

Concise Review of Atrial Fibrillation: Treatment Update Considerations in Light of AFFIRM and RACE

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Summary: Atrial fibrillation (AF) is the most common clinically significant arrhythmia seen by clinicians. Prevalence is as high as 9.0% in patients aged ≥ 80 years, and incidence is projected to be more than 5.6 million patients in the U.S. by 2050. Recently, new trials have challenged the traditional belief that rhythm control is inherently superior to rate control in these patients. This article reviews the basic tenets of treatment for AF and discusses how new trial data integrate into these protocols. A concise treatment algorithm is provided and new and upcoming more aggressive interventional treatment options are discussed. This review is designed to help the general practitioner decide how to treat patients in the outpatient setting, evaluate which patients should be hospitalized for management, and which patients should be referred to a cardiologist.

Key words: atrial fibrillation, antiarrhythmics, ablation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, affecting over 2 million persons in the US. With its increasing prevalence in our aging population, it is a problem that continues to expand. Atrial fibrillation carries with it significant potential for morbidity and mortality. Since there is still no effective, lasting cure for AF, there con-

tinues to be much research involving treatment options. Staying current in medical consensus is difficult for both primary care physicians and cardiologists. This review briefly summarizes current consensus, particularly in view of the recent clinical trials AFFIRM and RACE, released at the American College of Cardiology 2002 Annual Meeting.

Incidence

The Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study is a cross-sectional study examining the prevalence of AF and estimating the anticipated incidence by 2050. In a large California-based Health Maintenance Organization (HMO), 17,974 adults diagnosed with AF were identified. Of these, 45% were aged ≥ 75 years and the overall prevalence of AF was 0.95%. Atrial fibrillation was more common in men than in women (1.1 vs. 0.8%) and prevalence increased from 0.1% among adults aged < 55 years to 9.0% in persons aged ≥ 80 years. Among persons aged ≥ 50 years, prevalence of AF was higher in whites than in blacks (2.2 vs. 1.5%). The investigators estimate that approximately 2.3 million U.S. adults currently have AF, projected to increase to more than 5.6 million by the year 2050 with more than 50% of affected individuals aged ≥ 80 years.¹ This study agrees with prior known rates of prevalence and incidence in the Framingham study and other sources.

Definition

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by chaotic atrial activity with ineffective mechanical function. The ability to maintain AF is dependent on multiple factors including atrial size, fibrosis, stretch, mass, autonomic tone, and heterogeneity of atrial tissue. The electrocardiogram (ECG) is characterized by variable irregular, low-amplitude oscillations that correlate with atrial rates in excess of 300/min. Regular P waves are replaced by fibrillatory waves that vary in amplitude, frequency, and timing. It is a common misconception that if a visible P wave is present, the diagnosis of AF is excluded. In actuality, diffuse electrical ac-

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tivity is present in both atria, and the presence or absence of a visible P wave depends on the net vector sum of that electrical activity. This electrical activity, however, is unlikely to correspond to a mechanical contraction. These P waves will occur at an irregular rate, with a variable amplitude. The ventricular rate depends on characteristics of the atrioventricular (AV) node, the balance of sympathetic and parasympathetic tone, and the presence of medications that alter these conditions. If the AV node is normal, the ventricular rate can reach 200 beats/min or more.²

Mechanism

Atrial fibrillation requires two components, an initiator and the presence of substrate that will allow it to persist. Historically, there are two different proposed models for electrical activation: the “focal” hypothesis suggests that AF comes from multiple areas of ectopic automaticity,³ and the “multiple wavelet” hypothesis suggests that AF is the result of multiple tiny reentrant circuits that interfere with one another.⁴ Approximately 30 to 45% of paroxysmal cases and 20 to 25% of persistent cases of AF occur in younger patients without demonstrable underlying disease (lone AF).⁵ Lone AF is often attributed to idiopathic atrial fibrosis.⁶ In the last several years, electrophysiologists have observed that AF can be initiated by many different atrial tachyarrhythmias, most commonly premature atrial contractions (PACs). Many of these arise from residual left atrial musculature that surrounds the pulmonary veins and thus provide a possible source for potentially curative ablation.⁷

Clinical Presentation

Atrial fibrillation can be associated with virtually any cardiopulmonary or systemic disease. Hypertension is most common, and hyperthyroidism, alcohol abuse, mitral valve disease, and pulmonary embolism are other commonly associated conditions. Patients present with a range of symptoms: none, palpitations, systemic embolism or cardiovascular accident, syncope, angina, exercise intolerance, and congestive heart failure (CHF).

Clinical Evaluation

Patients need not be admitted to the hospital unless they are hemodynamically unstable, symptomatic of CHF, or are experiencing unstable angina. Even anticoagulation with coumadin can be safely started on an outpatient basis. Appropriate evaluation can be initiated in the outpatient setting in one visit, to include history and physical examination, ECG, transthoracic echocardiogram, and blood testing for thyroid function tests, electrolytes, and hemoglobin. If there is any suggestion of pulmonary disease or CHF on physical examination, chest x-ray should also be taken to evaluate both

parenchymal disease and vascularity. The echocardiogram is useful for prognosis and to evaluate for underlying heart disease, atrial size, and thrombus. If there is ambiguity in the diagnosis, frequency, or presence of paroxysmal disease, a Holter monitor may be indicated; if concern is high for thrombus, or if anticoagulation poses a high risk, a transesophageal echocardiogram (TEE) may be indicated; if the patient has recurrent, problematic symptoms after aggressive treatment, referral to an electrophysiologist is indicated.

Treatment (Fig. 1)

Atrial fibrillation can be divided into three categories: paroxysmal, persistent, and permanent. Paroxysmal AF is AF that has occurred and resolves, then recurs. Persistent AF is AF that does not resolve spontaneously, but aggressive attempts to perform cardioversion have not yet been attempted. Permanent AF is AF that has been unresponsive to multiple attempts to cardiovert.

Unstable patients should undergo immediate cardioversion. This discussion will be limited to outpatient treatment of AF in stable patients. The tenets of treatment consist of reducing symptoms and preventing stroke. Rate and rhythm control are the two basic treatment options. With rate control treatment, patients remain in AF and are given rate-controlling drugs to slow the ventricular response and anticoagulation therapy as appropriate. With rhythm control treatment, patients are given antiarrhythmic drugs and are cardioverted as necessary to obtain and maintain normal sinus rhythm (NSR). In either case, if symptoms are resistant to treatment, various device and ablation therapies are possible; these will be mentioned later.

Anticoagulation with coumadin to a target International Normalized Ratio (INR) of 2.0–3.0 is indicated for all patients who do not meet criteria for lone AF and who are not successfully maintained in sinus rhythm. Lone AF is defined as AF in a patient aged ≤ 65 years, with a structurally normal heart and who has never had a transient ischemic attack (TIA), a CVA, or a thromboembolic event.

Cardioversion is electrical or chemical, and should be done either within 48 h of onset of AF or after 4 weeks of therapeutic anticoagulation. Anticoagulation needs to be maintained for an additional 3–4 weeks after successful cardioversion. For recent onset AF, many patients convert spontaneously within 48 h of onset.⁸ No study has directly compared pharmacologic with electrical cardioversion; electrical cardioversion appears to be more efficacious. Drugs with proven efficacy when administered within 7 days include dofetilide, ibutilide, propafenone, flecainide, amiodarone, and quinidine. Only dofetilide is well documented to be efficacious in cardioversion of AF of > 7 days duration.⁹ (See Table I for drug options in atrial fibrillation.)

In the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial, 1,222 patients were randomized to conventional therapy versus TEE-guided cardioversion with a shorter period of anticoagulation.¹⁰ Eight-week results showed five embolic events in the TEE group (0.8%),

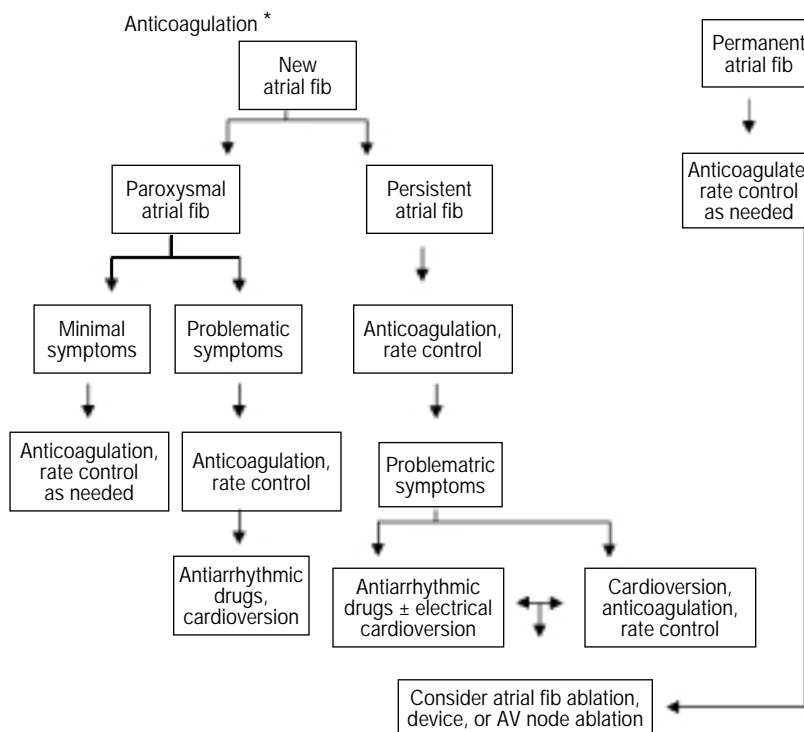


FIG. 1 Treatment algorithm.²⁰ *Anticoagulation with coumadin to INR of 2–3 for all patients with history of cardiovascular accident, transient ischemic attack, thromboembolism, age ≥ 65 years, structural heart disease, or prosthetic valves.

TABLE I Use of antiarrhythmic drugs²¹

Condition	Normal	CHF	CAD (normal EF)	LVH > 1.4 cm
First line	Flecainide, propafenone, sotalol	Amiodarone, dofetilide	Sotalol, amiodarone, dofetilide	Amiodarone
Second line	Amiodarone, dofetilide		Disopyramide, procainamide, quinidine	
Third line	Disopyramide, procainamide, quinidine			

Abbreviations: CHF = congestive heart failure, CAD = coronary artery disease, EF = ejection fraction, LVH = left ventricular hypertrophy.

and three embolic events in the conventional therapy group (0.5%) (p = 0.5). Both major and minor bleeds were more common in the conventional arm (5.5 vs. 2.9%, p = 0.03). In the TEE arm, mortality was higher at 2.4 versus 1.0% in the conventional treatment group, but just missed statistical significance (p = 0.06). Slightly more patients in the TEE arm were in sinus rhythm at the end of the study (52.7 vs. 50.4%). Many doctors use these results to justify TEE-guided cardioversion to reduce duration of anticoagulation in patients at higher risk for bleeding complications. Some believe, however, that the increased incidence of CVA and mortality in the TEE group requires further evaluation before utilizing this treatment option.

Prior to the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, initial therapies were usually attempts to restore and maintain NSR,¹¹ which was expected to lead to decreased morbidity. However, restoration and maintenance of sinus rhythm has proven difficult, time consuming, and expensive both for physician and patients. The AFFIRM trial was designed to examine whether this traditional rhythm normalization approach was beneficial compared with the less aggressive strategy of rate control and anticoagulation. The AFFIRM trial enrolled 4,060 patients at 213 sites in the U.S. and Canada. Included patients had AF and at least one other risk factor for stroke, including age ≥ 65 years, hyperten-

sion, diabetes mellitus, or CHF. Mean age was 69 (minimum 65). Patients were randomly assigned to rhythm or rate control and were followed for an average of 3.5 years. Patients treated with rate control could be treated with digoxin, beta blockers and/or calcium-channel blockers, and anticoagulation. Heart rate goal was <80 beats/min at rest and <110 beats/min during 6-min walk testing. Patients treated with rhythm control were given amiodarone, sotalol, propafenone, procainamide, quinidine, flecainide, disopyramide, and/or moricizine. At the end of the study, 63% of the rhythm group and 35% of the rate group were in NSR. There was no difference in the combined endpoint of death and CVA. The overall CVA rate was approximately 1%, with a slightly higher rate in the rhythm group. Hospitalizations were higher in the rhythm control group (1,374, 80% vs. 1,220, 73%). Deaths were slightly more prevalent in the rhythm control group, but did not reach statistical significance. Adverse drug effects were more common in the control group. There was no benefit to rhythm control in quality of life or improved cognitive function. Treatment in the rate control group was less costly due to the cost of antiarrhythmic drugs and the number of hospitalizations.

This outcome was reinforced by the Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation (RACE) trial, which was carried out in 35 hospitals in the Netherlands.¹² The hypothesis of RACE was that rate control of chronic AF is not inferior to rhythm control. In all, 522 patients with a mean age of 68 years were randomly assigned to rate or rhythm control. In the rhythm control group, patients underwent serial antiarrhythmic therapy, initially with sotalol, then flecainide or propafenone as the second agent, then amiodarone. Some patients underwent AV nodal ablation. In the rate control group, anticoagulation was given to a target INR of 2–3.5. Rate control drugs included beta blockers, calcium-channel blockers, and digoxin. Primary endpoint was a composite of cardiovascular death, CHF, hospitalization, thromboembolic complications, severe bleeding, pacemaker insertion, and “severe adverse effects.” At 3-year follow-up, 40% of the rhythm control and 10% of the rate control arm were in sinus rhythm. Primary endpoints were found in 17.2% of the rate control group and in 22.6% of the rhythm control group, with the conclusion that there is no difference in the composite endpoint between the two strategies. Thromboembolic events were again higher in the rhythm than in the rate control group (7.5 vs. 5.5%).

Discussion

The AFFIRM and RACE trials demonstrate that rate instead of rhythm control is an acceptable and possibly preferable therapeutic modality in a certain subset of patients. Careful examination of the patient populations shows that enrolled patients were older (average 68–69 years) and were minimally symptomatic. Thus, these results are not necessarily generalizable to all patients with AF, particularly those with symptoms. Optimal treatment for young patients with lone AF, or patients with highly symptomatic AF has yet to be ascertained.

It is of concern that higher rates of thromboembolism occurred in patients randomized to rhythm control in both studies. Most of these patients were either not undergoing anticoagulation therapy or had subtherapeutic INRs at the time of their events. That, combined with the poor success rates of maintaining sinus rhythm with antiarrhythmic agents, suggests that physicians must be extremely cautious in discontinuing anticoagulation in patients who are placed on antiarrhythmic therapy.

Catheter Ablation of Atrial Fibrillation

Programmed electrical stimulation of the heart was developed in the late 1960s as a way to study cardiac arrhythmias. It was not until the 1980s, when it was found that pathways that allowed the arrhythmia to persist could be successfully eradicated, that catheter ablation was developed as a potential therapy. In the last few years, increasing numbers of these ablative procedures have been performed in patients with AF. Atrial fibrillation often originates from the ostium of one or up to all four of the pulmonary veins. Therefore, in its simplest form, catheter ablation of AF consists of advancing a catheter with a loop at the tip containing 10 or 20 tiny electrodes (Lasso[®] Circular Mapping Catheter, Biosense Webster, a Johnson & Johnson company, Diamond Bar, Calif., USA) and positioning it sequentially at the entrance of each of the pulmonary veins. Radiofrequency current is then delivered to remove any electrical connection with the atria. There are several more complex methods, which frequently include various ways of drawing “lines” of tissue injury to isolate areas of the atria or pulmonary veins. In select patients, success rates have been as high as 90% with the initial procedure, but recurrence can be as high as 50%. At a few experienced centers, AF ablation can be performed in only a few hours, but most often procedure times are 4–6 h, or even longer. In addition, atrial flutter often coexists with AF and requires additional ablation sites, usually over the isthmus region in the right atrium.¹³

Although most ectopic beats originate from remnant myocardial tissue in the pulmonary vein orifices, ectopic beats can also originate from the superior vena cava, crista terminalis, coronary sinus, ligament of Marshall, or left atrial posterior free wall. Extra beats coming from these locations also complicate the procedure.¹⁴ A limitation to ablation of AF is that only very select groups of patients have been studied. The greatest successes are in younger patients with paroxysmal AF and no structural heart disease, or with some clinical suggestion of a focal source of their AF. Although cure rates of 60–85% have been reported in these groups, duration of cure is still unknown, as few long-term rates are available. Results for persistent AF are not as good. It is unclear whether these treatments will continue to protect individuals over time from recurrence and stroke. Because of the potential risk and complexity of catheter ablation, the ideal candidates should have frequent episodes, significant symptoms, drug refractory AF, and preferably paroxysmal rather than permanent fibrillation.¹⁵ Complications such as groin hematoma, pulmonary vein stenosis, cardiac perforation, tamponade, or stroke can occur during ablation, but serious complications are rare.

Open-heart surgical techniques have been developed to treat AF. Most common is the Maze procedure, which involves making a complex series of incisions designed to isolate the left and right atrium electrically, thus preventing the formation of atrial wavelets that result in AF. Cure rates of up to 85% have been reported, but morbidity is high and some mortality is present. Catheter-based maze procedures are currently under study and show some promise for future cure with less attendant risk than open surgery, but preliminary results are mixed.

Prognosis

The rate of nonvalvular CVA is 5–7% per year without anticoagulation. Based on Framingham data, the rate of CVA in patients with rheumatic heart disease is 17 times higher than in patients with other fibrillators.¹⁶ The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF increased from 1.5% in participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years.¹⁷ Mortality rates for patients with AF are approximately double those of the normal population; however, this appears to be strongly influenced by the presence and severity of other underlying disease, particularly heart disease. On the other hand, patients with metabolic causes, particularly hyperthyroidism, have remarkable success with long-term cure and minimal morbidity when the underlying metabolic problem is treated. Two trials of patients with CHF showed mixed influence of AF on mortality: the Veteran's Administration Heart Failure Trials (V-HeFTI and II) that studied outcomes of patients with heart failure found no increased mortality in patients with both heart failure and AF; the Studies of Left Ventricular Dysfunction (SOLVD) trial, however, showed a mortality of 23% in patients in NSR compared with 34% in similarly matched patients with AF. Death was due to CHF in these patients.^{18, 19}

Quality of Life

Although stroke accounts for a high percentage of functional impairment in patients with AF, treatment medications and the rhythm disturbance itself cause many symptoms. One study found that 68% of patients with paroxysmal AF considered their disease to disrupt their life significantly; this did not correlate with frequency or duration of events.

Conclusion

Atrial fibrillation remains a common problem in medicine; its incidence is projected to increase significantly over the next few decades. Optimal treatment strategy has yet to be clarified, especially because of the large variance in presentation and degree of symptoms among different patients. Effective stroke prevention remains an important consideration. Recent trials suggest that patients with minimal symptoms may be better served with simple rate control and anticoagulation rather than aggressive attempts to restore sinus rhythm, particularly as attempts to maintain sinus rhythm are costly,

time intensive, and ineffective. For patients with problematic symptoms, antiarrhythmic drug therapy is the first line of therapy, but newer, invasive procedures are being developed and refined. So far, these invasive therapies have shown efficacy only in limited patient populations. It is hoped that as medical knowledge of the mechanisms of AF continues to progress and technologies continue to be refined, improved options will become available.

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