Atrial Fibrillation

Review Article

Concepts in Disease Progression of Atrial Fibrillation and Implications for Medical Management

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Abstract. Despite recent advances in the understanding of atrial fibrillation (AF) pathophysiology, the disease remains incompletely understood. Evidence suggests that AF pathogenesis is multifactorial, involving structural and electrical remodeling and inflammation. AF is a progressive disease associated with increased risk of stroke, heart failure, and all-cause mortality, and incidence is expected to rise dramatically as the population ages. Physicians should utilize available guidelines including the 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) Focused Update on the Management of Patients With Atrial Fibrillation (update to the 2006 ACC/AHA/European Society of Cardiology (ESC) guidelines), ESC 2010 AF guidelines, and the 2010 Canadian Cardiovascular Society Atrial Fibrillation Guidelines as guiding principles of AF management, with a focus on individualizing treatment based on the patient’s symptomatic profile and comorbidities. New pharmacologic agents (antiarrhythmics and antithrombotics) are approved or in development, and catheter ablation is being improved to offer enhanced safety and efficacy. Newer data on AF pathophysiology and therapies argue for consideration of safety as well as efficacy, and include the concept of early intervention with rhythm-control strategies. Adherence to treatment guidelines and knowledge of new and emerging treatment options can aid in improving outcomes for this challenging disease.

Keywords. atrial fibrillation, cardiac arrhythmias, sinus rhythm.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. An estimated 3.03 million Americans had AF in 2005, and the prevalence is expected to rise to 7.56 million by 2050. AF ranges from 0.1% among persons aged below 55 years to 9.0% among patients aged 80 years or older. AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances, for a total of 5.0 million office visits, 276,000 emergency department visits, and 350,000 hospitalizations annually in the United States. A recent study showed that in the year following an initial hospitalization for AF, 12.5% of chronic AF patients and 10.1% of newly diagnosed AF patients were readmitted for AF. AF is a significant contributor to cardiovascular (CV) morbidity and mortality, as well as decreased health-related quality of life (HRQoL).

Owing to its complex pathophysiology and progressive nature, AF is a challenging disease to manage. Over the last decade, progress has been made in understanding AF pathophysiology. Despite these advancements, the underlying mechanisms remain incompletely understood,
and no specific etiologic factor has been identified as the main cause of AF. This review will focus on the current understanding of the various theories regarding the pathogenesis and progression of AF and discuss the clinical impact and treatment of this disease.

Classification of AF

AF is typically classified as either paroxysmal, persistent, or permanent. Paroxysmal AF refers to episodes of <7 days’ duration that generally stop spontaneously. When the arrhythmia is sustained beyond 7 days and is not self-terminating, it is categorized as persistent AF and often requires cardioversion to restore sinus rhythm. AF is deemed permanent if cardioversion has either failed or has not been attempted. Often, the clinical classification of permanent AF is ambiguous. If the duration of AF exceeds 1 year and AF is not responsive to therapeutic interventions, AF can be considered permanent. Approximately 30–45% of paroxysmal and 20–25% of persistent AF occurs in younger individuals (<60 years). If there is no underlying heart disease (including hypertension), the AF is referred to as “lone AF.” These categories are not mutually exclusive, and the pattern of the arrhythmia can vary over time.

Risk factors predisposing to AF

Several factors, both epidemiologic and clinical, can predispose patients to AF (Table 1). AF may be related to acute, temporary, reversible causes, including alcohol intake (“holiday heart syndrome”), myocardial infarction (MI), pericarditis or myocarditis, pulmonary embolism, hyperthyroidism, and other metabolic disorders, and is a common postoperative complication following cardiothoracic surgery. In some cases, treatment of a primary underlying condition such as atrial flutter, Wolff–Parkinson–White syndrome, or atrioventricular (AV) nodal reentrant tachycardia can prevent AF recurrence through the prevention of paroxysmal supraventricular tachycardia–triggered AF. Patients with congestive heart failure (CHF) are most likely to have permanent AF; however, permanent AF is also typically seen in patients with hypertension and ischemic heart disease. Mitral valve disease, coronary artery disease (CAD), CHF, and hypertension, particularly when accompanied by left ventricular hypertrophy (LVH), are coexisting conditions that contribute significantly to the occurrence and persistence of AF. Finally, the left atrial dilation that occurs with obesity and increasing body mass index is an emerging and potentially preventable risk factor for AF.

Pathophysiologic factors that may contribute to the development of AF

As depicted in Figure 1, several pathophysiologic factors, including electrical remodeling, structural remodeling, and inflammation, are thought to contribute to the development and progression of AF.

Atrial electrical remodeling

Atrial remodeling was first described in experimental studies and data correlating electrical remodeling with AF are mostly derived from animal models and, less frequently, from patients with AF undergoing surgery. Wolff and colleagues observed that AF is self-perpetrating—the longer the duration of AF, the lower the rate of success in cardioversion to restore and maintain sinus rhythm, leading to the adage that “AF begets AF.”

High atrial rate induces changes in the ionic properties of atrial myocytes, particularly the progressive shortening of effective refractory periods and slowing of the conduction velocity. Upon restoration of sinus rhythm, electrical remodeling is reversible, even after prolonged periods of AF (months to years); however, prolonged AF disrupts atrial contractile function, which may require significant recovery time following cardioversion, necessitating longer duration of anticoagulation use.

Structural remodeling

In 1995, Morillo and colleagues conducted the first study showing atrial structural changes and electrophysiologic abnormalities with sustained arrhythmia. Structural remodeling results in electrical tissue inhomogeneity, slowed conduction, and electrical uncoupling, which facilitate AF continuation without inducing changes in atrial action potential properties. In contrast to electrical remodeling, structural changes are less reversible and tend to persist after sinus rhythm has been re-established.

Although atrial fibrosis follows the onset of AF, it is not clear whether other observed structural changes precede or follow development of the arrhythmia. Structural remodeling may precede the onset of AF since it emanates from cardiac damage due to CAD, hemodynamic overload from valve disease, lung disease, hypertension, diabetes mellitus, or thyroid disease. Evidence that structural remodeling precedes AF is also substantiated by the fact that left atrial size, left ventricular fractional shortening, and the sum of left ventricular and posterior wall thickness were demonstrated to be independent echocardiographic predictors of AF. It is also possible that underlying cardiac pathologies may gradually create a structural substrate, potentially leading to arrhythmia influenced by electrical remodeling or inflammation. The AF substrate differs in diseased versus normal hearts. In a dog model of AF-induced heart failure, the presence of heart failure resulted not only in increased atrial fibrosis but slowing and organization of AF in the left atrium and pulmonary veins. Furthermore, the pattern of AF electrogram fractionation changes in heart failure and becomes more
heterogeneous in the posterior left atrium, suggesting autonomic remodeling. Autonomic neural remodeling contributes to AF persistence and recurrence. Vagal discharge enhances acetylcholine-dependent potassium current, reducing action potential duration and stabilizing reentrant rotors, and β-adrenoceptor activation increases diastolic calcium leak and promotes delayed afterdepolarizations-related ectopic firing by hyperphosphorylating ryanodine receptor. Such structural heart issues can affect the clinical manifestations of AF in humans. A study evaluating the influence of structural heart disease on AF frequency and duration in patients with implanted pacemakers demonstrated that the proportion of AF episodes longer than 6 h was greater in patients with structural heart disease than in patients without. Additionally, older patients (≥76 years) with structural heart disease had less frequent but longer AF episodes than younger patients. In this study, patients were considered to have structural heart disease if they had a history of MI, congenital heart disease, cardiomyopathy, CHF, or significant ventricular enlargement.

Inflammation

The first study to support the role of inflammation in AF pathogenesis demonstrated histologic changes consistent with myocarditis in the atrial tissue of patients with lone AF. These findings support that the infiltration of inflammatory cells and calcium overload during rapid atrial rate may contribute to oxidative damage in atrial tissue, which in turn leads to atrial fibrosis and promotes...

<table>
<thead>
<tr>
<th>Epidemiological Indicators</th>
<th>Clinical States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Male sex</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Ischemic heart disease</td>
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<tr>
<td>Left ventricular dysfunction</td>
<td>Myocardial infarction</td>
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<tr>
<td>Ischemic heart disease</td>
<td>Pulmonary disease</td>
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<tr>
<td>Myocardial infarction</td>
<td>Valvular heart disease</td>
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<tr>
<td>Hypertension</td>
<td>Cardiac or thoracic surgery</td>
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<tr>
<td>Left ventricular hypertrophy</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Left atrial dilatation</td>
<td>Congenital heart disease</td>
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<tr>
<td>Smoking</td>
<td>Rheumatic heart disease</td>
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<tr>
<td>Diabetes</td>
<td>Hyperthyroidism</td>
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<tr>
<td>Diuretic use</td>
<td>Alcohol poisoning</td>
</tr>
<tr>
<td>Cardiac/thoracic surgery</td>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td></td>
<td>Supraventricular tachyarrhythmia</td>
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</tbody>
</table>

CVA/TIA = cerebrovascular accident/transient ischemic attack.
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the maintenance of AF. It has also been shown that levels of C-reactive protein (CRP), a marker of systemic inflammation, are higher in patients with arrhythmias than in those without rhythm disturbances. Elevated CRP levels have also been associated with a greater incidence of AF in the general population.

The process that connects inflammation and structural remodeling has not been fully elucidated, but it is hypothesized that the two events are simultaneously the cause and consequence of the arrhythmia. Other researchers have hypothesized that the observed signs of inflammation in patients with AF could be a consequence of underlying CV disease rather than a direct effect of the arrhythmia.

**Progression of AF/clinical outcomes**

AF is a progressive arrhythmia characterized by a gradual worsening over time. Owing to the electrical, contractile, and structural remodeling of the atria, conversion of AF to sinus rhythm becomes increasingly difficult as the duration of AF increases. Disease progression can have devastating consequences. Although those with “lone AF” may have a favorable prognosis with respect to thromboembolism and mortality, patients may develop cardiac abnormalities such as left atrial enlargement as they age, at which point the risks of thromboembolism and mortality rise. Indeed, it has been estimated that 14–24% of patients with paroxysmal AF eventually progress to persistent AF. The 30-year cumulative probability of progressing from paroxysmal or persistent AF to permanent AF was found to be 29%, with most progressing to permanent AF within the first 15 years after initial diagnosis.

AF is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality. Women with AF have an approximately fivefold increased risk of any CV event, primarily stroke and heart failure, compared with a twofold increased risk in men. The primary risk factors for ischemic stroke in AF include increasing age, previous stroke or transient ischemic attack (TIA), diabetes, and a history of hypertension. Although patients with lone AF have a low risk of stroke, the risk increases with age. It has been proposed that AF may be causally related to the
development of heart failure through tachycardia-mediated cardiomyopathy. A 30-year follow-up study reported the fundamental role of comorbidities, including hypertension, diabetes, and heart failure, in association with aging, in AF progression and cerebrovascular complications. The study provides evidence that AF is a diverse condition and that comorbidities significantly change the progression of the disease and its complications. Since there is a low risk of progression to permanent AF in younger individuals, it is recommended that invasive therapies be reserved for highly symptomatic patients. As a young patient with lone AF ages or develops comorbidities such as hypertension, heart failure, or diabetes, the risk for thromboembolic events rises, and screening for comorbidities becomes crucial.

**Current treatment strategies for AF**

Recent practice guidelines/updates include the 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) focused updates (which have been incorporated into the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for the management of patients with AF), the ESC 2010 AF guidelines, and the Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines (2010). These guidelines emphasize that the management of patients with AF includes three non-mutually exclusive objectives: 1) prevention of stroke and thromboembolic events through anticoagulation therapy; 2) ventricular rate control during AF; and 3) rhythm control to restore and/or maintain sinus rhythm through cardioversion and treatment with antiarrhythmic drugs (AADs) or catheter ablation in selected patients. AF treatment guidelines recommend that drug selection be largely driven by drug safety issues and should be made with careful consideration of concomitant CV conditions, especially hypertension, LVH, CAD, and heart failure. In assessing the efficacy of AAD treatment, a number of factors should be considered, including the recurrence of AF, symptom control, HRQoL, and CV outcomes.

In patients with AF, stroke not only occurs more often (approximately 23.5% occurring in patients aged 80–89 years), but tends to be more severe. Consequently, guidelines recommend antithrombotic therapy to prevent thromboembolism for all patients with AF, except individuals with lone AF or contraindications to therapy.

**Rate control**

The symptoms of AF can often be relieved by controlling the ventricular response (rate control) with mono- or polypharmacy. β-Blockers and non-dihydropyridine calcium-channel blockers are the standard pharmacologic agents used for rate control in patients with AF, but digoxin can also be used. In the case of patients with AF (symptomatic or asymptomatic) with rapid ventricular response, initial treatment may consist of antithrombotic agents and rate control. Despite the benefits of symptom relief with the control of ventricular rate, rate control does not alter the pathophysiology of AF disease progression on cardiac structure and function.

According to the 2003 American Academy of Family Physicians and American College of Physicians clinical practice guidelines, rate control with chronic anticoagulation is the recommended strategy for the majority of patients with AF. These primary care recommendations are in distinct contrast to the guidelines put forth by specialist societies, who advocate the option of rate or rhythm control in selected patients. If rate control results in inadequate relief, restoration or maintenance of sinus rhythm becomes a long-term objective. The goals of rate control are to reduce the risk of hemodynamic deterioration, improve symptoms, and minimize the risk of death and hospitalization. The recent RACE II study showed that lentient rate control (<110 bpm) was non-inferior to strict rate control (<80 bpm). According to the 2011 ACCF/AHA/HRS recommendations, lentient rate control may be adopted as a reasonable strategy in patients with AF and an ejection fraction >40%, as it is generally more convenient and requires fewer outpatient visits and examinations. The ESC recommends a resting target rate <110 bpm and the CCS recommends <100 bpm.

Selection of the proper medication is determined first by safety and tolerability, and customized to the patient’s specific CV conditions, taking into consideration the number and pattern of prior episodes of AF. β-Blockers may be particularly useful in states of high adrenergic tone (e.g. postoperative AF). Non-dihydropyridine calcium-channel blockers may be preferred for long-term use over β-blockers in patients with bronchospasm or chronic obstructive pulmonary disease. Digoxin has limited efficacy for heart rate control when used alone, but has been shown to have a synergistic effect when added to β-blockers or non-dihydropyridine calcium-channel blockers. A study by Sticherling et al demonstrated that digoxin may predispose patients to short-term recurrences of AF when used to control ventricular rate. Because of controversial data, and given the availability of more effective agents, digoxin is no longer considered first-line therapy except in patients with heart failure or left ventricular dysfunction.

Although AADs are generally associated with a greater incidence of both CV and non-CV adverse events (AEs), the use of rate-control drugs results in significant AEs as well, especially CV, including bradycardia with an increased rate of permanent pacemaker implantation, syncope, heart failure, and hypotension. In a retrospective claims database analysis, 53.5% of patients on rhythm control and 45.5% on rate control had suspected AEs and/or function tests for AE monitoring. The most common suspected AEs were CV events. The mean number of CV events per 100 patients was 117 in the rhythm-control group and 106 in the rate-control group. Additionally, in the AFFIRM study, pacemaker implantation occurred in 11% of patients. Pacemakers
were mainly implanted in the setting of AV junctional ablation or bradycardia induced by rate-control drugs.\textsuperscript{55} Stricter rate control versus lenient rate control also results in the need for more permanent pacing.\textsuperscript{51} AV nodal ablation in conjunction with permanent pacemaker implantation provides effective heart rate control and improves symptoms in patients with AF. Patients likely to benefit from this strategy are symptomatic patients or patients with tachycardia-mediated cardiomyopathy related to rapid ventricular rate during AF that cannot be controlled adequately with antiarrhythmic or rate-control medications.\textsuperscript{1} Furthermore, patients with normal left ventricular function or reversible left ventricular dysfunction undergoing AV nodal ablation are most likely to benefit from standard AV nodal ablation and pacemaker implantation. For patients with impaired left ventricular function not due to tachycardia, a biventricular pacemaker with or without defibrillator capability should be considered.\textsuperscript{1}

Rhythm control

Prior to the approval of dronedarone in 2009, there were six commonly used AADs for the maintenance of sinus rhythm in the United States including amiodarone, disopyramide, dofetilide, flecainide, propafenone, and sotalol; clinical trials have demonstrated the efficacy of these agents. In the SAFE-T study, amiodarone was superior to sotalol (p=0.001) and placebo (p=0.001) for the maintenance of sinus rhythm.\textsuperscript{56} Several small, randomized trials support the efficacy of disopyramide to prevent AF after direct-current cardioversion and disopyramide may be considered first-line therapy in vagally induced AF.\textsuperscript{1} In the SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) study, dofetilide demonstrated 58% efficacy in maintaining sinus rhythm compared with only 20% in the placebo group 1 year after cardioversion (p=0.001).\textsuperscript{57} In the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group)-CHF trial, dofetilide had no effect on total mortality.\textsuperscript{58} Flecainide has been shown to delay the first occurrence of AF and decrease the time spent in AF.\textsuperscript{59,60} The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study demonstrated that sustained-release propafenone significantly lengthened the time to first symptomatic AF recurrence compared with placebo (p=0.014).\textsuperscript{61} Sotalol is also an effective agent for the maintenance of sinus rhythm.\textsuperscript{1}

The rhythm-control strategy attempts to restore and/or maintain sinus rhythm, with attention to rate control. Symptomatic relief can be accomplished either by maintenance of sinus rhythm or reduction of AF burden from both a rhythm and rate perspective. In addition, once AF occurs, early restoration of sinus rhythm can disrupt progression of atrial remodeling.\textsuperscript{62} Several studies, however, most notably the AFFIRM study,\textsuperscript{63–67} have failed to demonstrate a significant advantage of either a primary rate or rhythm-control strategy with regard to all-cause mortality or other measurements such as CV hospitalizations in an older AF population with CV risk factors for stroke or death. It is notable that one cannot necessarily extrapolate these results to a non-AFFIRM-like population (e.g. younger patients without risk factors for stroke, such as lone AF patients). Nevertheless, the majority of studies in AF patients have also failed to demonstrate a clear benefit in terms of CV outcomes with sinus rhythm maintenance over rate control, even with significantly higher rates of sinus rhythm.\textsuperscript{66,68} This was also evident in the heart failure population with AF.\textsuperscript{68}

There is evidence that restoration and maintenance of sinus rhythm is associated with beneficial reverse atrial and ventricular remodeling (through improved hemodynamics, improved cardiac output, and reduced filling pressures), but may also significantly improve patient HRQoL.\textsuperscript{50,69} As such, restoration and maintenance of sinus rhythm, using either electrical cardioversion or drug therapy (Figure 2), remain important components in the medical management of AF.\textsuperscript{1,34,35,44,50}

In the RECORD-AF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation), rhythm control and sinus rhythm reduced the likelihood of progression to permanent AF.\textsuperscript{70} Progression of AF can lead to cardiac remodeling and perpetuation of AF.\textsuperscript{19} Remodeling can occur within days and become permanent, resulting in more AF and eventually leading to fibrosis.\textsuperscript{19,71} Atrial fibrosis, increased left atrial volume, and increased risk for thromboembolic events such as stroke may manifest when structural remodeling occurs as AF progresses from paroxysmal to persistent to permanent.\textsuperscript{18,71–75} Prevention of AF or reduction in AF may potentially alter or slow down cardiac remodeling. Clinically, reducing the rate of progression to permanent AF or maintenance of sinus rhythm, as seen in RECORD-AF, can alter or slow down cardiac remodeling.

A variety of AADs have been studied for the prevention of AF recurrence after cardioversion, with demonstrated reductions of 30–50%; however, AF recurred in 42–67% of treated patients.\textsuperscript{76} Most of the currently available AADs are limited by modest or intermediate efficacy based on an AF recurrence standard\textsuperscript{77} or by AEs.\textsuperscript{78} All AADs result in AEs, with a differential profile depending on the AAD. Proarrhythmia is not uncommon with class I AADs, including flecainide, propafenone, and quinidine.\textsuperscript{1} Quinidine is rarely used for AF anymore. The more commonly used class IC agents should only be used in patients with no significant CAD and minimal to no structural heart disease (e.g. heart failure, LVH, prior MI, cardiomyopathy, congenital or valvular heart disease).\textsuperscript{3,4} A relevant AE concern for class IC agents is monomorphic ventricular tachycardia.\textsuperscript{1} Owing to AE concerns, treatment with these agents is often started in the hospital even though it is not required in all patients. Class III agents such as sotalol and dofetilide have the potential for polymorphic ventricular tachycardia and torsades de points.\textsuperscript{1} These agents are generally recommended to be initiated on an inpatient basis\textsuperscript{3} and both are FDA labeled for a 3-day patient admission;\textsuperscript{79,80} however, sotalol is increasingly being used on an outpatient basis due to the AF guidelines.
Figure 2: (a) Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation according to the 2011 ACCF/AHA/HRS guideline update. Adapted with permission from Wann et al.34 as modified from Fuster et al.84 (b) Antiarrhythmic drug therapy to maintain sinus rhythm according to the 2010 ESC guidelines.35 Drugs placed together in a single box are listed alphabetically. Reproduced with permission from Camm et al.35
recommending outpatient initiation in low-risk patients. Amiodarone has a host of organ side effects or AEs, including pulmonary toxicity, thyroid toxicity, liver toxicity, CV effects, gastrointestinal effects, neurotoxicity and cutaneous effects, and ocular effects. Rhythm control is associated with a high rate of discontinuation, especially early in therapy. Patients who discontinue treatment with a specific AAD are unlikely to restart therapy, and persistence with all AADs, including the two most commonly used, amiodarone and sotalol, is generally poor. This lack of persistence may be associated with an increased risk of hospitalizations and cardioversions when patients discontinue treatment. Potential reasons for discontinuation include lack of efficacy, AEs, and cost. A retrospective cohort study estimated that approximately half of AF patients receiving rhythm- and/or rate-control therapy had a suspected AE and/or function tests for AE monitoring. Lack of efficacy is an issue, and recurrence of any kind is often considered a “failure” of AAD therapy and thus may lead to a higher rate of discontinuation.

The AADs included in the 2006 ACC/AHA/ESC guidelines have comparable efficacy when used for the maintenance of sinus rhythm, with the exception of amiodarone. Amiodarone is the most effective drug for maintaining sinus rhythm, as determined by the AF recurrence standard at roughly 1 year; however, its use has been limited by its cumulative and potentially serious toxicities, especially with long-term therapy. Nevertheless, based on 1-year results, amiodarone was more effective in preventing recurrences of AF, caused fewer AEs and proarrhythmic effects, and was associated with less mortality than combined class I AADs. An AFFIRM substudy, which compared the efficacy of different AADs for the treatment of AF, reported that more patients were treated more successfully with amiodarone than were patients receiving sotalol (60% versus 38%; p = 0.002) or class I agents, including quinidine and procainamide (62% versus 23%; p < 0.001) at 1 year. The results of the Canadian Trial of Atrial Fibrillation demonstrated similar results. After 16 months of treatment, significantly more patients assigned to sotalol or propafenone had a recurrence of AF compared with patients receiving amiodarone (63% versus 35%, respectively; p < 0.001).

BECAUSE AF IS A CHRONIC DISEASE, MOST PATIENTS WILL likely experience AF recurrence at some point. However, the recurrence of AF in patients on AAD treatment should not necessarily be considered a treatment failure. Many patients will choose to continue AAD treatment if the frequency and severity of AF episodes decrease. This reduction in global arrhythmia or AF burden may constitute therapeutic success for some patients and occasional recurrences may be acceptable. On a more practical level, it is unrealistic to expect that any AAD will provide complete freedom from AF over the long term (more than 1 year), so significant benefit both from a symptomatic and AF burden perspective should be considered as an acceptable therapeutic result in most AF patients, especially older patients with CV risk factors.

New AADs for the maintenance of sinus rhythm

Over the past 10–15 years, alternative AADs have been developed to treat patients with AF, but only one AAD, dronedarone, has been approved (July 2009) for use in the United States and is the first oral AAD approval since dofetilide was approved in 1999. Given that dofetilide is not recommended by either the ESC or CCS guidelines, nor is it generally available in Europe or Canada, much of the world has not had a new AAD since sotalol was approved (US approval in 1992).

Dronedarone is a non-iodinated benzofuran amiodarone derivative that was structurally modified to improve the safety and tolerability profile. Dronedarone is indicated to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF. According to the 2011 ACCF/AHA/HRS guidelines update, dronedarone is recommended in patients with AF who have no or minimal heart disease, hypertension without LVH, or coronary heart disease (class IIa recommendation). The 2010 ESC guidelines recommend dronedarone in patients with AF with minimal or no heart disease, hypertension with or without LVH, CAD, and stable New York Heart Association (NYHA) class I or II CHF. The 2010 CCS guidelines recommend that dronedarone may be added for additional rate control in patients with uncontrolled ventricular rates despite therapy with β-blockers, calcium-channel blockers, and/or digoxin. The US guidelines do not recommend dronedarone as a rate-control adjunctive agent nor is it approved for this indication by the US FDA. Dronedarone should not be used in patients with permanent AF.

In a direct comparison, the incidence of the composite primary end point (time to first AF recurrence or premature drug discontinuation for intolerance or lack of efficacy) was 75.1% and 58.8% in the dronedarone and amiodarone groups, respectively, at 12 months of treatment (p < 0.0001). This primary end point was mainly driven by the AF recurrence component. More patients experienced AF recurrences with dronedarone (63.5%) than with amiodarone (42.0%) after electrical cardioversion, but more amiodarone-treated patients discontinued drug treatment prematurely because of AEs (13.3% versus 10.4%). Drug discontinuations were less frequent with dronedarone (10.4% versus 1.3%), which were mainly a result of fewer thyroid, neurologic, skin, and ocular AEs in the dronedarone group. Because this was a short-term study, it is likely that the AEs seen with amiodarone would not reflect the AEs that commonly occur with continued treatment, such as pulmonary events, which typically present at 2 years. The long-term toxicity associated with amiodarone therapy limits its use, especially in younger patients.

The ATHENA trial, the largest study conducted to date to evaluate benefits of a single AAD, included 4,628 patients with AF with at least one CV risk factor.
(excluding hemodynamic instability). This trial evaluated CV outcomes, both CV hospitalizations and CV mortality rather than the more familiar time to AF recurrence. This was an event-driven trial and resulted in a “paradigm shift” in thinking, as it is the only trial to show a benefit in CV outcomes, specifically a marked reduction in CV hospitalizations with an AAD. Total mortality was not significantly reduced, but CV mortality was reduced.

It is important to differentiate that the ATHENA patient is not the same as the ANDROMEDA patient who should not receive dronedarone. In contrast to ANDROMEDA, which enrolled patients who had been hospitalized with new or worsening heart failure with severe left ventricular systolic dysfunction, patients enrolled in ATHENA had documented AF or atrial flutter, were hemodynamically stable with no recent heart failure decompensation, and the majority of patients had preserved ventricular function. Patients in the ATHENA trial were treated on an outpatient basis with either dronedarone 400 mg bid or placebo as add-on therapy to standard rate-control medications and antithrombotics. Dronedarone demonstrated a 24% risk reduction in the primary end point, time to first hospitalization for CV reasons or all-cause mortality, compared with placebo. A total of 696 (30.2%) patients in the dronedarone group and 716 (30.8%) patients in the placebo group discontinued study drug prematurely, mostly because of AEs. The dronedarone group had higher rates of bradycardia, QT-interval prolongation, nausea, diarrhea, rash, and increased serum creatinine levels than the placebo group. Rates of thyroid- and pulmonary-related AEs were not significantly different between the two groups. Although sinus rhythm rates were not directly assessed, this is the first and only AAD to demonstrate a benefit in CV outcomes. Interestingly, these CV outcomes benefits were seen in patients that remained in normal sinus rhythm or developed recurrent AF in the study. There was also a trend toward benefit in patients that developed permanent AF, which was being further investigated in the PALLAS study (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy), an event-driven trial assessing other potential CV outcomes effects not related to AF itself. The PALLAS study was prematurely terminated by the recommendations from the study’s Operations Committee and Data Monitoring Committee after the finding of increased adverse CV events in the dronedarone arm. There were 25 deaths in the dronedarone group and 13 in the placebo group (p = 0.049); 21 deaths were from CV causes in the dronedarone group compared with 10 in the placebo group (p = 0.046). The first co-primary outcome was a composite of stroke, MI, systemic embolism, or death from CV causes, which occurred in 43 patients receiving dronedarone and 19 patients receiving placebo (p = 0.002). Compared with patients in the ATHENA study, patients enrolled in the PALLAS study were older (mean age 75.0 years versus 71.6 years). Heart failure was present in 66.9–68.4% of patients with NYHA class I–III and 53.9–54.0% of patients with NYHA class II–III in the PALLAS study and in 20.2–22.1% of patients with a history of CHF and/or NYHA class II–III in the ATHENA trial. These data show that dronedarone should not be used in patients with permanent AF who are at risk for major vascular events.

The US FDA recently completed a safety review of dronedarone based on data from the PALLAS and ATHENA trials. This review showed that dronedarone increased the risk of serious CV events, including death, when used by patients with permanent AF. The prescribing information for dronedarone has been revised to include recommendations from the FDA regarding the use of dronedarone to manage the potential serious CV risks with the drug. The European Medicines Agency’s Committee for Medicinal Products for Human Use has recommended that dronedarone should be used for maintaining heart rhythm in patients with paroxysmal or persistent AF for the maintenance of sinus rhythm after successful cardioversion. Owing to an increased risk of liver, lung, and CV AEs, dronedarone should only be prescribed after alternative treatment options have been considered. The ESC is currently working to develop an AF-focused update targeted for publication in 2012.

In a placebo-controlled study in patients with severe heart failure and severe left ventricular dysfunction (wall-motion index correlating to an ejection fraction ≤35%) and recent heart failure decompensation, patients given dronedarone had a greater than twofold increase in mortality. Thus, dronedarone is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA class IV heart failure and in patients in AF who will not or cannot be cardioverted into normal sinus rhythm. This trial is important, as it provides clinicians with information regarding patients who should not receive dronedarone, just as we learned about class I AADs and patients with CAD and structural heart disease in CAST (Cardiac Arrhythmia Suppression Trial). According to the 2011 ACCF/AHA/HRS guideline update, dronedarone is not recommended in patients with heart failure, and the 2010 ESC guidelines do not recommend dronedarone in patients with NYHA III/IV or “unstable or recently decompensated” NYHA II CHF.

There have been several post-marketing reports of hepatocellular liver injury and hepatic failure in patients receiving dronedarone, including two reports of acute hepatic failure that required transplantation and new-onset or worsening heart failure. Obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment with dronedarone, is recommended. Post-marketing cases of increased international normalized ratio (INR) with or without bleeding events have also been reported in patients on warfarin initiated on dronedarone.

The Prescribing Information for dronedarone has been updated since this publication and can be found at http://www.accessdata.fda.gov/scripts/cdrer/drugsatfda/.
interstitial lung disease including pneumonitis and pulmonary fibrosis have also been reported.93 Exposure to dabigatran is also higher when it is administered with dronedarone than when it is administered alone (1.7- to 2-fold).95 In patients with moderate renal impairment (creatinine clearance 30–50 ml/min), it is recommended to use the 75-mg (rather than the 150-mg) dose of dabigatran with dronedarone.105

AAs currently in development include vernakalant, azimilide, celivarone, and the potentially atrial-selective agent AZD7009. Intravenous vernakalant has recently been approved (September 2010) in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF to sinus rhythm in adult non-surgery patients with AF of ≤7 days duration and for adult post-cardiac surgery patients with AF of ≤3 days duration.106 Intravenous agents for AF conversion, however, have limited utility in AF disease management. The status of the oral formulation of vernakalant remains uncertain. A phase 2a study demonstrated that 33 of 54 patients (61%) in the vernakalant 300-mg group and 30 of 49 patients (61%) in the vernakalant 600-mg group were in sinus rhythm at study end compared with 24 of 56 patients (43%) in the placebo group.107 Administration of vernakalant has not resulted in any cases of proarrhythmia in studies conducted to date. Azimilide is also in late-stage clinical testing in implantable cardioverter-defibrillator patients, and if approved by the FDA, will be the first AAD indicated in this patient population.108 Phase II clinical trials examining the maintenance of sinus rhythm with celivarone were recently completed. In the ALPHEE study, a dose-ranging study of celivarone with amiodarone, celivarone was not effective at producing implantable-cardioverter defibrillator shocks or sudden death.109

Antithrombotic therapy
A stroke risk classification scheme in patients with AF, known as CHADS2 (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age over 75 years and a history of hypertension, diabetes, or recent heart failure.1 The original validation of this scheme classified a CHADS2 score of 0 as low risk, 1–2 as moderate risk, and ≥2 as high risk.35 This scheme is used primarily in the United States and Canada, as reflected by recommendations in the respective guidelines.1,38 However, the 2010 ESC guidelines have de-emphasized the use of these categorizations and emphasize a risk factor-based approach.35 The CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female)) score is based on a point system in which 2 points are assigned for a history of stroke or TIA or age ≥75, and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (MI, complex aortic plaque, and peripheral artery disease (PAD), including prior revascularization, amputation due to PAD, or angiographic evidence of PAD), and female sex.35 CHA2DS2-VASc extends CHADS2 by including additional stroke risk factors that may influence a decision to provide a patient with anticoagulation. The HAS-BLED bleeding risk schema for AF (the Birmingham AF bleeding schema: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) offers valuable predictive capacity for bleeding compared with other schemas.110 The 2010 ESC guidelines state it is reasonable to use the HAS-BLED score to assess bleeding risk in patients with AF.35

Anticoagulation with adjusted-dose warfarin has been shown to be very effective in reducing the risk of stroke (by 62%) in individuals with AF and stroke risk factors.111 A meta-analysis showed that therapy with adjusted-dose warfarin in patients with AF reduced the relative risk of all-cause mortality by 26%.112 Nevertheless, warfarin is underutilized in AF patients for a variety of reasons, including significant drug and dietary interactions, a narrow therapeutic window, and the need for frequent monitoring, which can be inconvenient when warfarin is used for chronic prophylaxis in AF patients.113

Newer antithrombotic agents, including rivaroxaban, apixaban, and dabigatran, which are selective for specific coagulation factors such as factor Xa and thrombin, have been studied for use in patients with AF.113–115 These newer anticoagulants appear to have several pharmacodynamic/pharmacokinetic advantages over existing antithrombotic agents in that they are highly targeted for a single coagulation factor, have a rapid onset of action and fewer drug interactions, and do not require dosage adjustment according to patient age, gender, body weight, or mild renal impairment.115 As such, these agents seem to produce a more predictable anticoagulant effect in a broader range of patients without the need for routine monitoring.115 These agents may reduce barriers to anticoagulation use due to the reduced need for blood draws, clinic visits, and fewer drug and dietary interactions.

Dabigatran, a direct thrombin inhibitor, has been approved in the United States (October 2010) to reduce the risk of stroke and systemic embolism in patients with AF.116 The 2011 ACCF/AHA/HRS guideline update states dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure, or advanced liver disease.34 The RE-LY study showed that dabigatran administered at a dose of 150 mg twice daily reduced the annualized risk of the primary end point of stroke (including both ischemic and hemorrhagic stroke) and peripheral embolic events compared with warfarin, with similar rates of major hemorrhage.117 In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range (2.0–3.0) was 64%,117 rendering dabigatran superior to “optimal” warfarin anticoagulation.118 Rates of all-cause mortality per year were lower with dabigatran
Disease Progression of Atrial Fibrillation

(3.75%, 110 mg; 3.64%, 150 mg) than with warfarin (4.13%), but these findings were not statistically significant.117

Clinical trials with other new anticoagulants (factor Xa inhibitors) in patients with AF include rivaroxaban (ROCKET-AF; rivaroxaban versus warfarin) and apixaban (ARISTOTLE; apixaban versus warfarin; AVERROES; apixaban versus aspirin in patients unsuitable for warfarin). The ROCKET-AF trial showed that rivaroxaban was non-inferior to warfarin with regard to stroke or systemic embolism in patients with non-valvular AF.119 In the primary efficacy population, stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) (p<0.001 for non-inferiority). Rates of major bleeding were 3.6% and 3.4% in the rivaroxaban and warfarin groups, respectively (p=0.58).119 Rivaroxaban is approved by the FDA for the prevention of stroke in patients with non-valvular AF.120 In the AVERROES study, apixaban reduced the risk of stroke or systemic embolism without significantly increasing major bleeding or intracranial hemorrhage.121 In the ARISTOTLE study, apixaban was superior to warfarin in preventing stroke or systemic embolism. Stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) compared with 265 patients in the warfarin group (1.60% per year) (p<0.001 for non-inferiority and p=0.01 for superiority). Apixaban resulted in a composite clinical outcomes benefit, reducing the combination of stroke, systemic embolism, major bleeding, or death from any cause (hazard ratio 0.85 [95% confidence interval 0.78–0.92]; p<0.001).122 Apixaban is currently undergoing FDA review.

An important limitation to the use of these agents is the lack of readily available reversal agents or antidotes. Patient compliance and the impact of once-daily versus twice-daily dosing given the lack of monitoring should also be assessed. These issues should be balanced by the limitations of warfarin from both a patient and pharmacodynamic perspective. There is also limited information regarding the use of these agents for pericardioversion of AF, whereas the use of unfractionated heparin, low-molecular-weight heparin, and warfarin for pericardioversion has been well documented.123,124 A recent post hoc analysis of the RE-LY trial compared dabigatran with warfarin for stroke prevention in patients with AF undergoing cardioversion.124 Rates of stroke and systemic embolism within 30 days of cardioversion were low and comparable between dabigatran (110 mg bid, 0.8%; 150 mg bid, 0.3%) and warfarin (0.6%), with and without transeosophageal echocardiography guidance. Results of this analysis suggest that dabigatran may be a safe alternative to warfarin in patients requiring cardioversion.124

Combining anticoagulant with antiplatelet therapy

Several recent studies have assessed the use of clopidogrel with aspirin for stroke prevention in patients with AF. In the ACTIVE-W trial, warfarin was superior to clopidogrel plus aspirin for the prevention of vascular events in patients with AF at high risk for stroke.125 The ACTIVE-A trial compared clopidogrel plus aspirin with aspirin alone in patients with AF who were considered unsuitable for therapy with warfarin. In this study, the addition of clopidogrel to aspirin reduced the risk of vascular events, especially stroke, and increased the risk of major hemorrhage.126 The updated 2011 ACCF/AHA/HRS guideline update recommend the addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable.34

Ablative interventions

The use of catheter ablation for AF has rapidly increased over the last decade. According to the 2011 ACCF/AHA/HRS guideline update, catheter ablation may be useful to maintain sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an AAD and have normal or mildly dilated left atria, normal or mildly reduced left ventricular function, and no severe pulmonary disease (class I recommendation upgraded from class IIa, but remaining a class IIa recommendation in both Europe and Canada); to treat symptomatic persistent AF (class IIa recommendation); and to treat symptomatic paroxysmal AF in patients with significant left atrial dilatation or with significant left ventricular dysfunction (class IIb recommendation).34 Catheter ablation may be performed in several ways (e.g. segmental pulmonary vein isolation (PVI), ostial/antral PVI, wide-area circumferential ablation, complex fractionated atrial electrogram, etc.), with no clear superiority of one technique over another. This high variability and individualization make comparing one surgical procedure with another complex, and make comparisons to AADs difficult.127,128 The CABANA trial, with a planned recruitment of 3000 patients in Europe and the United States and a primary end point of all-cause mortality, is designed to investigate the impact of AF ablation on survival compared with drug therapy.69 Currently, catheter ablation techniques are associated with an approximate 6% rate of major complications, including cardiac tamponade (1–4%), pulmonary vein stenosis (<2%), stroke (0.5–1%), and death (1 of 1000 patients, with cardiac tamponade and the development of atrioesophageal fistulae the first and second most frequent fatal complications, respectively).69,129 Catheter ablation is not necessarily a cure for AF. Patients may experience AF recurrence at any time; recurrences have been observed in patients who were AF-free at 12 months of follow-up.128 In a recent prospective, single-center, randomized study, the overall combined efficacy of an ablation strategy involving up to two ablation procedures was 70% for patients with paroxysmal AF and 56% for patients with persistent/permanent AF.130 A worldwide survey of 777 electrophysiology centers and 8,745 patients conducted in 2002 estimated the success rate of ablation in routine clinical practice to be 52% in the absence of any AAD therapy, with an additional 24% becoming asymptomatic with continued use of formerly ineffective AADs.131 Furthermore, even in patients presumably cured of AF, there is a significant recurrence rate over the subsequent 5 years.132 In a systematic
Future challenges

Broadly, two groups of AF patients may exist, those with lone AF and those with AF with structural heart disease and risk factors for stroke and death. Early and aggressive intervention may be appropriate in younger patients with minimal or no structural heart disease, whereas in older patients with structural heart disease, symptom control rather than simply the recurrence of AF may be a more appropriate treatment strategy. Ideally, CV outcomes should be improved in both groups of AF patients. Owing to the complex pathophysiology and significant clinical consequences associated with AF, it can be a challenging disease to manage. Given the increasing elderly population, the public health burden of AF is expected to rise. While prevention of all AF recurrence may not be a realistic goal, significant progress has been made in the long-term management of AF and its sequelae. The increasing prevalence of AF, the natural history of progression with age and CV comorbidities, and the associated morbidity and mortality all necessitate continued research into AF pathophysiology, pharmacologic and invasive therapies, and disease management strategies to achieve and sustain improvements in global AF burden (symptoms, rate, and rhythm) in addition to normal sinus rhythm as a primary objective in appropriate patients, such as those with lone AF. Multiple clinical guidelines, although with subtle differences due to variations in data interpretation, are available for the management of patients with AF, as discussed in this article. Owing to timing issues, regulatory approval of new agents is not fully incorporated into all guidelines; thus, periodic focused updates and revisions are important to health-care practitioners. Clinicians should utilize these guidelines, in addition to their clinical expertise, when treating patients with AF. A goal of reducing the public health burden of AF and CV outcomes should be a focused target.

References

Disease Progression of Atrial Fibrillation


