Case Studies with the Experts: Management Decisions in Atrial Fibrillation

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Case Studies with the Experts. Atrial fibrillation (AF) is the most common outpatient arrhythmia. The recent ACC/AHA/ESC guidelines outline a variety of approaches to the management of AF, but their implementation into clinical practice requires multi-faceted patient evaluations and assessments for optimizing patient care. Using a case-based approach, issues such as rate versus rhythm control, anticoagulation, cardioversion, pharmacological and catheter ablation for maintenance of sinus rhythm, and the pathophysiology of AF are discussed. These data were originally presented at a satellite symposium titled Case Studies with the Experts: Management Decisions in AF, held on May 10, 2007, during the annual Heart Rhythm Society meeting. (J Cardiovasc Electrophysiol, Vol. 19, pp. 1-12, Suppl. 1, 2008)

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Program Title
Case Studies with the Experts: Management Decisions in Atrial Fibrillation

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Activity Description
This journal supplement poses difficult clinical case scenarios to experts in the field of atrial fibrillation. Topics include complex decisions regarding indications for and timing and duration of cardioversion, effects of comorbidities and atrial remodeling on antiarrhythmic choices, mechanisms of action, indications, guidelines, and management implications of antiarrhythmic agent choices, and decisions about recommendations for ablation and outcomes expectations. The expert panel reviews clinical data and guidelines in the context of clinical case scenarios, and provides treatment options and evidence-based decisions for patient care.

The content of this supplement was originally presented at a satellite symposium of the same title on May 10, 2007, at the Heart Rhythm 2007 Scientific Sessions. The estimated time to complete this activity is 2 hours.

Learning Objectives
After participating in this educational activity, participants should be able to do the following:

- Recognize the burden, common comorbidities, and clinical progression of AF and the effect of atrial remodeling on management choices.
- Review indications and critical decisions for the initiation, duration, and choice of anticoagulation in patients with AF.
- Describe the current guidelines and their integration into patient care as well as new and emerging data affecting choices for antiarrhythmic therapy for the cardioversion and maintenance of sinus rhythm.
- Discuss the use, indications, and expected outcomes for ablation in patients with AF.

Target Audience
This educational activity has been designed for cardiologists and electrophysiologists.

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**Introduction**

The prevalence of atrial fibrillation (AF) is exploding, and its burden on both patients and the medical system is reaching alarming levels. This situation is occurring because of multiple facets, including an aging population, increased co-morbidities such as hypertension (HTN) and diabetes, and better understanding of its asymptomatic presentation, especially in the older population. The recently published ACC/AHA/ESC AF management guidelines provide the clinician with a variety of new therapeutic approaches to AF. At a satellite symposium titled *Case Studies with the Experts: Management Decisions in AF*, held on May 10, 2007, during the annual Heart Rhythm Society meeting, a panel of experts provided an in-depth discussion of the pathophysiology and treatment of AF using a case-based format. Each case provides an opportunity to review an area of AF. Issues covered range from mechanisms of AF to ablation. These data have been edited into a more concise publication.

**Anticoagulation: Difficult Decisions for Whom, Which Agent, and How Long**

**Case 1**

PRYSTOWSKY: A 48-year-old woman has a history of very symptomatic intermittent palpitations for 1 year that last from seconds to minutes, with occasional shortness of breath during the longer episodes. An event recorder documented AF as the cause of the symptoms. She also has a history of HTN treated with enalapril. Her physical examination is normal. Echocardiogram shows a normal-sized left atrium, normal left ventricular ejection fraction (LVEF), and no hypertrophy. Should this patient receive long-term anticoagulation therapy?

RUSKIN: I don’t think you have to use anticoagulants, but I think I’d be inclined to do so. I suppose if you did this strictly by the guidelines, you’d have a choice of aspirin or warfarin in this patient.

PRYSTOWSKY: Dr. Kowey, would you review the changes in the 2006 vs 2001 guidelines?

KOWEY: The guideline differences between 2001 and 2006 really aren’t very dramatic, but there are some things that required alteration. In the 2001 guidelines, HTN is a class I recommendation for warfarin anticoagulation. In the current 2006 guidelines, there’s been an adoption of the concept of the CHADS2 scoring system, whereby scores are allocated, in nonvalvular AF, according to a variety of factors, such as congestive heart failure (C), hypertension (H), age over 75 years (A), diabetes mellitus (D), and history of stroke or transient ischemic attack (S2) (Fig. 1). Using this scoring system allows you to determine the relative risk of stroke. A score of 0 requires aspirin only, and with a CHADS2 score of 1, either aspirin or warfarin can be used, as is the case in this patient.

That said, we need to understand how this recommendation was formulated. It did not come from the hardest data available, but from extrapolations in the literature and from people’s impressions, and so I would say that in the absence of compelling data to tell me that it’s safe not to anticoagulate with warfarin, I would use warfarin in this person. Of note, this patient represents a common problem because HTN is the most important pathogenetic factor in AF and often is the sole risk factor present for stroke. I suspect that if you open the door and give a choice to the patients, they most certainly will pick aspirin, so I think it is incumbent upon us to remain somewhat conservative.

PRYSTOWSKY: Don’t you feel it’s fair to the patients to tell them they have a choice? You could obviously say that you don’t agree with one option.

RUSKIN: What I do is to tell them what I recommend, but I also tell them I tend to favor warfarin, and they could see 10 other doctors and 8 of them might prescribe aspirin. Thus, the patient needs to know the choices, but also why I lean toward warfarin. I agree with Dr. Kowey that most patients given the opportunity would not want to take warfarin. However, I’m frequently surprised at how many will opt for warfarin after a pretty extensive discussion of the risks and benefits.

KOWEY: There’s actually as much violation of the guidelines using warfarin anticoagulation to anticoagulate people who don’t need to be anticoagulated as not anticoagulating people who need to be anticoagulated. Of course, you have the discussion with the patients and the patients do generally make the right decision, but I think there is a tendency among many physicians to be somewhat aggressive in many cases and decide to prescribe warfarin just to be on the safe side. That’s not fair either.

PRYSTOWSKY: I totally agree. Dr. Jais, what is the feeling about anticoagulation in France?

JAIŠ: I cannot speak for my colleagues, but the point I would like to make is that warfarin can be tried for a short period of time, e.g., 2 or 3 months, and the results evaluated. If the international normalized ratio (INR) has been difficult to stabilize, with substantial variability from 1.5 to 5, I would be reluctant to continue warfarin and would probably prescribe aspirin. However, if INR values have been relatively stable, e.g., 2 or 2.5, the risk appears low, and I would continue with warfarin treatment.

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**Figure 1. CHADS2 risk stratification scheme. CHADS2 = congestive heart failure (C), hypertension (H), age over 75 years (A), diabetes mellitus (D), and history of stroke or transient ischemic attack (S₂). Rockson SG, Alberts GW: Comparing the guidelines: Anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. J Am Coll Cardiol 2004;43:929-935 (A).**

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tr>
<td>C Recent congestive heart failure</td>
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<td>H Hypertension</td>
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<td>A Age ≥75 years</td>
<td>1</td>
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<td>D Diabetes mellitus</td>
<td>1</td>
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<td>S2 History of stroke or transient ischemic attack</td>
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PRYSTOWSKY: That’s an interesting approach. Dr. Ruskin, what do you think?

RUSKIN: I agree, it is interesting. In my opinion, this is a patient in whom I would have a low threshold for starting warfarin, but also a very low threshold for stopping it. Further, this is someone in whom I think we would try to control the AF, and I would be very comfortable with stopping warfarin if the AF were suppressed.

PRYSTOWSKY: Dr. Nattel, what is the approach in Canada?

NATTEL: I think it’s pretty similar. Unfortunately, we don’t have absolute answers, but one of the issues that we need to deal with is that the guidelines consider treated HTN the same as untreated HTN, and 1 episode of paroxysmal AF that lasts for 5 minutes no differently than persistent AF. In a patient like this, with relatively short-lived episodes of AF whose only risk factor is treated HTN, I would definitely give her a choice of aspirin or warfarin.

PRYSTOWSKY: Very reasonable. I am predisposed to use warfarin in patients with HTN. However, in the office I give patients with HTN as the only risk factor for stroke a choice of aspirin or warfarin. I tell them my bias is to use warfarin, and about 75% of such patients opt for warfarin. For patients who have been taking warfarin and have had reasonably stable INR levels, almost all continue taking warfarin.

RUSKIN: My question is whether you think aspirin is better than nothing.

PRYSTOWSKY: I do think so, in this group of patients.

RUSKIN: I think aspirin’s effectiveness is in the realm of possibility, and obviously the risk is pretty low, but the data are not compelling. There’s an ongoing clinical trial in which patients are being genotyped for the 2C9 metabolic pathway to try to determine whether or not patients are going to have this kind of variability before they start to get dosing. This is one way of trying to improve the safety of warfarin therapy, because what predisposes people to events are these wide fluctuations in INR, and if you can avoid them, possibly by knowing their genotype prospectively, this may be a step forward for a more effective and safer approach to warfarin treatment.

Case 2

PRYSTOWSKY: This is an 18-year-old man who was referred for a second opinion for recent onset of AF 2 months ago. The patient was undergoing a tooth extraction under anesthesia, and AF suddenly occurred on the monitor. They stopped the procedure, and he never got his tooth removed. He was asymptomatic, and his physicians decided to leave him in AF. At the office visit, he claimed to have no symptoms and there is no family history of cardiac arrhythmias. Physical examination was normal, except for an irregular heart rate of 81 beats per minute. Echocardiogram showed a normal LVEF without left ventricular hypertrophy (LVH) and a normal left atrium. Thyroid functions and electrolytes were normal. The 24-hour Holter monitor was very interesting, with a mean heart rate of 86 beats per minute in the absence of drugs. The electrocardiogram showed AF with some nonspecific findings.

This patient was left in AF by his local doctor because of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. However, this young man is nothing like the type of patient enrolled in AFFIRM. The AFFIRM population consisted of elderly people who typically were at risk for stroke, and the mean age was almost 70 years. Thus, it is not appropriate to base one’s clinical treatment plan for this patient on the results of AFFIRM. Dr. Nattel, now that this patient has been in persistent AF, what type of atrial changes have occurred?

NATTEL: The real question is: Does the presence of AF for a long period of time do anything to the atrium, and even to the ventricle? Atrial changes do occur during persistent AF. The atrial rate is increased by about 10-fold, and with each atrial activation, calcium enters the cell. So if you have 10 times as many atrial beats, you’ve got 10 times as much calcium going into the cell if nothing else happens, and if the cell had 10 times as much calcium in it, it would die. So, the cell has ways of dealing with this threat to cell viability, and the main way is by reducing the calcium current that brings calcium into the cell. In the short term, the calcium channels inactivate, and that’s over the course of minutes, and that reduces the calcium current. Over the course of hours to days, genetic reprogramming happens that decreases the production of the messenger RNA that encodes the calcium channel, which decreases the amount of calcium-channel protein being produced, and which then produces a form of long-term stable reduction in the calcium current.

The decrease in calcium current also shortens the duration of the atrial action potential. Calcium entry is the main process that keeps the cell depolarized, and so when you have less calcium going in, the action potential gets shorter. If the action potential is shorter, the refractory period is shorter, because the cell is available for firing sooner. If the refractory period is shorter, then the size of reentry circuits, or wavelength, is reduced, and that way it’s much easier to maintain AF. Thus, one of the things that happens with AF is that the cells adapt to the fast rate by changing their electrophysiology such that AF is more easily maintained, and that tends to perpetuate the arrhythmia.

Figure 2 shows the mechanism by which AF affects atrial tissue in heart failure (HF). The top panels are epicardial activation maps, and the lines show the propagation of an electrical impulse in the heart. In the control case, the lines are all nice and smooth, but in HF, there are areas of very slow conduction shown by the crowded lines, and the reason for that is shown in the bottom panels. These are histologic sections from canine atra that have been maintained either in HF or in normal rhythm. In the normal case, you have very fine, pale areas of fibrous tissue separating the myocytes, which are darker. The paler areas represent connective tissue and there’s very little there, the normal connective tissue distribution that’s necessary to hold the cells together. In the lower right-hand panel in HF, there are big bundles of pale tissue that represent extreme fibrosis. If you look at the bar graph at the left side, AF duration is greatly prolonged in HF because all of this fibrosis interferes with conduction.

What about AF in the absence of HF? A recent study was performed in pigs that were induced into AF by rapid atrial pacing and their ventricular rate was controlled, so they had no cardiomyopathy. There was, nevertheless, quite a substantial increase in the amount of fibrosis with AF and also an increase in collagen expression. This protein that creates connective tissue in this pig with AF suggests that if AF lasts long enough, scarring can occur in the atria and make them dilated and much more likely to stay in fibrillation.
Let’s examine the data from one other study done by Allessie’s group (Fig. 3). They studied goats kept in AF for up to 4 months by brief atrial burst-pacing whenever sinus rhythm (SR) occurred. The top left-hand panel is the AF cycle length (AFCL), which is an indication of the refractory period during AF. After 4 months of AF, the AFCL shortens compared with SR, and then 2 months after stopping the AF, and more so 4 months after stopping the AF, the AFCL recovers, so electrically the atria return to normal. The top right of the figure demonstrates that even 4 months after this goat has been in SR, the AF duration stays prolonged, and the reason is, presumably, that the 4-month histologic picture doesn’t look like SR. Therefore, if AF persists long enough, there are changes that happen to the atria that make it very much harder to restore and maintain SR.

So, the bottom line is that if you allow someone to stay in AF with a wait-and-watch policy, and then, maybe in 6 months or a year if they are not feeling well, decide to convert them to SR, you may have a much harder time doing so because of irreversible changes due to the AF itself.

PRYSTOWSKY: I’ve wondered whether we can extrapolate the data from animal models of HF to humans. For example, do you think that patients with HF and AF who have well-controlled ventricular rates have less atrial fibrosis than those in whom the ventricular rates are relatively fast?

NATTEL: Well, I think that certainly you’re much more likely to get atrial fibrosis if the ventricular rate is not controlled and you have an element of HF. However, the animal data and some clinical data suggest that even if there’s no clear HF and the ventricular rate is well controlled, there may still be, over longer periods of time, the development of atrial fibrosis. Another point is that the effect of AF on ventricular function is likely more complicated than simply rate control. I don’t think any of us really know what appropriate heart rate control is, and the heart rate control that we get with atrioventricular (AV) nodal blockers is not the same as a normal chronotropic response to the physiologic needs.

PRYSTOWSKY: Additionally, at his age, to have a controlled ventricular rate suggests he has some AV node disease, and this may become manifest in the future.

RUSKIN: Having AF at 18 is extraordinary and I’d look hard for family history, and if it’s not there, I would be worried about the patient having a sodium-channel mutation. I would observe his ventricular function and his left atrial size very carefully over time. Although we don’t have the data, I would try to keep him in SR.

Figure 2. Structural remodeling in CHF. AF = atrial fibrillation; CHF = congestive heart failure. Li D, Fareh S, Leung TK, Nattel S: Promotion of atrial fibrillation by heart failure in dogs: Atrial remodeling of a different sort. Circulation 1999;100:87-95, by permission of Lippincott Williams & Wilkins.

PRYSTOWSKY: Would you do a yearly echocardiogram?  
RUSKIN: At least yearly.

PRYSTOWSKY: Let me tell you what I did with this patient. Remember, he adamantly denied any symptoms. Since he had been in AF so long, I thought he’d probably revert to AF after cardioversion, so I treated him with flecainide for a couple of days in hospital, then cardioverted him. Two months later he returned for an office visit still in SR, at which point I stopped his flecainide. I asked him how he was feeling and, to my surprise, he stated that he hadn’t felt this good in months. Specifically, he said he no longer experiences those “skips,” which he had come to believe were simply normal for him and thus reported “no abnormalities.”

RUSKIN: It’s the kind of the thing you see often with more elderly patients, who have a slow heart rate and don’t know how much better they will feel in SR. The other thing about your patient’s rate is that I don’t think we fully understand why AF is harmful to the ventricle. Rate is only part of it, and I think irregularity is the other part.

PRYSTOWSKY: I agree with that.

RUSKIN: It clearly impairs filling on a regular basis, which has, ultimately, systolic consequences.

PRYSTOWSKY: Dr. Jaíś, your recent article on catheter ablation in patients with AF and HF had some interesting observations that I would like you to discuss.

JAÍŚ: We probably don’t know everything about the negative impact of AF on heart function, and it’s certainly not restricted only to heart rate. I’m not even sure that the regularity is the whole explanation. I think there’s much more than that, and in our study, we had a group of 58 patients with HF and AF. It was divided between 45% of them with reasonable ventricular rate control prior to AF ablation and 55% who were not properly rate controlled. The improvement in LVEF was greater in the group in whom heart rate was higher, but it was about a 23% increase in this group, absolute value of LVEF, as compared with 17% in the group with good rate control, so that’s a huge impact, given that the rate was properly controlled.

The impact of AF on heart function has probably been largely underestimated, and we all know that drugs have some impact, but also some deleterious effects. The substudy of AFFIRM showing that mortality was in fact higher in patients receiving drugs and lower in those in SR supports that if you can maintain SR without the negative impact of drugs, that’s probably beneficial for the patient.

Antiarrhythmic Drugs: Mechanisms, Algorithms, and Management Choices

Case 3

PRYSTOWSKY: A 62-year-old woman is referred with a history of HTN and a 3- to 4-year history of AF, which began as paroxysmal AF, and she was initially treated with a beta blocker. The episodes became more frequent, symptoms worsened, and propafenone was added with reasonable results and only occasional episodes of AF. She had a normal echocardiogram and stress test. Over the past year, the patient has had numerous recurrences, and she currently has persistent AF. Medications include metoprolol, propafenone, and warfarin, and she now presents for cardioversion.

If you cardiovert this patient, would you consider changing her antiarrhythmic agent prior to cardioversion? Also, are angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) useful in this patient? KOWEY: The issue of ACEIs and ARBs is a hot topic because people are very interested in the concept of adjunctive therapy for AF, and it’s basically in two modes. One mode is as an add-on to an antiarrhythmic drug, which is the question for this patient, and the other is for prevention in patients at high risk. The data from the Valsartan in Acute Myocardial Infarction (VALIANT) trial clearly show that there was a lower incidence of AF with valsartan.

In Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM), a trial involving candesartan, an analysis of the data showed that, especially in the low ejection fraction patients, there may be some benefit in terms of prevention of AF. Similarly, irbesartan added to amiodarone showed a reduction in AF after cardioversion versus amiodarone alone, but it was a relatively small trial (Fig. 4). So, based on this information, there’s a large initiative to try to study the effect of ACEI/ARB therapy on AF in a prospective way. One such trial is Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) (Fig. 5). ACTIVE is the study that’s looking at clopidogrel and aspirin, but in a multi-factorial design; it is also looking at irbesartan for the prevention of AF in this high-risk cohort. At present, I don’t think that the treatment effect you’re going to gain out of an ACEI or an ARB is adequate justification to just add that and perform cardioversion. I think that I would stop propafenone, load the patient with another antiarrhythmic drug, and then cardiovert to SR.

PRYSTOWSKY: I agree that there are no data to support ACEI/ARB use as a primary treatment yet, but when I have a patient with HTN and with AF or at risk for AF, I often use an ACEI or an ARB to control blood pressure.

Let’s discuss the choice of antiarrhythmic drugs. The treatment algorithm from the 2006 ACC/AHA/ESC guidelines uses a safety-first approach (Fig. 6). In people with minimal or no structural heart disease, drugs with minimal organ toxicity are preferred, such as flecainide, propafenone, and sotalol; amiodarone and dofetilide are second-line choices. Based on the concept that substantial LVH increases the risk of proarrhythmia with most drugs, amiodarone is suggested as first-line treatment in this category. For coronary artery...

disease, dofetilide and sotalol are initial choices, with amiodarone as second-line. Finally, amiodarone and dofetilide are the only drug choices in HF based on data from trials. Note that catheter ablation is second-line in all categories. Dr. Nattel, please comment on this approach from your viewpoint.

effects. LVH seems to be a moderate risk factor for the IC agents, and the patients probably not at increased risk are those with a normal heart, female sex, diuretic therapy, and renal failure.

The class III drugs have a totally different risk profile. For them, coronary artery disease is not much of a risk factor. CHF is a risk and LVH very much increases one’s risk. There are a lot of data suggesting that the risk of torsade de pointes is substantially increased with LVH or HTN. Female sex is an important risk factor, although exactly why is not clear. Diuretic therapy and renal failure, which are not necessarily a problem for IC agents, are a problem for class III agents. In the case of amiodarone, the good side is that the cardiac risks in general are very low, although CHF is a moderate-risk group. Torsade de pointes does occur with increased rate with amiodarone in HF patients, but all the other categories are not at increased risk.

Although toxicity is the most important consideration, we still are concerned about efficacy, and there, amiodarone is by far the most efficacious, with flecainide, propafenone, sotalol, and dofetilide basically equal. Beta blockers are the least efficacious.

We talked about cardiac risks, but we can’t forget extracardiac risks, and beta blockers, propafenone, sotalol, and dofetilide are all pretty much equivalent and fairly low. Amiodarone is by far the worst. So in the AF management guidelines, there’s a pretty simple general rule. The rule is that amiodarone is kept in reserve because of its significant risk of extracardiac toxicity, particularly with longer term therapy, so it’s not a first-line drug unless the risks of the alternatives are too high. The simple rationale is that you use what’s least dangerous first, and if nothing else, then amiodarone; catheter ablation is coming second, but it might come a lot higher in the future.

PRYSTOWSKY: Catheter ablation was discussed in-depth as first-line therapy for patients with no or minimal heart disease. I suspect it will be positioned as first-line treatment for 1 or more categories in the next guideline update with more trial data being available.

In reviewing the literature, I came across an interesting study in Nature on a tarantula peptide that can antagonize stretch receptors and, in a model of increased pressure in the atria, prevent AF. Dr. Kowey, will you enlighten us on investigational drugs for AF?

KOWEY: Looking at the guideline algorithm, it’s amiodarone across the board. We’ve really got to come up with some better ideas, because we seem to be stuck on the same old drugs. The good news is that there is a fair amount of work being done. Figure 7 shows some of the possible mechanisms by which some of these newer agents may work. Many of us have been mystified by the fact that some of the most effective drugs we’ve ever seen are so-called “dirty drugs”—drugs that have multiple mechanisms of action. Certainly amiodarone fits into that category, and so there are a number of drugs in the pipeline that have a combination of ion-channel effects that perhaps in aggregate may be more beneficial than anything in particular.

Dronedarone has been under regulatory review for an approval for the specific indication of prevention of recurrent AF and symptomatic AF, and this is a drug that is like amiodarone but lacks the iodine moiety. The promise of dronedarone is that it should be devoid of the thyroid and pulmonary toxicity that plagues amiodarone use.

There have been a series of clinical trials evaluating dronedarone. In a phase 2 trial that was a dose-finding experiment, a reverse dose response for dronedarone was identified, and based on these data, the 400 bid dose was selected for use in the pivotal phase 3 trials.

The phase 3 trials were EURIDIS (EUropean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm) and ADONIS (American–Australian trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm), which were extraordinarily important in establishing the safety and efficacy of dronedarone. The results of those two trials look very similar, showing clear efficacy superiority for dronedarone compared with placebo for the primary end point of first recurrence of AF or flutter (Fig. 8). Even more importantly, the pooled tolerability and safety data for this experiment indicated that the drug was just about as safe as placebo for patients who had some heart disease (Table 1). These were patients who had coronary disease and hypertensive heart disease. These were not patients with normal hearts, but an appropriate target population. I would point out that there have not been any cases of torsade de pointes reported with the use of dronedarone.

The ANDROMEDA (Antiarrhythmic trial with Dronedarone in Moderate to severe CHF Evaluating morbidity Decrease) study evaluated dronedarone in patients with substantial HF and showed a mortality disadvantage for the drug. There were lots of caveats around that observation, and it has mandated another study called ATHENA (A placebo-controlled, double-blind Trial to assess the cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation and Flutter), which is currently in progress.

My final comments are about vernakalant. This is one of four drugs now in regulatory review. Its indication would be terminating AF when used intravenously. Vernakalant is a novel drug with some mixed ion-channel effects, including ultrarapid potassium current, sodium current, and transient outward current. A robust clinical trial experience demonstrated fairly conclusively that the drug has efficacy, especially in patients who have AF of relatively short duration.

- β-Blockers with class I or III effects
- Amiodarone congeners
- Atrial-selective antiarrhythmic drugs
  - \( I_{KUR} \) and \( I_{KACH} \) blocker
  - Atrial-selective Na channel blocker
  - 5-HT\(_4\) receptor antagonist
- Stretch-activated channel blockers
- ACEI/ARB
- NCX (Na/Ca exchanger) inhibitor
- Anti-inflammatories (statins)
- Gap junction conduction facilitation

Figure 7. New antiarrhythmic drug development: possible mechanisms. ARB = angiotensin-receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; Ca = calcium; Na = sodium; NCX = sodium/calcium exchanger.
Figure 8. Primary end point for the EURIDIS and ADONIS trials: patients with adjudicated first recurrence of atrial fibrillation or atrial flutter. 

EURIDIS = EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of sinus rhythm; ADONIS = American-Australian trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of sinus rhythm. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH; EURIDIS and ADONIS Investigators: Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-999 (A). Copyright © 2007 Massachusetts Medical Society. All rights reserved.

and will probably work best in patients with AF of less than 48–72 hours’ duration.

Figure 9 shows the ACT (Atrial Arrhythmia Trial) III results presented at the American College of Cardiology Annual Meeting in 2006, with an efficacy of somewhere around 50–60% for patients with relatively recent onset AF. This drug, by the way, is now being investigated as an oral formulation for maintenance of SR in patients with AF. So far, its tolerability and safety profile have been acceptable.

PRYSTOWSKY: All points well taken. To finish this case, we switched drugs prior to cardioversion, but I also added an ARB for blood pressure control with the hope it may also have a salutary effect to minimize AF recurrences. She is also considering catheter ablation.

Ablation: Which Patients and When to Incorporate Into Clinical Options

Case 4

PRYSTOWSKY: A 45-year-old man had paroxysmal AF for 10 years that has been persistent for 3 months. He’s been symptomatic and sotalol has failed. He is afraid to take a class IC drug. His echocardiogram demonstrates mild LVH (13 mm), the LVEF is 65%, and the left atrium is 48 mm. This is a case of Dr. Jáïs, who will give us more details.

JÁIS: This patient’s best friend died when he was about 50, taking an IC drug. He did not want to take an antiarrhythmic agent. So what we did in this patient was pulmonary vein isolation (PVI), but PVI alone in persistent AF is not usually enough to get success. We started with PVI, but had no conversion of the AF. In the upper right-hand panel of Figure 10 you can appreciate that the tracing from the lasso placed in the left inferior PV had very fast bursts of PV activity, and we felt that there was a good chance that the patient would convert to SR by isolating this vein, but it was not enough. The lower left-hand panel of Figure 10 shows the final ablation site at the inferior part of the left septum, where fractionated potentials were recorded. It has been difficult to define what fractionation is and what electrograms to target for success, and the initial description suggested they be fairly consistent, more than 10 seconds, and usually low amplitude. This is an example of high amplitude potentials, and they were acting by bursts of 3 seconds, and then were much more regular, but it was the effective site to terminate AF. In this case, there was very organized activity after PVI in the vast majority of
TABLE 1
Pooled tolerability and safety data for the EURIDIS and ADONIS trials. ADONIS = American-Australian trial with Dronedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm; EURIDIS = EUropean trial In atrial fibrillation or flutter patients receiving Dronedarone for the Maintenance of Sinus rhythm. Singh BN, Connolly SJ, Crijs HJ, Rog D, Kowey PR, Capucci A, Radzik D, Alist EM, Hohnloser SH; EURIDIS and ADONIS Investigators: Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-999 (A). Copyright ©2007 Massachusetts Medical Society. All rights reserved.

<table>
<thead>
<tr>
<th>Event</th>
<th>Dronedarone (n = 828)</th>
<th>Placebo (n = 409)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Death – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>8 (1.0)</td>
<td>3 (0.7)</td>
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<tr>
<td>Sudden death</td>
<td>4 (0.5)</td>
<td>1 (0.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke – no. (%)</td>
<td>4 (0.5)</td>
<td>3 (0.7)</td>
<td>0.69</td>
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<tr>
<td>Pulmonary event – no. (%)</td>
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<td></td>
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<tr>
<td>Cough</td>
<td>19 (2.3)</td>
<td>7 (1.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>27 (3.3)</td>
<td>15 (3.7)</td>
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<td>Endocrine event – no./total (%)</td>
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<td></td>
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<tr>
<td>Hyperthyroidism</td>
<td>67/801 (8.4)</td>
<td>56/396 (14.1)</td>
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<td>Hyperthyroidism</td>
<td>44/801 (5.5)</td>
<td>14/396 (3.5)</td>
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<td>Cardiac event – no. (%)</td>
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<td>Bradycardia or conduction block</td>
<td>22 (2.7)</td>
<td>8 (2.0)</td>
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<tr>
<td>Heart failure or shock</td>
<td>8 (1.0)</td>
<td>3 (0.7)</td>
<td>1.00</td>
</tr>
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<td>Neurologic event – no. (%)</td>
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<tr>
<td>Insomnia or other sleep disorder</td>
<td>12 (1.4)</td>
<td>6 (1.5)</td>
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<td>Memory impairment</td>
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<td>1.00</td>
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<tr>
<td>Peripheral neuropathy</td>
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</tr>
<tr>
<td>Paresthesia</td>
<td>11 (1.3)</td>
<td>4 (1.0)</td>
<td>0.78</td>
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<td>Tremor</td>
<td>6 (0.7)</td>
<td>2 (0.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gastrointestinal or hepatic event</td>
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<td></td>
<td></td>
</tr>
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<td>Diarrhea – no. (%)</td>
<td>59 (7.1)</td>
<td>20 (4.9)</td>
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</tr>
<tr>
<td>Nausea – no. (%)</td>
<td>36 (4.5)</td>
<td>14 (3.4)</td>
<td>0.54</td>
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<tr>
<td>Abnormality of liver function – no./total (%)</td>
<td>100/822 (12.2)</td>
<td>55/405 (13.6)</td>
<td>0.52</td>
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<td>Dermatologic event – no. (%)</td>
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<td></td>
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<td>Photosensitivity or skin discoloration</td>
<td>6 (0.7)</td>
<td>1 (0.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Other elevation of serum creatinine – no. (%)</td>
<td>20 (2.4)</td>
<td>1 (0.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Figure 9. ACT III results: conversion from AF to SR or termination of AF or AFL. ACT = Atrial Arrhythmia Trial; AF = atrial fibrillation; AFL = atrial flutter; NS = not significant; SR = sinus rhythm. Pratt C, Roy D, Juel-Moller S, Torp-Pedersen C, Toft E, Wyse DG, Nielsen T, Rasmussen SL, on behalf of the ACT III Investigators. Efficacy and tolerance of RSD1235 in the treatment of atrial fibrillation or atrial flutter: Results of a phase III, randomized, placebo-controlled, multicenter trial. J Am Coll Cardiol 2006;47 Suppl A:10A (A).

The left atrium, except at that site. If the whole left atrium harbors this kind of activity, it’s a much more difficult situation. You don’t know where to start, but in those patients with AF that persists for weeks or months, not years, areas showing complex electrogams are usually limited.

PRYSTOWSKY: Dr. Jaïs, what would be your success if you only did PVI?

JAïS: In our data, AF termination during the ablation procedure is predictive of a very good outcome in patients in whom we achieve SR during the procedure, or at least convert the AF into atrial tachycardia—95% of them have a successful outcome, most without taking drugs. On the contrary, if we don’t achieve SR or conversion, only 50% have a successful outcome. Thus, it’s possible that this patient would have been doing well with just PVI. It’s even more likely in this case because there was just one site outside the pulmonary veins, so possibly only PVI would have been successful. I would guess a 70% chance in this patient.

PRYSTOWSKY: So in other words, you would go ahead and try to isolate the veins, but if you were still in AF at that point, then you would say that’s a low-yield long-term. You would then proceed with further ablations. However, if the AF terminated, you might stop ablation?

JAïS: Most certainly.

PRYSTOWSKY: That’s a very rational approach. Dr. Ruskin, I’m trying to understand the pathophysiology of these complex atrial electrogams, because in SR you often don’t see them. First, what do you think is producing the complex electrogams, and second, do you believe in the concept of targeting them to get a successful outcome?

RUSKIN: Well, I’ll give you a very short answer to the first part, and that is I certainly don’t know. I think Dr. Jaïs alluded to the problem of defining these electrogams. My sense in watching these is that a lot of this is in the eye of the beholder in terms of which ones are really targets. Because if you followed Dr. Nademanee’s algorithms, I think we ablate a lot more than what he does. We will include as fractionated electrogams much more than what he might, the high voltage ones being an example of that. We don’t require that they be low voltage, for example. In fact, some of the high voltage ones that are very fast I think are among the most productive sites to target. I don’t think there’s a science to this, but I can tell you in watching these, they’re not easy, and there’s a lot of subjectivity to it, and a lot of intuition and instinct about which sites really are important. Dr. Jaïs, is that a fair statement?

JAïS: I fully agree with Dr. Ruskin, and I’m very uncomfortable giving a definition for these complex electrogams. Even more difficult is building the software that could identify them for you. It really is extremely challenging, but it works, even if we don’t completely know why.

RUSKIN: It does work, but I think that there’s a huge difference between a standard PVI for a classic patient with
paroxysmal AF and a moderately small left atrium, and dealing with this kind of patient—it’s a whole different category.

PRYSTOWSKY: Dr. Nattel, do you have any thoughts on the pathophysiology of complex fractionated atrial electrograms?

NATTEL: I think some of the complex fractionated electrograms may represent regions of slow conduction that are crucial to reentry circuits, some of them may represent very rapid local activity and some of them may not be so obviously meaningful, and I have a feeling that sometimes people get success with AF ablation without necessarily having a very good pathophysiologic rationale. I think the rapidly firing PV sources that are responsible for maintaining paroxysmal AF is one specific example of a successful target, as identified by the Bordeaux group, and this has revolutionized our field. I also think a lot of the extensive ablations that are being done today and that use all kinds of different formulas may be successful, more because they know the general region that’s important to ablate than having a really precise pathophysiologic concept.

PRYSTOWSKY: Some of these complex electrogram areas may be due to vagal innervation. Even the literature from decades ago demonstrated that stimulating the vagus could yield very rapid firing in these areas.

NATTEL: Yes, it’s absolutely conceivable, and we have been doing some studies looking at ablation for vagal AF in the dog, epicardial ablation, and ablating the ganglia to see what role they might play. The electrograms near or under-neath the ganglia often are very disorganized, fractionated, and extremely fast, so that may be part of the story.24

RUSKIN: I’m hoping that Dr. Jaïs and Dr. Haïssaguerre are going to do this, as they’ve done so much in this field. The issue here is specificity; which electrograms/sites really matter. Because if you could figure out which of these abnormal electrograms really mattered, you could enhance the precision of the procedure, decrease the time, and minimize the amount of atrium ablated.

References
7. Muszkat M, Blotnik S, Elami A, Krasilnikov I, Caraco Y: Warfarin metabolism and anticoagulant effect: A prospective, observational study...