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Cardioversion or rate control for atrial fibrillation: balancing risks and benefits

This article is based on a discussion held at the Cleveland Clinic Heart Center's "Controversies in Cardiology" conference.

In managing atrial fibrillation, should physicians try to restore and maintain sinus rhythm, or take a more conservative approach and try only to control the heart rate and prevent thromboembolism? Although restoring sinus rhythm seems preferable, antiarrhythmic drugs may have unacceptable side effects. But does opting for the conservative approach of rate control and anticoagulation deny some patients the opportunity for optimal benefit (such as better exercise tolerance and the prevention of electrical remodeling of the heart) and expose them to other risks (such as bleeding)?

In this month's Cardiology Dialogue, Dr. Kenneth Ellenbogen, from the Medical College of Virginia, lays out the argument for restoring sinus rhythm, while Dr. Patrick Tchou, from the Cleveland Clinic, gives the rationale for rate control and anticoagulation; however, both discussants agree that the answer in the real world depends on the individual patient.

They also discuss the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), which is comparing clinical outcomes in patients with atrial fibrillation receiving ventricular rate control or drug therapy to maintain sinus rhythm.

THE CASE FOR AGGRESSIVE TREATMENT WITH ANTIARRHYTHMIC DRUGS

DR. ELLENBOGEN: For the sake of argument, let me point out several reasons why antiarrhythmic drugs to restore and maintain sinus rhythm should be the first line of therapy for a patient who presents with atrial fibrillation.

The window of opportunity for restoring sinus rhythm is limited

The longer a person is in atrial fibrillation, the harder it is to restore

sinus rhythm, and by using heart-rate control (with drugs such as calcium channel blockers or beta blockers) and anticoagulation alone, we squander the opportunity of restoring sinus rhythm. In recent studies in humans, in which we used intravenous ibutilide, a new class-III drug that can rapidly restore sinus rhythm, the single most important clinical factor that predicted successful pharmacologic conversion to sinus rhythm was duration of atrial fibrillation.[1]

Electrical remodeling, in which prolonged atrial fibrillation alters the electrophysiological structure of the heart, may explain this phenomenon. This was demonstrated by Maurits Allessie, whose experiments in goats showed that such electrophysiologic changes occurred after 2 days to 4 weeks of atrial fibrillation (induced by rapid pacing). After the rapid pacing was stopped, these changes took a week to reverse.[2]

There is also some evidence that persons in atrial fibrillation for long periods actually have progressive atrial dilatation and, in some studies, cardiomyopathy. I believe that most cases of cardiomyopathy in atrial fibrillation are due to poor heart-rate control, but a few may be related to the atrial fibrillation itself.

The longer a person is in atrial fibrillation, the harder it is to restore sinus rhythm

Because there is a limited window of opportunity for correcting atrial fibrillation, I am concerned about the possibility that some patients enrolled in the AFFIRM trial may have a difficult time being converted to sinus rhythm at some later time. If, 5 years from now, we find that antiarrhythmic drug therapy is the optimal strategy, it may be too late to restore sinus rhythm in some patients who were randomized to receive heart-rate control and anticoagulation alone.

The advantages of restoring sinus rhythm

AV-nodal blocking drugs (beta blockers, calcium channel blockers, and digoxin) do not control the heart rate nearly as well as the sinus node does. Specifically, they never really match what the heart rate should be during exercise or daily activities. They also have many side effects that limit their usefulness, such as fatigue, exacerbation of asthma, constipation, and depression.

Better exercise tolerance. Many studies in the early 1900s, when digoxin and digitoxin were the only drugs available for heart-rate control, showed that patients in atrial fibrillation had a marked and exaggerated increase in heart rate in response to exercise, compared with when they were in sinus rhythm. Patients in sinus rhythm can exercise longer than patients in atrial fibrillation even while receiving rate-control drugs, and also have lower filling pressures than patients in atrial fibrillation with rate-control drugs.

The risk of stroke is less. The risk of stroke increases markedly after 48 hours of atrial fibrillation. In sinus rhythm, the risk of stroke is practically nonexistent.

■ THE CASE FOR CONSERVATIVE TREATMENT WITH RATE CONTROL AND ANTICOAGULATION

DR. TCHOU: I agree that sinus rhythm is better than atrial fibrillation, and if I can maintain the patient in sinus rhythm without antiarrhythmic drugs, I prefer it. But maintaining sinus rhythm with antiarrhythmic drugs has limitations.

The limitations of antiarrhythmic drugs

Many patients have cardiomyopathy. Many patients with atrial fibrillation have advanced cardiomyopathy of various etiologies, and keeping them in sinus rhythm is very difficult to start with. These patients are at the greatest risk of serious, life-threatening ventricular arrhythmias caused by antiarrhythmic drugs. Therefore, while they may stand to benefit the most from the use of antiarrhythmic drugs, they are also at the greatest risk from them.

Antiarrhythmic drugs may have proarrhythmic effects, even in patients without cardiomyopathy. Several meta-analyses demonstrated that patients taking antiarrhythmic medications have an elevated mortality rate.[3,4]

In addition, all of the antiarrhythmic

medications have "nuisance" side effects that the patients do not like.

Antiarrhythmic drug therapy often fails. Besides the side effects, antiarrhythmic drugs are not 100% successful in controlling atrial fibrillation; in fact, they fail for half the patients who take them. And treatment failure can be insidious, with patients experiencing few or no symptoms when they go back into fibrillation. Stopping anticoagulation therapy in a patient likely to go back into atrial fibrillation without coming to medical attention may well expose that patient to stroke.

The advantages of rate-control drugs

Symptom relief. The main reason many patients feel poorly in atrial fibrillation is the uncontrolled, rapid, irregular heart rate. Rate-control therapy helps them feel better.

Fewer side effects. Compared with antiarrhythmic drugs, the drugs and the nonmedication approaches to controlling rate have fewer serious or life-threatening side effects. Although some people cannot tolerate beta blockers, if I had a choice between taking a beta blocker or quinidine, or between a calcium channel blocker and amiodarone, I would choose the beta blocker or calcium channel blocker.

Catheter ablation available. For patients who cannot tolerate these medications or who cannot achieve adequate rate control with them, we have catheter ablation, in which we essentially disconnect the atrium from the ventricle electrically, and control the ventricular rate with a pacemaker.

Balancing risks and benefits of medications

I agree that the risk of stroke is less in sinus rhythm. The real question is whether the potential reduction of stroke achieved by maintaining sinus rhythm is worth the difficulties of using antiarrhythmic medications, which have significant day-to-day side effects, and in occasional patients have life-threatening side effects. Therefore, one should use antiarrhythmic drugs judiciously and weigh their potential complications carefully. I would seriously consider rate control, with its lower risk, provided the continuing atrial fibrillation, rate-control medications, and anticoagulant medications do not severely inhibit the patient's lifestyle.

REBUTTAL: RISK STRATIFICATION REDUCES THE RISKS OF ANTIARRHYTHMIC DRUGS

DR. ELLENBOGEN: Yes, we must balance the side effects of the antiarrhythmic drugs with the risks and side effects of anticoagulation and AV nodal blocking drug therapy. But by using antiarrhythmic drugs judiciously and with in-hospital monitoring, we can significantly decrease the risk of proarrhythmia. Patients will still have some side effects, but the incidence and severity is less at lower doses.

Meta-analyses of antiarrhythmic drug studies done in 1960s and 1970s showed a risk of proarrhythmia that would be unacceptable today.[3] But in many of the studies, the patients were not routinely monitored for QT prolongation, which might warn of impending *torsades de pointes*. About 80% to 90% of the cases of *torsades de pointes* that occur with type IA drugs occur in the first 48 hours of therapy.

In the 1960s, 1970s, and even the early 1980s, many physicians were not aware of how diuretics caused hypokalemia and hypomagnesemia, which could interact with antiarrhythmic drugs and predispose to the development of *torsades*. In addition, other commonly used drugs, such as tricyclic antidepressants, erythromycin, and antihistamines, can prolong the QT interval, and in combination with an antiarrhythmic drug can also predispose to *torsades*.

Finally, the patients who received antiarrhythmic drugs in those days were a heterogeneous group. It is not fair to cite proarrhythmic risks based on studies done 1 or 2 decades ago, when risk stratification of patients was not done.

The real question is whether the potential reduction of stroke is worth the difficulties of using antiarrhythmic medications

Newer antiarrhythmic drugs are better than older ones

Newer antiarrhythmic drugs, such as amiodarone, cause a negligible incidence of proarrhythmia in patients with heart failure. There has been a considerable worldwide experience with amiodarone, particularly at low doses and in patients with atrial fibrillation; some patients have been taking it for 10 or 15 years, with great success. Some of our most effective antiarrhythmic drugs can be given for long periods, prevent recurrent atrial fibrillation in many patients, and obviate the use of anticoagulation in some.

Anticoagulant therapy also has risks

Although antiarrhythmic drugs have their risks, so do anticoagulant drugs. Anticoagulants (eg, warfarin) are associated with increased risk when patients do not get their prothrombin times checked regularly, or drink alcohol in excess.

Warfarin also poses special risks for the elderly, because they fall, they are frail, and they bleed easily. Their risk of stroke is greatest in atrial fibrillation, yet it is also great with anticoagulation therapy. In an 80-year-old patient we need not worry about the side effects of antiarrhythmic agents 10 to 15 years down the road. For such patients, therapy with a drug such as amiodarone can prove remarkably effective in preventing atrial fibrillation.

HOW COMMON IS ASYMPTOMATIC ATRIAL FIBRILLATION?

The risk of stroke is relatively low when atrial fibrillation lasts less than 24 hours

AUDIENCE QUESTION: In analyzing Holter monitor records from patients with histories of atrial fibrillation, we have seen episodes of completely asymptomatic atrial fibrillation lasting 30 minutes or an hour. How often does this actually happen?

DR. ELLENBOGEN: It is probably the rule. We have data from approximately 100 patients with paroxysmal atrial fibrillation caused by sick sinus syndrome, who have pacemakers with data-logging abilities, and many of them do have short episodes of atrial fibrillation. Several years ago, Dr. Ed Pritchett from Duke University reported on a group of patients with paroxysmal atrial fibrillation. He followed those patients with a combination of transtelephonic monitors and a random Holter monitor once a month. For every symptomatic episode of atrial fibrillation, there were approximately 18 or 19 asymptomatic episodes.[5] The numbers may be even higher when you can constantly monitor the patient with a pacemaker.

Fortunately, the risk of stroke is probably relatively low when the atrial fibrillation lasts less than 24 hours. A paper from the Cleveland Clinic suggested the risk of stroke goes up after 48 hours.[6]

When to stop warfarin therapy

Many patients will still need warfarin therapy long-term, even with antiarrhythmic therapy, and there are risks and benefits. If a patient presents with asymptomatic or minimally symptomatic atrial fibrillation, and I give him or her an antiarrhythmic drug, particularly one that can slow conduction through the heart, such as sotalol or amiodarone or probably even propafenone, I would continue the warfarin long-term because the patient could be totally asymptomatic if the atrial fibrillation were to recur, and it might be 2 or 3 months until I see the patient again.

On the other hand, if a patient presents with symptomatic atrial fibrillation, such as a fast ventricular response, I would start an antiarrhythmic drug and follow the patient every 2 or 3 months. If the atrial fibrillation never recurs, and the patient never complains of any palpitations, it is probably reasonable to stop the anticoagulation. But that decision needs to be individualized. If there is a strong argument, such as risk factors for bleeding or problems with anticoagulation, or fluctuating international normalized ratios (INRs), I might try stopping the anticoagulation sooner. I would not stop the warfarin if the patient has multiple risk factors for stroke, a dilated cardiomyopathy, or a history of stroke or transient ischemic attacks.

WHAT IS "ADEQUATE" HEART-RATE CONTROL?

AUDIENCE QUESTION: I am also concerned about the AFFIRM trial, which is ostensibly testing rate control as an entity. The "ablate-and-pace" trial showed a marked improvement in quality of life when people with resistant atrial fibrillation had AV nodal ablation and a VVIR pacemaker placed, or paroxysmal atrial fibrillation and had even dual-chamber pacemakers.[7] However, the AFFIRM trial is using rate-control drugs, and reserving the ablate-and-pace procedure for patients who do not

achieve a certain heart rate.

I am concerned that patients in the AFFIRM trial will not have their heart rates lowered enough. Maybe more strict rate control is more important.

DR. ELLENBOGEN: Your experience at the Cleveland Clinic is very similar to the experience described by Dr Natale from Duke University,[8] who reported on a group of patients who had heart-rate control, but not what we would consider strictly optimal. After ablation of the AV junction and initiation of VVIR or ventricular pacing, he noted an improvement in quality of life and exercise function.

The Cleveland Clinic's observations and those of others suggest that as many as 50% of people whom we say have "adequate heart-rate control" do not really have optimal heart-rate control. Many physicians who care for patients with heart failure feel that atrial fibrillation may in fact cause cardiomyopathy, but I feel that more often it is caused by suboptimal heart-rate control.

The design of the AFFIRM trial does lead to suboptimal rate control. That is a major criticism, because if 25% to 50% of patients in the heart-rate control group do not really have good rate control, then the antiarrhythmic drug therapy may look better than it really is.

DR. TCHOU: I think the heart rate during exercise is more important than the resting rate. Digitalis does not work well because it primarily works at rest, and not when sympathetic tone is high (or parasympathetic tone is low). Beta blockers, on the other hand, work much better because they block sympathetic tone (and may not affect vagal tone at rest). They probably do not slow the heart rate much below its spontaneous rate, but start to act when the sympathetic tone starts to increase.

HOW TO TELL IF PHARMACOLOGIC CARDIOVERSION WILL SUCCEED

AUDIENCE QUESTION: Duration of atrial fibrillation seems to be the best predictor of whether pharmacologic cardioversion will succeed, but patients often cannot tell when atrial fibrillation begins. Are there are any other markers that predict successful cardioversion?

DR. ELLENBOGEN: Most patients do know when atrial fibrillation starts; they have some symptoms, if only palpitations.

As for the factors that predict whether cardioversion will succeed, study after study has found that the best clinical predictor is the duration of atrial fibrillation, with shorter duration predicting greater success.[9–11]

DR. TCHOU: While the studies have found that the duration of fibrillation is key, physicians sometimes misapply that information and tell patients who have been in atrial fibrillation for 1 or 2 years that cardioversion will not work.

Although the risk of recurrent atrial fibrillation increases with time, and cardioversion and maintenance of sinus rhythm become less likely to succeed, the success rate is still high enough that if a patient might benefit from conversion to sinus rhythm, either in reduced symptoms or improved cardiac function, it is worth trying. I see a fair number of patients who have been told there is no sense in trying cardioversion, but if pharmacologic cardioversion is attempted, many of them do respond.

HOW MANY TIMES TO TRY ANTIARRHYTHMIC THERAPY?

AUDIENCE QUESTION: It is not always so easy to keep a patient in sinus rhythm. So how hard should we try? And how many times should we try?

As many as 50% of people whom we say have "adequate heart-rate control" do not have optimal heart-rate control

DR. ELLENBOGEN: Therapy has to be individualized; we generally try once or twice, depending on the patient's age and symptoms. The younger the patient, the more we are willing to persevere, because I believe that eventually a catheter cure for atrial fibrillation will be developed, and I think it will be easier to accomplish in someone who spends most of the time in sinus rhythm. But there is no substitute for good clinical judgment. For some patients, one trial is enough, particularly an elderly person taking amiodarone. In a younger person, such as a middle-aged woman with hypertension, I might try disopyramide first, and then go to other agents such as sotalol, flecainide, or low-dose amiodarone.

AUDIENCE QUESTION: What is your approach to anticoagulation after pharmacologic or electrical cardioversion?

DR. ELLENBOGEN: We are participating in the ACUTE (Assessment of Cardioversion

Utilizing Transesophageal Echocardiography) trial and have enrolled a number of patients. This trial is comparing transesophageal-guided anticoagulation with standard anticoagulation.

Basically, all patients with new-onset atrial fibrillation get anticoagulant therapy unless they have a contraindication to it. We generally bring them into the hospital, start them on heparin and warfarin, and send them home 4 or 5 days later with warfarin therapy alone. Then we try to get therapeutic INRs for 3 or 4 weeks in a row.

How long they must continue taking warfarin has to be individualized, as I mentioned. In a 40-year-old patient with a first episode of atrial fibrillation and no risk factors, we might continue warfarin and antiarrhythmic therapy for 3 months and then stop both, and have the patient take aspirin instead.

If a patient needs cardioversion while in the hospital, we start heparin, obtain a transesophageal echocardiogram, and perform electrical or pharmacologic cardioversion. Then, if the risk of bleeding is so high that we would not send the patient home with warfarin, we keep him or her on heparin for at least 3 days, but usually up to 5 to 7 days after they are back in sinus rhythm, and we presume they will stay in sinus rhythm. ■

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