The Editor's Roundtable: Medical Management of Atrial Fibrillation

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Introduction

Atrial fibrillation (AF) is defined as "a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function."[1] Among all cardiac dysrhythmias, it is the most common sustained abnormality, and its prevalence increases with age. Prevention and treatment of AF are complex, especially concerning an ongoing debate about rhythm versus rate control, and, as emphasized in this Editor's Roundtable, must be highly individualized for optimal care.

Dr. Friedewald: Describe the pathophysiology of AF.

Dr. Olshansky: AF is caused by many conditions. It also can occur as an isolated condition that originates in the pulmonary veins, but that mechanism is uncertain, perhaps involving autonomic changes or specific sites of ectopic activity in the pulmonary veins. Patients with left atrial (LA) enlargement due to cardiac disease (e.g., mitral stenosis, mitral regurgitation, left ventricular [LV] dysfunction) all are due to anatomical changes within the LA such as fibrosis and LA "stretch." Hypertension with LV diastolic dysfunction causes increased stretch, and the stretch triggers AF, which perhaps also originates in the pulmonary vein. There many other initiators and perpetuators of AF. Thus, the most common underlying pathophysiology is either a trigger from the pulmonary vein or a reentry mechanism within the left atrium. Other mechanisms include Wolff-Parkinson-White syndrome–related AF after a supraventricular tachycardia, and there also is emerging evidence for inflammatory mediators that are arrhythmogenic.

Dr. Friedewald: What is the evidence for inflammation as a factor in AF?

Dr. Olshansky: Inflammatory conditions such as postoperative AF, in which there are increased levels of inflammatory cytokines such as interleukin (IL)–6, IL-18, and elevated serum levels of C-reactive protein suggest that AF may in part be caused by an inflammatory process inherent to some conditions.

Dr. Kowal: I agree with Dr. Olshansky's perspective. I believe that there is interplay between primary cellular electrophysiologic issues, ion channel defects, and enhanced susceptibility to electrical factors. In addition, there is a neural autonomic component in diseases such as hypertension, leading to structural and electrical remodeling at the cellular level. The relative importance of these factors varies among different disease states, leading to the same common end point, which is AF.

Dr. Friedewald: Dr. Roberts, how do you view AF, from the perspective of a specialist in cardiovascular morphology?

Dr. Roberts: The common denominator of AF at necropsy is LA dilatation. Does AF occur in the absence of LA dilation?

Dr. Olshansky: There is a dynamic between AF and LA dilatation, with electrical and mechanical remodeling over time, so when AF occurs, it leads to LA dilatation. With AF correction, the LA size may revert to normal, depending on the underlying cause. AF changes the electrophysiology of the atria in many ways that allow AF to self-perpetuate. Lone AF, however, can occur in normal-sized atria. Larger atria are associated with various medical conditions, including hypertension, heart failure (HF), and coronary heart disease. In patients with very large atria, it is very difficult to correct AF.

Dr. Roberts: A few years ago here at Baylor University Medical Center, we looked at about 50 patients who had mitral valve operations for mitral valve prolapse, and the frequency of AF was only about 10%. In contrast, we also looked at a group of patients who had surgery for MS (mitral stenosis), and their frequency of AF was much greater. The patients with mitral valve prolapse had larger atria than did those with MS, but the histology of the LA wall in MS patients is abnormal, whereas the LA wall of the patients with mitral prolapse tends to be normal.

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Dr. Kowal: Those observations point out that the electrocardiographic (ECG) diagnosis of AF is a final common *electrical* diagnosis for multiple different *primary* diseases. With mitral valve disease, AF is secondary to structural remodeling. There is a subset of patients in whom AF is primarily an electrical disease causing remodeling.

Dr. Friedewald: Dr. Yancy, what is the mechanism of AF in patients with HF?

Dr. Yancy: AF is a co-morbidity in about 1/3 of all HF hospitalizations and occurs in about 50% of approximately 6 million people in the United States with HF. It is relatively easy to attribute the relation as a simple function of stretch, but I suspect the underlying mechanism goes beyond that. HF involves remodeling probably driven by neurohormonal activation, which also likely causes atrial remodeling. This concept is supported by observations that angiotensin receptor antagonists may reduce the incidence of AF in patients with HF. Other common factors would be aging and senescence of the conduction system.

Dr. Roberts: Dr. Yancy, by "remodeling," do you mean dilatation?

Dr. Yancy: I regard remodeling as a combination of dilatation and a decrement in functionality.

Dr. Roberts: So you are talking about both atrial cavity size and wall function.

Dr. Yancy: Yes.

Dr. Olshansky: There are several things that happen in the atria in the presence of AF, but it is unclear whether they are causally related, such as abnormalities in intracellular connections. There also can be the development of LA wall fibrosis, which may contribute to AF. There is a dynamic between AF and HF. The Framingham data suggest that over time, patients with HF develop AF at a fairly high rate, and patients who first have AF also develop HF by a variety of mechanisms, including a unique integrated disease process comprised of loss of atrial function secondary to ventricular diastolic dysfunction, rhythm irregularity, and the rapid heart rate itself, culminating in the process of *tachycardia-mediated cardiomyopathy*. As found in CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)[2] and other trials, the combination of LV dysfunction and AF is bad, with a high mortality.

Dr. Yancy: There is a negative synergy when AF and HF are combined.

Dr. Olshansky: Do HF patients do better in sinus rhythm, and does mortality improve if you correct AF, or is AF simply a marker for severity of HF? These are unresolved but very important issues.

Dr. Roberts: There is systolic HF and there is diastolic HF, and there may be a combination of both. Patients with hypertrophic cardiomyopathy with diastolic HF do poorly with AF. What about AF in the usual hypertensive patient with diastolic HF compared to the patient who has a healed myocardial infarction with systolic HF?

Dr. Yancy: When you change the substrate from LV systolic dysfunction or reduced LV ejection fraction (EF) to preserved-EF HF, the companion presence of AF is significant in the setting of HF with preserved LVEF. The combination of hypertension, AF, diabetes mellitus, and coronary artery disease probably encompasses 90% of the patient population with HF and preserved LVEF. Thus, as we wrestle with how best to treat HF with preserved EF, the first objective is to treat the relevant co-morbidity for which there are specific guidelines, such as AF. The more provocative question is whether it is the development of AF and a change in LV filling that tends to provoke the presentation of those patients who have either intact or slightly impaired LVEFs but develop symptomatic HF. Is it a *forme fruste* of what we see so dramatically in hypertrophic cardiomyopathy where AF can cause low systemic arterial pressure due to the decrement in cardiac performance? There is a suggestion that the AF would have a negative influence in the setting of HF with preserved LVEF if the issues about stiffness and compliance are pertinent and are correct. AF is an important cofactor that demands respect.

Dr. Olshansky: The relation between AF and HF is complex, because in systolic HF, there are substrates of post–myocardial infarction and nonischemic cardiomyopathy. Among older patients with diastolic HF, AF is 1 of the most common presentations. What are the risks for mortality in that population and in patients with systolic HF? According to Framingham data and other data, among patients who have AF, including both men and women, the presence of AF in an older population with hypertension is associated with excess mortality compared to persons without AF but who otherwise have similar co-morbidities.

Dr. Roberts: Does that mean the best way to prevent AF in older people is to treat more aggressively the hypertensive population to prevent diastolic HF, and to use statins more often to prevent coronary artery disease and its complications such as systolic HF?

Dr. Olshansky: This is an issue of "upstream therapies" in AF, such as the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for both HF and AF. There are data suggesting that these drug classes reduce AF, but the mechanism is unknown. Statins also may have pleiotropic effects in preventing AF, although the data are not strong for this effect.

Dr. Friedewald: The number of noncardiac conditions *associated* with AF is very long, such as diabetes mellitus, hyperthyroidism, chronic obstructive pulmonary disease, and infections such as diphtheria and pneumonia. Is there any evidence that better control of associated conditions, especially diabetes mellitus, reduces the likelihood of AF?

Dr. Olshansky: The mechanism of the AF-diabetes link and whether tighter glucose control is effective in preventing AF are unknown issues. It is important to consider risk of the combination of AF plus another condition, such as diabetes mellitus, compared to the risk of patients with AF as an isolated condition. For example, systolic HF with AF is a very bad combination, as is hypertrophic cardiomyopathy and AF. Thus, AF treatment varies depending on the underlying condition. Treatment algorithms in cardiology are often related mainly to mortality reduction, but when treating the patient with AF we also are trying to improve symptoms and reduce hospitalizations and a variety of issues related to cardiovascular hemodynamics.

Dr. Friedewald: Let's discuss rate versus rhythm control in AF.

Dr. Kowal: There are not appreciable differences in mortality between strategies that focus either on rhythm or rate control. Being in sinus rhythm is probably better than

not being in sinus rhythm; the problem is how this is best achieved. This comes down to the interplay between patients' co-morbidities and symptoms when deciding upon a treatment strategy. In general, if a patient is asymptomatic, I am less aggressive in trying to maintain normal rhythm unless there are other clinical features that suggest it might be beneficial. In patients with AF-induced symptoms, however, I am aggressive.

Dr. Friedewald: Among asymptomatic patients with AF, what factors favor a rhythm control strategy?

Dr. Kowal: I often attempt to restore sinus rhythm in patients with a first episode of AF, either with an antiarrhythmic drug or electrical cardioversion. In asymptomatic patients with clear evidence of a tachycardia-related cardiomyopathy, rate control should be the first goal, but if the cardiomyopathy does not improve, cardioversion may be indicated to try to improve LV performance. An important issue is how to adequately identify the patient with AF who is *truly asymptomatic*. Some patients with AF are profoundly bothered by palpitations. Other patients, however, have no sense that the heart rhythm or rate is abnormal; rather, their main symptom is subtle fatigue and exercise intolerance, with a spectrum of symptoms in between. In such patients, a detailed history about limitations in exercise capacity or performance over the previous several months' period of time is important to assessing their symptoms. It is common for patients referred with "asymptomatic" AF who are actually quite limited, which can be confirmed by an exercise test.

Dr. Friedewald: Have you ever seen anyone with AF who did not have at least *some* amount of physical limitation?

Dr. Kowal: I have 1 patient aged about 55 who cannot discern when he is in AF, which we proved with ambulatory monitoring. He even plays tennis with a ventricular response of >150 beats/min. I am uncertain how best to treat him.

Dr. Olshansky: Rate and rhythm may be relatively unimportant in the overall scheme of how best to treat patients with AF, so why treat AF at all? There are several potential reasons, including symptom control, mortality reduction, and reduction in hospitalizations. Much of the data on rhythm versus rate control relate to mortality, stroke, and HF outcomes and do not support *either* approach. Thus, I treat my AF patients for *symptom control* as the most important objective. Symptoms due to AF, however, are often difficult to assess. Every AF patient presents differently, some denying *any* symptoms until they have returned to normal rhythm, and then they suddenly feel a lot better. They might have been fatigued for 6 months and attributed this to aging. After cardioversion, however, they discover more energy. There are many AF patients, however, who are truly asymptomatic regardless of activity, and it is difficult to determine how aggressively to treat their AF, although patients with uncontrolled rates for many years sometimes develop a cardiomyopathy. When I manage a patient, I do not decide that I am going to take a specific rhythm-control approach or rate-control approach. I first assess the symptoms and what these mean for the particular patient and his or her family. If the AF is recent and perhaps reversible, which might make the patient feel better, I would probably attempt cardioversion. There is a lot of trial and error in managing many AF patients.

Dr. Friedewald: How does the risk for embolic stroke influence rate control versus rhythm control?

Dr. Olshansky: This is a very complicated issue. Data in AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management),[3] for example, which are probably the best data on this topic, suggest that it is very dangerous to discontinue warfarin in patients who are maintained in normal rhythm with an antiarrhythmic drug. There are some newer anticoagulants, such as direct thrombin inhibitors and factor Xa inhibitors, that also are effective. The antiarrhythmic dronedarone also may reduce stroke risk through an unknown mechanism other than its antiarrhythmic effect, although this has not been confirmed. There is, however, a lot we do not know about drug effects on AF outcome.

Dr. Yancy: I agree that stroke risk is not necessarily mitigated by achieving sinus rhythm or rate control, but we should acknowledge the risk and appropriately deploy anticoagulant strategies. Regarding rhythm versus rate control, my thinking has changed in recent years. I used to believe that *any* patient with HF and AF would benefit hemodynamically from conversion to sinus rhythm. Data have convinced me, however, that except for patients who are overtly symptomatic due to an excessive rate response or some other consequence of AF, cardioversion is not necessarily beneficial. Thus, our current approach is to focus on controlling the rate response, and 1 of the ways to achieve optimal rate response is with drugs for HF, specifically β blockers. This simplifies the treatment of AF in the setting of HF and avoids circumstances in which patients go in and out of sinus rhythm with the attendant risk of peripheral embolism. I believe that rhythm control ought to be relegated to the patient who clearly develops significant compromise due to AF.

Dr. Friedewald: What is the role of anticoagulation in AF?

Dr. Kowal: Anticoagulation is a separate issue. Restoration of sinus rhythm *does not reduce stroke risk*, which is a common misconception. Stroke risk is probably more complex than just a simple quantification of time in AF.

Dr. Yancy: I agree.

Dr. Friedewald: Are anticoagulants underprescribed for patients with AF?

Dr. Kowal: I believe that anticoagulants are more often prescribed for younger patients with AF than for older patients, who are more likely to benefit.

Dr. Yancy: Symptoms should not dictate whether patients should be anticoagulated. Only 60% of patients with AF and HF treated by cardiologists are prescribed anticoagulants.

Dr. Friedewald: This is consistent with the general tendency of physicians to undertreat many conditions.

Dr. Kowal: Not only is the initial prescribing rate for anticoagulants low, it falls further with time as many physicians discontinue anticoagulation in patients who remain in sinus rhythm. *This is a common practice that is neither guideline nor evidence-driven.*

Dr. Friedewald: Is there *any* type of patient with AF in whom you would eventually discontinue anticoagulation?

Dr. Kowal: Yes, *select* patients who have successfully had catheter ablation with low stroke risk, but this is an ill-defined area.

Dr. Yancy: That is another of our dilemmas about treatment of patients with AF. There are no measurable indicators of when anticoagulants can be discontinued following successful AF ablation. Some experts believe the decision should be driven by the $CHADS_2$ (cardiac failure, hypertension, age, diabetes, Stroke [doubled]) score,[4] with a score of 0 to 1 acceptable for *considering* anticoagulant discontinuation. The purpose of ablation, however, is not to eliminate the need for anticoagulation.

Dr. Olshansky: I agree. Many ablations are performed in young, otherwise healthy patients with frequent episodes of paroxysmal AF and do not have a high stroke risk. The $CHADS_2$ score is very important in determining the need for anticoagulation, because there is an incremental increase in risk of stroke with higher $CHADS_2$ scores. There is a new score, termed CHA_2DS_2-VASc (cardiac failure or dysfunction, hypertension, age >75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, and sex category), which incorporates additional, intermediate risk factors.[5] The $CHADS_2$ score includes an age of ≥ 75 years, whereas CHA_2DS_2-VASc includes an age of ≥ 65 years and places additional risk for women. Women with AF have a much higher risk of stroke than men, with a hazard ratio of about 1.6, independent of other risk factors. The presence of peripheral arterial vascular disease is another risk factor.

Unfortunately, patients at highest risk (i.e., those with the highest $CHADS_2$ scores), however, often are not anticoagulated. It also is important that the higher the $CHADS_2$ score, the higher the risk for bleeding, and so it's a "2-edged sword." Thus, with anticoagulation, it is important to maintain an INR (international normalized ratio) score in the therapeutic range of 2 to 3. This is a critical value, because outside this range, there is no protective effect of the anticoagulant, but there is an increased risk of bleeding. In patients with high $CHADS_2$ scores, the risk for stroke is ameliorated more by warfarin than is the increased risk for bleeding.

Dr. Friedewald: Does the $CHADS_2$ score equally apply to the newer anticoagulants?

Dr. Olshansky: There are some potential advantages of some of the new anticoagulants. If you can give a drug that anticoagulates quickly and is easy to take without monitoring, it would probably be given to more older people, and it might even be more valuable if the risk of bleeding is low enough that it could be given to people even with lower $CHADS_2$ scores, although *every* patient with AF, regardless of the $CHADS_2$ score, is at increased stroke risk. Thus, the main issue of anticoagulation is the risk-benefit ratio. In other words, we want to reduce the risk of stroke but we do not want to increase the risk of bleeding. Partially based on data and partially arbitrary, the usual approach is that when the $CHADS_2$ score is ≥ 2, the risk for bleeding is less than the potential benefit from warfarin. Thus, it is efficacious to use warfarin when the $CHADS_2$ score is ≥ 2. When it is <2, the risk for bleeding and the benefit of stroke reduction are similar, and it is in these patients that there is benefit in using 1 of the newer anticoagulants.

Another population in which we would consider short-term anticoagulation is patients who have a 1-time precipitant of AF, such as AF that is cardioverted after coronary artery bypass grafting, if the CHAD is low.

Dr. Friedewald: Let's discuss drug treatment of rate control and rhythm control.

Dr. Olshansky: Three to 5 million people have AF in the United States, so there *should* be a lot of data about rate control, but there are not, just a lot of small studies. Further, the reasons for controlling rate and end points for controlling rate have not been defined, and these vary among different populations. I believe the largest data we have on rate control in AF comes from the AFFIRM trial,[3] in which about 2,000 patients were in the rate-control arm and was very stringent, including exercise testing and ambulatory monitoring. AFFIRM looked at all the different methodologies to control rate, which included digoxin, various long- and short-acting β blockers, combinations of digoxin and β blockers, calcium channel blockers including verapamil and diltiazem, and combinations of all these agents. From these data, the best way to control rate is unclear. The RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation) trial,[6] in contrast, had much more lenient criteria for control: basically a ventricular response rate <100 beats/min with medication. Comparing those 2 trials, there is no real difference in outcome, except patients in AFFIRM had a slightly higher incidence of pacemaker implantation, suggesting an overly aggressive attempt at controlling rate. According to AFFIRM, the best long-term rate controlling combination is a β blocker with or without digoxin. The question remains, however, exactly what we are trying to achieve with rate control, which was highlighted recently in the RACE II trial,[7] in which a "lenient" approach was found at least as good as a more aggressive approach to rate control.

Dr. Friedewald: Do symptoms correlate with the ventricular response rate in AF?

Dr. Olshansky: Many AF patients are unaware of a fast heart rate. If, however, they do have symptoms and you treat them with a β blocker, they may become fatigued, and although the rate is controlled, new symptoms are created from the treatment. The goal should be to keep the AF patient's rate in a normal physiological range with exercise and at rest so that it mimics, as close as possible, what happens in sinus rhythm. The main problem is the trade-off of side effects from the rate-control medication.

Dr. Kowal: I agree with that approach to rate control. Although β blockers are often a first choice, each AF patient's co-morbid conditions, if any, must be taken into account in drug selection. For example, many patients with AF also have chronic obstructive pulmonary disease, which may worsen with a β blocker. Most patients, analogous to the treatment of hypertension, require >1 agent to attain optimal rate control. Another issue is that there are subsets of patients who get a tachycardia-related cardiomyopathy, and it is difficult to identify which patients are susceptible to this condition and which ones are not. There are patients who come to the office with heart rates of 150 beats/min who are minimally symptomatic and whose LV performance is normal, and others' LV function plummets when they are going that fast. Thus, the level of aggressiveness for rate control is dictated by multiple factors.

Dr. Friedewald: How much do you rely on the resting ECG, exercise testing and ambulatory monitoring versus symptoms alone for rate control?

Dr. Kowal: The resting ECG itself is useful. I encourage the use of heart rate monitors with exercise, and I often just walk a patient around the hall outside my office to see what their rate does.

Dr. Yancy: This is a great application for a very "low-tech" hall walk test so you can be certain that the resting heart rate that appears to be under control with whatever rate-limiting drug you use is still effective when the patient is active. I do not believe that an actual stress test or a tilt table or any other sort of elaborate provocation is more valuable. I will echo that part of what has been such an enigma about the treatment of AF is that the medical therapies are, in some patients, worse than the disease itself. Beta blockers make people feel sluggish, and those that are doing cognitive work do not feel quite as crisp. Calcium channel blockers, especially the nondihydropyridines, cause constipation. The prototypical antiarrhythmic drugs have a whole different set of side effects. Thus, there are many choices for rate control, but all of them suboptimal from the perspective of patient tolerability and outcomes.

Dr. Olshansky: There is no absolute *best* number for rate control. For example, in my experience, there are older persons who have very rapid rates and feel poorly, especially with fatigue, and their rates cannot be controlled with reasonable doses of medication. In AFFIRM, the rate could not be controlled in about 5% of AF patients. In such patients, an ablation of the AV (atrioventricular) junction and pacemaker insertion should be considered, because many patients treated this way have excellent improvement in symptoms. There is a question whether a resynchronization-type pacemaker, a single VVI pacemaker, or a dual-chamber pacemaker should be used in patients who are going in and out of AF. It is not successful in everyone, and I certainly would not recommend it for the majority of such patients. With this approach, however, the patient remains in AF at least part of the time, so anticoagulation is indicated because the risk of stroke is not lessened.

Dr. Friedewald: What is the role, if any, of dronedarone or amiodarone in rate control?

Dr. Yancy: Amiodarone is a more effective agent for rate control, but the advantage of dronedarone is in less morbidity, except in patients with symptomatic, NYHA (New York Heart Association) class III or IV HF.

Dr. Olshansky: Both amiodarone and dronedarone can control rate. In the EURIDIS and ADONIS trials there was approximately a 10 beat per minute reduction in rate with dronedarone.[8]

Dr. Friedewald: Let's discuss AF rhythm control with medications.

Dr. Kowal: Each situation is different, so matching drugs to specific patient types, especially as they relate to co-morbidities, is important. It is not as simple as "Give this drug with the first episode, this drug with the second," et cetera. Drugs effective for AF function differently according to their class, and their side effects and adverse effects also differ.

Dr. Olshansky: All drugs that are effective for rhythm control have toxic risks. Thus, the goal is to balance the benefits of the drugs against their toxic effects. Antiarrhythmic drugs are only partially effective, so AF recurrences usually occur with drug rhythm control. There may be only *less* recurrence of AF while taking an antiarrhythmic drug, and in many patients that might suffice. In some cases, however, perfect control of AF is the goal, and that is hard to attain with antiarrhythmic drugs. Amiodarone is the most efficacious antiarrhythmic drug for maintaining sinus rhythm in patients with AF but has potentially very severe side effects, including toxic effects on the lung, skin, thyroid, and nervous system. Amiodarone is *not indicated for maintaining sinus rhythm* in patients with prior AF, but it is the most commonly used drug for this purpose. This points to the fact that rate- versus rhythm-control drug studies do not favor sinus rhythm maintenance because of the side effects.

Antiarrhythmic drugs have a role in maintaining sinus rhythm in patients with recurrent episodes after cardioversion. Most of the drugs for rhythm control are class III antiarrhythmics, including sotalol, dronedarone, amiodarone, and dofetilide. Dofetilide has a very small role, but nevertheless, it is a good drug to maintain sinus rhythm and needs to be started in the hospital under observation because of its risk of QT interval prolongation. Sotalol also must be started in the hospital and is contraindicated in patients with structural heart disease and with LV dysfunction (ejection fraction $<35\%$) secondary to ischemic heart disease. The role of dronedarone is growing and has been used in patients who are at low risk for severe HF or acute exacerbations of HF; in such patients, there is outcome improvement. Dronedarone has a short half-life and must be given twice a day. Compared to placebo, over time, patients taking dronedarone have a decreased risk of mortality and cardiac hospitalization, which is a unique end point and the basis for its indication, not maintenance of sinus rhythm or symptom reduction. The other drugs sometimes used for AF rhythm control are the IC antiarrhythmic drugs like flecainide and propafenone, which *cannot be given to patients with structural heart disease or ischemic heart disease*. Thus, evaluation for these conditions is needed before prescribing them. Such evaluation includes an echocardiogram showing an LV wall thickness of ≤ 1.4 cm, and there needs to be evidence, at least by a noninvasive approach, such as an exercise thallium test, that no ischemic heart disease is present. The IC drugs also have proarrhythmic effects, including atrial flutter with 1:1 conduction and ventricular tachycardia, and cannot be given to patients with bundle branch block.

Dr. Friedewald: Patient adherence to medication is a huge issue in cardiovascular medicine. Amiodarone, however, has an extraordinarily long half-life, and I wonder whether at least part of the difference in efficacy between amiodarone and dronedarone is attributable to the need to take dronedarone twice daily. Any patient prescribed dronedarone should receive special emphasis on the need to take it twice daily, as the second dose of medications in general is missed as often as 20% to 25% of the time.

Dr. Kowal: That point is important and also applies to dofetilide, flecainide, and sotalol, which are all twice-a-day drugs. Non-extended-release propafenone should be taken 3 times per day.

Dr. Yancy: We must emphasize the side effect profile of amiodarone. There is no way you can prescribe a toxic compound like that and, either as the practitioner, as the person working in the office, or as a pharmacist dispensing the med, not discuss these effects. Patients who are fully aware of those concerns are much less likely to take amiodarone.

Dr. Kowal: In our institution, we emphasize the importance of taking dronedarone every 12 hours.

Dr. Olshansky: Dofetilide also is a good drug, but you do have to start it in the hospital and the risk, I believe, is probably similar to many other drugs in terms of Torsades and the potential for QT prolongation. Dronedarone, however, does not need to be started in the hospital, because its risk for Torsades is low, although it can cause small degrees of QT prolongation.

Dr. Roberts: Do you ever use quinidine?

Dr. Olshansky: No.

Dr. Roberts: What is the role of digitalis in AF?

Dr. Olshansky: As a rate-controlling drug it has a small effect, but its exact role in rate control is unclear. Also, it is toxic in high doses.

Dr. Kowal: Digitalis is synergistic with β blockers and calcium channel blockers.

Dr. Olshansky: Digitalis is much more effective when used in conjunction with those drugs.

Dr. Yancy: Its utility is best when added *after* a β blocker, but not as a starting drug.

Dr. Friedewald: What dose of digoxin do you recommend for AF?

Dr. Yancy: I prescribe whatever dose is required to achieve rate control, an approach that makes many people unnecessarily toxic. The best dose is probably 0.1 mg/day, with the goal of a drug level that is significantly $<$1.0 ng/dl.

Dr. Roberts: Are drug levels of digitalis important?

Dr. Yancy: Yes, because digitalis serum level monitoring is the best way to avoid toxicity.

Dr. Yancy: From the perspective of a physician involved with AF in the setting of HF rather than as a primary condition, we do not have sufficient agents to effectively manage either rate or rhythm. My concern about AFFIRM is that there was no ideal agent to test in that study. Therefore, I am not surprised that so much crossover occurred, which confounds the interpretation, because by an intent-to-treat design, a significant 30% to 40% of the patients in each arm ended on a different treatment assignment than the original intention; such results are difficult to interpret.

Dr. Olshansky: I agree. AFFIRM tried to do a very rigorous study of rate control as part of an initial substudy by randomizing patients to either β blockers or calcium channel blockers followed by adding digitalis. When we started randomizing patients, we found that we could not control rate very well. But when we looked at the way people use these medicines clinically, and they kept switching them around, they ultimately got a rate-control strategy. In our analysis in the AFFIRM database, we incorporated a statistic to look at that switching approach because by switching drugs, you eventually get a proper rate control, which varies from patient to patient. There was no "magic number" for any patient, and most patients ended up on β blockers. This is the art of medicine in the sense that with AF, there is no 1 approach that allows for putting patients on a particular drug and they are then permanently controlled. Rather, AF rate control requires constant monitoring, with frequent follow-up clinic visits. AF is a complex condition to manage.

Dr. Roberts: How many cardioversions do you generally perform before considering more radical therapy such as ablation?

Dr. Olshansky: That also is a complex question. When you mention cardioversion, some patients run for the hills—and there are not many hills in Iowa! Other patients, however, welcome the suggestion for cardioversion and willingly return for repeat procedures with AF recurrence. Cardioversion, however, has some potential negative effects on the heart when several are repeated in a period of time, so there is a small risk with that approach. It does not make sense to repeat the procedure if they return 3 days later back in AF. Once per year cardioversion, however, is a reasonable frequency, even carried out over 10 years. This is a matter of clinical judgment. You do not want to perform cardioversions too frequently, and when you get to 2 or more in a year, you need to reassess the strategy, such as new drug combinations or ablation. The procedure itself, however, is reasonably safe, provided the patient is properly anticoagulated in advance.

Dr. Kowal: There is new insight about the utility of the drug approach compared to ablation, particularly for patients with paroxysmal AF, such as studies that have randomized patients who have failed to convert with a first drug who are then given a second drug versus proceeding to ablation. If the first drug has a 50% effectiveness over a 1-year period, the second drug is much worse, with second drug success as low as $<$10%. Thus, when 1 drug fails, use of a second drug to control rhythm is likely to fail as well.

Dr. Friedewald: Dr. Yancy, what is the correlation between HF control and AF control?

Dr. Yancy: The main objective is to determine the driver of the patient's symptoms. If the patient has documented low LV ejection fraction, HF treatment based on appropriate evidence-based therapy is the first goal, recognizing that a β blocker will be strongly indicated, as well as digoxin. If AF remains a problem after appropriate HF treatment, the AF should be the treatment target, recognizing that antiarrhythmics bring their own set of arrhythmia problems, especially soltalol and ibutilide. In some patients, correcting the AF dramatically improves the HF.

Dr. Roberts: What about treatment of AF in the setting of HF with normal LV ejection fraction?

Dr. Yancy: This is *totally* driven by the indications for AF management. For example, the reasons for anticoagulation are the same. HF alone achieves a $CHADS_2$ of at least 1 and unless the patient is very young, the $CHADS_2$ is at least 2, thereby indicating the need for anticoagulation. There are emerging data suggesting that direct thrombin inhibitors may be more efficacious alternatives to warfarin. It appears that at a standard dose, they may be more efficacious for stroke prevention than INR-adjusted use of anticoagulation with warfarin. The lower dose of a thrombin inhibitor may be of similar efficacy but with less bleeding risk. The bleeding risk is not zero with dabigatran, and in standard dose, the bleeding risk is similar to the bleeding risk with warfarin, but the freedom from serial assessment is a patient comfort advantage. The main side effect with dabigatran is gastrointestinal upset.

Dr. Kowal: Another common clinical conundrum is the combination of drug-eluting stents and AF (i.e., how to manage the combination of aspirin, clopidogrel, and warfarin in the safest and most efficacious manner). We have little data about this situation.

Dr. Roberts: What do you do?

Dr. Kowal: This is very patient specific. In the setting of a drug-eluting stent, I typically use warfarin and clopidogrel. Aspirin for a short period and clopidogrel is a reasonable alternative in some instances, but we need guidelines for such patients.

Dr. Roberts: AF after cardiac surgery, especially coronary artery bypass grafting, is common. How do you manage AF in that setting? Also, what is the current status of LA appendage occluders?

Dr. Yancy: Left atrial appendage occluder, LA appendage resection, and percutaneous ablation *appear* to be effective, but outcome studies are lacking.

Dr. Olshansky: Which AF patients get percutaneous ablation and who gets an occluder is an important issue, but we again do not have good data. Postoperative AF management has many possible approaches that are currently based solely on clinical judgment, and usually is comprised of amiodarone, β blockers, and warfarin. The new Xa inhibitors and direct thrombin inhibitors could revolutionize AF management in the sense that patients with lower risk for stroke but $CHADS_2$ scores of 1 may be candidates for these drugs.

Dr. Friedewald: What is the current and future status of ablation for AF?

Dr. Olshansky: Ablation is highly effective for certain subpopulations with AF, but we are just starting to understand who those subpopulations are. The highly symptomatic patient with an otherwise normal heart and paroxysmal, lone AF is an ideal candidate for ablation. Patients with persistent AF, older patients with AF, and even patients with persistent AF also may benefit. Ablation may even have a role in AF patients with HF. Ablation, however, is not a perfect solution as some patients require more than 1 ablation; ablation has proarrhythmic effects such as atrial flutter; patients sometimes get worse in the first several weeks or months after the ablation before they get better; and there are risks of perforation and esophageal injury, which are infrequent but need to be explained to patients who are otherwise healthy.

We have much to learn about the new therapies, because the prevalence of AF is increasing. We also need to know more about the different mechanisms responsible; AF is not simply a condition with 1 potential mechanism. This is an exciting time in electrophysiology, with the need to address a lot of unanswered questions about AF.

Dr. Yancy: With all of the interventions that are seemingly effective and increasingly so, we have to remember that these low-frequency events of complications have serious consequences. This must force us to recall exactly *why* we are treating AF from the outset. We need to think about the risk factors that drive the conditions that cause AF: coronary artery disease, HF, hypertension. Paying attention to the blood pressure and achieving blood pressure control, controlling dyslipidemia, managing obesity: these are issues that continue to be implicated in virtually the entire portfolio of cardiovascular diseases. We have excellent drug treatments and procedures, and a great future to anticipate, but we cannot ignore the importance of preventing the processes that lead to AF in the first place.

One additional and fascinating point are the biomarker data in asymptomatic community populations, such as intranormal elevations of β natriuretic peptide (BNP), which are predictive of stroke, HF, and AF over relatively short periods of time. If we could identify an appropriate way to screen patients at risk for AF and other cardiovascular diseases, there may be preemptive therapies that are safe and effective (e.g., statins and renin-angiotensin blockers) that could attenuate the disease before it starts. This concept relies on precise disease markers. BNP is crude, but if we could find a more precise marker that would allow us to anticipate risk *before* AF occurs and then treat the risk, that would be a fundamental breakthrough.

Dr. Olshansky: We also are learning more about genomics, and there are some interesting data that there is a predisposition to AF that can be predicted by certain gene markers. Currently, we are treating "after the fact." AF is a huge problem because up to 10% of the population >80 years have this condition.

Dr. Yancy: And that is the fastest growing segment of our population.

Dr. Friedewald: Thank you.

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