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Reviews

Antiarrhythmic Drug Therapy for Atrial Fibrillation: Are the Guidelines Guiding Clinical Practice?

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Summary: The AFFIRM study showed no clear survival advantage for a rhythm versus rate control strategy in patients with atrial fibrillation (AF). However, rhythm control with antiarrhythmic drugs (AADs) is appropriate in a large number of patients with AF. The American College of Cardiology/American Heart Association/European Society of Cardiology AF management guidelines include a safety-based algorithm for selection of AAD therapy. Class 1C agents are recommended as first-line therapy in patients without or with minimal structural heart disease. However, market research and clinical study data indicate a growing use of class III agents (mainly amiodarone) despite long-term safety and tolerability concerns, suggesting that clinical practice does not adhere to current guidelines.

Key words: antiarrhythmic drugs, class IC drugs, propafenone sustained release, Rhythmol SR Atrial Fibrillation Trial, structural heart disease, amiodarone

Introduction

Whether atrial fibrillation (AF) is paroxysmal or persistent, if symptoms become troublesome, physicians are faced with choosing between rhythm control or controlling ventricular rate response as the initial strategy.[1] The relative benefits of these two strategies were widely debated until the publication of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study results, which demonstrated that management of AF with rhythm control strategy offered no clear survival advantage over rate control strategy in patients with AF.[2] The results of the smaller European Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study[3] were consistent with those from the AFFIRM trial.

Patients enrolled in the AFFIRM study were required to have ≥ 1 risk factor for stroke or death, including older age, and had to be able to tolerate AF if rate-controlled, and patients in the RACE trial had persistent AF refractory to electrical cardioversion. Consequently, these patients generally had more serious cardiac disease or other coexisting illnesses. In contrast, younger patients without or with minimal structural heart disease (SHD), who may represent ~30% of patients with AF,[4] were not included in the AFFIRM or RACE trials due to their low risk of fatal events. Therefore, the results of these studies probably cannot be generalized to younger patients without risk factors for stroke, such as those with primary or "lone" AF, and particularly those with paroxysmal AF, or to those with symptoms despite rate control. Therefore, while the rhythm control strategy can no longer be considered imperative, there remains a population of symptomatic patients with AF for whom rhythm control with antiarrhythmic drugs (AADs) is still appropriate.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) Guidelines

The most comprehensive practice guidelines for management of patients with AF, developed jointly by the ACC/AHA/ESC and sanctioned by the Heart Rhythm Society (HRS), were published in 2001[5] and relate to appropriate selection of pharmacologic therapy for maintenance of sinus rhythm.

The stated goal of maintenance antiarrhythmic therapy is suppression of symptoms and sometimes prevention of tachy-

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cardia-induced cardiomyopathy due to AF when rate control fails. Selection of an AAD should generally be based on arrhythmia burden, type of underlying heart disease, severity of symptoms, risk of side effects, and patient preference.[5] The guidelines present a safety-based algorithm for drug therapy selection based on the presence or absence of SHD.[5]

Recommendations for Antiarrhythmic Drug Selection

As shown in Figure 1, the guidelines recommend a class IC agent (flecainide or propafenone) or sotalol as first-line therapy in patients with no or minimal SHD. Amiodarone and dofetilide are second-line choices based on the high incidence of side effects and organ toxicity associated with amiodarone, the early proarrhythmic risk of dofetilide, and the large number of potential drug interactions with both drugs.

Additional data supporting propafenone use, specifically a sustained-release formulation, as first-line therapy come from the recently published randomized, placebo-controlled Rythmol SR Atrial Fibrillation Trial (RAFT) that studied 523 patients with a history of AF, most of whom had no SHD.[6] Patients in sinus rhythm were randomized to receive either placebo or one of three doses of propafenone SR: 225, 325, or 425 mg twice daily (b.i.d.) for a maximum of 39 weeks. Recurrent episodes of symptomatic AF were documented using transtelephonic electrocardiogram (ECG) monitoring. Compared with placebo, all three doses of propafenone SR significantly lengthened the median time to first symptomatic AF recurrence by > 300 days with 425 mg, 291 days with 325 mg, and 112 days with 225 mg, versus 41 days with placebo. Of patients treated with propafenone SR 425 mg b.i.d., 70% experienced no symptomatic arrhythmia recurrence during the study. Propafenone SR was well tolerated, and the overall incidence of serious side effects was similar to placebo, except that side effects leading to study withdrawal were slightly higher in the 425 mg group.

In the ACC/AHA/ESC guidelines, patients with heart disease are divided into three populations: those with heart failure (HF), coronary artery disease (CAD), or hypertension without ischemic disease. The latter group is further differentiated according to the severity of left ventricular hypertrophy (LVH). In 2001, a left ventricular (LV) wall thickness ≥ 1.4 cm was suggested as the cut point for severity. Since patients with LVH are at increased risk for torsade de pointes from drugs that prolong the QT interval, agents that do not prolong the QT interval are preferable as first-line therapy. Therefore, in the absence of HF, CAD, or substantial LVH, propafenone or flecainide are reasonable and recommended first-line choices. With more severe LVH, all AAD classes will have an increased risk of proarrhythmia. Although no clinical data support the recommendation, the 2001 guidelines suggest amiodarone for patients with ≥ 1.4 cm LV wall thickness.

In patients with HF, amiodarone or dofetilide are the recommended first-line agents based on several randomized survival trials.[7–9] Sotalol is not recommended in the overt HF population given its negative inotropic and proarrhythmic potential.

In patients with CAD without HF, sotalol is the recommended first-line AAD due to its substantial beta-blocking activity, neutral effect on survival,[10] shorter half-life, and lower toxicity than amiodarone, although amiodarone would be preferred in those patients who also have HF. Dofetilide, based on neutral survival from the Danish Investigations of Arrhythmia and Mortality ON Dofetilide-Myocardial Infarction (DIAMOND MI) trial,[11] is a reasonable alternative. Class IC agents (flecainide and propafenone) are not recommended in this population because studies such as the Cardiac Arrhythmia Suppression Trial (CAST) found an increased mortality risk in the presence of ischemia or prior myocardial infarction (MI).[12, 13]

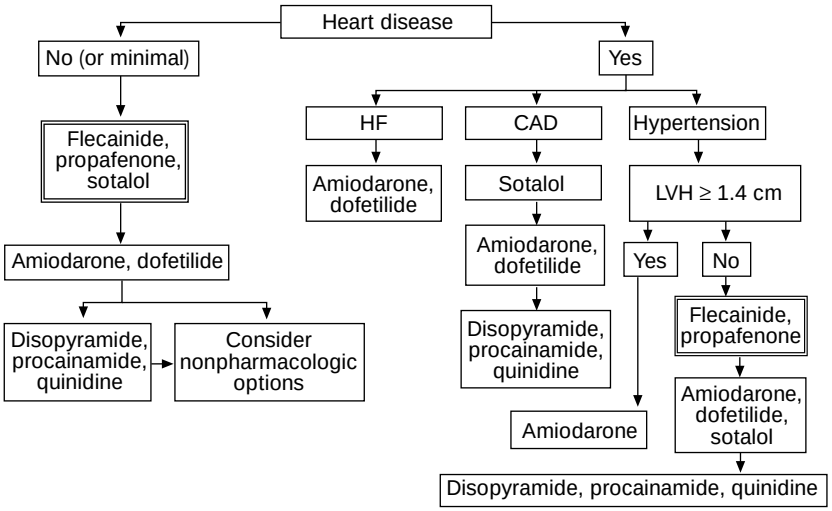

FIG. 1 Algorithm for selection of drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. CAD = coronary artery disease, HF = heart failure, LVH = left ventricular hypertrophy. Reprinted from Ref. No. 5 with permission.

Does Heart Disease Matter in Patients with Atrial Fibrillation?

The focus on safety in AAD selection is important since many patients with AF also have ≥1 cardiovascular conditions such as HF, CAD, or LVH that pose an increased risk for proarrhythmic events. The prevalence of such comorbid conditions was reported in two recent studies. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study found that in a cohort of 17,974 adults with AF, 49% had hypertension, 29% had HF, and 24% had a history of angina and/or MI.[14] Similar findings were reported in the Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle (FRACTAL) study.[15] Of 1,005 patients enrolled in this AF registry, 49% had a history of hypertension, 25% had CAD, and 17% had valvular heart disease. The high prevalence of comorbid conditions was also demonstrated in the AFFIRM trial. Of 4,060 randomized patients, 51% had hypertension, 26% had CAD, and 23% had a history of HF, while 12% had no apparent cardiac disease.[16]

Since concomitant heart disease frequently accompanies and/or underlies AF, the unresolved issue is how SHD can be best defined, identified, or at least ruled out in clinical practice.

How Should "Significant" Structural Heart Disease Be Identified?

Rather than being defined strictly by anatomy, SHD for antiarrhythmic drug purposes generally can be described as the presence of an abnormal ventricular pathophysiologic state that can promote proarrhythmia. Conversely, a patient with a "normal" heart can be characterized as someone with a "normal" history, a "normal" cardiac physical examination, a "normal" 12-lead ECG, no significant ventricular abnormalities or dysfunction on echocardiogram, and a "normal" exercise stress test in appropriate patients.

Given the importance of identifying patients with "significant" SHD, a thorough workup is imperative in all those with AF. The goal is to detect provocable ischemia, LVH, ventricular dilation, or regional or global ventricular dysfunction, which may result from previous ischemia, fibrosis, calcification, infiltration, or inflammation. Even though precise definitions of, or criteria for, SHD are not provided by the guidelines, minimal and additional evaluations of patients with AF are outlined.[5]

A detailed medical history and physical examination should focus on symptoms of, risk factors for, or detection of cardiac disease. A 12-lead ECG should be obtained with emphasis on detecting atrial and ventricular hypertrophy, MI, conduction disturbances, QTc prolongation, or nonspecific repolarization abnormalities. Echocardiography should also be performed because LVH and regional and global ventricular enlargement can be symptomatically silent and undetectable on ECG.

However, these evaluations do not detect silent, exertional ischemia, latent QT prolongation, exertionally manifesting ventricular dysfunction, and most ventricular arrhythmias. When appropriate, a stress test should be performed to rule out obstructive CAD in high-risk patients. Because exercise ECG testing may yield false positive or false negative results, repeated testing with associated imaging or coronary angiography may be required in certain patients. In patients with ventricular ectopy and equivocal findings by other assessments, a signal-averaged ECG may be useful. Finally, a chest x-ray can be helpful if the patient has dyspnea but no other evidence of cardiac disease.

Antiarrhythmic Drug Use in Community Practice

Market research data provide a broad picture of prescribing trends.[17] Changes in the number of new prescriptions for AADs from July 2002–June 2003 to July 2003–June 2004 indicate a predominant and growing use of class III agents (amiodarone and sotalol), which increased from 71% of all new prescriptions during 2002–2003 to 74% during 2003–2004; of these, new prescriptions for amiodarone increased by 4.4%. Among the class IC agents (flecainide and propafenone), only new prescriptions for propafenone increased by 4.3%. New prescriptions for all other AADs decreased by nearly 16%, possibly due to the findings of AFFIRM and RACE. Therefore, although the guidelines would suggest that ≥50% of patients should receive a class IC agent, the actual use is only 19%.[17]

Fang *et al.* analyzed national trends from 1991 through 2000 in AAD use from the National Ambulatory Medical Care Survey.[18] Although there was a slight, nonsignificant, overall increase in AAD use (9.8 vs. 12.2% of visits) during this period, amiodarone use increased from 0.2 to 6.4% of visits ($p < 0.001$ for trend), and the use of class IC agents also increased from 0.5 to 2.9% of visits ($p < 0.001$ for trend), resulting in a 5.8-fold difference in amiodarone use versus the use of propafenone and flecainide combined. Use of class IA agents decreased.

In the FRACTAL study,[15] a total of 481 patients (48%) received an AAD during the first year of follow-up. Of these, 14% received a class IA agent, 29% received a class IC drug, 23% received sotalol, and 34% received amiodarone. However, there was a significant difference ($p < 0.001$) in utilization according to the prescribing physician's specialty (Table I).

TABLE I Variation in use of antiarrhythmic drug medications

	Cardiologists, % (n = 221)	Electrophysiologists, % (n = 168)	Internists, % (n = 92)
Class 1A	15	7	23
Class 1C	37	22	27
Sotalol	24	23	22
Amiodarone	24	48	28

$p < 0.001$.

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Electrophysiologists tended to use amiodarone, while general cardiologists appeared to prefer class IC agents; a clear-cut preference among internists was not evident. Preferential use of amiodarone by electrophysiologists may reflect nonconformity with the guidelines, or more likely, the effect of referral patterns in which they are sent more difficult patients who may have failed prior AAD therapy. These data also suggest that cardiologists and internists use more class IA agents and fewer class IC drugs than the guidelines would suggest.

A recent survey by the HRS conducted among member and nonmember electrophysiologists also found a relatively greater preference for class III agents, primarily amiodarone, as first-line therapy in AF.[19] When asked whether they were familiar with the ACC/AHA/ESC guidelines, 60% reported familiarity with them, and > 90% agreed with the recommendation that a class IC agent (flecainide, propafenone) or sotalol should be considered as first-line treatment in patients with no or minimal SHD, and > 80% agreed that flecainide or propafenone should be the first choice AAD in patients with AF and hypertension if the LV wall thickness is < 1.4 cm.[19] These stated beliefs, however, do not appear to be consistent with clinical practice and guideline recommendations.

Guidelines versus Clinical Practice: Why the Difference?

These data strongly suggest that, in contrast to the guideline recommendations, class III agents, particularly amiodarone, are being prescribed for most patients with AF and that the trend is continuing.

The choice of AAD based on safety has been a clinical recommendation for a long time. Guidelines are not novel in this regard, making the clinicians' lack of compliance even more puzzling. Although available evidence suggests that amiodarone is effective for maintenance of sinus rhythm in patients with AF, its use is limited by potentially severe extracardiac side effects,[5] even at low doses.[20] Therefore, amiodarone should be used as second-line treatment, except in patients with HF, in whom amiodarone appears to offer advantages regarding relative risks and benefits, and in patients with substantial LVH.[5]

Numerous possible reasons exist regarding the extensive use of amiodarone. Although ignorance of the guidelines is a partial explanation, inherent biases of the practicing physician or alternatives chosen due to unique aspects of a patient's case may also be important. In refractory patients, second- and third-tier choices may be appropriate. The fact that amiodarone as well as disopyramide and procainamide are not approved for the treatment of AF does not appear to be an issue in management decisions. Practical issues likely play a role in selecting amiodarone. For example, amiodarone as well as class IC therapies can be initiated in an outpatient setting—usually more convenient for the patient and the clinician and incurring lower costs. Efficacy is another factor that may favor amiodarone. However, a recent randomized study comparing amiodarone and immediate-release propafenone found that, although the recurrence rate with amiodarone (34%) was lower than with propafenone (46%), 17% of patients receiving amiodarone discontinued because of adverse effects versus 3% in the propafenone group.[21] Therefore, the overall benefit (efficacy without drug withdrawal) was 49% with amiodarone and 53% with propafenone.

Amiodarone has been associated with low incidences of arrhythmic events, particularly torsade de pointes, but significant sinus bradycardia is frequent and significant enough to necessitate pacemaker implantation within 1 year in ~ 2.4% of patients.[22] Therefore, the issue of long-term safety of amiodarone identified in the guidelines[5] appears to be of less concern with clinicians in light of their level of prescribing. Amiodarone is a complex drug with multiple electrophysiologic effects, unusual pharmacokinetics, and numerous potentially harmful drug interactions and adverse effects.[23, 24] The prevalence of adverse effects has been reported to be as high as 15% in the first year of use and up to 50% during long-term use, even at low doses.[5, 22–25] Clinically significant extracardiac adverse effects, particularly with long-term use, include pulmonary and liver toxicity, hyper- and hypothyroidism, photosensitivity, neuropathy, blindness, and a blue discoloration of the skin. None of these occur with the class IC agents flecainide and propafenone, or with sotalol and dofetilide. Amiodarone has clinically important drug interactions with digoxin, warfarin, simvastatin, procainamide, quinidine, and quinolone antibiotics, among many others.[23, 24] Given the potential for extracardiac adverse effects and drug interactions, the amiodarone dosage should be kept at the lowest effective level, and regular and appropriate monitoring and follow-up of patients is essential. In patients taking digoxin and warfarin, for example, digoxin levels and prothrombin time should be monitored, keeping in mind that interactions with amiodarone do not peak until 7 weeks after initiating concomitant therapy.[23] Monitoring of liver and thyroid function are recommended at least every 6 months, and ongoing eye and pulmonary surveillance is also needed.[23] A recent Food and Drug Administration (FDA)-mandated patient information guide about amiodarone is now available with all prescriptions. The guide describes approved indications, potential side effects, appropriate use, and monitoring needs, which are likely to result in the reduction of amiodarone use.

Discussion

The current and most agreed upon algorithm for selection of an AAD for maintenance of sinus rhythm is in the ACC/AHA/ESC guidelines, which are based on the premise that the presence or absence of concomitant SHD is a pivotal consideration; however, these guidelines appear to be underutilized.

Suboptimal compliance with evidence- and consensus-based management guidelines is not unique to AF. For example, a study from the Centers for Disease Control and Prevention analyzed data from 6,736 hypertensive patients to determine whether they had been prescribed a diuretic and/or a beta blocker as first-line therapy as recommended by the Sixth

Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI).[26] Only 38% were on a diuretic and less than a third were prescribed a beta blocker. In comparison, approximately half of the hypertensive patients with certain comorbidities received non-first-line therapy. A recent study that assessed compliance with the National Cholesterol Education Program (NCEP) III guidelines for statin use by physicians in a large urban cardiology practice found that, among patients with documented dyslipidemia of ≥ 2 years duration and no contraindications to statin therapy, only 43% had received this treatment, and 38% of those who were on statin therapy had a suboptimal lipid profile despite > 2 years of therapy.[27]

Noncompliance with guidelines is not limited to the United States. A recent study from New Zealand found that only 47.5% of patients presenting to the emergency department with AF received antithrombotic therapy (primarily warfarin) as recommended by the 2001 ACC/AHA/ESC and American College of Chest Physicians (ACCP) guidelines.[28] At follow-up, 5% of patients, all of whom did not receive warfarin, had a stroke. A survey of the implementation of European guidelines for the management of chronic HF among cardiologists in six European countries found that, overall, adherence to guidelines for appropriate use of five classes of drugs was 60%.[29] Important is the fact that analysis of 6-month follow-up data from 1,410 patients found that adherence to guidelines was a significant predictor of fewer cardiovascular hospitalizations.

Perhaps one reason for the pattern of clinical use of antiarrhythmic drugs is that clear, evidence-based definitions of "significant" SHD are not always adequately detailed to guide decisions. This is not a fundamental failing of the guideline development process but rather reflects the current lack of clinical data on which to base the definitions and distinctions. Thus, some clinicians may not feel comfortable in deciding whether a given patient has or does not have "significant" CAD. In such circumstances, the fallback choice could be amiodarone.

This issue is not trivial, since as many as 30% of patients with AF have "lone AF,"[4] and an additional number of patients have minimal SHD and may be candidates for class IC drugs. Clinicians must understand the interrelationships between SHD and AADs regarding not only proarrhythmic risk, but also toxicities and drug interactions.

If physicians choose to not follow the guidelines, they should examine their practice patterns to determine why, and they should have a defensible rationale for these differences. In the absence of a sound rationale, a change in clinical practice patterns should be encouraged so that their practices are in keeping with the recommended internationally sanctioned guidelines for the best medical practice in the management of patients with AF.

What can be done to improve or change clinical practice so that it conforms better to the ACC/AHA/ESC AF management guidelines? Multitiered, practice-oriented education would provide the foundation for improvement. This could include live and web-based continuing medical education programs directed at cardiologists and internists, as well as on-site initiatives such as Grand Rounds and Visiting Professor programs. Availability of concise, decision-focused handbooks of the guidelines on the AHA, ACC, or HRS websites could provide a convenient reference for busy physicians. In addition, "patient-friendly" information on antiarrhythmic drugs would help patients understand their regimen and query their physician. A more ambitious initiative could be modeled on the AHA's "Get With the Guidelines" collaborative, quality improvement programs on CAD, CHF, and stroke that include didactic best-practice presentations, interactive multidisciplinary team workshops, a customized guideline tool kit, and interactive web-based patient management tools. Given the increasing number of individuals with AF, it would be appropriate for public health agencies and major medical organizations to disseminate the message directly to the public that guidelines for physicians exist for many major cardiovascular and other medical conditions, including the management of AF. Patients with such conditions would be well served to review their care with their physicians in the context of such guidelines.

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