REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will manage newly diagnosed atrial fibrillation appropriately

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Managing newly diagnosed atrial fibrillation: Rate, rhythm, and risk

ABSTRACT

The treatment of atrial fibrillation focuses on controlling the heart rate, preventing thromboembolic events, and, depending on the symptoms, restoring and maintaining sinus rhythm. In most cases, the rate or rhythm can be quickly controlled, and a long-term plan can be started that will minimize the impact of this disorder on the life of the patient.

KEY POINTS

When atrial fibrillation is newly diagnosed, reversible causes and commonly associated processes should be sought.

Agents to control the heart rate, eg, beta-blockers or nondihydropyridine calcium channel blockers, are often started and titrated intravenously and then changed to oral dosing.

The benefit of rhythm control has not been firmly established. Although we try cardioversion at least once when atrial fibrillation is first diagnosed, rhythm control is generally reserved for patients whose symptoms persist despite rate control, or for patients in whom the heart rate cannot be controlled.

The need for short-term or long-term anticoagulation must be estimated.

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THREE GENERAL CONCERNS dictate the management of atrial fibrillation:

- Controlling the heart rate
- Controlling symptoms
- Preventing thromboembolic events, including stroke.

When seeing a patient with newly diagnosed atrial fibrillation, these same three concerns should be kept in mind, but several additional issues must be addressed:

- Reversible causes of atrial fibrillation must be ruled out
- The true time of onset of the atrial fibrillation and the frequency of the episodes should be ascertained, if possible
- A careful estimation of the patient's symptom burden should be made.

Atrial fibrillation is common and has a huge impact in terms of the morbidity, death, and costs associated with it. It affects more than 2.2 million Americans.[1] Approximately 1 in 10 people over the age of 80 has atrial fibrillation, and for those over the age of 40, the lifetime risk of developing it is one in four.[2] Framingham data suggest that the risk of death is approximately twice as high for patients with atrial fibrillation compared with a similar cohort without.[3–5]

IMPORTANT QUESTIONS DURING THE INITIAL WORKUP

Does the patient have a reversible cause of atrial fibrillation?

Atrial fibrillation is thought to be due to triggers that initiate it and to a myocardial sub-

strate that supports it. While it may develop in the absence of other heart disease, it is often associated with hypertension, diabetes, obesity, structural heart disease (including congenital heart disease), obstructive sleep apnea, advanced age, and alcohol abuse.

Therefore, once atrial fibrillation has been diagnosed, the history, examination, and diagnostic workup should be directed toward looking for potentially reversible causes and for frequently associated comorbidities. Common reversible causes include:

Hyperthyroidism. The laboratory evaluation should include a thyrotropin (thyroid-stimulating hormone, or TSH) level.

Alcohol use, especially binge drinking.

Obstructive sleep apnea, if suspected on the basis of the history or the body habitus.

Structural heart disease such as valvular heart disease or congenital heart defects may also predispose to atrial fibrillation. Therefore, listen carefully to the heart and obtain a transthoracic echocardiogram if one has not already been done or if you suspect a change in valvular disease or systolic function since the most recent study.

How long has the patient been in atrial fibrillation?

The duration of the atrial fibrillation often affects the treatment strategy. Therefore, when the diagnosis has been made, it is important to try to estimate how long the patient has been in atrial fibrillation.

Often, we must settle for an estimate, as the patient's recollection may be vague. However, in some cases, the symptoms are pronounced or electrocardiographic or telemetric data are available, allowing the time of onset to be clearly defined.

In addition, it is helpful to know if the patient has had prior episodes that were never brought to medical attention. To this end, elicit the patient's spectrum of symptoms and encourage him or her to think back months or years and try to recall other times when similar symptoms might have occurred.

How do the symptoms affect the patient's quality of life?

The clinician must also estimate the extent to which the symptoms affect the patient's quality of life. This is best done when the heart rate is under control. If the patient still has significant symptoms despite adequate rate control, then a rhythm control strategy should probably be pursued.

MANAGING NEWLY DIAGNOSED ATRIAL FIBRILLATION

Control the heart rate with a beta-blocker, a calcium channel blocker, or digoxin

Many patients present during their first episode of atrial fibrillation with a rapid ventricular rate, especially if they are not already taking a drug to slow conduction through the atrioventricular node. If the symptoms are particularly profound, one should try to get the heart rate under control quickly.

Oral agents take time to be absorbed and are not always easy to titrate. Intravenous beta-blockers such as metoprolol (Lopressor) and labetalol (Normodyne, Trandate) or intravenous diltiazem (Cardizem) can slow the heart rate quickly and can be titrated. Once the heart rate is controlled, the oral form can be started, to allow weaning from the intravenous agent. In acute management, we seek a heart rate of less than about 100 to 110 beats per minute.

We try to restore sinus rhythm at least once when atrial fibrillation is first found

If the patient's blood pressure is marginal, loading with intravenous digoxin may be considered. The dosage is 0.5 mg intravenously, then 0.25 mg intravenously in the first 6 hours and another 0.25 mg intravenously in another 6 hours. In patients with renal insufficiency the dosage should be less, or digoxin should be avoided altogether. Often, the blood pressure will improve once the heart rate is decreased, allowing other agents to be initiated. However, if the patient is frankly hypotensive with chest pain, shortness of breath, or a diminished level of consciousness, then emergency electrical cardioversion is indicated even if anticoagulation has not yet been started (more about anticoagulation below).

Oral forms of these same agents are the workhorses for heart rate control in the outpatient setting. Oral beta-blockers and nondihydropyridine calcium channel blockers (ie, diltiazem or verapamil [Calan, Verelan]) are the first-line agents, because when digoxin is used alone, it is relatively poor at controlling the heart rate,

especially when the patient is not at rest.

The choice between these agents should be dictated by whether the patient has comorbidities such as coronary artery disease, heart failure, or reactive airway disease. Nondihydropyridine calcium channel blockers are relatively contraindicated in patients with heart failure, while beta-blockers can exacerbate reactive airway disease.[6]

It is also important to document that the heart rate is adequately controlled outside the hospital or outpatient clinic, where the patient is typically sitting or supine. This can be done with a 6-minute walk, exercise test, or Holter monitor once rate-controlling agents have been titrated.[7]

When to try to restore sinus rhythm

When atrial fibrillation is first diagnosed, it may not be possible to determine if it is paroxysmal (ie, self-terminating) or persistent. If the episode does not quickly end on its own, consideration may be given to restoring sinus rhythm.

Although experts debate the merits of a rate control approach vs a rhythm control approach for managing atrial fibrillation in the long term, many, including ourselves, recommend trying to restore sinus rhythm at least once when atrial fibrillation is first discovered. It is not always clear if atrial fibrillation is truly asymptomatic. Symptoms such as fatigue or decreased exercise tolerance can be subtle. Additionally, these symptoms may be attributed to other factors such as deconditioning, obesity, or advancing age. Thus, in many cases, only restoring normal sinus rhythm for a time allows the patient and clinician to fully assess the symptoms attributable to atrial fibrillation.

If atrial fibrillation has lasted > 48 hours or if you are not sure, anticoagulate before cardioversion

Therefore, in patients with newly diagnosed atrial fibrillation, an attempt to restore sinus rhythm is often warranted. Exceptions are in select patients who have no apparent symptoms and who are very old or are deemed too frail to tolerate cardioversion.

Direct-current cardioversion is typically the treatment of choice when attempting to restore sinus rhythm. The procedure can be done without anticoagulation within 48 hours of the onset of atrial fibrillation, if the time of onset is clear.[7] However, clinicians must be careful in defining the onset of atrial fibrillation for this purpose.

Symptoms such as fatigue or shortness of breath can be vague in terms of the exact time of onset and often cannot be relied upon for the purpose of deciding whether cardioversion can be done without anticoagulation. When in doubt, it is best to err on the side of safety and assume that the atrial fibrillation has been going on for more than 48 hours.

If the time of onset is unclear or if more than 48 hours have passed, there are two general strategies for proceeding to electrical cardioversion.

One is to **order transesophageal echocardiography** and begin anticoagulation therapy at the same time. If there is no thrombus in the left atrium, then cardioversion can be done.[8] Therapeutic anticoagulation with heparin, low-molecular-weight heparin, or warfarin (Coumadin) should be achieved within 24 to 48 hours of transesophageal echocardiography and cardioversion to minimize the risk of thromboembolic events, which can occur even after sinus rhythm has been restored.

At our institution, we typically strive to achieve therapeutic anticoagulation with either heparin or low-molecular-weight heparin before cardioversion in this scenario so as to avoid situations in which a patient may undergo cardioversion but then fail to achieve therapeutic anticoagulation for some time due to unforeseen factors.

The other approach is to **start warfarin** and maintain a goal international normalized ratio (INR) of 2 to 3 for 3 weeks, at which time cardioversion can be performed safely without transesophageal echocardiography.[8]

Regardless of which strategy is used, anticoagulation should be continued for at least 4 weeks after cardioversion,[8] as atrial dysfunction and the risk of stroke may persist for days to weeks after normal sinus rhythm is restored.[9]

Role of antiarrhythmic drugs

Antiarrhythmic drugs can be used for chemical cardioversion or, more often, to help maintain sinus rhythm after direct-current cardioversion.

Because most of these drugs have at least a small chance of restoring normal sinus rhythm, we need to follow the same rules when starting them as when performing direct-current cardioversion. Patients should not be started

on an antiarrhythmic medication until they have had adequate anticoagulation for at least 3 weeks or adequate anticoagulation and a transesophageal echocardiogram confirming that there is no thrombus in the left atrium.

Antiarrhythmic drugs should be started in select patients with newly diagnosed atrial fibrillation in whom a rhythm control strategy will be pursued. For patients whose history suggests a single episode, or episodes that previously self-terminated, an antiarrhythmic may not be necessary. For those with frequent episodes or whose history suggests ongoing atrial fibrillation for a long period, an antiarrhythmic will likely be required to provide a reasonable chance of achieving freedom from atrial fibrillation.

The choice of antiarrhythmic drug should be tailored to the specific patient.

Propafenone (Rythmol) and **flecainide** (Tambocor) are first-line drugs[7] but are contraindicated in patients with coronary artery disease and significant structural heart disease.[10]

Sotalol (Betapace) and **dofetilide** (Tikosyn) can be used in patients with coronary artery disease. However, sotalol is contraindicated in patients with congestive heart failure, and dofetilide carries a long list of drug interactions. Both must be used with extreme caution in patients with renal insufficiency, and hospital admission is required for initiation or upward titration of the dose.

Amiodarone (Cordarone) is effective, and in the short term it is typically very well tolerated. However, it has a long half-life, and its potential for long-term toxicity often makes it a poor choice for long-term treatment. The toxicity of amiodarone increases with the cumulative dose. Therefore, this drug should be avoided for long-term therapy of atrial fibrillation in younger patients.

The 'pill-in-the-pocket' strategy

The "pill-in-the-pocket" strategy, in which patients are instructed to take their medication only when they have a bout of atrial fibrillation, is a reasonable option for patients with symptomatic recurrences of paroxysmal atrial fibrillation. This strategy is mainly reserved for patients who have relatively infrequent recurrences. Those who have frequent recurrences are usually more effectively treated with daily dosing of an antiarrhythmic. Flecainide and propafenone are the agents of choice for this approach because of their safety profile and efficacy in chemical cardioversion.

While this strategy may be started on an outpatient basis in patients with lone, paroxysmal atrial fibrillation, those with structural heart disease or conduction abnormalities should be observed in the hospital during initiation of therapy to observe for excessive PR prolongation or development of dangerous or worrisome arrhythmias.[11–13]

Additionally, these agents can decrease the refractory period of the atrioventricular node, thereby increasing the ventricular rate. In the case of atrial flutter, patients may be converted from variable or 2:1 response to a 1:1 conduction. Thus, one should consider also using a beta-blocker with this strategy.

Since the goal of this approach is to convert the patient to sinus rhythm within a few hours of the onset of atrial fibrillation, it may be implemented without the use of warfarin. Patients are instructed that if they do not convert to normal sinus rhythm within a few hours, they should notify the physician so they can undergo electrical cardioversion within the 48-hour window from the onset of atrial fibrillation.

Continue anticoagulation for at least 4 weeks after cardioversion

Dronedarone, a new antiarrhythmic drug

Dronedarone (Multaq) is now available and has been shown to be effective in treating atrial fibrillation.[14] It has a long half-life and a mechanism of action similar to that of amiodarone. However, it may be inferior to amiodarone in terms of efficacy.[15] It is metabolized by CYP3A4. No dosage adjustment is needed for patients with renal insufficiency.

Because dronedarone lacks the iodine moiety found in amiodarone, it should not carry the same toxicity profile. No pulmonary or thyroid toxicity was reported in early trials.[16]

Nevertheless, dronedarone has several important limitations. It carries a black box warning stating it is contraindicated in patients with severe or recently decompensated heart failure, as the mortality rate was twice as high when this drug was used in such patients in initial studies.[17] Additionally, there have been reports of hepatotoxicity requiring liver

transplantation in a small number of patients. The extent of this problem and strategies for avoiding it are not yet defined as of the writing of this paper. As with any new medication, patients who are started on dronedarone should be observed closely for any side effects, and these should be reported to assist in the development of the drug's safety profile.

Pulmonary vein isolation

In a procedure that can potentially cure atrial fibrillation, catheters are inserted into the left atrium and rings of scar tissue are created around the ostia of the pulmonary veins using radiofrequency energy, electrically isolating them from the rest of the left atrium.

Some debate exists as to whether this procedure may be reasonable as a first-line therapy for some patients with atrial fibrillation.[18,19] It may be considered as an early treatment strategy in a small subset of patients, specifically young patients with symptomatic, recurrent atrial fibrillation, especially if they are averse to long-term antiarrhythmic therapy.

Because patients may still be more prone to atrial arrhythmias for several weeks to months after the procedure, they must be able to tolerate anticoagulation with warfarin for at least several months.

With a $CHADS_2$ score of 1, the risk of stroke off warfarin equals the risk of bleeding on warfarin

Rate control vs rhythm control

The choice between a rate control strategy or a rhythm control strategy in the long term is not always straightforward. While atrial fibrillation is clearly associated with higher morbidity and mortality rates, there are few data to date showing that restoring and maintaining sinus rhythm in patients with atrial fibrillation reduce the incidence of morbid complications or the likelihood of death.

Thus, current guidelines recommend a rate control strategy in patients who have no symptoms, and a rhythm control strategy if rate control cannot be achieved or if symptoms persist despite adequate control of the heart rate.[7] The circumstances and preferences of the individual patient should carry weight in this decision.

Trials are under way that may shed more light on the relative benefits of rhythm control with ablation or antiarrhythmics and rate control.

PREVENTING THROMBOEMBOLIC EVENTS

Warfarin

In the short term, warfarin therapy may be dictated by plans to restore sinus rhythm. Patients need warfarin for at least 4 weeks after cardioversion unless it is performed within 48 hours of the onset of atrial fibrillation.

The $CHADS_2$ score (1 point each for ***c***ongestive heart failure, ***h***ypertension, ***a***ge 75 or older, and ***d***iabetes mellitus; 2 points for prior ***s***troke or transient ischemic attack) is useful when deciding whether to give long-term anticoagulation.

For patients with a score of 0, the risk of stroke is lower than the risk of a major bleeding complication while on therapeutic warfarin.[20,21] For these patients, aspirin 81 to 325 mg daily is recommended for stroke prophylaxis.

For those with a score of 2 or greater, the risk of stroke without warfarin is greater than the risk of a major bleeding complication with warfarin. These patients should receive warfarin with a goal INR of 2.0 to 3.0.[7]

Patients with a $CHADS_2$ score of 1 present a dilemma, as their risk of stroke without warfarin is about the same as their risk of a major bleeding complication with warfarin. They can be managed with either warfarin or aspirin, according to the physician's judgment.[7] In these cases, factors such as hobbies or professions that might increase the risk of bleeding, perceived frequency of atrial fibrillation episodes, and even patient preconceptions about warfarin are often used when deciding between aspirin and warfarin.

Patients with a $CHADS_2$ score of 2 or greater with a single episode of atrial fibrillation and a likely reversible cause may also pose a dilemma when deciding whether to start warfarin. These patients have demonstrated they at least have the substrate to maintain atrial fibrillation. This situation again calls for physician judgment. Bear in mind that asymptomatic recurrences are common in patients with atrial fibrillation.[22,23] A higher $CHADS_2$ score denotes a greater risk of stroke and may influence this decision. It is usually beneficial to enlist the patient in this decision-making process, as patients often have very strong opinions about tolerance of the risk of stroke or of warfarin therapy itself.

Another strategy is to start anticoagulation with warfarin and aggressively monitor for recurrences. If the patient has no recurrences of atrial fibrillation after 6 to 12 months and the reversible cause is resolved, one can then revisit the need for warfarin.

Role of aspirin and clopidogrel

Aspirin, alone or in conjunction with clopidogrel (Plavix), may provide an alternative for stroke prophylaxis in patients in whom warfarin is contraindicated. While inferior to warfarin, the combination of aspirin and clopidogrel has been shown to decrease the incidence of major thromboembolic events, especially stroke.[24] However, the risk of a major bleeding complication was also significantly increased.

This combination may be a reasonable strategy in select patients with a $CHADS_2$ score of 2 or greater in whom warfarin cannot be used for reasons such as personal aversion to the medication, side effects, or nonbleeding complications or in patients whose INR is exceedingly difficult to keep within the therapeutic range.

Dabigatran, a new anticoagulant

The newest option for anticoagulation in patients with atrial fibrillation is a direct thrombin inhibitor, dabigatran (Pradaxa).

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[25] dabigatran was studied head-to-head with warfarin. The doses of dabigatran studied were 110 mg and 150 mg twice a day. At 150 mg twice a day, patients on dabigatran had a lower rate of stroke than with warfarin (1.11% vs 1.69%, $P < .001$), as well as a lower rate of central nervous system bleeding (0.10% vs 0.38% with warfarin, $P < .001$). The rates of major bleeding were comparable in the patients receiving warfarin or dabigatran 150 mg twice a day, but the rate of gastrointestinal bleeding was higher in the dabigatran group (1.51% vs 1.02% with warfarin, $P < .001$).[25]

Dabigatran was recently approved by the US Food and Drug Administration for use in patients with atrial fibrillation. Doses of 150 mg and 75 mg are available.

Dabigatran is renally excreted, and the 150 mg twice-a-day dosing is intended for patients with a creatinine clearance greater than 30 mL/min. The 75-mg twice-a-day dosing is intended for patients with a creatinine clearance of 15 to 30 mL/min. However, it should be noted that currently there are no data to support the 75-mg twice-a-day dosing.

Dabigatran does have several advantages over warfarin. Patients do not need to avoid foods containing vitamin K, and routine serial monitoring does not appear to be needed. As with any new medication, patients who are started on dabigatran should be observed closely for any side effects, and these should be reported to assist in the development of the drug's safety profile.

SPECIAL CIRCUMSTANCES

After cardiac or noncardiac surgery

Atrial fibrillation is common after open heart surgery, occurring in approximately 25% to 50% of patients.[26–28]

When this happens, at least one or two attempts are made to restore sinus rhythm. Especially in the early postoperative period, anticoagulation with heparin or warfarin may be contraindicated, so careful attention must be paid to the patient's heart rhythm so that atrial fibrillation can be recognized quickly and cardioversion performed within a 48-hour window of onset. Beta-blockers, diltiazem, and verapamil are typically used for rate control.

Aspirin, with or without clopidogrel, may be an alternative if warfarin is contraindicated

When atrial fibrillation recurs in patients who have undergone open heart surgery, antiarrhythmics are started early to help prevent further recurrences. At our institution, we usually use amiodarone, as it is highly effective and well tolerated in the short term. When started on amiodarone for postoperative atrial fibrillation, patients are informed that the drug will be stopped after about 2 to 3 months. For patients who continue to have bouts of atrial fibrillation, the need for antiarrhythmic medications can be reassessed, and, if needed, the optimal antiarrhythmic medication for long-term therapy for the patient can be chosen.

Atrial fibrillation in severe, acute illness

Atrial fibrillation is common in the setting of extreme systemic stressors such as shock and sepsis and when the patient is being supported with inotropic agents. In this setting, patients

may be in a high-catecholamine state, and both the heart rate and the heart rhythm may be very difficult to control.

Beta-blockers and nondihydropyridine calcium channel blockers should not be used when patients are on medications to support blood pressure, and in this setting, when the patient's hemodynamic status permits the use of these agents, their effect may be minimal.

Amiodarone or perhaps digoxin may slow the heart rate somewhat without too much effect on the blood pressure. However, with amiodarone, one may have to accept a risk of chemical cardioversion.

Electrical cardioversion with or without the assistance of an antiarrhythmic drug may control the heart rate by restoring sinus rhythm. However, atrial fibrillation often recurs, and if it recurs quickly one may have to accept elevated heart rates until the underlying process is addressed.

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