Update on Drugs for Outpatient Management of Atrial Fibrillation

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Biographical Information

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Purpose and Overview

To provide an update on recently-introduced drugs for the outpatient management of atrial fibrillation.

Educational Objectives

- Recognize the advantages and disadvantages of rate vs. rhythm control strategies for management of atrial fibrillation.

- Understand the advantages and limitations of recently-introduced antiarrhythmic agents.

- Understand the advantages and limitations of recently-introduced oral anticoagulants with respect to convenience, safety and efficacy.

- Appreciate the efficacy of drug-based rate- and rhythm-control strategies in older patients.

Introduction

The experience of atrial fibrillation varies substantially from patient to patient and for many there are no overt symptoms. However, this should not obscure the importance of the diagnosis of atrial fibrillation. The impact is substantial. It is the most common sustained arrhythmia. The prevalence among patients less than 60 years old is less than 1% but at age 60 the prevalence begins to increase exponentially and by age 80, the prevalence is > 10%. It is an important cause of stroke, particularly in the elderly, and unfortunately a stroke may be the first presentation of AF. AF may also cause significant morbidity including palpitations, malaise, loss of exercise tolerance and reduced quality of life. The presence of AF may precipitate worsening symptoms in patients with coronary disease or congestive heart failure or significant mitral valve disease. Even in the complete absence of symptoms, a continuous tachycardia may cause left ventricular dysfunction, the so-called tachycardiomyopathy. Atrial fibrillation is associated with increased mortality and increased expenses.

Management of atrial fibrillation focuses on control of either heart rate or heart rhythm, plus antiembolic therapy. Although this concept has been standard teaching for decades, the evaluation and therapeutic options have changed dramatically over the past few years, for several reasons. First, new technologies to detect and monitor arrhythmias have become more flexible and widely used. Second, ablation methods are now widely available for rate control and prevention of recurrent atrial fibrillation. Third, we have gradually accumulated information about the safe and effective use of potent antiarrhythmic agents to maintain sinus rhythm, and dronedarone was introduced recently. Finally, the introduction of novel direct oral anticoagulants (NOACs) provides new options for embolism prophylaxis. With the development of additional drugs and new information about existing drugs, therapeutic options have become increasingly complex.

Terminology

Paroxysmal: AF that terminates spontaneously or with intervention within 7 d of onset.

Persistent: Continuous AF that is sustained >7 d.

Long-standing persistent AF: Continuous AF >12 months in duration.

Permanent: No (further) attempts to restore SR. Attitude, not pathophysiology.

Nonvalvular: AF in the absence of MS, a mechanical or bioprosthetic heart valve, or mitral valve repair.

Recommendations from the American Heart Association, the American College of Cardiology and other groups were recently updated (1 , 2). One recommendation was to improve our precision of the language used to describe AF. The writing team recommended that terms like "lone fibrillator" and "chronic AF" be avoided.

For the purposes of this short update, it is assumed that the patient has had a complete evaluation including history, physical exam, ECG, lab studies to assess thyroid, renal and hepatic function, a transthoracic echocardiogram to assess ejection fraction, septal thickness and the possibility of valvular heart disease, and a chest x-ray.

Mechanisms

Many cardiac arrhythmias are due to reentry which refers to a continuous circuit around some anatomical obstacle. Typical examples are WPW and atrioventricular nodal re-entrant tachycardia. Atrial fibrillation, on the other hand, is thought to be a continuous chaotic activation of the atria by "wavelets" of depolarization that circulate in the atria without a reentry circuit. Consequently there is no AF circuit susceptible to ablation of a small volume of tissue.

However, like other arrhythmias, a premature or other triggering beat can provoke atrial fibrillation (3). In the 1960s, "sleeves" of atrial tissue that invest the pulmonary veins for variable distances were described. Subsequently it was shown that a large portion of the premature beats triggering AF arise from ectopy in the

pulmonary veins which probably represent an arrhythmogenic border zone. Isolation of the pulmonary veins by ablating conducting tissue around the ostia is an effective means of preventing AF, although the precise role of pulmonary vein isolation awaits completion of randomized trials. Other atrial arrhythmias may also provoke AF including atrial flutter, atrial tachycardias and atrial premature beats.

In addition to the triggering arrhythmia, the overall electrical properties of the atria influence the persistence of atrial fibrillation. It is now clear that AF itself injures the atria and that "AF begets AF" in animal models (4, 5). For example, in dogs with experimentally induced AF, myocytes become edematous, and mitochondria become spherical with loss of organization of cristae. Among patients undergoing cardiothoracic surgery for other indications, about 2/3 were in sinus rhythm and 1/3 in AF. In biopsies of right atrial tissue, there was an association between the presence of interstitial fibrosis and the duration of atrial fibrillation, suggesting that atrial fibrillation actually damages atrial tissue and that prolonged atrial fibrillation encourages atrial fibrillation. Other aspects of atrial tissue increase the risk for AF and there are now numerous associations that are thought to increase the susceptibility of atrial tissue to maintenance of atrial fibrillation. Many other factors such as aging-related fibrosis, fatty infiltration of atrial tissue, hormonal effects such as thyrotoxicosis or hyperadrenergic states, ethanol, caffeine, and mechanical stretching of atrial tissue increase the likelihood of persistent AF. Chronic AF leads to both atrial enlargement and probably continuous atrial injury.

It is a reasonable approximation to describe the mechanism as the sum of both triggering arrhythmias and abnormal atrial substrate. Paroxysmal AF is probably due to triggering arrhythmias and transient changes in the atrial substrate, whereas persistent AF likely reflects more permanent remodeling of the atria. Although with chronic remodeling the arrhythmia is self-perpetuating and more difficult to convert to sinus rhythm, there is no specific electrophysiology that characterizes permanent AF.

Prevention

Prevention of AF is an important goal. We know from epidemiological studies that AF is associated with the traditional cardiovascular risk factors including hypertension, diabetes, smoking and dyslipidemia. It would seem reasonable that prevention of AF would include treatment of hypertension, diabetes, dyslipidemia, and smoking cessation. There may be a role for angiotensin converting enzyme inhibitors, angiotensin receptor blockers or statins, but to date the evidence is not convincing for large populations. Other interventions including proper programming of RV pacemkers, management of sleep apnea and management of obesity may be important.

In fact, management of obesity may be an opportunity (6). In a single-center Australian randomized controlled trial, 150 patients with paroxysmal or persistent AF, Age 21-75 yrs, and BMI > 27 were allocated to a very low-calorie diet (800-1200 kCal/d), an exercise plan (20-45 min, 3x/wk), behavioral counseling and support. Remarkably, the AF symptom burden score decreased in parallel with the BMI, total AF burden was decreased significnatly in the weight-loss group, and left atrial size and LV wall thickness both decreased. This was not an AF prevention study since by definition all patients had AF to enter the trial. But it does suggest a useful nonpharmacological approach. It raises the question that the efficacy of many other interventions may be enhanced by weight loss.

Strategy

The two strategies for management of atrial fibrillation are rate control and rhythm control (1). Rate control refers to the acceptance of AF by the patient and physician. This approach is recommended for many patients because many have few or no symptoms attributable to AF. Rate control is conceptually

straightforward and often relatively simple for patients, in practice. Many AF patients have few or no symptoms, and this approach generally avoids invasive procedures as well as the antiarrhythmic drugs and their toxicities. The approach is probably overall simpler and less costly than rhythm control.

Prevention of stroke and systemic emboli is the critical requirement. Control of heart rate with preserved exercise tolerance and quality of life is also important. A reasonable goal is probably a resting heart rate in the range of 70 – 90 bpm. Typically the heart rate can be controlled with inhibition of the AV node with calcium channel blockers or beta adrenergic blockers. For some patients, ablation of the AV node is required, in combination with implantation of a permanent pacemaker.

Conversion to sinus rhythm and maintenance of sinus rhythm offers numerous advantages, in principle, including better hemodynamics due to the left atrial contribution to ventricular filling. There are numerous small studies of the hemodynamic benefits of conversion to sinus rhythm for patients (7, 8, 9). Although some patients deny hemodynamic symptoms, it is not uncommon for patients to report that they feel better after cardioversion. In addition to avoiding the symptoms attributable to impaired hemodynamics and palpitation, sinus rhythm assures not risk of tachycardiomyopathy. The methods available include antiarrhythmic drugs, often with direct current cardioversion, pulmonary vein isolation, and AF surgery (the maze procedure). The goals are maintenance of sinus rhythm, presumed reduction of the risk of CVA, and avoidance of adverse events related to the anti-arrhythmic drugs.

Antiarrhytmic Drugs

Six drugs are recommended for rhythm control in AF (1). Some knowledge of the mechanisms of action of antiarrhythmic drugs and drug classification schemes is essential because the FDA and various recommendation documents all refer to the Vaughan Williams scheme as a convenient shorthand. This scheme is based on the role of various ion channels in the generation of the cardiac action potential (see table).

I. Sodium Channel Blockers
Inhibit Depolarization,
Slow conduction

II. Beta adrenergic blockers
Indirect effects on fluxes

III. Potassium Channel Blockers
Prolong repolarization

IV. Calcium Channel Blockers
Verapamil, diltiazem
Major effects on AV node

The class I agents, the sodium channel blockers, are subdivided into there subclasses. The 1A agents include quinidine, procainamide (only available i.v.), and disopyramide. These agents have intermediate kinetics when associating with the sodium channel, and all agents have some class III effects, meaning that prolongation of the action potential is observed. The resulting prolongation of the QT interval is can be associated with torsade. All of these agents are negative inotropes. The IB agents are lidocaine (only available i.v.) and mexiletine. These agents have little effect on atrial tissue and are probably most useful in suppression of ventricular arrhythmias in ischemic tissue. The IC agents are flecainide and propafenone. These drugs have slow kinetics in their binding to the sodium channel. These are the most potent sodium channel blockers and have the greatest effect on ECG of all class I agents. Both are negative inotropes.

Flecainide was studied in the Cardiac Arrhythmia Suppression Trial (CAST) which was designed to evaluate the effects of potent antiarrhythmic thereapy among patients who were post-MI with frequent ventricular ectopy. Three ddrugs were studied - encainide, flecainide, and moricizine vs. placebo – and all drugs effectively suppressed premature ventricular beats and nonsustained VT. However, as is well known, mortality was roughly 2X for active drug therapy and as a result flecainide now carries a “black box” warning on the package insert. Propafenone was not studied in CAST, but because it is in the same Vaughan Williams class, we assume that the results of CAST apply. Although flecainide was associated with doubled mortality after MI, it has

proven safe for chronic suppression of supraventricular tachycardias, AF, and Wolf-Parkinson-White. If a patient with AF is going to be started on flecainide, it should be administered with a beta blocker or calcium channel blocker simultaneously. Flecainide or propafenone may cause AF to organize to slow atrial flutter with 1:1 conduction. Some AV nodes can conduct at 210 bpm.

Mortality in Studies Targeting VT / VF

propafenone	**mortality increased**	Assume CAST data are representative
flecainide	**mortality increased**	CAST: 2x increase in mortality rate JAMA 1993: 270: 2451
D-sotalol	**mortality increased**	SWORD, Lancet 1996; 348: 7
dofetilide	neutral	DIAMOND, Lancet 2000; 356: 2052
dronedarone	**mortality increased**	ANDROMEDA, NEJM 2008; 358: 2678
amiodarone	overall neutral	GESICA, Lancet 1994; 344: 493 CHF-STAT, NEJM 1995; 333: 77 EMIAT, Lancet 1997; 349: 667 CAMIAT, Lancet 1997; 349: 675

As noted, propafenone was not used in CAST but we assume the results apply. Propafenone is similar to flecainide except that it has some intrinsic beta adrenergic blocking activity. It also has an aactive metabolite, 5-OH propafenone.

The class III agents, the potassium channel blockers, refer to sotalol, dofetilide, amiodarone and dronedarone. Amiodarone is a unique drug because it possesses electrophysiolgcal properties of all four Vaughan Williams classes. Dronedarone is electrically similar to amiodarone. While dofetilide is probably the purest potassium channel blocker, all four ages block the potassium channel and prolong the action potential duration and the effective refractory period.

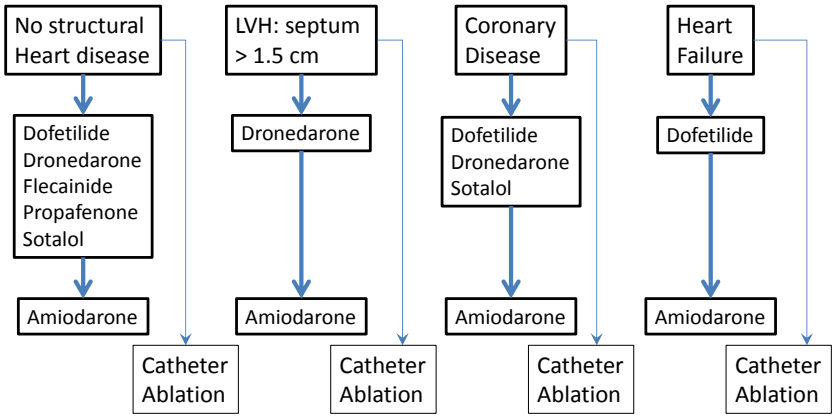
All six drugs are recommended for maintenance of sinus rhythm after conversion from atrial fibrillation, based on numerous placebo-controlled and head-to-head comparisons. Comparative trials such as DIONYSOS trial compared amiodarone to dronedarone and found that amiodarone was superior for maintenance of sinus rhythm (10). The Canadian Trial of Atrial Fibrillation (CTAF) found that propafenone and sotalol were essentially equivalent and that both were inferior to amiodarone for maintenance of sinus rhythm (11). The SAFE-T trial compared placebo to sotalol and amiodarone in 665 patients, overwhelmingly male because the study was performed by the VA. Sotalol was superior to placebo, and amiodarone was superior to either sotalol or placebo (12). Together, these and other studies indicate that amiodarone is superior to other antiarrhytmic agents for maintenance of sinus rhythm.

Although amiodarone is the most effective agent for preventing recurrence, it also has numerous extracardiac toxicities. Essentially every organ system except the kidney is involved. As described below, there is rare torsade. Other complications include pulmonary fibrosis, hypo- or hyperthyroidism, neurological complications including ataxia and tremors, corneal deposits, blue skin and numerous drug interactions including with warfarin, some statins, and digoxin.

Dronedarone, the newest antiarrhythmic agent, was developed specifically to retain the electrophysiological properties of amiodarone but with two major modifications (13 14). Iodine was removed with the intent of reducing the risk of thyroid toxicities. A methylsulfonamide group was added to increase the polarity of the molecule and reduce the apparent volume of distribution by reducing lipophilicity. Interestingly, dronedarone inhibits the renal tubular secretion of creatinine

	Amiodarone	**Dronedarone**
FDA approval	VT/VF	AF
Dosing	Once daily	Twice daily
Half life	Long	Short
Expense	Less	More
Extracardiac adverse effects	Many	Fewer
Experience	Long	Short
Safety with CHF	Safe	Unsafe

which causes an increase in plasma creatinine without a change in renal function. With the much shorter half-life, it is dosed at 400 mg twice daily, and appears to be associated with a much lower risk of thyroid and pulmonoary complications compared to amiodarone.



ATHENA was a very large (4628 patients) study of dronedarone vs. placebo (15). Patients with AF or atrial flutter within the past 6 months were enrolled but permanent AF was not required; 25% were in AF at randomization. Dronedarone reduced cardiovascular hospitalization due to reduced AF recurrences and slower ventricular response in those patients in AF. There was no effect on mortality in this relatively healthy population. Gastrointestinal toxicity was observed but there were no other major toxicities over the 21 months of the study. In particular there was no indication of ventricular tachyarrhythmias induced by dronedarone.

ANDROMEDA enrolled patients with a depressed left ventricular ejection fraction (<35%) and CHF (16). Only about 40% of the patients had atrial fibrillation and the study was terminated early because of a significant excess mortality in the dronedarone group, attributable to cardiovascular causes including CHF. The PALLAS study (17) examined patients with permanent AF, age>65, and vascular risk factors for stroke, with the hypothesis that dronedarone would reduce vascular events. Only a very small fraction of patients converted to sinus rhythm during the study, and all endpoints were worse in the dronedarone arm.

Although excess ventricular tachyarrhythmias were not observed in ATHENA, post marketing surveillance indicates that dronedarone, like all class III agents, is associated with torsade de pointe, and the risk may be substantially higher than with amiodarone. In summary, the population in the ATHENA trial was less sick than in the ANDROMEDA trial, so the positive findings in ATHENA cannot be extrapolated to patients with CHF. Dronedarone is not a major step forward in terms of efficacy but it offers fewer noncardiac side effects compared to amiodarone.

Novel Oral Anticoagulants

Atrial fibrillation cause a thrombus in the left atrial appendage, presumably because of blood stasis and perhaps other factors such as endothelial dysfunction or hypercoagulability. The danger, of course, is embolism to the brain, intestine, coronary artery or extremity.

It is worth emphasizing that the clinical presentation and outcome of strokes associated with AF is different than “ordinary” strokes. Specifically, if a patient presents with a stroke in the setting of AF, that patient is more likely to have a more severe stroke by scoring systems, and that patient is more likely to die in hospital or be discharge to an extended care facility rather than to home. Although the reason for this effect of AF is not known, it seems plausible that an embolism originating the atria is likely to be larger.

Various scoring systems have been proposed to assist with decision making regarding anticoagulation. Warfarin poses significant challenges because of the risk of bleeding, numerous drug interactions and the need for frequent monitoring. One popular system, the CHADS2, has been validated in several trials and this scoring system was used in reporting the large trials of novel oral anticoagulants. Thus it is worth being aware of the

details. The following risk factors are considered: hypertension (1 point), congestive heart failure (1 point), age >= 75 years (1 point), a history of diabetes (1 point), and a history of stroke, TIA or systemic embolism (2 points). The CHADS2 system is valuable but it will likely be supplanted by the CHA2DS2-VASc system which may improve stratification for lower-risk patients. For two or more points, oral anticoabulation is recommended, and other factors such as LVH, enlargement of the left atrium, and other risk factors may be considered. In general, patients with AF plus hypertrophic cardiomyopathy, rheumatic mitral stenosis and amyloidosis are anticoagulated. A perceived fall risk or history of minor bleeding is probably not sufficient to withhold anticoagulation (2, 18, 19).

Warfarin, of course, is unquestionably effective for prevention of systemic embolism in AF. But it has limitations, including the following. First, it may be difficult to maintain the target INR, even under optimal circumstances with the most cooperative patients. Second, the INR testing and sometimes-frequent dose adjustments are costly and inconvenient. Third, is the risk of bleeding. The perceived risk and actual risk of hemorrhage may not always be consistent, but peptic ulcers, fall risk, prior bleeding events, nosebleeds, etc. are real concerns. Fourth, there are numerous drug and diet interactions of warfarin. Fifth, and probably because of the difficulty in monitoring INR is the risk of breakthrough thromboembolism: a stroke or systemic embolism in spite of warfarin.

Dabigatran (20) is a direct-acting thrombin inhibitor that has been shown to be non-inferior to warfarin for prevention of stroke in atrial fibrillation. Two doses were studied in a trial of 18,113 patients, 110 mg or 150 mg. The lower dose had equivalent efficacy and less major bleeding compared to warvarin, and the higher dose had better efficacy with equivalent major bleeding. The risk of intracranial hemorrhage was reduced by dabigatran. Apixaban (21, 22) is an oral Factor Xa Inhibitor. At 5 mg twice daily vs. warfarin, it was associated with a lower risk of stroke or embolism, and a lower risk of major bleeding. About 70% of clearance is hepatic, so inducers of CYP 3A4 such as rifampin should be avoided since lower apixiban levels may increase the risk of stroke. Unlike the other agents, it has a “2/3” recommendation for dose adjustment: reduce to 2.5 mg twice daily if two of the following three conditions are met: age > 80 yrs, weight < 60 kg, creatinine > 1.5. Rivaroxaban (28) is also an effective oral factor Xa inhibitor with about 50% renal excretion. Consequently, the manufacturer recommends dose adjustment based on estimated creatinine clearance. Avoidance of drugs that interact with P-gp and CYP3A4 is recommended.

	Warfarin	**NOACs**
Trial design	Many small	Few large
Indications	AF, DVT, PE, valves	Non-valvular AF (DVT/PE for R/D)
Expense / pill	Less	More
Onset	Slow	Rapid
Excretion/metabolism	Liver	Kidneys and some liver
Monitoring	INR	None
Correction	FFP, vit K	None specific, not dialyzable
Food interactions	Many	Minimal
Drug interactions	Many	Variable or few

The key decision, rather than fine-tuning issues about each NOAC, is whether a patient should take warfarin or a NOAC. Patient selection is crucial. The patients who are likely most suited to NOACs are those with normal renal function, difficulty with regular INR monitoring, or a poorly controlled INR that is not due to noncompliance. There are some patients who should not take a NOAC, for example those with a mechanical heart valve, although only dabigatran has been studied in this context. Renal function is an important consideration for any of the NOACs, particulary dabigatran since it is primarily excreted by the kidneys. Apixaban may be the better agent for moderate renal dysfunction since it has somewhat less renal clearance. NOACs should not be prescribed for patients who may not be compliant, and a patient with conflicting concerns (for example atrial fibrillation in the setting of prior GI bleeding or ulcer disease) may be better managed with warfarin.

Strategy Revisited

Several studies have examined the consequences of selecting one or the other. The largest was the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) in which 4060 patients, all asymptomatic, with AF (23, 24). In the rhythm-control group the AAD was chosen by the primary physician. Options included Class I agents (quinidine, disopyramide, procainamide, flecainide, moricizine or propafenone), or Class III agents (amiodarone, dofetilide and sotalol). Continuous anticoagulation was encouraged but could be stopped if sinus rhythm had apparently been maintained for at least 4 consecutive weeks with antiarrhythmic-drug therapy. In the rate control group, the target was heart-rate control using essentially any combination of digoxin, beta-blockers and calcium-channel blockers (verapamil and diltiazem). The goal was heart rate less than 80 beats per minute at rest and less than 110 beats per minute during a six-minute walk test. Continuous anticoagulation with warfarin to an INR of 2-3 was required.

All-cause mortality was 17.5% in the rhythm control group and 15.1% in the rate control group. The risk of stroke was 7.3% in rhythm and 5.7% in rate control. There was no survival advantage of rhythm control over the rate-control strategy. Retrospective stratification by age, rhythm at randomization, the presence of coronary disease, ejection fraction, clinical heart failure, the duration of atrial fibrillation or a history of hypertension did not identify a group that apparently benefited. In summary, drug-based rate- and rhythm-control strategies have comparable efficacy in older patients.

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