Choice of an initial antiarrhythmic medication is often dictated by the presence of structural heart disease, coronary artery disease, or heart failure as outlined in Figure 4. In addition, the presence of accompanying renal, hepatic, lung, or other systemic disease also guides the initial choice of an appropriate antiarrhythmic medication. Importantly, all antiarrhythmic medications have both potential toxicities and risk of proarrhythmia, and the risk/benefit ratio of antiarrhythmic drug therapy should be considered by clinicians and patients prior to initiation of treatment.

For patients with a structurally normal heart, either flecainide or propafenone is an appropriate initial medication choice. This includes patients with hypertension but without left ventricular hypertrophy. Several placebo-controlled trials demonstrated that flecainide and propafenone delay the recurrence of atrial fibrillation [86–88]. Dofetilide and sotalol also represent reasonable choices for patients with structurally normal hearts [79,89]; however, the QT interval and renal function should be carefully monitored during an inpatient drug initiation. Sotalol should be used with caution in patients with reactive airway disease and heart failure.

For patients with coronary artery disease, sotalol has significant beta-blocking activity and represents the initial choice for maintenance of sinus rhythm [90]. Amiodarone may represent a reasonable alternative but given the risk of long-term toxicities, it should not be used initially [91]. Finally, dofetilide has been shown to be safe in this population but inpatient monitoring is required [92]. The class Ic agents should not be used...
in patients with coronary artery disease given the previously increased mortality risk observed in the CAST trial, though it should be noted that propafenone was not used in this trial [93].

In patients with heart failure (LVEF < 35%), dofetilide and amiodarone should be used to prevent episodes of atrial fibrillation. In the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy trial, amiodarone was associated with greater likelihood of conversion to sinus rhythm and improved survival compared to placebo [94]. In the Danish Investigators of Arrhythmias and Mortality on Dofetilide in Heart Failure trial, patients treated with dofetilide were more likely to maintain sinus rhythm compared to those receiving placebo. The risk of proarrhythmias (torsades de pointes) occurred in 3.3% of patients receiving dofetilide and occurred within the first 3 days of therapy [95]. Class Ic agents, sotalol, and dronedarone should be avoided in patients with heart failure.

Hypertension and associated left ventricular hypertrophy (LVH) are common among patients with atrial fibrillation. Ventricular ectopy can be common in LVH, and therefore class III antiarrhythmic medications, which further prolong repolarization, should not be used in LVH. In patients without LVH, class Ic agents and amiodarone are favored. However, in patients with LVH, only amiodarone and dronedarone have been shown to be safe, where the QT prolonging activity of these medications does not increase the risk of proarrhythmia.

Although dronedarone has been shown to be safe and effective in patients with atrial fibrillation, it does deserve special consideration given that several of the trials leading to its release and postmarket research have indicated that this medication may not be appropriate for all patient groups [96,97]. In the EURIDIS and ADONIS trials, which tested the efficacy of dronedarone compared with placebo in patients with normal LVH.
function, dronedarone was more effective at maintaining normal rhythm and controlling ventricular rates when atrial fibrillation recurred [98]. There was no difference in the rate of adverse effects in the dronedarone group with the exception of an increased serum creatinine. In the Effect of Dronedarone on Cardiovascular Event in Atrial Fibrillation (ATHENA) trial, dronedarone was associated with a 24% relative risk reduction of the primary endpoint of all-cause mortality or cardiovascular hospitalization [99]. For the most part, patients in ATHENA had normal left ventricular function with only 11.9% having a LVEF < 45%. These trials contrast with those performed in patients with persistent atrial fibrillation or heart failure. The PALLAS trial tested the effect of dronedarone compared to placebo on major vascular and cardiovascular events in permanent atrial fibrillation and found that dronedarone was associated with increased rates of heart failure, stroke and cardiovascular mortality [96]. Patients included in the PALLAS trial were at least 65 years old and had at least 1 risk factor for a vascular event and included approximately 20% of patients with a LVEF ≤ 40%. In patients with severe heart failure (LVEF ≤ 35%), the ANDROMEDA study demonstrated an increased mortality associated with dronedarone compared to placebo that was mostly associated with worsening heart failure. The FDA has also reported rare liver failure associated with dronedarone use. Currently dronedarone is FDA-approved to reduce the risk of hospitalization in patients with paroxysmal or persistent atrial fibrillation, with special warnings in patients with advanced heart failure and permanent atrial fibrillation.

Ablation for Atrial Fibrillation

Ablation for atrial fibrillation is assuming a more prominent role in the treatment algorithm for maintenance of normal sinus rhythm. The goal of ablation is to isolate atrial tachycardias that degenerate into atrial fibrillation and are for the most part located in the pulmonary veins (PV) [3,100]. Focal firing from the pulmonary veins originate from muscular sleeves that extend from the left atrium into the pulmonary veins [3]. There is also evidence that action potentials are shorter in the pulmonary veins due to larger delayed-rectifier K⁺ currents and smaller inward Ca²⁺ currents in the PV [101,102]. As atrial fibrillation progresses from paroxysmal to persistent, ion channel remodeling occurs, which may increase the activity of triggers to perpetuate the rhythm and subsequently results in structural changes within the atria [103,104]. Ablation around the pulmonary veins, or PVI or pulmonary vein antral isolation (PVAI), is the common ablation strategy for paroxysmal atrial fibrillation and part of the ablation strategy for persistent atrial fibrillation. Surgical options for ablation of atrial fibrillation also exist, including both cut-and-sew approaches and also ablation-assisted approaches; in the hands of at least some surgeons, these Cox-Maze III and IV procedures are associated with greater than 85% freedom from atrial fibrillation at 2 years among patients with lone paroxysmal atrial fibrillation [105].

There is some data to suggest that an ablation strategy may lead to superior patient outcomes compared with antiarrhythmic medications. In a nonrandomized study, Pappone et al compared ablation (PVI) to antiarrhythmic therapy and found that ablation was associated with decreased all-cause mortality, less stroke and heart failure, and improved quality of life [106]. Since this was a nonrandomized, single-center trial, these results should be considered preliminary. Wazni et al randomized 70 patients to first-line ablation (PVI) or antiarrhythmic medication and found less atrial fibrillation recurrence and improved symptoms in the ablation group [107]. Wilber et al found similar decreased atrial fibrillation recurrence and improved quality of life in the ablation group among 167 patients randomized to ablation or antiarrhythmic medication who had previously failed one treatment [108].

Although these results are encouraging, larger trials are needed before ablation can be recommended for all atrial fibrillation patients and to investigate if there are other benefits besides symptom relief. The CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial is an ongoing multicenter trial funded by the National Heart Lung and Blood Institute that compares ablation to current antiarrhythmic medications for the treatment of atrial fibrillation. Eligible patients are over 65 years of age or less than 65 years old with 1 stroke risk factor. The primary endpoint is total mortality with a composite secondary endpoint of mortality, stroke, serious bleeding, and cardiac arrest. The Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) is a national registry effort that, if successfully implemented, will track the real-world safety and durability of the procedure [109].

The most recent Heart Rhythm Society guidelines recommend ablation for symptomatic paroxysmal atrial fibrillation for patients who have failed at least one
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Class 1 or 3 antiarrhythmic medication (recommendation class I) [110]. Ablation of persistent and long-standing atrial fibrillation that is symptomatic for patients who have failed at least 1 antiarrhythmic medication is also considered reasonable, though with a lower strength of recommendation (class IIa and IIb, respectively). For patients undergoing cardiac surgery for another indication, surgical ablation is reasonable, regardless of whether patients have failed an antiarrhythmic medication (recommendation class: paroxysmal IIa, persistent IIb). Surgical ablation is also recommended as a stand-alone procedure for patients who prefer a surgical approach (recommendation class IIb). The guidelines emphasize that the primary goal of ablation for atrial fibrillation is for symptom relief in patients who are adequately rate controlled.

CONCLUSION

Atrial fibrillation is the most common cardiac arrhythmia encountered in clinical practice. It has many different presentations and may occur in isolation or in association with other medical conditions. Therefore, the approach to newly diagnosed atrial fibrillation needs to be individualized based on the patient’s comorbidities. Treatment options are evolving and focus on prevention of systemic thromboembolism, rate control, and rhythm control.

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