Atrial fibrillation (AF) has become the most common cardiac arrhythmia, particularly in elderly persons. A Kaiser Permanente cross-sectional study of patients enrolled in its health maintenance organization (the ATRIA Study, 2001) estimated that approximately 2.3 million U.S. adults currently have AF. It predicted that this figure will continue to increase to more than 5.6 million in the next 20 years.

While very uncommon in patients under the age of 40, it is seen in as much as 10 to 15 percent of patients over the age of 80, which is a quite a lot. Men are at greater risk than women. The most common conditions that underlie this arrhythmia include hypertension, obesity, obstructive sleep apnea, and alcohol excess. A significant portion of patients, particularly those under the age of 50, likely have a genetically based predisposition.

Atrial fibrillation is classified into four categories. First diagnosed or new onset: only one diagnosed episode; paroxysmal: recurrent episodes that stop on their own and usually within no more than seven days; persistent: recurrent episodes lasting more than seven days and usually requiring cardioversion to restore sinus rhythm; permanent: continuous atrial fibrillation wherein a decision has been made to not restore sinus rhythm.

Figure 1. Natural Time Course of AF

From an etiological standpoint, the arrhythmia can also be classified according to coexisting structural heart disease or conditions. “Lone” atrial fibrillation implies an absence of any structural heart disease and is seen in younger populations. Nonvalvular atrial fibrillation exists in the absence of significant valve disease and includes such disorders as hypertension or coronary artery disease. The “valvular” reference emphasizes the importance of rheumatic mitral valve disorders, prosthetic heart valves, or mitral valve repairs, wherein a specific form of anticoagulation (warfarin) is necessary for the prevention of stroke. Secondary atrial fibrillation occurs in the setting of a primary diagnosis such as hyperthyroidism, pericarditis, pulmonary embolism, cardiac surgery, pneumonia, or other infections, and may be reversible.

The majority of patients who develop AF exhibit a reasonably predictable progression from a paroxysmal to
permanent behavior over time. Patients with “lone” atrial fibrillation tend not to progress as much, likely because of their younger age and absence of coexisting structural heart disease, which tends to promote a more persistent behavior. Atrial fibrillation not only causes disabling symptoms such as palpitation, dyspnea, and activity intolerance; it can contribute to the eventual development of heart failure among patients with existing heart disease, particularly when the heart rate is uncontrolled. The second major consequence, embolic stroke, accounts for roughly 30 percent of all stroke cases. In one particular group of patients, those with asymptomatic atrial fibrillation, the risk of developing a “tachycardia-mediated” cardiomyopathy is significant. Luckily, the impairment in ventricular function is reversible once sinus rhythm is restored and maintained. This is also the subgroup of patients at even higher risk of stroke simply because they have no symptoms and never make it to the doctor’s office for a diagnosis.

**Number of Concomitant Conditions**

The actual risk of stroke is not just due to the presence of fibrillation. More importantly, it relates to the number of coexisting morbidities, which promote cardiac impairment, inflammation, and a more hypercoagulable state when in the company of fibrillating atria. The above graph emphasizes that as one progresses from paroxysmal to permanent, there is a greater proportion of patients having more coexisting morbidities. Or stated another way: as you own more risk factors, you are more likely to belong to the permanent group. The greater the number of these conditions in an individual, the greater the stroke risk. Hence, a system to establish the best advice to prevent stroke is based on a scoring system known as the CHADS\textsubscript{2}VASC score (Figure 3), not on whether you are still experiencing atrial fibrillation.

**CHADS\textsubscript{2}VASC Score**

Added up, a score of 0 or 1 can be safely managed with aspirin regardless of the atrial fibrillation behavior (paroxysmal, persistent or even its duration at any time). A score of \(2\) prompts the recommendation for oral anti-coagulation (OAC) with either a novel anticoagulant such as dabigatran, rivaroxaban, apixaban, endoxaban, or with warfarin. Until our guidelines change, even if you think you have permanently eliminated the atrial fibrillation, OAC will be a lifelong requirement. Atrial fibrillation’s biggest morbidity is stroke, so there is no doubt that the most significant impact we have made in treating patients with AF is the ability to prevent stroke. Since the left atrial appendage is the source of the clots that embolize and cause stroke, an occluding device has been developed for use in patients who are unable to take OAC drugs.

Management strategies are generally divided into rate control and rhythm control categories. Rhythm control refers to restoring and maintaining sinus rhythm using antiarrhythmic drug therapy or catheter ablation. The antiarrhythmic drugs to which I am referring are “membrane stabilizing” drugs whose purpose is to prevent AF. Class I and III antiarrhythmic drugs are included in this category.

Rate control implies that the atrial fibrillation is left alone, but the ventricular response is kept within a normal heart rate operating range (50–80 bpm). This is achieved with medications that depress AV nodal conduction such as class II (beta blockers) and IV (calcium channel blockers) antiarrhythmic drugs. These drugs are not intended to prevent AF. The definitive endgame involves ablation of the AV node coupled with placement of a permanent pacemaker. The AFFIRM trial showed no significant differences in all-cause deaths when comparing rhythm to rate control. Because this was somewhat counterintuitive, a more detailed analysis disclosed that the anticipated beneficial effect on survival by maintaining sinus rhythm was offset by the adverse effects of the antiarrhythmic drugs used to maintain sinus rhythm. This is just one of many examples in which our treatment can be worse than the disease.

The recent randomized trial known as CABANA (Catheter Ablation versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation) intended to clarify this. It examined mortality outcome comparing ablation versus drugs in maintaining sinus rhythm. The trial showed only a trend toward improved mortality with catheter ablation. The
difference was not statistically significant. It’s complicated. After a thorough reanalysis looking at the data as “per protocol” instead of the original “intention to treat” approach (which is what makes it a randomized trial), an ablation approach won out. The biggest criticism of the trial was that the reanalysis violated the rules of the game. Milton Packer (not related to Doug Packer, the primary investigator) aptly stated, “Why would you design a randomized trial if you are going to analyze it in a way that is inconsistent with randomization?”

Most electrophysiologists would agree that restoring and maintaining sinus rhythm is preferred to rate control, particularly in the younger patient, because it is easier to halt the arrhythmia progression by intervening earlier, at a time when the substrate is more likely to respond.

Pathophysiology

As is the case with nearly all sustained tachycardias, there is a requirement of a trigger to initiate the arrhythmia and a substrate to sustain it. Substrate refers to some structural feature of the involved cardiac tissue.

Pulmonary Vein Sleeve

Triggers appear in the form of premature atrial complexes or nonsustained atrial tachycardias. Their origins are predominantly from within the muscular sleeves that wrap around the base of each of the four pulmonary veins and provide an anatomic transition from cardiac (atrial) to vascular tissue. The basis for the arrhythmogenic behavior of the pulmonary vein sleeves relates to their cells’ ability to develop abnormal pacemaker behavior—a mechanism referred to as “triggered” activity. Triggered activity stems from one’s genetic make-up, but is also made worse by the volume or pressure overload conditions that accompany the various types of heart disease: cellular “stretch” is arrhythmogenic. Triggers also reside within the left atrial posterior wall.

The substrate is primarily a reference to the structural features that exist within the left atrial muscle tissue and, in my view, extend to the entirety of the left atrial posterior wall. Here, complex myocardial tissue architecture, fibrosis, and abnormal neural activity promote the conditions that facilitate perpetuation of fibrillation once initiated by the triggers.

Management Issues

The primary intent of this article is to provide better insight into the issues we commonly face in the management of atrial fibrillation. Three clinical circumstances are discussed: new onset atrial fibrillation, managing atrial fibrillation in the emergency room, and dealing with the asymptomatic patient. Additional commentary includes anticoagulation choices, selecting the proper antiarrhythmic drug, and some insights into ablation of atrial fibrillation.

The following four questions pertain to all clinical circumstances and should be taken into consideration when formulating an initial treatment strategy:

1. How long has the patient been in AF?
2. Is the patient currently adequately anticoagulated?
3. Is the patient really asymptomatic?
4. Are you going to use a membrane stabilizing antiarrhythmic drug (class I or II) or an AV nodal blocking drug (class II or IV)? They aren’t the same thing.

New Onset or First Diagnosed Atrial Fibrillation

When a patient appears in your examining room and is found to be in atrial fibrillation for the first time, it’s probably not the first instance—especially if he/she is unaware of it. Because the fundamental approach to managing AF is to prevent stroke and eliminate symptoms, step one begins with the appropriate antithrombotic agent based on the patient’s CHADS2-VASC score. That’s the easy button.

Typical symptoms of atrial fibrillation include palpitation, racing heart, resting or exertional shortness of breath (elevated LV filling pressure), and activity intolerance (reduced cardiac output). Chest discomfort can occur. Syncope is rare. I would recommend a short-term event monitor (at least one-week duration) to establish if there is a more persistent behavior that implies the likely need for cardioversion. If heart rate average exceeds 100 bpm, I would also initiate a beta blocker or calcium channel blocker (verapamil or diltiazem) to bring the rate under control.

Cardioversion should be pursued if the AF is present 100 percent of the time on the event monitor, referred to as 100 percent burden. Because it is the patient’s “first” episode, one has no idea when the next episode is likely to occur. Thus, there is no compelling reason to initiate antiarrhythmic drug therapy. The exception is if his/her average rate was over 100 bpm, in which case temporary “rate control” with an AV nodal...
blocking episode would be just fine. If the next episode were not to occur for six months or more, placing the patient on drug therapy would be overindulgent. Imagine if you had one episode of AF per year. How long will it take to convince yourself the drug is working? The answer is two years without an episode. In general, I would want to give most or all patients the benefit of the doubt and embark on a rhythm control strategy if recurrences are subsequently observed regardless of symptoms.

For those patients who will go on to have recurrent episodes of AF, their frequency will determine whether they should have maintenance therapy or the “cocktail” approach. Maintenance therapy implies daily dosing while the cocktail approach involves a single, large dose of a membrane-stabilizing drug taken within an hour of onset, and not to be repeated in a 24-hour period. It’s like taking 800 mg ibuprofen for a headache. This approach is limited to the drugs propafenone and flecainide. As a guide, episodes occurring more frequently than one per month should be managed with maintenance approach while those fewer than one every three months could be handled with the cocktail approach. Your patient can certainly contribute to the decision-making on this topic.

Additional initial evaluation will include their past medical history, and looking for treatable disorders known to cause AF such as hypertension, thyroid disorder, sleep apnea, and alcohol excess. An electrocardiogram and echocardiogram will provide you with a good baseline assessment of cardiac structure and function, and give additional insight into other issues that may need attention.

**AF in the Emergency Department**

Invariably, patients presenting to the emergency room with AF are significantly symptomatic. The ECG findings are: no identifiable P waves and an irregular ventricular response. Often, there is no visible atrial activity at all, and the baseline seems flat. This still qualifies as “no identifiable P waves.”

The worst-case scenario is a patient with hypotension, angina, or heart failure symptoms in conjunction with their AF. Ventricular rate response is usually rapid. Emergent cardioversion is most appropriate followed by temporary rhythm control until more information can be made available, and this includes their anticoagulation status.

The hypertensive patient with AF and rapid ventricular response is more readily approachable since drugs controlling rate generally also lower blood pressure. This patient and the one who is normotensive are not urgent concerns and don’t generally mandate DC cardioversion. Rather, the first consideration in these patients is the duration of the atrial fibrillation, as you should avoid restoring sinus rhythm if it has been ongoing for more than 48 hours and appropriate antithrombotic therapy has not been in place for at least three to four weeks.

Note that if warfarin is the patient’s anticoagulant, that three-to-four week period doesn’t begin until the day the patient has a therapeutic INR. Subsequent therapeutic INRs should be documented for the entire three-to-four week period. This is information you probably don’t have access to on a Sunday afternoon. If anticoagulation is inadequate or you don’t know, a rate control strategy should be initiated until three to four weeks of anticoagulation is completed. In cases involving adequate anticoagulation, intravenous ibutilide is a very good option to restore sinus rhythm enabling the patient to be discharged home in sinus rhythm. Caveats regarding ibutilide are found below.

For the patient who has not been anticoagulated, if the CHADS2-VASC score is low (0 - 2) and they have been in AF <48 hours, it’s reasonable to restore sinus rhythm pharmacologically or by DC cardioversion. For scores ≥2, they may be better served with temporary rate control, initiation of appropriate antithrombotic therapy, and plans to restore NSR after three to four weeks. The fast-track alternative, especially for the symptomatic patient, is to perform a transesophageal echocardiogram to verify absence of left atrial appendage thrombus and then promptly proceed with DC cardioversion, with or without antiarrhythmic therapy. Follow up with an electrophysiologist should be arranged within the week.

The Asymptomatic Patient

The asymptomatic patient presents a problem for two reasons. One is because the duration of the arrhythmia is unknown. If the patient has not been adequately anticoagulated, sinus rhythm should not be restored until it is complete. If the patient is pondering whether he/she has symptoms in order to establish when the arrhythmia started, you must assume the duration is unknown.

The second reason is because there may be a tendency to assume sinus rhythm needn’t be restored—because, after all, there are no symptoms to eliminate. Most often, the mistake made here is that the patient actually does have symptoms but they are subtle. Not until sinus rhythm is restored, does the patient realize how good they really feel.

**Anticoagulation and the CHADS2-VASC Score**

Once AF is documented, a commitment to antithrombotic therapy needs to be made. It needs to be made clear to the patient that it is a lifelong commitment. Only patients who qualify (according to guidelines) should receive a left atrial appendage occlusion device, as there can be significant risk surrounding the procedure. Also, it needs to be made clear that OAC must be continued indefinitely even when we think we have eliminated the arrhythmia by whatever means. A very big error of omission can occur when you stop anticoagulation believing you have eliminated the arrhythmia, and then a very long asymptomatic episode comes along and causes a stroke.

This brings up another unresolved issue: we still don’t know how much AF is enough AF to make stroke a real threat. This actually applies to both the decision to start anticoagulation and to justify its eventual discontinuation. Even if one had a perpetual implantable loop recorder, there’s no mechanism to mind the store often enough for it to be considered meaningful surveillance. Clinical trials are in place to answer this.

CHADS2-VASC score of 0 or 1: enteric coated aspirin, 81 (baby) or 325 mg. CHADS2-VASC score of ≥2: warfarin, apixaban, rivaroxaban, dabigatran or edoxaban.
Choosing an Antiarrhythmic Drug

In the context of AF management, antiarrhythmic drugs are considered either membrane stabilizing drugs (class I or III) or AV nodal blocking agents (class II or IV). If your plan is to restore sinus rhythm, a membrane stabilizer should be your pick. For rate control, class II or IV drugs are best.

All class I agents block the sodium inward current, which has the effect of impairing impulse conduction, a form of antiarrhythmic drug action. All class III antiarrhythmic drugs prolong repolarization as the mechanism of antiarrhythmic action. However, please note we have never been able to apply the knowledge of these drug actions to tailor drug selection to a particular case in mind.

Drug Classes

When choosing an agent, one must know the underlying disease and the structural/functional features of the patient’s heart, all available from the echocardiogram. The following are top choices, not the only choices.

Follow-Up Choices

- Flecainide and propafenone can be used with beta blockers, but with caution.
- Sotalol is more likely to cause torsades des pointes than amiodarone.
- QT prolongation is common to all class III drugs.
- Dofetilide and sotalol are the only drugs requiring three-day hospitalization to initiate.
- Ibutilide should be avoided in patients with low EF, low K’, or concomitant class III use.
- Ibutilide is a particularly helpful drug in the emergency room. It is the only intravenous drug that can quickly convert AF to sinus rhythm by intravenous injection without creating bradycardia or dropping blood pressure.

Serious adverse effects are uncommon but include polymorphic ventricular tachycardia in patients with markedly reduced ejection fractions and/or hypokalemia. Its use has dramatically reduced the need for DC cardioversion and hospitalizations.

One should be familiar with the predominant routes of metabolism and excretion of all these drugs to avoid toxicity when used in patients with hepatic or renal impairment.

Ablation of AF

Elimination of atrial fibrillation became a reality in 1998 when a group of electrophysiologists in Bordeaux, France, discovered that the origin of the AF triggers resides within the pulmonary veins. By ablating a circular area at the base of the vein where it is connected to the atrium, they were able to demonstrate that the spontaneous electrical discharges from within the vein were no longer able to propagate into the adjacent left atrium and the arrhythmia immediately became quiescent. This is referred to as pulmonary vein isolation (PVI).

Catheter ablation is a technique in which alternating current is delivered through the tip of an intracardiac catheter in contact with a region of abnormal cardiac tissue to deliberately destroy it. As little as 15–30 sec of energy application can turn viable tissue into scar tissue. In principle, it is identical to the heat production during welding but with many orders of magnitude less current and voltage. Unlike household current (60 Hz frequency), the frequency used in catheter ablation is 600–700,000 Hz. Because this frequency is in the radio-wave range, the technique is referred to as radiofrequency catheter ablation.

Left Atrium

While there is a vast array of tools and considerable variation in the techniques used to perform catheter ablation, common to all is PVI. In my experience, the additional isolation of the entire left atrial posterior wall (PWI) results in even higher long-term success rates. Typically, PVI alone yields 60–75 percent success rate at one or two years. In my series of 350 patients undergoing both PVI and PWI, the 10-year success rate is 88 percent. Taking into account the learning curve, the success rate during the last five years is 93 percent. Success means no symptoms and no drug. The percent of repeat procedures is only 15 percent, compared to 30–35 percent with PVI alone.

Figure 7 (following page) shows an example of the appearance of a patient’s left atrium prior to (left) and following (right) combined PVI and PWI. The image is produced by moving a catheter with multiple electrodes throughout the left atrium. Because the heart is located within an electromagnetic field, the metal electrodes’ locations are constantly tracked and the computer program “paints” a rendition of the shape of the chamber. The view is the rear of the left atrium with the four pulmonary veins projecting out (A–D). The color
reflects viability: purple is intact, excit- able tissue, and red is inexcitable tissue. In the left-hand image, the portions of the pulmonary veins farthest away from the atrium are normally red because this region is “vein only” and venous tissue does not exhibit excitability. The base of each vein is purple, owing to the atrial muscle tissue known as the pulmonary vein sleeves.

Preablation, the sleeves, the poste- rior wall, and the remainder of the left atrium are all purple. In the right-hand postablation image, the black lines define the location of the ablation lesions placed with the catheter. Once completed and with no breaks in the lines, the ablation lesions prevent electrical activation of the portions of the atria and veins contained within the lines, rendering them electrically silent. It is remarkable that this much of the atrial wall can be rendered inactive and yet have little or no significant effect on overall cardiac function. Because the posterior wall also contains areas that are arrhythmo- genic, sparing them is the reason the PVI-only success rates are between 60–75 percent and why there is a 30 percent repeat procedure rate within as little as two years.

**Whom to Ablate**

In general, the best candidates are symptomatic patients, whether or not they have failed drug therapy. Younger patients are more likely to benefit because we presume the disease process hasn’t progressed as far as it would have in older patients. Based on a recent meta-analysis as well as the CABANA trial, one population characteristic that is associated with improved mortality was having the ablation at ages under 65. As in the case with any type of therapy, the more frequent the symptoms, the sooner a successful result can be appreci- ated. If a patient was having an episode twice a year and underwent catheter ablation, it would take an entire year free of any symptoms to convince you the procedure may have worked—and this just seems overindulgent.

Ablating asymptomatic patients is a bit more difficult to justify knowing that they will not recognize and appreciate what has been done to them, since they had no symptoms in the first place. But we do it and, to some extent, what really matters here is the operator’s procedural experience and his comfort level in performing it. Nothing is worse than having a procedural complication when the procedure’s benefit would never be obvious to the patient.

There is one category of the asymptomatic patient in whom catheter ablation is highly recommended: the patient who developed tachycardia—cardiomyopathy because of a prolonged period of high heart rates that never got their attention. After their ablation, a special effort becomes necessary to verify that the patient stays in sinus rhythm. This is most easily accomplished by a daily heart rate determina- tion (bp cuff, pulse palpation, pulse ox, Fitbit, or AliveCor). If a patient’s resting rate is always between 50–80 bpm, he/she is most likely in sinus rhythm. Resting rates in excess of 90 bpm are suspicious but resting rates over 100 bpm merit a closer look with an EKG.

**Outcomes and Expectations**

Most electrophysiologists do not maintain a database to track their own performance and it is not required by hospitals or professional organizations. As a result, their success rates are really a “gut feeling,” and one often quotes the general experience as reflected in the literature. The literature does indicate a 60–75 percent success rate at one year for PVI-only, regardless of the technique: radiofrequency catheter ablation, the cryo-balloon method, or the “hybrid” approach in which your second procedure is actually being done anyway. The hybrid approach, fashioned after the original surgical ablation technique, aims to ablate atrial tissue “from the outside” and requires thoracoscopy, either through the rib cage on both sides or a single access beneath the xiphoid process. Once the “epicardial” surgical approach is completed, you are scheduled to have the more traditional “endocardial” catheter ablation within a month or two. As this constitutes two initial procedures, success rates in some centers may be higher than reported. Of note is that the original surgical literature emphasized the importance of including the posterior wall in the isolation process.

In my series of patients, in addition to an overall success rate of 88 percent, the repeat procedure rate is only 15 percent, significantly less than the currently reported 30–35 percent rate of a second procedure. Three-fourths of the repeat procedures were performed
within the first two years after the index procedure. After that, the likelihood of a second procedure fell to a very low level. While a very late recurrence necessitating a second procedure occurred, it was unusual.

**Follow-Up**

Typically, I see patients at one, three, six, and 12 months post-procedure. If, at the 12-month visit, they are having no symptoms and were previously clearly symptomatic, I will discharge them from clinic. We can see them at any time in the future should the need arise. For the asymptomatic patient or those who developed a tachycardia-mediated cardiomyopathy, I follow them for two to three years, knowing this is the most likely timeframe a second procedure may become necessary. Nonetheless, they will be held to the responsibility of checking their resting heart rate on a daily basis.

Antiarrhythmic therapy is usually continued for two to three months post-ablation and then stopped. We refer to this as the “blanking period” because in most all of the clinical trials examining ablation of AF, a very early recurrence of the arrhythmia didn’t predict a later recurrence. Therefore, the patient is simply kept on a drug for a short period of time until the “dust settles.”

In patients with a CHADS$_2$VASC score of 0–1, OAC can be stopped at two months and they can resume aspirin. For all others, plan on lifelong oral anticoagulation until our guidelines change.

As a concluding comment: because AF is far more complicated than all of the other types of arrhythmias we ablate, one must remain vigilant to ensure all of the conditions known to cause AF, such as hypertension, coronary artery disease, sleep apnea, and alcohol excess, are kept under control. If not, the arrhythmia will be back. It’s only a matter of time.

*Ed. Note: In addition to his work as a cardiac electrophysiologist, Dr. Moulton and his wife, Linda Moulton, RN, have conducted courses on electrophysiology nationwide for the past 26 years.*

*Email: kriegh.moulton@ncmahealth.com*

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**Recommended References**