DR. BERNARD GERSH: Hi, this is Bernard Gersh at the Mayo Clinic. And with me today are two of my colleagues, Dr. David Holmes and Dr. Doug Packer, to discuss the really very topical issue of left atrial occlusion devices to reduce thromboembolism and atrial fibrillation. Perhaps, Doug, I can just ask you to start and sketch out the background behind-- so basically, the theory behind-- these mechanical approaches.

DR. DOUG PACKER: I think the first issue, Bernie, is there are a lot of people who have atrial fibrillation.

DR. BERNARD GERSH: Three million in this country, at least.

DR. DOUG PACKER: At least. And probably 200,000 new patients a year. They're not all at stroke risk, but a lot of them are. And we've worked with coumadin for years and years. Coumadin is a flat-out pain to use. Patients don't like using it.

In our studies, when we've looked at quality of life, the biggest impactor on quality of life is an anticoagulant. So the question is, are there alternatives? And are occlusive devices really the alternative? Is this the greatest thing since sliced bread, or is this just yet another approach?

And so I think that the big issue becomes one of patients who can't, or won't, take coumadin.

DR. BERNARD GERSH: So let me just stop you right there, and ask you, how frequently in your practice-- both you and I see a lot of patients with atrial fibrillation. And there are some who absolutely cannot take anticoagulants. They have GI bleeds. They can't do it. They're at high risk of falls.

I think I've seen maybe three or four such patients in the last year, and I've seen a lot of atrial fibrillation. But yeah, in general, you're right. Warfarin is not a popular drug. It's a very effective drug. It's very cheap, and it works. But it's not a popular drug. And we also have the new anticoagulants. Don't know how that will change the scene.

DR. DAVID HOLMES: I think there are a lot of issues about that. Although you have mentioned that you've only seen two or three patients who can't take it, there are a fair number. And the literature is very replete with information to suggest that, at least with warfarin, that perhaps 50% of patients in whom it is prescribed, they never pick up the prescription. That's the data that's available. That's the first piece of information.

DR. BERNARD GERSH: Well, the second is also. And we just looked at this in the ORBIT registry out of Duke. And that is that a significant number of eligible patients never get a prescription. We underutilize these drugs.

DR. DOUG PACKER: But even if they have the prescription, and even if they use it-- I think if you're talking about a 60-year-old who has atrial fibrillation, I'm not sure it's that big of a problem. But I think that as patient's age, then other comorbidities become more of a problem.

If you look at a trial like PROTECT, and you have the data on that, there could have been more patients enrolled in PROTECT. But some of the inclusion criteria and exclusions were a little bit restrictive. If we had a device, and the device works well, and it can be put in, and it can be done safely, and if it shows good efficacy, I think that there are actually more patients out there than we otherwise would think. And that's something we'll see on the [INAUDIBLE].

DR. BERNARD GERSH: I would accept that, particularly as we're getting into the 80 and 85 year plus age group. It's interesting to me that when you look at all the risk stratification scores for stroke, they also risk stratify bleeding. So the higher the risk of stroke, the greater the risk of bleeding. So the Murphy's law. David, what's out there? You've been very close to the trials and to one of the devices. What's the state of play at the moment?

DR. DAVID HOLMES: The state of play is this, the number one. Prior to the trials-- happen to be PROTECT AF-- although there was the hypothesis that, indeed, based upon echo studies and other pathology studies, that the left atrial appendage was the source of the putative stroke invasions with nonvalvular atrial fibrillation. We didn't know that for sure.

So the very first piece of information that we know now about devices is, by virtue of the result of the trials, that indeed that confirms the hypothesis, that in patients with nonvalvular atrial fibrillation, stroke comes from left atrial appendage. Not at 100%. But overwhelming majority, that's the case.

And so that's an important piece of information because it opens the door for mechanical approaches to occlude the left atrial appendage, or to dramatically decrease for a left atrial appendage. The present time, we have a single randomized trial that has been published. We have another one that is completed. We have multiple registries. And we have some very--

DR. BERNARD GERSH: With different devices.

DR. DAVID HOLMES: With different devices. The field is increasing in terms of the number of players that are in that field. By virtue of what both of you have suggested, the large number of patients, that is expected to increase as the patient population grows. That's the first piece of information.

The second piece of information is that, of course, we have new oral anticoagulant therapies. However, as we think about those, they're expensive, number one. Number two, they have side effects. Number three, the information that is available is that, at least with some of them, at two years, 20% of the patients in whom they have taken them as part of a trial, at the end of two years when the trial is over, they're finished with them. They don't like them. They have side effects associated with them, and they're concerned about bleeding.

For example, if they are on a trip, they fall, and begin to bleed. And they're in a small town. And people don't know what to do with rivaroxaban. They can't deal with that, or apixaban. How do you reverse it? What happens if they're going to have surgeries?

DR. BERNARD GERSH: Well, I mean, at this stage, we have no ability to reverse those, either the direct antithrombins or the factor Xa inhibitors. It's interesting. There are at least two or three compounds that should be available in two years that will, at least, look like they will reverse the effect of these drugs.

But what is interesting is, how are we ever going to test that? How are you going to do a trial of people who are bleeding and randomize them to a compound that may reverse the effect of apixaban, or dabigatran, versus placebo?

So we may, actually, have agents that are developed that will reverse anticoagulant effect. But we may never be able to test them properly. So it's a sort of interesting kind of paradox. In the era of randomized trials, we just may not be able to do that. It is an issue. I mean, the fact that you can't reverse the bleeding.

And personally, I think the novel anticoagulant drugs, overall, do show efficacy. They clearly show less intracranial bleeding. I think they are safer. As you point out, they're much more expensive. They do have some side effects. And they don't obviate bleeding. Every time you prevent clotting, you run the risk of bleeding. And it doesn't matter what you do it with.

DR. DAVID HOLMES: One of the other issues is, as we see patients over the course of their life, some of them are not all that keen about adding another medication to the polypharmacy that they are already on in terms of drug interactions. So we see patients that come in with an acute coronary syndrome that have a drug-eluting stent. And they then have atrial fibrillation. And then they are faced with triple therapy and the potential for bleeding.

So there are a group of patients that, as Doug has said, if you have a device that works, it is safe, and it is very effective, it's going to be a device that I think will be used in a large number of patients, particularly after ablation, for example. Ablation, while it's been a tremendous thing, and those patients that have a high CHADS2-VASc score, they still need to be on an anticoagulant-- at least that's the information that the guidelines would suggest-- and so that devices like that will be used in concert with ablation.

DR. BERNARD GERSH: I really like the idea that the population that really could benefit are those with acute ischemic syndromes. Because whichever registry you look at, triple antithrombotic therapy causes bleeds. There's large Scandinavian registries, and there are a number of them. And we don't quite know the duration of dual antiplatelet therapy. And that's the subject of a number of trials right now. But it's certainly a year, if not two, and at minimum, six months.

But if you're going to be in dual antiplatelet therapy and an anticoagulant, the risk of bleeding is really very high. So that may be a group where there is real potential. Maybe I can just ask both of you.

One thing that, I think, is unresolved-- I mean, it's clear that thrombi come from the left atrial appendage, and we learned that from the era of arterial stenosis. But as you look at the data, there are many aspects of the natural history of stroke and atrial fibrillation that really support the possibility that this is from the left atrial appendage.

But there are other data that are much more confusing. People who have atrial fibrillation have stroke. But the relationship between the stroke and the episodes of atrial fibrillation-- there is no relationship. It's like atrial fibrillation is a marker of something else going on in the vasculature. Just like CHADS2 doesn't predict left atrial thrombus. CHADS2 predicts stroke.

DR. DOUG PACKER: And I have to tell you. You and I have had that argument a number of times. I actually don't believe that all of thromboembolic events come from the left atrial appendage. I think that there's a lot of other things going on. I think that there's a ischemia involving the left atrium. I think that there's carotid problems. I don't think, though, that that's the death knell for an occlusive device.

What it just means is we need to get better at defining who should get it and who doesn't. Who has the left atrial appendage thrombus, and who has something else? We still have to say that, if you look at PROTECT, if you're looking for non-inferiority, it won on the non-inferiority side.

So if you're looking at warfarin, and you're looking at an occlusive device, they both had equivalent effect, even though there may have been other sources of the embolic events. So I think the best is one of those things where we're going to have to get better at this idea of who is the patient.

DR. BERNARD GERSH: I think we're getting into an incredibly interesting time in terms of risk stratification for stroke. Just simply CHADS and CHADS2 VASc, I think, in five years time, we'll look back upon that as the beginning of our attempts to risk stratify.

I think the biomarker data is absolutely fascinating, with troponins and NT-proBNP that predict both stroke, and bleeding, and other events. And I think it's really interesting that, hopefully, one will be able to take this pool of people with atrial fibrillation and say, these are the ones where the left atrial appendage should be occluded, and these are the ones that we need to do other things.

DR. DAVID HOLMES: There are risks with that data set, however. You mentioned, obviously, all of the inflammatory markers. One of the issues has been that inflammatory markers, when they are studied in a population of 50,000 patients, you're going to find some relationships. When those relationships hold true for the individual patient who is sitting in the office with you, is not at all clear. And so although we get better and better with risk prediction, the patient wants to know, am I going to have it or not?

DR. BERNARD GERSH: I think what we can say from the Aristotle database-- which is a trial database, so it's not the real world in that way-- is it does appear that these biomarkers add a lot of information, after you've stratified by CHADS. So you can, perhaps, identify a group where you're at very low risk.

What I find so interesting about it is, why? Why does this troponin in BNP-- BNP, I think, I can understand more easily. But what is troponin got to do with left atrial thrombus? I don't know. Why is it so predictive?

You're absolutely right, David, that in the individual patient, it's not going to help you. But conceptually, it's very interesting. Let's give you the last word. Continue again with the state of play. What can we look forward to over the next year or two?

DR. DAVID HOLMES: I think we will have an increasingly robust data set on long term follow up. For example, this year at HRS, the superiority of the Watchman device over warfarin-- it's true, it's warfarin, not a new anticoagulant, one of the newer oral anticoagulants-- was documented for the very first time in just 700 patients. So Vivek Reddy presented that. And you probably were there.

And that's probably the first time that we've seen superiority of any device, as compared to warfarin, in a small number of patients. It wasn't like it was 15,000 patients. So I think we will see long term data. I think we'll see the development of new approaches that are safer, that are more effective, that have more complete closure, in the field of left atrial appendage occlusion.

DR. BERNARD GERSH: Can I just ask you to define the safety aspect? When you say they're safer, in what specific areas?

DR. DAVID HOLMES: At present time, the very first concern with the PROTECT AF data, was that pericardial effusion occurred in about 5%. While it did not result in mortality, it prolonged hospital stay and wound up being a big deal. In the subsequent trials, both the continued Nexus registry, as well as in PREVAIL, that's down to about 1 and 1/2 percent, or 1.7%. It's not going to be zero. And Doug, you can probably comment on that.

DR. DOUG PACKER: And it's clearly different in the group of patients that are operated on by somebody who's done a bunch of these. The success rate for getting one of these in is about 98% if you've done a number of these. It may be 93% for a first time user. So I think the [INAUDIBLE] is going to be that kind of an issue to deal with.

DR. BERNARD GERSH: Well, I think, just in closing, release of the devices is going to have to be controlled. I think we've done a very good job, and you were pivotal in all of this, with tava. Not every single cath lab in the country is going to do tavas. And that will apply here. Thank you very much, gentlemen.

DR. DAVID HOLMES: Thank you.

DR. BERNARD GERSH: Thank you for listening.