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### 5 Key Takeaways on Managing Afib in the Post-CABANA Era

#### Dr. Epstein:

So, my charge today is to address these 5 points, and I'll review them, and you'll see this slide again as a segue in between the comments that I'll make. So, one is to use CABANA in a discussion with patients in shared decision-making about how to be treated, talk a little bit about quality of life, and how do we judge how much AF is important to an individual. We'll talk about patients with asymptomatic AF where quality of life really isn't an issue because they don't feel bad. Heart failure is something that we see. And as Dr. Singh mentioned, 15% only of patients in CABANA had heart failure, but this is an important group because our choices of drug versus ablation is influenced by that diagnosis. And finally, what do we do with the patients who are not candidates for ablation?

So let's start with the first bullet, a selective approach to AF ablation. This just again reminds us of the CABANA endpoint, that for the composite endpoint that was discussed, there was no significant difference. And I think one of the things that all of us will want to talk about afterwards—and Jag and I may fall on different sides of the street a little bit on this—is when you are a statistician and you look at a trial where the primary endpoint is negative, many believe that it's statistically improper to make the assessments of secondary endpoints when the primary endpoint is negative.

So, in this context, Cabana was really more than a negative trial, I think. First of all, it tells us that either ablation or drug therapy are acceptable treatments for AF, and that's very different than saying, well, ablation isn't better and therefore the trial failed or ablation is better if you look at mortality. There is a place for 2 players in the room; that is drugs and ablation. Then for higher-risk patients, the risk of adverse events was, in fact, very low in both arms, as Dr. Singh mentioned. The estimates of events was overestimated when the trial was being designed, and so, when things like that happen, trials are often negative because they don't have the power to show a difference. And then finally, that ablation reduced the secondary endpoints of mortality and cardiovascular hospitalization, as was discussed, as well as AF has to be viewed in the context of the primary endpoint being negative and statistical issues that I mentioned.

So, how does CABANA fit into the AF guidelines? And you'll see 2 dates here. The 2019 update was based on the 2014 guideline, which Jag showed and I will re-allude to, but the important thing here is that adherence to the recommendations in the guidelines is really enhanced when we talk to patients and to use shared decision-making, having patients engaged is important, and we really need to know what their values, preferences and associated conditions are that can impact outcomes of either drug or ablation therapy. We do need drugs, and we need drugs because both in the guideline are acceptable treatments as first- and second-tier options in the management of AF. Second, even after ablation, drugs often remain needed. And when we read ablation articles in the literature, often times complete success is defined as prevention of atrial fibrillation even when drugs are continued. And then we cannot forget that not only does ablation have adverse effects, so do drugs, and conversely, both of them are efficacious.

This is an important slide, and this is from the 2014 iteration of the AF guideline, and an important branch point for us is to determine whether or not someone has structural heart disease, and I'm going to speak to this on the next slide. If there is no structural heart disease, our options for AF management are much broader, especially with regard to drug choices. We can use dofetilide, dronedarone, flecainide, propafenone, sotalol. If you notice, amiodarone is relegated to a second tier there. And again I would like to emphasize that this is a drug with baggage associated with it, and I'll show you that in a moment.

Catheter ablation can be either used as a primary intervention—that's the dotted lines there—and that is after shared decision-making

with patients. It is a Class I recommendation, certainly after failure of drug therapy ablation is warranted. Structural heart disease is a little bit more difficult because the Class IC drugs, specifically flecainide and propafenone, are contraindicated. Ablation falls into first tier there, first tier, and for people with heart failure, amiodarone and dofetilide are really your only choices.

This is something that is not discussed very often, but what defines a structurally normal heart, that is someone with no structural heart disease? What we're really looking at is the ventricle. By definition, if you've got atrial fibrillation, you've got heart disease because you've got a rhythm abnormality. But these individuals have a normal history, a normal physical exam, a normal 12-lead electrocardiogram, no ventricular abnormalities or dysfunction on an echo, and certainly, they cannot have ischemia when a stress test is done if the patient is in an appropriate age group for a stress test to be done.

This is from the Kaiser database showing that in terms of all-cause mortality after catheter ablation for AF, whether or not you're on a drug doesn't make any difference. This is almost 4,000 patients on a variety of drugs. And the take-home message from this slide is that antiarrhythmic drugs are not detrimental after catheter ablation when they are used thoughtfully.

Quality of life has been discussed a little bit, and I'd just like to make a couple of points, that the data are mixed here. There is no question that AF adversely affects quality of life, and this is from a study of Paul Dorian's in Canada showing that compared to control groups, post-infarction as well as AF patients have impaired quality of life scores. In the AFFIRM trial, which was the NIH study that looked at rate versus rhythm control, even with a rhythm control strategy, quality of life was actually no different than with rate control if that is done well and the heart rate for AFFIRM was kept at less than 100 beats per minute on a resting electrocardiogram.

And then in contrast, like CABANA, quality of life can be shown to improve with restoration of sinus rhythm. These comparisons are a little bit tricky when you think about it because is there a control group that doesn't have an antiarrhythmic drug; is it just ablation; and is it successful ablation? So, is it leaving you an AF with a controlled rate, or are you in sinus rhythm? I think the bottom line is that people feel better in sinus rhythm or with rate control, and if you get there by drug therapy, ablation therapy or a combination, it's okay.

Third is what to do with asymptomatic AF, and this is an area of expertise for Dr. Mittal, actually, and he touched on this a bit with the large armamentarium we have now of ways to look for AF in patients. The more intense the monitoring, the greater is the yield of looking. Maybe one thing we can talk about in our discussion is the Apple watch study from last year, because although it's gotten a lot of press, I'll just say that for over 450,000 patients that were in the study, only 153 patients were AF or actually diagnosed with AF that was treated.

Another area of controversy, when we look at the literature in AF, is what defines recurrence and success of treatment. Actually, in our guidelines it's 30 seconds of AF, so somebody who has had 60 episodes of AF a week and they get put on a drug and at 5 months they have had 1 episode, that is a failure according to the guidelines, but that can be a very, very happy patient. So we have to consider what is the AF burden and could that be the frequency of AF or actually the AF burden, as we call it, which is the percentage of time that somebody is in AF. And then the longest duration of AF is another important endpoint.

Now, this is important because of the stroke risk. SCAF stands for Subclinical Atrial Fibrillation. And importantly, the feeling is, is that the more AF that somebody has, the greater is the risk for stroke, and this certainly has implications on how we manage the patients, especially with anticoagulation. And this just shows in a broad sense that as the AF burden increases, however you define it in these different trials, the risk of stroke also increases. This slide was shown showing that by the time we're over 65, the incidence of AF and stroke attributable to it increases. Actually, by the time we're 80 years of age, over one-third strokes are attributable to AF. It's a terrible problem.

Now, here is the real thing that's difficult for us in electrophysiology. This is a slide that is from the TRENDS study, and it looks at the relationship of the timing of atrial fibrillation with 24/7 monitoring to the occurrence of stroke. The gray bars are the time when somebody was monitored, the black fill-ins was when AF was present on the monitor, and the red line in the middle is the zero point when a stroke occurred. You can see that from the top... I guess I can use this here. On the top here you can see that there is no AF at the time when stroke occurred. Here there is a little bit of AF before it, but it comes more persistent after that. Here, this person really didn't have any AF. So there is something more than the presence of AF that is related to stroke in these individuals, and this is why all of us I think here on the panel believe that once you have had AF, the cat's out of the bag and lifelong anticoagulation is warranted if at all possible.

The guidelines tell us that for patients with cardiac implantable electronic devices, such as pacemakers or defibrillators, the presence of recorded high-rate episodes should prompt further investigation. And for us to decide about whether or not anticoagulation can be turned on and turned off, if you will, depending on whether AF is present or not is under study, and this is 1 of 2 studies that is currently ongoing called ARTESiA, which is randomizing patients to using a NOAC at the time of atrial fibrillation when it's discovered by monitoring. But I think until this study and the other one are published and released, people with atrial fibrillation should be permanently anticoagulated.

Next up here is: What about patients with heart failure? And there are a number of studies that have been done in the ablation and drug area, the drug fields in this area. One which has gotten a lot of notoriety because it was published in the New England Journal of Medicine is Dr. Nassir Marrouche's paper from the CASTLE-AF study, and you can see that cardiovascular death here is decreased by ablation. It's higher in the pharmacologic group. Cardiovascular hospitalization as well as stroke is also benefited by ablation in people with heart failure.

The guidelines tell us that AF catheter ablation is reasonable in selected patients with symptomatic AF and heart failure, especially with low ejection fractions, but that doesn't mean that drugs can't be used. And this was an important trial from now almost—well, 2 decades ago called the DLaMonD study, which led to the approval of dofetilide for the treatment of AF with heart failure, and importantly, survival was identical in the patients treated with placebo versus dofetilide, so there is a place for drug therapy as well as ablation in patients with heart failure.

And then finally, how do we manage patients who have AF but are not great candidates for ablation? And this is where drug therapy really plays an important part. Now, we've known for a number of years that—as my pharmacology professor in medical school, Dr. Louis Lasagna, said—all antiarrhythmic drugs are poisons with a few beneficial side effects. And in 1990, Sharon Coplan published this first sentinel paper really showing that quinidine was associated with almost a 3-fold increase in mortality in this sort of meta-analysis—it was called then. It's not the way we think of meta-analyses now. The study gave a signal that antiarrhythmic drugs can be associated with mortality. And then this was highlighted by the Cardiac Arrhythmia Suppression Trial which, as you all know, used encainide, which is no longer available, flecainide, which is available, and moricizine, which is no longer available, showing that suppression of PVCs at least in patients post-infarction with structural heart disease can lead to increased mortality.

So, when we think about drugs and how to choose them, there are many factors that we have to consider. One is adverse effects. Proarrhythmia has already been mentioned. We think about ventricular proarrhythmia in the form of torsades de pointes with a Class IA and III drugs, but actually, with the Class IC drugs, atrial flutter can be a severe, lethal arrhythmia that occurs, because what happens with the IC drugs is the flutter rate is slowed, for example, from 300 to 240 beats per minute, but the ventricular response then changes from 2 to 1, or a ventricular rate of 150 beats per minute to suddenly 240 beats per minute. Heart failure is also a complication with drugs that depress left ventricular function. Amiodarone interacts with warfarin and digitalis, both increasing sensitivity to these agents. Dofetilide has interactions with a number of drugs. Dig we know about. And organ toxicity, we can't say enough about the adverse effects of amiodarone on virtually every organ in the body, but especially the lungs, thyroid, skin and eyes.

To highlight that amiodarone is not a panacea, this was one of the first signals from the COMET beta-blocker trial for carvedilol, and you can see that for patients with the New York Heart Association Class II, III and IV heart failure, patients receiving amiodarone for whatever reason had higher mortality. And similarly, in the SCD-HeFT trial, which was a combination of prophylactic defibrillator, prophylactic amiodarone, versus optimized medical therapy for heart failure, with time, after you get past about 1¼ years, mortality is actually higher in the amiodarone arm in this prospective randomized trial.

So, how do we choose which drug to use? Well, certainly, one is what the patient wants in terms of where drugs can be started. Just to highlight, the class IA drugs sotalol and dofetilide, because of their QT-prolonging effects, should be started in the hospital. Amiodarone and dronedarone can be started as outpatients. And as I said, because amiodarone with its organ toxicities is now really a second-line drug for us, a drug like dronedarone is something very, very reasonable to consider if somebody doesn't want to come into the hospital. You can also use this for the Class IC drugs. The X in parentheses here is because when you use a IC in an elderly person, especially with a slow ventricular response, if they convert on the drug, you don't know if they will have sinus bradycardia afterwards, and you want to make sure that they're not too slow when sinus rhythm occurs.

This just shows for dronedarone the trial called ATHENA, which randomized dronedarone to placebo showing decreased hospitalization. It decreases the time to first recurrence of atrial fibrillation and flutter in these 2 trials, EURIDIS and ADONIS, and this was the combined analysis of those trials. And at the end of the day, when you choose a drug, whether it be amiodarone, dronedarone, sotalol, Class C drugs or placebo, the effect or the efficacy in all of these is about 50% with the exception of amiodarone, which gets you to maybe 60% efficacy, but that extra 10% is probably not worth it given the organ toxicity.

So, at the end of the day, we, I think, all feel that we should follow the guidelines, consider the pros and cons of ablation versus antiarrhythmic drug therapy, talk to the patient, and sometimes we end up using both.

Thank you very much.