KONSTANTINOS SIONTIS: Greetings, I'm Konstantinos Siontis, electrophysiology fellow, Mayo Clinic. During today's roundtable, we'll be discussing the CABANA trial. I'm joined today by Dr. Doug Packer, Dr. Tom Munger, and Dr. Peter Noseworthy. Welcome, everyone.

PETER NOSEWORTHY: Thank you.

THOMAS MUNGER: Good morning.

KONSTANTINOS SIONTIS: Dr. Mungo, let me start with you. What was the CABANA trial and why was it done?

THOMAS MUNGER: Sure, CABANA was a trial actually conceived by Doug more than a decade ago to look at patients who had atrial fibrillation, who had at least one risk factor for stroke. And then we randomized those patients between both ablation procedures versus antiarrhythmic therapy serially. And so that's the general conception of CABANA was looking at mortality stroke events, symptoms, and other endpoints.

DOUGLAS PACKER: We did want it to be fairly early patients.

THOMAS MUNGER: Yeah.

DOUGLAS PACKER: Patients that really have not been treated to any large extent. And we wanted it to be an opportunity to really find out if there was a difference between those therapies.

THOMAS MUNGER: The average age of the patients in the trial ended up being in their--

DOUGLAS PACKER: 68.

THOMAS MUNGER: --60s, yeah.

DOUGLAS PACKER: Yeah, 68 in both groups.

THOMAS MUNGER: Yeah.

KONSTANTINOS SIONTIS: Dr. Packer, in a little more detail, what are the strengths and limitations of the CABANA trial?

DOUGLAS PACKER: CABANA is a great trial from the standpoint that it was 2,200 patients. So it's probably the largest ablation trial that's ever been done. It is one that enrolled, well, I'll be at a little bit slowly, with about 1,000 patients in each arm. So some are randomized to drug therapy, some are randomized to overall a blade of therapy. And it turns out that 90% finished with a median time of the trial 48 months.

Now I think the strengths are clearly that it demonstrates that ablation is substantially better than drug therapy for preventing the recurrence of atrial fibrillation. By far and away, that's the strongest point. The second point is that it appears to be fairly safe. And we'll talk about that in a minute.

When we look at total mortality and the hospitalization, then patients who were ablated did better than those that didn't. Now there are a couple of liners in CABANA. And the liners in CABANA really are what about the primary endpoint? The primary endpoint was a composite of total mortality, disabling stroke, sudden death, or serious bleeding, kinds of things that have to do with atrial fibrillation treatment.

In the primary endpoint, we didn't see the difference that we thought we would. We didn't see that ablation was going to be substantially better than drug therapy. They were fairly equivalent. And from the standpoint of the secondary endpoints, the most important one would be the primary, secondary endpoint, which is total mortality. And they were about the same.

Now that was done with the intention to treat the approach. And so I think that if you put it in a nutshell, that's what CABANA says. And I think that if you use intention to treat, and it's an important clinical trial and statistical analysis tool, that's what CABANA showed.

KONSTANTINOS SIONTIS: Dr. Munger, considering all of the above, what does the CABANA trial mean for the practicing clinician, electrophysiologist, [INAUDIBLE] cardiologist.

THOMAS MUNGER: Sure, so I think the initial take-home points I got from CABANA were again, some of the secondary endpoints that Doug mentioned in the intention to treat analysis. Really, to me, it confirmed that it reduces symptoms. Significantly, ablation does better than antiarrhythmic therapy does.

Two, there was reduced hospitalizations in the ablation group compared to the drug arm, and that's again, important for clinicians no matter what you're doing since we're all under the gun to try to reduce hospitalizations and cost of medicine. So I think that was a very important take home point for me.

The mortality signal was negative in the intention to treat analysis. But there is data. And Doug may mention this later in the conversation about looking at some of the patients who did crossover as far as how they did long term and if there was an effect on mortality. So in a nutshell, that's what I leaned from it.

KONSTANTINOS SIONTIS: Great, Dr. Packer, you already talked a little bit about this. But as with any clinical trial, there can be questions that come up after the first results are presented. Tell us a little bit more about specific analysis and outcomes issues that came up and how you put this all together as the clinical trial is being presented now.

DOUGLAS PACKER: When you look at those issues, with any clinical trial, there can always be questions. And if you look at the questions that were raised even before the trial came out, one of them was how would quality of life look like? Would quality of life really tell us anything?

And in point of fact, if you look at Dan Mark's work, the quality of life was substantially better in those patients who were ablated just like the issue of freedom from recurrence of atrial fibrillation. So that's important.

So this is a strategy trial. It looks at an interventional approach. If it were a drug trial, this would have been easy because you randomized to one or the other. And most of the time patients staying in their arm of randomization, that makes life substantially easier. And you can do that with drug trials.

It's very, very easy, and it's the way it should be done. The problem with CABANA is that there were 301 patients who started out on drug therapy and crossed over. And the reason why they crossed over is because drugs didn't work. And then there were 102 patients in the ablation arm that didn't get ablated.

So immediately you have two crossover issues and some patients that checked out of the trial early. And it creates a problem with intention to treat. That's the one area where intention to treat can actually be biased and can push towards the null, and that is not intended to be a tremendous criticism of intention to treat. That's the way it should be.

But in point of fact, if you go to textbooks, or if you go to a number of different documents or different manuscripts, you'll see that even intention to treat has a problem. So what we did with that is we looked at per protocol analysis and as treated analysis.

And if you look at the two of those, then in those-- and I think it's important to talk about per protocol because in per protocol, those patients were randomized. And they stayed in their treatment arms. If they crossed over, then they were taken out of the trial. That means you're going to have fewer subjects.

But it doesn't mean that you're going to lose the benefit of randomization. And I think that's the thing that some people had troubles with with the blogging early on in the trial. But I do think what it does is it clarifies. It's explanatory.

It's not exploratory. It's explanatory, and it gives you a fairly good idea of whether there really wasn't a mortality benefit or not.

And I think that if you look at those, then the relative risk reduction for the primary endpoint and the secondary endpoint were on the order of 25% to 45%. And I think it's fair to talk about that. And I think it's fair to point out that many of the early blogs that were out there, number one, didn't have the data and so they didn't have anything to go by.

Much of the information was wrong, and they weren't peer reviewed. So those are some of the issues that come up. But at the end of the day, I think that CABANA does say that there is a substantial benefit to patients that are treated with ablate of therapy.

KONSTANTINOS SIONTIS: Dr. Noseworthy, you recently led a large scale analysis based on observational data and administrative claims database analysis. Looking at the real world outcomes of AF ablation and medications, what did this study tell us in addition to CABANA and how does that tie into the findings of the CABANA trial?

PETER NOSEWORTHY: Right, well CABANA, of course, is one of the most hotly anticipated trials certainly in our career and in electrophysiology. A couple of years ago, Dr. Packer and I were talking at one of the CABANA meetings.

I said, what's it going to show? What do you think? What's your hunch?

And he said, I don't know. But whatever it shows, it's going to raise as many questions as it does answers, and that was clear. So if the trial hit it out of the park with a mortality benefit, people were going to say, are the results generalizable to everyday practice into community practice, into outside these expert centers?

If there was an equivocal result, we were going to need more numbers. If there were interesting subgroups that couldn't be resolved with 1,000 ablation patients, we had to look. So we went to a large administrative data set, and its national data. 180,000 patients with atrial fibrillation. And it allowed us to answer a lot of those questions.

So what we saw was that about 2/3 or actually 3/4 of patients in practice looked like CABANA patients. So whatever you believe about CABANA, it's likely to be applicable to the patients that we encounter in everyday practice. The remarkable thing was that the hazard ratio in our analysis was very similar to the per protocol analysis.

So patients that are selected for ablation in everyday practice look like those that underwent ablation in the trial and relative to medical therapy had very similar outcomes. Lastly, we see that trial eligibility had a lot to do with the likelihood of a benefit of ablation.

So patients who were lower risk, who had no chance CHA2DS2-VASc risk factors, who were less than 65, actually had very low event rates. So I often hear from clinicians, if maybe there is a hint of a mortality or a stroke benefit with ablation, should we ablating earlier. Should we try to ablate those people at 50, or 45 years old when they present, even if they're minimally symptomatic.

But what I take from our data is that those patients have very low event rates. And we have to focus on the things that we know benefit those patients-- so anticoagulation when there's an indication, risk factor modifications, diet, exercise, et cetera, and then ablate for symptoms in those patients. So I think it's a nice example of the complementary nature of observational data and randomized trial data. And presenting these together, I think round out a full picture of the data.

KONSTANTINOS SIONTIS: Extremely interesting. I will definitely look forward to seeing those results fully published.

PETER NOSEWORTHY: Yes.

KONSTANTINOS SIONTIS: Now Dr. Munger, does CABANA tell us anything about the safety of ablation and medications?

THOMAS MUNGER: Sure. Well, it was remarkable. I thought that again, the ablation data set in CABANA showed a really great safety profile of ablation. Of course, there's been data from registries and then also looking at population studies and large data sets. But the safety profile of ablation was actually quite remarkable, I thought. And that is, again, a concern we had thinking about the antiarrhythmic drugs and the post MI trials from the '80s and '90s.

And then the MUSST data set from the early 2000s, we clearly saw antiarrhythmics had their own downsides depending on the substrate of the patient. Doug, anything else about the safety profile at all, or--

DOUGLAS PACKER: I think we were a little bit surprised.

THOMAS MUNGER: Yeah.

DOUGLAS PACKER: You know, if you look at the drug patients, they kind of look like they've been on amiodarone, but they all weren't. You look at the ablation of them, the only place where there really was an issue was perforation. And even that, the event rates were low.

THOMAS MUNGER: Yeah.

DOUGLAS PACKER: So--

THOMAS MUNGER: I was quite impressed with them.

DOUGLAS PACKER: Yeah, I suppose you could say, well, they're healthier patients, but they weren't. They're 68 or older. Their median CHA2DS2-VASc score was three.

THOMAS MUNGER: Yeah.

DOUGLAS PACKER: And so they weren't cherry picked.

THOMAS MUNGER: Correct, correct.

KONSTANTINOS SIONTIS: Dr. Packer, final question to you to summarize and get your final thoughts in the overall high level take-on points from the CABANA trial.

DOUGLAS PACKER: I think that we have to say upfront with CABANA that using an intention to treat analysis-- and that's the way you should start-- we didn't see that much more benefit with ablation than we did with drug therapy in the primary endpoint and in the total mortality. So those were about equivalent.

Now we view that as being or suggesting that the trial in those regards was indeterminate. It was a little bit slower enrollment. It was fewer events than what we anticipated, and I think those are important points that need to be kept in mind.

But there is a substantial difference in the patients who are ablated had better freedom from recurrent atrial fibrillation and less mortality in composite with hospitalization. And then if you look at the protocol component of this, then there was a clear difference with ablation versus patients who are treated with antiarrhythmic drugs. Now, again, that's where there's some conflict.

And I think that there'll be more information coming out in the manuscripts. And I think that they will be incredibly helpful as we go on in trying to decide how to treat patients over the next decade.

KONSTANTINOS SIONTIS: Great discussion. Thank you all for these very important insights. And thank you all for joining us on the heart.org and Medscape cardiology.