PRACTICAL LESSONS FROM THE NEW ATRIAL FIBRILLATION GUIDELINES

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INTRODUCTION

Atrial fibrillation is the most common arrhythmia in the country, and its prevalence is increasing as the U.S. population ages.[1] Frequently associated with hypertension and/or coronary artery disease (CAD), atrial fibrillation results in serious morbidity, mortality, hospitalization and emergency room visits.

Since 2000, five clinical trials have been published regarding the question of whether the use of long-term prophylactic therapy with antiarrhythmic drugs to maintain sinus rhythm (rhythm control) in patients with atrial fibrillation results in a better outcome than a strategy aimed at controlling heart rate and anticoagulation appropriate to the atrial fibrillation guidelines (rate control).[2-6] In all five trials, there was no improvement in clinical outcome (stroke, death, heart failure, hospitalization) in patients comparing the two strategies.

It is useful to focus on the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial since it is three-times the size of the other four trials combined.[2] AFFIRM studied 4,060 patients to assess the benefits of prophylactic antiarrhythmic therapy, and patients were randomized to either a rate control or rhythm control strategy. Despite the fact that patients in the rhythm control group stayed in sinus rhythm nearly twice as often as the rate control group (62.6% vs. 34.6%), there was no difference in mortality, heart failure or stroke between the two strategies. Although it is still recommended to restore sinus rhythm during a first or second episode of atrial fibrillation, physicians are left with the conundrum of whether to adopt a rate or rhythm control strategy. This review will focus on selected aspects of the updated atrial fibrillation guidelines and the clinical trials impacting these alternatives.[7]

RATE CONTROL: A STEPCHILD IN ATRIAL FIBRILLATION MANAGEMENT

A 48-year-old male presented with progressive symptoms of congestive heart failure (CHF), without palpitations, over a period of 4 to 6 weeks. He had no prior history of structural heart disease and no chest pain that suggested CAD. In the emergency room, he was noted to be in rapid atrial fibrillation with the initial rate being between 150 to 170 beats per minute. ECGs and cardiac enzymes were negative. In-hospital management consisted of diuresis, ACE inhibition and rate control, which was achieved with a combination of digitalis and diltiazem. After initial acute stabilization, the patient underwent an adenosine SPECT sestamibi study that was negative for ischemia and a 2-D echocardiogram that revealed a dilated left ventricle and left atrium, no segmental wall motion defect, an estimated left ventricular ejection fraction of 30-35%, and an estimated pulmonary artery pressure of 56 mmHg. Because of the unknown duration of atrial fibrillation, attempted cardioversion was carried out only after three weeks of outpatient warfarin therapy with the INR ≥ 2.0. Two attempts at electrical cardioversion were unsuccessful; therefore, the emphasis was on rate control.

The patient received oral digoxin (0.25 mg) and oral diltiazem, titrated from 120 mg to 360 mg over a five-week interval. Once CHF was stabilized, carvedilol was started at 3.125 mg and titrated over two months to 25 mg. His progress is summarized in Table 1. Heart rates at rest and during normal activity and maximal hourly heart rates by Holter were all reduced sequentially. Tachyarrhythmic cardiomyopathy was reversed. Ejection fraction increased from 30-35% to 52%, and left ventricular end-diastolic dimension was reduced

	Rest HR	(Holter) Mean HR	(Holter) Max HR	Echo LVEF	Echo LVEDD
AF admission	110-170	NA	NA	30-35%	6.6 cm
Clinic follow-up					
Week 2	100	110-115	130	--	--
Week 3	90	98	118	42%	5.9 cm
Week 8	82	84	96	--	--
6 Months	76	70	86	52%	5.6 cm

AF = atrial fibrillation; HR = heart rate; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension

Table 1. Case study in rate control.

from 6.6 cm to 5.6 cm over a six-month period. The patient improved from NYHA class IV to functional class I. The resting heart rate in clinic (Table 1) did not accurately reflect hourly heart rates during normal activity on Holter. This emphasizes the need for 24-hour ambulatory ECG monitoring or at least walking the patient in clinic to better regulate heart rate during clinical visits.

In this case, the extent to which the improvement in left-ventricular systolic function was due to rate control versus the remodeling effects of ACE inhibitor and carvedilol is debatable. The relatively rigid rate control achieved in this patient probably was a substantial contributing factor to his improvement. The patient currently walks one hour a day without dyspnea, has no symptoms suggesting clinical congestive heart failure, and has returned to full-time work. Tachycardia-induced cardiomyopathy is often poorly managed, but improvements in ejection fraction of the magnitude exemplified by this patient are common if strict rate control is achieved.[8-10]

The following are key aspects from the current atrial fibrillation rate control guidelines:

1. Beta blockers and nondihydropyridine calcium blockers are choices for rate control. The exceptions to this rule are patients with decompensated CHF and left-ventricular systolic dysfunction.
2. To achieve optimal heart rate control, attention to heart rate during normal activities of daily life and moderate exercise is necessary: Relying on the resting heart rate taken in clinic is a clinical error. Clinic personnel should take the apical pulse for 30 seconds to one minute.
3. Digitalis is the drug of choice for rate control in patients with atrial fibrillation and clinical CHF with systolic dysfunction. Adding amiodarone is reserved for resistant cases given its non-cardiac toxicity profile.
4. The recommended heart rate targets in the guidelines are modest, with a resting heart rate of 60 to 80 and of 90 to 115 during moderate exercise. Stricter management of heart rate, as exemplified by the above patient, may result in additional symptomatic improvement.[7]

In summary, once the clinical decision has been made that sinus rhythm cannot be achieved or maintained, heart rate control is often poorly managed. When the ventricular response during modest activity is well-controlled, clinical improvement (e.g. energy level, dyspnea, endurance) will result.

ANTICOAGULATION: SYNOPSIS OF THE ATRIAL FIBRILLATION ANTICOAGULATION GUIDELINES

The following are key aspects from the anticoagulation guidelines for nonvalvular atrial fibrillation:[7]

1. Antithrombotic therapy is recommended for all patients with atrial fibrillation except lone atrial fibrillation without cardiovascular risk factors or in patients for which anticoagulation therapy is contraindicated.
2. For nonvalvular atrial fibrillation, vitamin K (warfarin) antagonists are recommended for patients with ≥1 of the modifying risk factors, including age ≥75 years old, hypertension, heart failure, impaired systolic function (ejection fraction ≤ 35%), and diabetes.
3. The INR should be measured and maintained at a frequency allowing careful control within a range of 2 and 3. For valvular atrial fibrillation, especially in patients with valve replacement, an INR between 2.5 to 4.0 is recommended.
4. Aspirin (81 to 325 mg) is recommended as a substitute for vitamin K antagonist only if the risk of vitamin K antagonist is high or for a very low-risk patient.
5. The above rules apply equally to patients with atrial flutter.
6. Long-term anticoagulation with warfarin has not been demonstrated efficacious in the primary prevention of stroke in patients ≤ 60 years old with no structural heart disease and no risk factors for thromboembolism (i.e., low intrinsic risk).

CLINICAL APPLICATION OF THESE GUIDELINES

In the AFFIRM trial, 211 of the 4,060 patients incurred a stroke (8.2% of the population). Of these, 157 (6.3%) were considered ischemic, and half of those were considered embolic.[11] Stroke rates were not significantly different between the rhythm and rate control arms. Patients in atrial fibrillation at the time of the stroke were at 60% higher risk. Those patients on warfarin had a nearly 70% diminished chance of stroke. The "not subtle message" is that patients consistently on warfarin were benefited.

This data from AFFIRM leads to a very practical question: How do you know your patients are continuously in sinus rhythm when you rarely see them? An occasional clinic visit with a history and 12-lead electrocardiogram does not define the weeks and months between visits. Is the absence of palpitations and dizziness adequate evidence to assume there is no atrial fibrillation? Unfortunately, the answer is no. My first patient example (tachyarrhythmic cardiomyopathy) complained of heart failure symptoms, not palpitations, despite atrial fibrillation rates of 150 to 170.

Consider another example, this time a 51-year-old male with new-onset atrial fibrillation referred to Methodist DeBakey Heart Center for cardioversion. He had a modest non-ischemic cardiomyopathy. After successful anticoagulation and cardioversion to sinus rhythm, the patient was asked to wear ten 24-hour ambulatory ECG monitors over a period of one month (Figure 1). Symptoms suggesting arrhythmia occurred during monitored days when

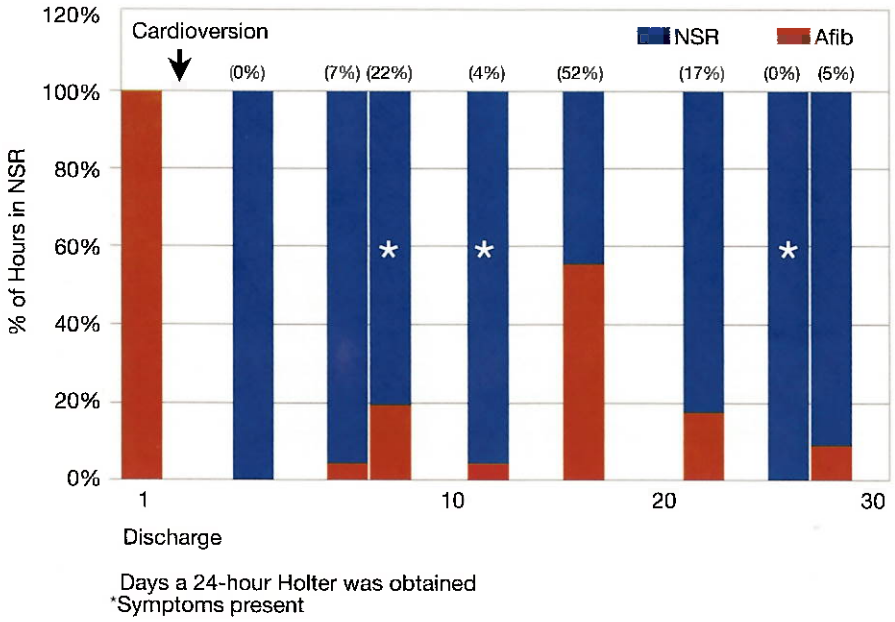

Figure 1. A month in the life of a patient with atrial fibrillation.

no atrial fibrillation was on the Holter, whereas on asymptomatic days the patient had atrial fibrillation for up to half the day. Given the AFFIRM data on stroke and this typical example of the poor correlation between symptoms and atrial fibrillation, I have evolved to a conservative approach, preferring to continue warfarin even in relatively low-risk patients and keeping the INR at the lower limit of the target range (2 to 3) even if they manifest "normal sinus rhythm" in clinic. Stroke is a very satisfying event to prevent!

PHARMACOLOGIC THERAPY TO MAINTAIN SINUS RHYTHM: FOCUS ON THE ATRIAL FIBRILLATION GUIDELINES

Most patients experience improved subjective symptoms if sinus rhythm can be maintained. The atrial fibrillation guidelines for prophylactic antiarrhythmic therapy are based on best available clinical trials. There are two well-accepted principles for considering antiarrhythmic drug selection:

1. Even with the best pharmacologic therapy, the majority of patients experience recurrence of atrial fibrillation.[12]
2. The available antiarrhythmic drugs have, in general, a narrow therapeutic/toxic ratio, making safety a primary motivation in drug selection. This is especially relevant since sinus rhythm has not been associated with improvements in death, heart failure and stroke.

SELECTED ASPECTS OF THE DRUG SELECTION ATRIAL FIBRILLATION GUIDELINES FOR MAINTAINING SINUS RHYTHM

The current drug selection recommendations are presented in Figure 2. To optimally use this algorithm, baseline testing should include an echocardiogram, a 12-lead electrocardiogram, and additional testing necessary to eliminate the presence of ischemia (CAD). Preexisting high blood pressure should be treated to appropriate guideline levels. Optimization of precipitating and reversible causes of atrial fibrillation is assumed in this discussion and is a Class I recommendation (e.g. hyperthyroid, alcohol abstinence).[7]

PROPHYLACTIC ANTIARRHYTHMIC THERAPY IN PATIENTS WITH NO STRUCTURAL HEART DISEASE

Atrial fibrillation is a frequent problem in patients without structural heart disease. This category may account for up to 30% of the atrial fibrillation cases. The term "no structural heart disease" resulted from a FDA committee review of the Cardiac Arrhythmia Suppression Trial (CAST), which showed that both flecainide and encainide were associated with increased mortality in a post-myocardial infarction population with frequent ventricular ectopy. The term "structural heart disease" has evolved to include patients with CAD, myocardial infarction, reduced left-ventricular ejection fraction, CHF, or substantial left-ventricular hypertrophy.[13] Whether minimal enlargement of the left atrium or borderline left ventricular wall thickness by echocardiogram qualifies as structural heart disease is left to the individual physician's judgment. The FDA does not and should not practice medicine!

As seen in Figure 2, flecainide, propafenone, and sotalol are the initial considerations in this category. The largest and best clinical trial data are from the Rythmol Atrial Fibrillation Trial (RAFT) and the European Rythmol/Rythmonorm Atrial Fibrillation Trial (ERAFT) studies.[14,15] As seen in Figure 3, there is a dose-proportional increase in the maintenance of sinus rhythm over six months as propafenone dose is increased from 225 mg to 425 mg. The RAFT study result characterizes the majority of propafenone, flecainide, and sotalol data. During the 39-week study, 70% of placebo patients versus 30% high-dose propafenone patients had an arrhythmia recurrence. A key principal is exemplified by these results: atrial fibrillation recurrence is common with all antiarrhythmic drugs. It is important to counsel patients that this recurrence may not connote drug failure. Repeat cardioversion and dosage adjustment is

an acceptable approach.

In the new guidelines, propafenone and flecainide may be preferable to sotalol in patients with no structural heart disease because sotalol has a 1-2% torsades de pointes ventricular tachycardia risk, especially in females. Also, sotalol requires dosage adjustment for patients with decreased renal function. A representative example of sotatol's efficacy was reported by Benditt.[16] Doses of 120-160 mg increased the maintenance of sinus rhythm from 27 days on placebo to 175-229 days on sotalol. The lower dose (120 mg) appears to have the best risk-benefit ratio. Two-thirds of recurrence of atrial fibrillation occurred in the first 30 days, typical of the majority of antiarrhythmic drugs tested.

THE BASIS FOR GUIDELINES OF ANTIARRHYTHMIC DRUGS FOR ATRIAL FIBRILLATION AND HEART FAILURE

The Danish Investigations and Arrhythmia on Dofetilide (DIAMOND) and the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trials tested dofetilide and amiodarone, respectively, in more than 3,600 patients with CHF.[17,18] The atrial fibrillation guideline selection focused upon these studies (Figure 2). There were 506 patients with atrial fibrillation in the DIAMOND trials and 103 in the CHF-STAT trial.

The maintenance of sinus rhythm in these trials is summarized in Table 2. Atrial fibrillation was common in both trials and as high as 25% of patients in the DIAMOND-CHF trial. The placebo-subtracted efficacy was 25% for dofetilide and 23% for amiodarone (Table 2). While these results are similar, it is not appropriate to directly compare efficacy between the two drugs since the patient population and study designs are not comparable.

The justification of selecting these two drugs as preferred therapy to prevent recurrence of atrial fibrillation in heart failure patients is based on this data, especially the fact that in both trials the mortality on dofetilide and amiodarone was comparable to placebo.

AMIODARONE TOXICITY: A WORD OF CAUTION

Why not simply select amiodarone for all atrial fibrillation patients? The myocardial infarction and CHF trials comparing amiodarone to placebo allows objective estimates of serious

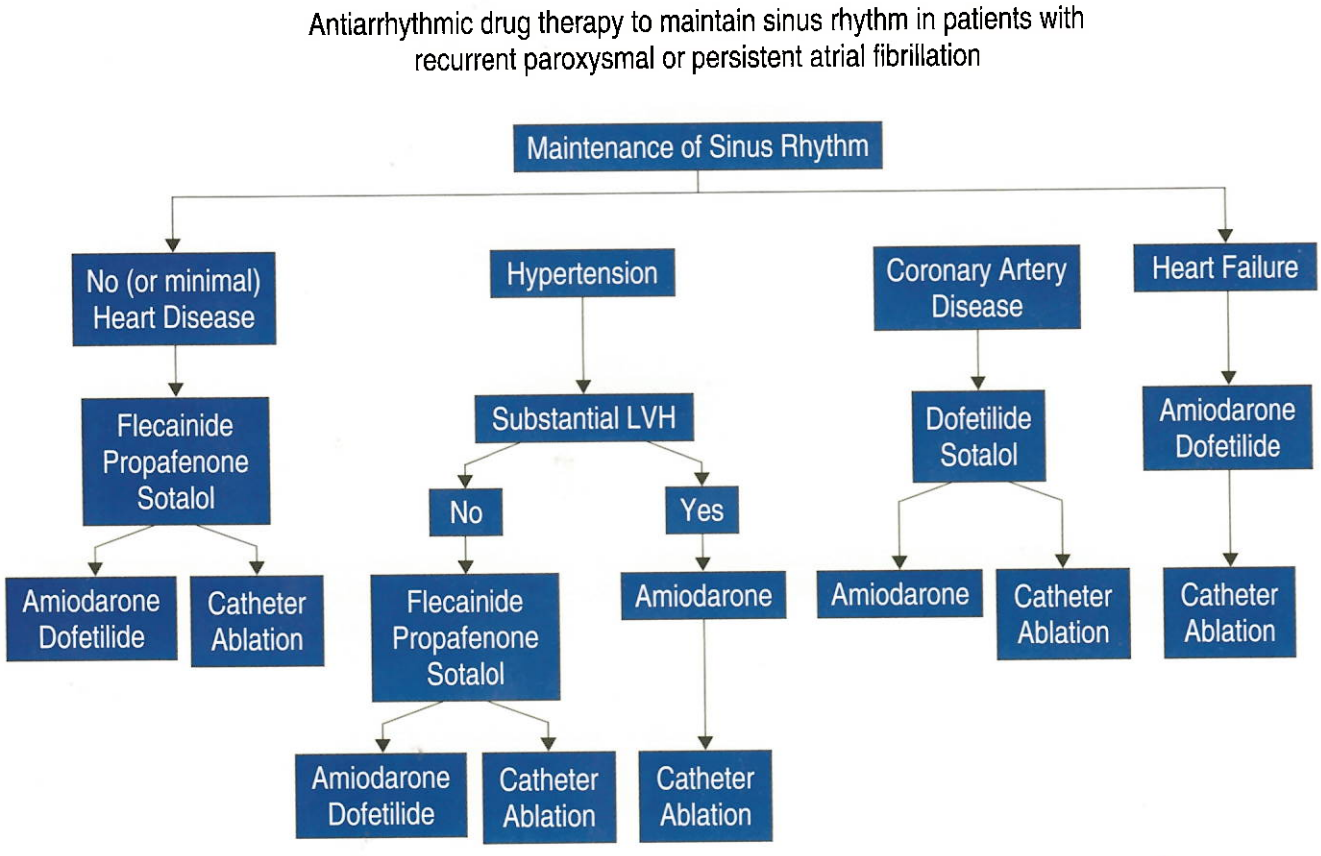

Figure 2. Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation: guidelines algorithm.[7]

	DIAMOND Trials (Dofetilide)	CHF-STAT Trials (Amiodarone)
Total number of patients with AF	506	103
% patients with AF	16.7%	15.4%
Efficacy		
Active	59%	34%
Placebo	34%	8%
Placebo-subtracted efficacy	25%	23%

Abbreviations as before

Table 2. Achievement of sinus rhythm during the congestive heart failure trials: patients with atrial fibrillation at baseline.

Disease Category	Incidence*	Placebo-Subtracted Incidence
Pulmonary	39/1,685 = 2.3%	25/1,685 = 1.5%
Thyroid	72/1,685 = 4.3%	51/1,685 = 3.0%
Neurologic	39/1,685 = 2.3%	27/1,685 = 1.6%
Cutaneous	27/1,685 = 1.6%	12/1,685 = 0.7%

Counts only "severe" cases or drug discontinuations.

*Represents all amiodarone-assigned patients in CHF-STAT, EMIAT and CAMIAT.[18-20]

Table 3. Incidence and placebo-subtracted incidence of severe non-cardiac toxicities associated with amiodarone therapy (N=1,685 patients treated).

toxicities attributable to amiodarone. The relevant placebo-controlled trials are the CHF-STAT, European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), together comprising more than 3,200 patients with follow-up of one and a half to three and a half years.[18-20] The toxicities are listed in Table 3 and were considered serious, some even lethal or requiring discontinuation of the study drug.

The frequency of pulmonary, thyroid, neurologic and cutaneous toxicities make amiodarone a very poor first choice in patients without heart failure for whom there are alternative therapies (Figure 2). In addition, minor thyroid and cutaneous complaints occur in up to 10% of patients. With regard to mortality, however, there were no episodes of torsades de pointes ventricular tachycardia in the three amiodarone-controlled trials. Mortality was comparable to placebo. The clinical tradeoff is significant efficacy and a good cardiovascular safety profile versus a poor non-cardiac toxicity profile. Toxicity concerns emphasize why amiodarone is not a preferred treatment in patients with atrial fibrillation and a structurally normal heart, as reflected in the guidelines (Figure 2).

PHARMACOLOGIC PREVENTION OF ATRIAL FIBRILLATION: PATIENTS WITH CORONARY ARTERY DISEASE OR HYPERTENSIVE HEART DISEASE

Guideline recommendations for hypertension and CAD are presented in Figure 2. The discussion of the pharmacologic prevention of atrial fibrillation recurrence in patients with hypertensive heart disease and CAD assumes optimal medical management of other factors (blood pressure, use of ACE inhibitors or angiotensin receptor blockers, and statins using appropriate guidelines).

Atrial fibrillation commonly occurs in patients with CAD and/or significant, poorly controlled hypertension. In patients with atrial fibrillation and CAD, sotalol is a logical choice because it has beta blocker properties in addition to its class III electrophysiologic effects. It also has a safety profile based on a previous post-MI trial in which there was no increase in mortality.[7] Amiodarone is relegated to a second-tier selection based on its non-cardiac toxicities highlighted in the heart failure section. Propafenone and flecainide are contraindicated based on extrapolation of the CAST trial results, in which flecainide increased mortality in a post-MI population with frequent ventricular ectopy.[21] Dofetilide is a reasonable option to sotalol in patients with CAD despite its logistic disadvantages of inpatient initiation and telemetry monitoring. Both sotalol and dofetilide require renal adjustment for impaired renal function. Amiodarone is a second-tier choice based on its safety profile. However, it has been more effective than comparator drugs (sotalol, propafenone) in well-controlled randomized clinical trials, making amiodarone a good alternative in cases of poor efficacy.[22]

MAINTENANCE OF SINUS RHYTHM IN PATIENTS WITH ATRIAL FIBRILLATION AND HYPERTENSIVE HEART DISEASE

One cannot overemphasize the importance of blood pressure control in these patients. This is especially true for reducing stroke risk in the elderly, in whom systolic hypertension commonly companies atrial fibrillation. By achieving guidelines, stroke risk can be reduced by 50-70%.[23,24] Although the data is sparse to guide antiarrhythmic drug selection in patients with hypertensive heart disease, amiodarone (Figure 2) is considered the first choice for patients with severe left-ventricular hypertrophy and atrial fibrillation. This is driven primarily by cardiac safety issues. Although amiodarone increases

the QT interval on the ECG, in well-controlled clinical trials it has not been associated with increased mortality. In three studies comprising more than 3,000 patients, there were no episodes of torsades de pointes ventricular tachycardia.[18-20]

CONCLUSION

Meticulous control of anticoagulation with warfarin and carefully documented rate control are the mainstays of good atrial fibrillation management. Conversion to sinus rhythm and its maintenance is still desirable in most patients. Careful attention to the guideline recommendations of prophylactic antiarrhythmic drug alternatives is necessary to safely use this challenging class of drugs.

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