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Who Needs Pharmacologic Therapy?

Christopher P. Porterfield, MD MPH and Rohit Malhotra, MD

Department of Internal Medicine, Division of Cardiology, University of Virginia Health Center, Charlottesville, VA 22908.

Abstract

Treatment of atrial fibrillation has evolved significantly in the last ten years, with ablation becoming a far more common form of treatment for this most common type of arrhythmias. However, while ablation has become more common, certain populations derive continued benefit from the use of pharmacologic therapy for treatment. We review the use of pharmacologic therapy and novel considerations for treatment of atrial fibrillation.

Atrial Fibrillation Demographics And Prevalence

Atrial fibrillation (AF) continues to be the most common sustained cardiac arrhythmia.[1] In the Framingham Heart Study, 2326 men and 2866 women were followed for two years and the risk of developing permanent AF was 8.5% for men and 13.7% for women.[2] Paroxysmal AF was seen in 8.2% of men and 20.4% of women. In those without prior or concurrent congestive heart failure or myocardial infarction, the lifetime risks for atrial fibrillation were approximately 16%. In diastolic heart failure, approximately 25% to 30% of patients have evidence of atrial fibrillation.[2]

In the United Kingdom, an attempt at determining the general population prevalence was sought in the Echocardiographic Heart of England Screening (ECHOES) study where 3960 patients were randomly selected from the population.[3] These patients were 45 years of age and older and were followed for 8 years. The overall prevalence was 2% (1.6% in women and 2.4% in men). Over half of all cases were in patients aged 75 and older. The most common comorbid disease state was heart failure in which 22.4% of patients had atrial fibrillation. Mortality was 1.57 times higher for patients with atrial fibrillation.

With the prevalence of atrial fibrillation increasing in the elderly population, treatment strategies are often different than those chosen for younger patients. Consideration of antiarrhythmic drug adverse effects, drug interactions, bleeding risks and frailty score will determine available management strategies. Patients with hypertrophic cardiomyopathy (HCM), valvular heart disease and infiltrative cardiomyopathies often have a higher risk of developing atrial fibrillation and higher treatment failure rates.[3] Treatment options are frequently limited and these patients can be more challenging to treat. As the numbers of patients with atrial fibrillation increase worldwide, the number of available operators to perform ablation has not kept pace. As a result, medical therapy remains a cornerstone of treatment. While the Thermocool AF study did demonstrate greater efficacy of ablation in drug refractory patients after 9 months, Nielsen et al did not find ablation to be more effective over 2 years than medical therapy.[4-5] Finally, follow-up of post-ablative patients only extends to two years post treatment. Most of these trials do not have intensive monitoring with implanted recorders or long-term event monitoring, thus potentially underestimating the rate of recurrence.

Rate Vs. Rhythm Control

Often, the first question that must be addressed in patients with recurrent atrial fibrillation is whether a rate control or a rhythm control strategy is most appropriate. Factors that should be considered include the temporal pattern (paroxysmal versus persistent) of the arrhythmia, the frequency of episodes, the severity of symptoms, patient factors and the probabilities for maintaining sinus rhythm or effectively controlling ventricular rates.

Although a rhythm control strategy would seem intuitively to be superior to a rate control strategy, a series of randomized trials have been unable to demonstrate this with pharmacologically based therapies. The two most relevant trials for heart failure patients were the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) and the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Trial.[6-7] AFFIRM randomized 4060 patients, 23% of whom had heart failure, between rate control and rhythm control strategies. No difference was seen in total mortality or stroke between the two strategies with a slight trend favoring rate control. Patients in whom sinus rhythm was maintained during the study had improved outcomes but this likely represents a "healthy

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Corresponding Author:
Rohit Malhotra, MD,
Assistant Professor,
Department of Internal Medicine, Cardiology Division,
Heart Rhythm Center,
University of Virginia Health Sciences Center,
PO Box 800158.

responder" phenomenon. A second trial, AF-CHF, compared rate control and rhythm control strategies in patients and was required to have heart failure and depressed left ventricular systolic function. There was no significant difference between the two strategies within the three primary endpoints: mortality, stroke, and heart failure hospitalizations. In addition, even when patients were grouped into those with high and low prevalence of sinus rhythm during the course of the study, no benefit on these outcomes could be demonstrated. However, it must be remembered that entry into all of the rate control versus rhythm control strategy trials required that patients be candidates for both approaches. Highly symptomatic patients therefore were unlikely to be randomized. Therefore, most clinicians would recommend that patients with persistent symptoms related to their atrial fibrillation should have at least an initial attempt to restore and maintain sinus rhythm with rate control as a fall back approach if rhythm control is unsuccessful or poorly tolerated.

The optimal range for ventricular rates during atrial fibrillation is still controversial. In AF-CHF the heart rate goals were < 80 bpm at rest and <110 bpm during a 6-minute walk test. Similar heart rate targets were used in AFFIRM. In RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation), a trial specifically designed to assess strict and lenient rate control, however, no adverse effects were seen with a more lenient heart rate target.[8]

Ablation

Patients with symptomatic atrial fibrillation who have failed antiarrhythmic therapy should be considered for atrial fibrillation ablation. The 2014 guidelines for management of Atrial Fibrillation also now include ablation as a first line therapy.[9] This may necessitate ablation of left atrial tachycardia that may arise post ablation. Furthermore, the basic technique of pulmonary vein antral isolation alone is rarely successful in patients with long-standing atrial fibrillation due to left atrial enlargement, chronic left atrial hypertension and diffuse atrial scarring. Additional linear lesions, both left and right atrial, and lesions targeting atrial electrograms that are fractionated are often placed with a modest increase in efficacy.[10] Nevertheless, even though only intermediate success rate should be anticipated, catheter or surgical ablation may be a useful option in selected patients. Catheter ablation should probably be attempted before AV junctional ablation in younger patients without AV block since the latter procedure is irreversible and creates a situation of life-long pacemaker dependency. However, the ablate and pace trial JICE trial does demonstrate good outcomes with this strategy.[11]

Patients undergoing atrial fibrillation ablation remain at risk for thromboembolic event and require anticoagulation. Current guidelines recommend continuing anticoagulation based on risk assessment utilizing the CHA_2DS_2VASc score.[9] It is also not uncommon for patients to remain on their antiarrhythmic therapy post ablation for at least a short period of time. Patients should not undergo catheter ablation solely to eliminate the need to take anticoagulants.

Pharmacologic Therapy

Beta-blockers are typically the first-line therapy for rate control in patients with AF. In addition to controlling rates in AF, several beta-blockers have been shown to reduce mortality in heart failure and post-myocardial infarction patients in general. Non-dihydropyridine calcium channel blockers, verapamil and diltiazem, may be used in patients with heart failure and preserved systolic function, but their negative inotropic actions make them contraindicated in patients with a depressed ejection fraction. Digoxin remains a potentially useful adjunct to beta-blockers' for rate control but must be used with caution due to its narrow therapeutic range and its use should be avoided in patients with advanced renal dysfunction.[12]

Additional medications are available to patients without structural heart disease. Outcomes with use of flecainide over two years[13] and propafenone for 6 months[14] and propafenone verus sotalol at 1 year,15 demonstrate high rates of maintenance of normal sinus rhythm (66%, 66%, 63%/73%). In patients with CAD (Coronary Artery Disease), sotalol has been demonstrated to be effective in 40% maintaining sinus rhythm in patients with persistent atrial fibrillation for one year.[16] Dronedarone can be effective for maintenance of sinus rhythm in patients with CAD and normal EF (Ejection Fraction). Dronedarone, however, is contraindicated in heart failure patients based on the data from the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease) and PALLAS (Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy) trials, both of which showed increased mortality with dronedarone therapy in patients with heart failure.[17-18] Dofetilide and amiodarone are highly effective for patients with atrial fibrillation and reduced ejection fraction. Dofetilide can be cumbersome for patients due to the need for inpatient drug loading. However, even in patients with persistent atrial fibrillation, dofetilide can maintain normal sinus rhythm for long periods of time.[19] While amiodarone is the most effective medication for maintenance of sinus rhythm, due to its associated toxicities, it is often reserved for older patients with other co-morbidities.

For patients with permanent AF in whom rate cannot be controlled and for those with drug refractory highly symptomatic recurrent episodes, AV junctional ablation can be an effective strategy. The potentially deleterious effects of RV apical pacing must be considered. In some patients, poor rate control alone may be responsible for the low ejection fraction, and these patients may be managed with just RV pacing. If LV function is depressed even when the patient is in sinus rhythm, biventricular pacing for cardiac resynchronization will be the method of choice.

Anticoagulation In Atrial Fibrillation

Non-rheumatic atrial fibrillation has been associated with a five-fold increase in the risk of ischemic stroke. It has been estimated that 15% of all ischemic strokes occur in patients with atrial fibrillation. Patients with stroke and atrial fibrillation are at higher risk for recurrent stroke and more severe stroke leading to greater disability and loss of independence. Stroke in patients with AF are 1.5-3.0 times more likely to be fatal than those in patients in sinus rhythm. Balanced against the increased risk for stoke and systemic embolism in patients with AF is the risk of bleeding associated with long-term anticoagulant therapy. For each patient, these risks must be carefully weighed to achieve optimal outcomes.

Several scoring systems for stroke risk in patients with AF have been proposed. Although all the proposals have limitations, they remain clinically useful. In North America and Europe, the $CHADS_2$ and CHA_2DS_2-VASc schemes being most commonly employed. Heart failure is a risk factor in both these scoring systems so virtually all patients with heart failure and AF are candidates for chronic anticoagulation. In the absence of contraindications, oral

anticoagulation is recommended for patients with $CHADS_2$ or CHADSVASc scores of 2 or greater and should be considered for scores of 1. Bleeding risk is also a critical factor in decisions about long-term anticoagulation and scoring systems to predict risk have also been described (i.e. HASBLED).[20-21]

Warfarin has long-been the primary oral anticoagulant for patients with atrial fibrillation. In a series of randomized trials in patients with nonvalvular AF, warfarin was shown to decrease stroke rate by approximately 2/3rds. Similar effects were seen in patients with both paroxysmal and permanent AF. The target INR should be 2.0 to 3.0 with increased rates of stroke clearly seen below an INR of 1.7 and increased bleeding when INR values were over 4.0. Recently, new oral anticoagulants have been introduced. Dabigatran, a direct thrombin inhibitor, and 3 factor 10a inhibitors, rivaroxaban, apixaban, and endoxaban have been shown to be non-inferior to warfarin in large randomized clinical trials in non-valvular AF.

In the last several years, additional non-pharmacologic options for stroke prevention have been developed. The two currently available options in the United States, the LARIAT procedure, and the Atriclip, allow patients to avoid long-term use of oral anticoagulants. While the LARIAT device has been approved for use, there have not been extensive studies to demonstrate long-term efficacy. The Atriclip is approved for use at the time of sternotomy, and it is undergoing clinical trials to evaluate its safety and efficacy as an isolated thoracoscopic procedure. The Watchman device, which has undergone the most extensive clinical trials, is undergoing FDA evaluation. Other similar devices are in development.[22] These devices may raise another question for patients with atrial fibrillation: What form of stroke risk reduction will they choose to pursue: medical or structural?

Currently there is not a complete single reversal agent for bleeding in patients on factor Xa inhibitors or direct thrombin inhibitors. Fresh frozen plasma (FFP), prothrombin complex concentrate has been proposed to help temporarily manage patients with acute bleeding. Recently, andexanet, a lyophilized reversal agent for factor Xa inhibitors, was granted breakthrough therapy status by the FDA. It is, however, not an antidote for dabagitran, which is a direct thrombin inhibitor. Another drug, aripazine (PER-977) was developed as a non-specific reversal agent for Factor Xa inhibitors, dabigatran, unfractionated heparin, and low molecular weight heparin. This agent has just completed Phase 1 clinical trials.[23]

Discussion

Atrial fibrillation may adversely influence prognosis both by increasing the risk of thromboembolic events and by aggravating or directly causing heart failure or ischemia. Pro-arrhythmic responses to drug therapy or bleeding from anticoagulants may also contribute to an increase in mortality in patients who have atrial fibrillation. In the Framingham study, atrial fibrillation was associated with an OR for death of 1.5 (95% CI 1.2–1.8) among men and 1.9 (95% CI 1.5–2.2) among women after adjustment for multiple clinical parameters. The greatest absolute impact of atrial fibrillation on prognosis is seen when it occurs in patients who have advanced heart disease or other comorbid diseases. In patients who do not have significant heart disease, atrial fibrillation has lesser effects on survival.[24] As strategies for appropriate anticoagulation, effective rate control and heart failure management continue to evolve; it may be that the magnitude of the independent effect of atrial fibrillation will be lessened in the future. Atrial fibrillation is the most common sustained arrhythmia in adult populations. Although atrial fibrillation itself is usually not life threatening, it leads to significant patient morbidity and economic costs, and contributes to stroke and heart failure. Clinical decisions in patients who have atrial fibrillation are often difficult, and no uniformly effective therapies are available. In some patients, ventricular rate control and anticoagulation may be preferable to aggressive attempts to maintain sinus rhythm with repeat cardioversions and antiarrhythmic drug therapy.

Conclusions:

The new 2014 AHA/ACC/HRS guidelines for treatment of atrial fibrillation made several important changes to how patients are managed. One change was the shift from $CHADS_2$ to CHADSVASc score for risk stratification of anticoagulation in patients with atrial fibrillation. Another shift was in the decreased emphasis of aspirin in patient's with atrial fibrillation in reduction of stroke. As previously mentioned, catheter ablation was increased to a Class 1 recommendation for first line therapy in patients with symptomatic atrial fibrillation.[9]

Newer strategies, such as less toxic antiarrhythmic agents, catheter ablation, improved surgical approaches and new oral anticoagulants, offer promise for the future, but their efficacy and optimal uses still need to be demonstrated.

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