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## Update in Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia in adults. It is a significant public health problem in the United States where it affects 2.2 million Americans and almost 10% of the population older than 80 years. It should be emphasized that the prevalence of AF increases with advancing age and with worsening cardiac function. AF is an independent risk factor for death and greatly increases the risk for embolic stroke. In addition, this arrhythmia can be associated with hemodynamic instability, tachycardia-

induced cardiomyopathy, and systemic embolism. The management of atrial fibrillation today is directed toward the prevention of thromboembolism, control of the ventricular rate and conversion to sinus rhythm. It is the purpose of this review to summarize the most recent information about the clinical implications and treatment of this common rhythm disorder.

*Key words: Atrial fibrillation, Epidemiology, Classification, Diagnostic evaluation, Management, Anticoagulation, Rate control, Rhythm control*

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**A**trial fibrillation (AF) is considered the most common sustained cardiac arrhythmia found in clinical practice (1). Electrocardiographically, it is characterized by the presence of fibrillatory waves that are seen as rapid, irregular waves with different shape and size. The disorganized atrial activation results in poor atrial mechanical function. This results in a rapid irregular ventricular response highly dependent on the performance of the AV node so that when AV block is present regularization of ventricular response takes place, with a subsidiary AV junctional pacemaker taking control of the ventricles. During fibrillation there is blood stasis within the atria that may lead to clot formation and potential liberation of emboli to other parts of the body and particularly to the brain.

In recent years there has been special interest on the pathogenetic mechanisms of atrial fibrillation and the structuring of strategies for its management. In the recent past, the preferred therapeutic objective was restoration and maintenance of sinus rhythm. Recently published trials have changed the traditional approach to the management of atrial fibrillation. It is the purpose of this review article to summarize the information available at

this time and describe the current approach to the management of this frequent cardiac arrhythmia.

### Epidemiology and Natural History

Atrial fibrillation (AF) affects approximately 2.2 million adults in the United States (2), Braunwald in the Shattuck lecture alludes to the growing epidemic of AF (3). The rate of AF increases as the patient gets older reaching a prevalence of around 10% among persons aged 80 years or more in whom it is very important to identify the arrhythmia for proper prevention of embolic events. Also AF has a substantial impact in morbidity and mortality and it is an independent risk factor for death with a relative risk of 1.5 for men and 1.9 for women (4). Nowadays it is found more frequently in death certificates as an important contributor to mortality (5).

Data gathered from many studies on atrial fibrillation showed a prevalence of 0.5-1.0% in the general population (6). The Cardiovascular Heart Study evaluated 5,207 men and women with age greater than 65 years to assess

risk factors for coronary artery disease and stroke. They reported a prevalence of 4.8% in women and 6.2% in men. It is noteworthy that in those patients with cardiovascular disease, the prevalence of atrial fibrillation rose to 9.1%.

In the SOLVD prevention study (7) the prevalence of atrial fibrillation for patients in functional class I was 4.2% whereas it was 49.8% for those in functional class IV in the CONSENSUS study (8). Not only is AF a frequent companion of heart failure but it can also lead to tachycardia-induced cardiomyopathy. In this condition,

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left ventricle dysfunction may be reversed if sinus rhythm is established and maintained.

## Classification

AF presents in different way and occurs in the presence or absence of heart disease. It is very important to recognize the onset of AF and it can be difficult because it may or may not be associated with symptoms.

- *Permanent AF*: is considered to be present if the arrhythmia last for more than one year and cardioversion either has not been attempted or has failed.
- *Paroxysmal AF*: the episode generally lasts less than seven days, usually less than 24 hours and may be recurrent.
- *Persistent AF*: fails to self-terminate and lasts longer than seven (7) days but can be terminated by cardioversion.
- *Recurrent AF*: when the patient experiences two or more episodes.
- *"Lone" AF*: atrial fibrillation in individuals without structural heart disease.

## Diagnostic Evaluation

Symptoms of AF range from simple palpitations and fatigue, to syncope, acute pulmonary edema or the neurologic consequences of cerebral embolism. Many cardiovascular and systemic conditions occur in association with atrial fibrillation (Table 1) (e.g., hypertension, coronary artery disease valvular heart disease and cardiomyopathy). Thus it is very important to determine the cause of the AF. Sometimes there is no apparent cause for the atrial fibrillation and we apply the diagnosis of lone or solitary AF. More commonly we find AF associated with structural heart disease such as mitral stenosis, cardiomyopathy hypertensive or coronary artery disease.

In the patient that comes with a totally irregular rhythm the electrocardiogram is the first diagnostic test after the history and the physical examination. The characteristic feature is fibrillatory atrial activity without distinct P waves, and an irregularly irregular ventricular rate. Atrial fibrillatory waves are best seen in lead V<sub>1</sub> and are usually clearly evident in II, III ad AVF.

The echocardiogram is an important part of the evaluation and it is recommended in all patients with AF. It provides information on ventricular function, atrial size, state of the cardiac valves and a good estimate of the severity of any existing disease. Thyroid function tests

**Table: 1.** Conditions Associated with Atrial Fibrillation

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| <b>Cardiovascular</b>                                      |
| Hypertension   |
| Coronary artery disease                                    |
| Cardiomyopathy (dilated, hypertrophic, infiltrative, etc.) |
| Valvular heart disease                                     |
| Congenital heart disease                                   |
| Cerebrovascular disease                                    |
| Peripheral vascular disease                                |
| Pericarditis   |
| Myocarditis  |
| <b>Pulmonary</b>   |
| Pulmonary embolus  |
| Chronic obstructive lung disease                           |
| Pulmonary hypertension                                     |
| <b>Metabolic</b>   |
| Hyperthyroidism  |
| Alcohol intoxication ("holiday heart")                     |
| Electrolyte abnormalities                                  |
| <b>Primary dysrhythmic states</b>                          |
| Wolff-Parkinson-White syndrome                             |
| Sick sinus syndrome (bradycardia-tachycardia syndrome)     |
| <b>Miscellaneous</b>                                       |
| Postoperative state  |

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*Adapted from Ganz LI. In Crit Path Cardiol 2002;1:3-11.*

and ambulatory ECG monitoring (Holter) are also included in the initial evaluation but no test is a substitute for a careful, focused history and a meticulous physical examination.

Detailed testing for other conditions such as myocardial infarction or acute pulmonary embolism is only indicated in those patients presenting with symptoms or signs suggestive of those entities. New diagnostic tests have been recently developed such as brain natriuretic peptide and D-dimer to detect impaired cardiac function and hypercoagulability. However, both are still under investigation and should not be part of the initial work up of AF at this point in time.

## Management

The present day management of atrial fibrillation addresses three objectives: anticoagulation, control of the ventricular rate, and rhythm control. In patients with persistent AF there are two ways to manage the rhythm disorder: to restore and maintain sinus rhythm or to allow AF to continue, control the ventricular rate and anticoagulate the patient.

**Anticoagulation.** Systemic embolization from atrial thrombi can occur with any form of atrial fibrillation (AF), spontaneously, or in association with cardioversion. Thus

anticoagulation is considered in most of the patients and becomes one of the primary therapeutic goals. Clinical trials have shown that anticoagulation with warfarin reduces the risk of ischemic stroke by 68% (10). However, clinicians must decide whether the benefits of long-term anticoagulation outweigh the risk of bleeding for individual patients, and, they must aim for the optimal level of anticoagulation needed to prevent stroke.

The prevalence of AF increases with age and is thought to be responsible for approximately one-sixth of all ischemic strokes in people over 60 year of age (11). Guidelines from the American College of Chest Physicians (ACCP) and the Joint Task Force of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) (1) recommend anticoagulation therapy for the prevention of stroke in patients with AF based upon the presence of risk factors for stroke. Many risk models have been proposed in an attempt to predict risk and the likelihood of benefits from therapy with warfarin (1, 12, 13, 14, 15).

There is general agreement on the factors that represent a high risk for stroke: old age, hypertension, previous stroke, transient ischemic attacks, heart failure and diabetes. Patients with rheumatic mitral valve disease and those with a mitral prosthesis constitute a very high risk group even when they are in sinus rhythm. The risk becomes extraordinarily high if they develop atrial fibrillation.

Patients younger than 65 years, without structural heart disease (so-called lone atrial fibrillation), carry a low risk for stroke and can be treated with aspirin alone. It is important to emphasize age as a risk factor. Before 65 years of age, the relative risk for stroke is 1.4. However, as the patient gets older the risk for stroke doubles with each decade. Surprisingly, the ATRIA study (15) showed that the older the patient the lesser is the probability that the patient is receiving anticoagulation therapy. In that study only 35.4% of patients 85 years of age or older were using warfarin even though they had no contraindication for the use of that drug. In a small study (16) of 10 patients with AF, aged 90 or more years, it was found that chronic anticoagulation was effective and safe when given under

close supervision and appropriate monitoring.

The ACC/AHA/ESC guidelines present recommendations based on an integration of the ACCP consensus risk stratification scheme with an evidence based analysis of risk factors for stroke (see table 2). The low-risk patients should receive aspirin (325 mgs) daily. In very high risk patients, the target INR is 2.5 to 3.5. However, in patients with valvular disease or a history of a previous stroke, there is no data to indicate that the efficacy of anticoagulation is improved in patient with AF when the INR exceeds 2.5. In all other instances, the desired anticoagulation level has been defined as an INR of 2.0 to 3.0.

**Table 2:** Risk of Stroke and General Approaches to Anticoagulation in Atrial Fibrillation

| Age Group | Risk Factors* | Annual Event Rate If Untreated (95% Confidence Interval) | Recommendation        |
|-----------|---------------|--|-----------------------|
| < 65      | Absent        | 1.0 (0.3 – 3.1)  | Aspirin or no therapy |
|           | Present       | 4.9 (3.0 – 8.1)  | Warfarin              |
| 65-75     | Absent        | 4.3 (2.7 – 7.1)  | Warfarin (Aspirin)    |
|           | Present       | 5.7 (3.9 – 8.3)  | Warfarin              |
| > 75      | Absent        | 3.5 (1.6 – 7.7)  | Warfarin              |
|           | Present       | 8.1 (4.7 - 13.9)   | Warfarin              |

\*A presence of one or more of the following features: previous stroke or transient ischemic attack, hypertension, heart failure (HTN), Coronary Artery Disease (CAD), prosthetic heart valve, diabetes or hyperthyroidism.

*Adapted from the American College of Physicians recommendations for anticoagulation for patients with atrial fibrillation. Arch Intern Med 1994;154:1449-1457.*

Low-dose warfarin plus aspirin with a goal of INR between 1.2 and 1.5 in combination with aspirin (325 mg/day) should not be used to reduce the stroke risk in patients with AF and has been associated with significant higher mortality and morbidity than adjusted-dose warfarin. The only exception to this recommendation is the subset of patients older than 75 years considered to have increased risk of bleeding in which a target INR of 2 range (1.6 to 2.5) for primary prevention should be sufficient. Patients with atrial fibrillation that are candidates for electrical or pharmacological cardioversion require anticoagulation.

Atrial fibrillation of more than 48 hours duration, or of unknown duration, should be anticoagulated for 3-4 weeks before and after elective cardioversion. An alternative approach is to screen for the presence of thrombus in the atria with transesophageal echocardiography (TEE). If no thrombi are seen, a bolus of IV heparin is given followed by a continuous infusion to prolong the activated PTT to

1.5-2 times the control value. Concomitantly with the heparin infusion, one may proceed with electrical cardioversion. If thrombi are seen in the atria, the patient should have oral anticoagulation with warfarin for 4 weeks before cardioversion is considered.

## Control of Ventricular Rate

There are two important reasons to prevent rapid ventricular rates in atrial fibrillation: to avoid symptoms of hemodynamic impairment (such as palpitations, shortness of breath, lightheadedness and poor exercise capacity) and to prevent the development (over the long term) of tachycardia-mediated cardiomyopathy(17).

The adequacy of rate control should be assessed both at rest and with exertion. Heart rate targets include:

1. An average heart rate at rest of 80 beats/min
2. A heart rate of 100 beats/min in a 24 hour Holter study
3. A maximum heart rate of 110 beats/min in a six minute-walk test

For a long time digitalis was the only drug available to control the ventricular rate. Now it is recognized that digitalis by itself is usually insufficient to provide adequate control in most activities and achieves control mostly at rest. The availability of beta blockers and calcium channel blockers (such as verapamil and diltiazem) have rendered rate control more effective and easier to maintain.

*Digoxin* may still be the most widely used drug for control of ventricular rate and acts primarily by vagotonic inhibition of AV nodal conduction, a mechanism that can take several hours to become apparent. It is considered the preferred drug only in patients with atrial fibrillation due to heart failure and in those patients that can not take or who respond inadequately to beta blockers or calcium channel blockers.

*Intravenous beta blockers* like esmolol, metoprolol, atenolol, propranolol, etc., are effective for acute control of ventricular rate, mostly in situations such as angina pectoris induced by a rapid ventricular rate, hyperadrenergic states like hyperthyroidism, and post-cardiac surgery. Esmolol is a rapid acting agent that is metabolized by red blood cell cholinesterase resulting in a very short duration of action (10 to 20 minutes).

The *nondihydropyridine calcium channel blockers* verapamil and diltiazem are useful when given intravenously and can provide long term rate slowing when used orally.

*Combination therapy* is recommended when adequate rate control can not be achieved with a single agent. Sometimes it is difficult to attain adequate heart rate

control and the physician needs to resort to non-pharmacological approaches such as radiofrequency catheter ablation of the AV junction accompanied by the implantation of a permanent pacemaker.

## Rhythm Control

Restoration of sinus rhythm is generally attempted with the first documented episode of AF or when associated with symptoms of hemodynamic instability.

The ACC/AHA/ESC Guidelines recommend immediate electrical cardioversion in patients with paroxysmal atrial fibrillation and rapid ventricular response who have ECG evidence of acute myocardial infarction or symptomatic hypotension, angina, or heart failure that does not respond promptly to pharmacological measures.

Another indication are those patients with persistent symptoms in a rate control strategy (e.g., palpitations, weakness, dizziness, dyspnea) or if there is strong patient predilection for sinus rhythm.

Predictors of a lesser chance of long-term success after cardioversion are: AF duration of more than one year and increased echocardiographic left atrial dimension (4.5 to 5 cm). DC cardioversion has been associated with high rate of success when none of those characteristics are present and it has ranged from 75 to 90%.

Maintenance antiarrhythmic drug therapy is usually not recommended after the first episode of AF in those patients where a transient or correctable cause is present, or when the episodes have a very short duration. In other patients maintenance antiarrhythmic drugs may be given to reduce the rate of recurrence.

For many physicians the use of antiarrhythmic drugs is the preferred method for cardioversion of AF. It is most important that the clinician be very much aware of the potential for toxicity of the available antiarrhythmic drugs. Ibutilide proved to be effective for pharmacological cardioversion but there is a small risk of inducing *torsades des pointes* particularly in patients with low ejection fraction. If conversion to sinus rhythm is attained with ibutilide, the patient should be monitored at least for the next 4 hours.

*Amiodarone* also has been used in different doses and routes and is modestly effective but is associated with long term adverse effects. Irrespective of the modality used for cardioversion there is a high incidence of recurrence of AF. Subsequent maintenance of sinus rhythm is sometimes difficult and usually requires different drugs that must be carefully selected keeping in mind the presence of heart failure; left ventricular hypertrophy and coronary artery disease. Even more important is to be aware of the risk of proarrhythmia.

**Rhythm control versus rate control in atrial fibrillation.** Before the results of recent clinical trials were published (18-22), most clinicians preferred aiming for rhythm control for the first few episodes of atrial fibrillation. Recent clinical trials such as PIAF(18), STAF(19), RACE(20),HOT CAFÉ (21) and AFFIRM(22), have shown that rhythm control and rate control give comparable results in terms of symptoms and the risk of stroke provided that the patient is adequately anticoagulated. In some studies, rate control may have a lower risk of adverse events, a trend toward lower risk of death, and fewer hospitalizations. Today, the available data indicates that rate control is not inferior to rhythm control in most patients with persistent atrial fibrillation.

Attempts to obtain rhythm control are warranted in patients with new-onset AF, in young patients, and in those that remain symptomatic despite adequate rate-control.

**Non-pharmacologic therapy of atrial fibrillation.** In the recent past several techniques have been developed for the management of drug refractory atrial fibrillation and maintenance of sinus rhythm. When an initiating focus for the AF can be identified in an electrophysiologic study, focal radiofrequency ablation can be successful. The maze operation designed by James Cox(23) can be performed in patients with AF that are undergoing thoracotomy for other reasons. Catheter based approaches for internal atrial defibrillation are currently under active investigation.

## Conclusions

Atrial fibrillation is the cardiac arrhythmia most frequently encountered in adults and may be associated with devastating complications. It is a major risk factor for embolic stroke which is an important cause of morbidity and mortality.

It behooves the practicing physician to be aware of its epidemiology, natural history, pathogenesis, classification, and of the modern diagnostic techniques available. It is most important to know the major therapeutic approaches that include anticoagulation, rate control and rhythm control. This article summarizes the most current information collected in the most recent clinical trials.

## Resumen

La fibrilación auricular (FA) es la arritmia sostenida encontrada más frecuentemente en la clínica. Afecta millones de personas y aumenta su prevalencia con la edad y con el empeoramiento de la clase funcional cardíaca. La fibrilación auricular constituye un factor de riesgo importante de muerte así como de eventos

cerebrovasculares. En adición, puede asociarse con inestabilidad hemodinámica, miocardiopatía inducida por una frecuencia ventricular rápida y embolismos sistémicos. El manejo de la FA está dirigido hacia la prevención de complicaciones embólicas mediante el uso de anticoagulantes, el control de la frecuencia cardíaca y la conversión a ritmo sinusal. El propósito de este trabajo es resumir los avances más recientes en este tipo de arritmia cardíaca, y presentar los métodos más aceptables para su manejo, a la luz de recomendaciones ofrecidas por las guías establecidas por el Comité de la Asociación Americana del Corazón, El Colegio Americano de Cardiología y la Sociedad Europea del Corazón.

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