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Atrial fibrillation: current epidemiology, noninvasive imaging, and pharmacologic therapy

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Atrial fibrillation (AF) is an increasingly common supraventricular arrhythmia. In this review, we will discuss the changing epidemiology of AF, the impact of noninvasive imaging on the evaluation of patients with AF, and the role of pharmacologic therapy in the treatment of this condition.

Epidemiology

The Framingham Study generated some of the early epidemiologic data concerning AF in the early 1970s. The investigators found then that there was a 3.2% prevalence of AF in adult males.[1] They also noted that the incidence of AF increased with age. In their most recent analysis, based on 1987-1989 data, the age-adjusted prevalence of AF had increased to 9.1% in men and from 2.8% to 4.7% in women (aged 65-84).[1] Over this same time period, the age-dependence of AF has persisted at 0.5% in those aged 50-59 years, while increasing steeply to 9% in the octogenarian. The reason for the increase in AF prevalence is unclear but, as the population ages, it is increasingly a cause for concern.

Several clinical features are associated with heightened risk for subsequent development of AF (Table 1). These clinical risk factors include age (as noted above), hypertension (age-adjusted risk odds ratio: 1.5 in men,1.4 in women),diabetes (1.4 in men, 1.6 in women), heart failure (4.5 in men, 5.9 in women), valvular heart disease (1.8 in men,3.4 in women), and myocardial infarction (1.4 in men, 1.2 in women).[2] It is unknown whether effective treatment of these risk factors and disease processes will lead to a reduction in the occurrence of AF.

Certain echocardiographic correlates of these clinical risk factors are associated with increasing likelihood of AF development. In a Framingham cohort of about 1900 men and women, echocardiographic evidence of structural heart disease markedly increased the risk of AF. Those in the highest quartile of left atrial size had a 2.5 times increased risk of having AF.[3] Similarly, echocardiographic evidence of reduced fractional shortening or increased wall thickness were associated with a 2- to 3-fold greater prevalence of AF.[3]

Hazards of atrial fibrillation

The most well-known hazard of AF is the augmented risk of stroke. From an epidemiologic standpoint, AF accounts for approximately 0.5% of all strokes in patients aged 50-59.[4] This attributable risk increases with age such that nearly a quarter of all strokes in octogenarians may be accounted for by underlying AF.[4] A more serious hazard is an increased incidence of death in patients with AF. Benjamin *et al* have looked at the mortality risk incurred by patients aged 55-94 after being diagnosed with AF and compared it to age-matched patients without AF.[5] AF was associated with an odds ratio for death of 1.5 (1.2,1.8) in men and 1.9 (1.5,2.2) in women. Also, patients with AF were more likely to have other cardiovascular risk factors. After 10 years of follow-up, death had occurred in 61.5% of men with AF,

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Table 1: Clinical and echocardiographic risk factors for developing AF

Clinical predictors of AF	Echocardiographic predictors of AF
•Age	•Dilated left atrium
•Heart Failure	•Increased left ventricular wall thickness
•Hypertension	•Depressed fractional shortening
•Diabetes mellitus	
•Valvular heart disease	
•Myocardial infarction	

but in only 30% of men without AF. In women, 58% with AF and 21% without AF had died at 10 years.[5] The mechanism of this increased mortality at one year appeared to be related to stroke, coronary heart disease and other comorbidities, as well as cardiovascular disorders in both men and women.

The reduction in stroke with warfarin has been investigated in several multicenter studies. These have demonstrated that warfarin is extremely effective in reducing the risk of stroke in patients with nonvalvular AF.[6-8] In particular, warfarin has been found uniformly to decrease the risk of ischemic stroke in patients with AF. Aspirin is also associated with a reduction in the risk of stroke, but is less potent in this regard than warfarin. Risk factors associated with an increased risk of embolism include hypertension, left ventricular dysfunction, increasing age (>75 years old in women),prior transient ischemic attack (TIA) or stroke, and diabetes.[9-11] Patients who are < 65 years old without risk factors for embolism may be treated with aspirin. Patients who have one or more of these risk factors should benefit from therapy with warfarin. The recommendations from the Fifth ACCP Consensus Conference on Antithrombotic Therapy are shown in Table 2.[12]

While death and stroke are clearly the most serious hazards, AF can produce other morbidities. The development of AF can result in decreased functional capacity. Patients may develop shortness of breath as well as palpitations, decreasing their ability to perform their daily activities when in AF. Recently, attention has been given to the development of cardiomyopathy after AF has occurred. Attempts to treat AF promptly and effectively may decrease these symptoms as well as prevent the development of cardiomyopathy.

Use of noninvasive imaging in AF

Echocardiography

Much of the early echocardiographic data focused on left atrial size as the predictor for developing and sustaining AF.[3] Most studies have made measurements of left atrial size from parasternal echocardiographic imaging windows. Every 5 mm increase in atrial diameter was found to be associated with a 39% increase in the risk of developing AF.[3] In addition, atrial volumes from apical views were found to correspond to an increased likelihood of AF. Left atrial size also appeared to be a possible predictor of responsiveness to antiarrhythmic or

Table 2: Recommendations for anticoagulation in AF in patients considered candidates for anticoagulation[12]

Age	Risk Factors*	Recommendation
< 65 years	Absent	Aspirin
< 65 years	Present	Warfarin (target INR 2.5 [range 2.0-3.0])
65-75 years	Absent	Aspirin or warfarin
65-75 years	Present	Warfarin (target INR 2.5 [range 2.0-3.0])
> 75 years	All patients	Warfarin (target INR 2.5 [range 2.0-3.0])

*Risk factors include prior TIA, systemic embolism or stroke, hypertension, depressed left ventricular function, rheumatic mitral valve disease, prosthetic heart valve.Note that the target INR may be higher for a patient with a prosthetic heart valve.

electrical cardioversion therapy. Early data obtained by several investigators defined a critical left atrial size of 4-4.5 cm. Those patients with left atrial sizes greater than this dimension had a decreased likelihood to maintain sinus rhythm long-term. However,subsequent studies by Brodsky *et al* suggest that patients with left atrial dimensions up to 6 cm may be effectively converted back to sinus rhythm.[13] Whether these data are related to the use of amiodarone rather than traditional antiarrhythmics such as quinidine, or are perhaps due to variations in arrhythmia duration or less severe myocardial or valvular disease remain unclear.

Left atrial size is a dynamic dimension that changes in response to the underlying rhythm status. The concept "AF begets atrial enlargement" was studied by Gosselink *et al*.[14] These investigators studied patients with AF, measuring apical left and right atrial volumes at baseline and 20 months later. During this time left atrial volume increased from 45 to 64 ml and right atrial volume increased by a comparable amount.[14] This is consistent with the concept that disorganization of atrial conduction leads to further expansion and stretching of the atrial myocardium. The inverse physiologic finding is also true: those patients who are converted to and sustained in sinus rhythm have a decrease in left atrial volume. Sanfilippo measured atrial volumes prior to and six months following restoration of sinus rhythm.[15] Left atrial volume decreased from an average of 73 to 59 ml demonstrating that a determinant of atrial volume is underlying rhythm status.[15]

Adding Doppler techniques

The availability of advanced noninvasive imaging modalities and Doppler techniques provide the opportunity to go beyond left atrial size. Early Doppler-based insights investigated the relationship between the transmitral Doppler profile in sinus rhythm and patient symptoms. A typical transmitral profile consists of an E wave (early diastolic filling) which is typically of a larger magnitude than the A wave (ventricular filling associated with atrial contraction). Patients who have abnormal relaxation of their left ventricle may develop prominent A waves. This is most common in patients who have

underlying coronary disease or hypertension. Sixty patients with a history of atrial fibrillation who had echocardiograms performed in sinus rhythm were studied at Brigham and Women's Hospital.[16] Those patients with a markedly elevated A wave velocity relative to the E wave velocity in sinus rhythm were the ones most likely to become symptomatic upon developing AF.[16] These patients are more dependent on atrial contraction for ventricular filling.

Doppler echocardiography has also led to important insights into the recovery of mechanical function. There have been several elegant studies performed which examined changes in the transmitral flow profile over time in patients following restoration of sinus rhythm. As anticipated prior to cardioversion, no A wave is found to be present while patients are in AF. Following conversion to sinus rhythm there may be subsequent development of an A wave, demonstrating restoration of effective atrial mechanical function. Despite the prompt electrocardiographic restoration of the P wave, mechanical function may lag. The magnitude of this A wave may be small initially, returning to normal over time. Approximately 75% of patients recover atrial function (return of an effective A wave) a week following successful cardioversion.[17] Return of effective atrial contraction with restoration of normal sinus rhythm may be more rapid in patients with a briefer duration of AF. Manning *et al* demonstrated an improvement in peak A wave velocity over the first 24 hours following cardioversion with continued improvement between one and three months thereafter.[17]

The availability of transesophageal echocardiography has led to further Doppler and imaging-based insights. The risk of stroke may be related either to the presence of thrombi or stasis of blood flow within the left atrial appendage. The atrial appendage velocity patterns may be interrogated using transesophageal echocardiography. One pattern is with well developed filling and emptying waves at velocities greater than 25 cm/sec consistent with low embolic risk. A pattern with diffuse irregular low filling and emptying patterns is associated with echocardiographic appearance of smoke, thrombus formation, and greater embolic risk.[18]

Echocardiography with cardioversion

Manning and investigators speculated that this transesophageal echocardiographic information from the left atrial appendage could be used to help direct the initial therapy of patients with AF. Their initial study enrolled 65 patients who presented with AF.[19] These patients were placed on heparin in the hospital but were not pretreated with warfarin. These patients underwent transesophageal echocardiography and prompt cardioversion was performed if no left atrial thrombi were visualized. Long-term anticoagulation was begun without cardioversion if a thrombus was seen. In those patients undergoing cardioversion there was a 0% embolic rate.[19] These investigators subsequently expanded their enrollment to 233 patients and found similar results, underscoring the safety of prompt cardioversion in the echocardiographic low risk group.[20] However, since these numbers remain low, this experience cannot be considered definitive. Subsequent to the initial report of the transesophageal guided cardioversion strategy by Manning et al, there have been several cases of patients who underwent transesophageal echocardiography and cardioversion who ultimately developed an embolic event despite a clear transesophageal echocardiogram.[21]

To reach a definitive answer, a larger scale trial is needed. This trial must enroll thousands of patients since historical data show that the general risk of stroke with cardioversion in patients without rheumatic heart disease is approximately 1% with conventional anticoagulation and 2.8% without full anticoagulation for 3-4 weeks.[22] In addition, the likelihood of detecting a thrombus in the left atrium of a patient in AF on a transesophageal study is in the range of 6-16%.[20,23,24] Many investigators have argued that the transesophageal echocardiography strategy ultimately reduces the stroke risk since transesophageal echocardiography most accurately visualizes the left atrial appendage and identifies not only the thrombus and spontaneous echo contrast, but also allows evaluation of the aorta for atheroma.

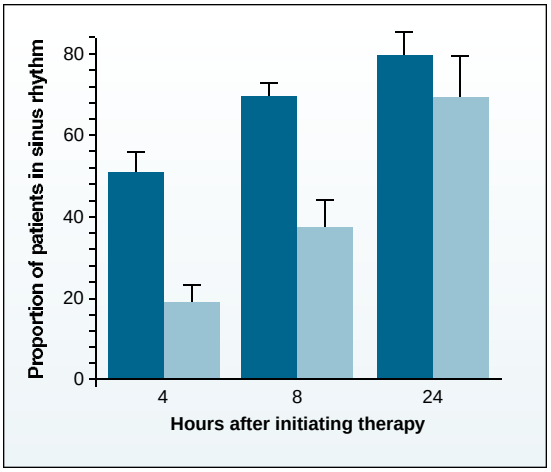
In some cases, there has been variability regarding the post-cardioversion anticoagulation regimen. The initially published strategy recommended anticoagulation for three to four weeks following cardioversion. Because of the concerns of many investigators concerning the risks/benefits of the use of transesophageal echo in AF, a multicenter trial called the ACUTE Trial (Assessment of Cardioversion Using Transesophageal Echocardiography) has recently been initiated.[25] This randomized trial will enroll 3000 patients with AF lasting more than two days from 65 sites, and will compare transesophageal echocardiography-guided prompt cardioversion versus standard anticoagulation prior to cardioversion. The primary endpoints will include stroke, embolization, and transient ischemic attacks after eight weeks with secondary endpoints of mortality, bleeding, cost-effectiveness and maintenance of sinus rhythm. This trial will likely define the role of transesophageal echocardiography in the early management of patients with AF.

Pharmacologic therapy in the management of AF

How to treat patients with acute AF is a common clinical question. These patients may not have "declared" their pattern, but we now know that up to 90% of them will revert to sinus rhythm within 72 hours even if no therapy is given.[26] For pharmacologic therapy to be more effective than time alone, an increased proportion of patients must convert to sinus rhythm or patients must convert to sinus rhythm more promptly.

In order to investigate this situation, a meta-analysis was recently performed of 27 studies in which propafenone was administered for acute termination of AF.[27] Over 1800

Figure 1. The proportion of patients with acute AF who convert to sinus rhythm is shown for propafenone treatment (dark bars) and control treatment (lighter bars). The proportion (%) of patients converting to sinus rhythm is significantly greater for propafenone at 4 and 8 hours after starting therapy ($p<0.01$) but is not different at 24 hours.[27]



patients were treated with both oral and intravenous propafenone. Within four hours of initiating therapy, over 50% of patients reverted to sinus rhythm. The proportion of patients in sinus rhythm increased to 86% at 48 hours after starting propafenone therapy.[27] These results look favorable but must be compared to data from placebo patients. In a comparison of propafenone-treated patients with controls, propafenone was found to be more effective than placebo at four and eight hours after starting therapy in the proportion of patients converting to sinus rhythm. However, by 24 hours after starting therapy, no treatment difference was observed (Figure 1). Thus, propafenone more promptly restored sinus rhythm within the first eight hours without markedly changing the ultimate proportion of patients converting to sinus rhythm.[27]

While the objectives of treating paroxysmal AF are to decrease the frequency, intensity, and duration of symptoms, the goal of treating persistent AF is restoration and maintenance of sinus rhythm. For both of these arrhythmia patterns, it is important to understand the risks associated with not treating the arrhythmia. Data from different studies on the treatment of patients with paroxysmal AF may be difficult to compare since study endpoints are quite variable, ie, time to first recurrence, number of episodes over time, duration of episodes.

Quinidine has been used since the 1940s to treat paroxysmal and persistent AF. Data from six randomized controlled trials suggested that the efficacy of quinidine to maintain sinus rhythm was approximately 50% at 12 months compared to 25% in the placebo group.[28] While quinidine appeared effective during this period of time, this meta-analysis also revealed a slightly increased mortality associated with the use of quinidine. Subsequent studies with other antiarrhythmics have shown comparable six-month efficacy with sotalol for the treatment of persistent AF.[29] The Brigham Arrhythmia Group randomized 100 patients with paroxysmal or persistent AF to propafenone or sotalol and followed their rhythm status over time. Six months after starting therapy, nearly equal proportions of patients (40-45%) remained in sinus rhythm regardless of arrhythmia pattern, atrial dimension (< or >4.5cm), and pharmacologic therapy.[30] In the last few years there has been increasing interest in the use of amiodarone to treat AF. While there are no randomized trials of amiodarone in the treatment of AF, there are several trials suggesting that maintenance of sinus rhythm (50-70% at 20 months) is improved more with amiodarone than with other antiarrhythmics.[9,31,32]

Instead of using a single agent over time, a common strategy for treating the patient with persistent AF may include serial cardioversion and antiarrhythmic therapy. Van Gelder and colleagues have used this approach to maintain patients in sinus rhythm (27% at four years).[33] These results show that even though initial antiarrhythmic therapy may be effective for maintaining sinus rhythm, the arrhythmia is likely to recur over time. Ongoing clinical trials which randomize sotalol versus amiodarone, such as AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) as well as a current VA trial, may better define the role of antiarrhythmic therapy in the management of AF. AFFIRM is addressing an even more fundamental question: should the clinical objective of therapy be a strategy for rate control of AF or maintenance of sinus rhythm with antiarrhythmic agents and cardioversion. It is important to note that both approaches are based on a chronic anticoagulation regimen.

Nonpharmacologic therapies

Mechanical interventions may offer an alternative to pharmacologic therapies for patients with AF (Table 3). These mechanical interventions include percutaneous procedures such as radiofrequency ablation of foci of AF near the pulmonary veins or in the right atrium, atrial cardioverters, radiofrequency modification of the atrioventricular node, and surgical disruption of the atrial circuitry needed for maintenance of AF (MAZE Procedure).[34-36] Enthusiasm for the early descriptions of ablation of AF foci near the pulmonary veins have been tempered by reports of pulmonary venous obstruction that have developed as a complication of this procedure.[37] Mechanical procedures offer promise in the treatment of AF, but data on safety, as well as long-term efficacy are still unknown.

Table 3. Interventional treatments of AF

Percutaneous interventions	Surgical interventions
• Radiofrequency modification/ablation of the AV node	• MAZE procedure
• Radiofrequency ablation of AF foci near the ostia of the pulmonary veins	• Corridor procedure
• Radiofrequency ablation of AF foci in the right atrium	• Open radiofrequency ablation
• Atrioverter	

An integrated approach to patient management

The integrated approach to patient management encompasses everything from the determination of etiology of AF to the pharmacologic management of this disorder. In addition to the physical examination, most patients who present with AF should have an assessment for metabolic disorders (electrolyte disorders, thyroid dysfunction) as well as structural heart disease (echocardiogram, possible exercise testing) which may be responsible for precipitating the disorder and may influence therapy.

Long-term management of the patient should involve a determination of the patient's candidacy and requirement for anticoagulation (see Table 2). In general, patients with AF for >48 hours should not undergo cardioversion without appropriate anticoagulation or a transesophageal echocardiogram documenting a low risk of embolic events. Patients with AF for less than this period generally have a lower risk of embolization from acute cardioversion with the exception of those patients with rheumatic disease and prosthetic heart valves.

After considering the need for anticoagulants or antiplatelet therapy, the clinician should determine the indication for therapy: termination of acute AF, prevention of paroxysms of AF, or restoration and maintenance of AF. In acute AF, the physician should first address rate control of AF using beta-blockers, digoxin, or calcium channel blockers. Antiarrhythmic therapy for acute conversion may be indicated to decrease the duration of time in the arrhythmia for some patients.

The decision to institute therapy to prevent paroxysms of AF will depend on the frequency and severity of symptoms. Chronic prophylactic therapy may vary from beta-adrenergic blocking agents to antiarrhythmic agents ranging from Type IA agents to amiodarone. Some patients may be better suited for cocktail therapy, ie, taking a beta-blocker at the time of development of a paroxysm.

Pending the results of the AFFIRM trial, therapy for restoration and maintenance of sinus rhythm should be attempted in those patients with significant symptoms associated with AF. Invasive therapies for AF are currently usually reserved for patients with difficult rate control issues or those with problems from frequent arrhythmia recurrences.

Conclusions

Atrial fibrillation is an increasingly common arrhythmia in the elderly for whom only some risk factors are recognized. Future research should focus on identifying other risk factors and on preventing and treating the dysrhythmia. Transthoracic and transesophageal echocardiography may provide insight into the risk of AF for a given patient and may guide medical therapy in selected patients.

Current pharmacologic therapy is aimed at decreasing symptoms and embolic risk. Mechanical therapies such as ablation or AV nodal modification may lead to an improvement in functional capacity, but long-term safety and efficacy issues have yet to be resolved. Future trials of pharmacologic as well as mechanical interventions should focus on efficacy as well as safety.

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