SEAN PATRICK WHALEN: Thank you, Fran. So I'm in charge of the electro fiddlers. My task today is to talk a little bit about the dirty work that we do in terms of the nuts and bolts of managing atrial fibrillation and to update you on the new novel oral anticoagulants

So we'll start with a clinical scenario. And this will be familiar to most of you in this room, who take care of patients. So this is J.S. or Dr. J.S is a 66-year-old female. She has a history of paroxysmal atrial fibrillation, has a couple of episodes a year. Most of the time, she's well and active.

She's a retired physician. She's internet savvy. And she's done her homework before she comes to clinic.

She has a history of hypertension. And she's been on an aspirin, and flecainide, and toprol. And she wants to talk about her stroke risk.

So I think this is a framework for us to talk about the role of anticoagulation and atrial fibrillation. Because I have a captive audience, I'd like to start by taking a step back and just talk about a general approach to patients with tachycardia.

So when I see somebody with tachycardia, the first thing that I ask myself is it a wide complex rhythm or a narrow complex rhythm? Wide complex tachycardia is VT until proven otherwise. But we do see some exceptions to that rule.

Narrow complex tachycardia is going to come from above the AV node, from the atrium. In the differential of SVT, I always ask whether the rhythm is regular or irregular with irregularly irregular rhythms being AFib until proven otherwise. Sometimes, we'll see things like MAT or SVT with variable conduction in that group.

This is the patient we're talking about here with a atrial fibrillation. When we see someone with a regular tachycardia, I ask myself is this atrial flutter? And we look at heart rates at 150 beats per minute with a fine-tooth comb looking for flutters. And then I ask about whether I can see P-waves. And we designate SVTs by short RP and long RP.

And the reason why I step back from atrial fibrillation in order to give you this background is that in today's world we try and just say no to drugs for these patients. OK. So ablation is primary therapy for SVT, primary therapy for atrial flutter. And we will offer ablated therapies, because they are curative for these patients.

So rather than put someone on a beta blocker or calcium channel blocker for life, we can effectively eliminate rhythms 95% of the time with a catheter. And we can cure them. And cure is not a word we use in medicine very often. I think most of the things that we do, we palliate.

But atrial fibrillation is different. OK. So AF is different than these rhythms. And the reason is AF is more complicated.

So AFib involves triggers and substrate. So in order to have atrial fibrillation you have to have two things. You have to have skipped beats, PAC, atrial tachycardia to initiate the arrhythmia. And you've got to have enough electrical disease in the heart, that once the heart goes out of rhythm, it can stay there for a period of time. OK.

All arrhythmias require trigger and substrate. And AFib is a progressive disease. So what it takes to put a 30-year-old out of rhythm is very different from what it takes to put an 80-year-old out of rhythm. And that's sort of the natural progression of the disease. And if you talk to patients with atrial fibrillation, they will give you this story.

So this is actually from a goat model of atrial fibrillation, where they put in a pacemaker. And they burst pace the atrium for a couple of minutes. And they have AFib that lasts a couple of seconds. If you burst pace the atrium for 24 hours, the AFib will last for a longer period of time, and then it will convert.

And if you burst pace the atrium for two weeks, it will go out of rhythm. And it will stay out of rhythm. And this is what patients will tell you.

They say I had this when I was in my 30s, or 40s, or 50s, and it would come and go. And I'd only have it if I had a really tough week, if I'd been up all night, if I drank too much caffeine, drank too much alcohol, my thyroid was out of whack, what have you. But over time, the episodes last longer. And they come closer together, until they start to bleed together, and AFib goes from paroxysmal atrial fibrillation to persistent disease.

Now how long this takes is a variable process. Some folks, it's the first episode, and they're stuck out of rhythm. Other folks can take 20 or 30 years and never get to this stage. But from a big picture, population-base perspective, most AFib patients will progress from this point to this point over time.

And treating atrial fibrillation is kind of like ordering food in a Chinese restaurant. OK. So you order something from column A, something from column B, and everybody gets an anticoagulant appetizer. OK.

So when I talk to patients in the clinic about AFib, I tell them we can use drugs to control your rhythm, to keep your rhythm normal. We can use ablation to keep your rhythm normal. We can use drugs to slow your heart rate. But the most important thing that we do is thin the blood in order to prevent stroke.

So if you want to save lives, treating atrial fibrillation, you don't do it in the EP lab doing fancy procedures and catheter ablation. So you do it by thinning the blood and preventing stroke. OK. So these are quality of life interventions.

So we use drugs to control the heart rate and to restore normal rhythm and use ablation and pacemakers to control symptoms. But if you really want to make people live longer, you have to understand their stroke risk. And you have to anticoagulant them, at least for now. OK.

So AFib is a big problem. We have six million people in the US with atrial fibrillation. It's expected to triple in the next 40 years, 66% increase in hospitalizations for atrial fibrillation in the last 20 years. This is because we have an aging population. The baby boomers are starting to get into this curve.

We have an epidemic of obesity in sleep apnea. And we have a rising prevalence of structural heart disease. Atrial fibrillation is not a benign condition.

So if you look at patients with AFib and you compare them to healthy controls, where you take patients with atrial fibrillation and co-morbid diseases, like coronary disease, myocardial infarction, patients with AFib have increased mortality compared to their matched controls. And that's primarily driven by stroke and heart failure. OK. That goes back to the point that if you want to make people live longer with a atrial fibrillation, you prevent stroke.

So how do we predict who is at risk for stroke? We don't put everybody on Coumadin. We use a risk ratifications scheme. The original scheme we use is called the CHADS2 score. OK.

So you have points designated to whether you have heart failure or hypertension, how old you are, diabetes. You get two points if you've had a prior stroke. And the higher your score, the higher your risk of stroke.

The idea being if you can take the low-risk patients and not treat them with rat poison and take the high-risk patients and treat them with anticoagulation, you can be smarter about how you treat the patients. And this works pretty well. The problem is that even the CHADS2 score patients have somewhere between a 1% and 2% risk per year of stroke. OK.

These folks, the high-risk patients have a 20% per year risk of stroke. So it's a no-brainer that these patients need to be anticoagulated. There's debate about what to do with these lower risk patients.

But if you look at the data across multiple studies done over many years, it's very clear that warfarin prevents stroke. OK. It reduces stroke risk by 60% to 70% compared to placebo. And it reduces stroke risk by 40% to 50% compared to aspirin.

So the question you get in clinic is, doc, why can't I just take an aspirin for this? This is what I've always taken. But in point of fact, you're getting twice the benefit from full anticoagulation than you get from aspirin. Aspirin reduces stroke risk by 30% to 40%, but that's not enough in most patients.

And if you take the risk of bleeding, which is the primary concern that patients have who are on warfarin, there's a sweet spot. So if your very, very low-risk, if your CHAD score is zero or your stroke risk is very, very low, then the risk of bleeding outweighs the benefit. If your risk is very high, the risk of benefit outweighs you're bleeding risk.

And in somewhere between one and two in the CHAD scoring system, we have a trade-off in terms of risk and benefit. And so current recommendations are CHADS2. If you're in Europe, you get nothing. If you're in the US, you get an aspirin.

And there's a deviation between the groups writing consensus statements, at this point. If your CHADS1, it's dealer's choice. Now point of fact, diabetes and hypertension are probably not equal here.

Some risk factors are more significant than others. Age greater than 75 probably means more than hypertension and things like that. But I will typically offer full anticoagulation in these patients and encourage it.

CHADS2 or greater you really need warfarin in order to minimize stroke risk in these patients. CHADS2 VASc score, which is the newer modality for risk ratification includes vascular disease and coronary disease. You get an extra point for being a woman. And you get two points if you're 75 or older, one point if you're 65 or older.

So this is a little more comprehensive in terms of how we stratify the patients. The advantage to that is that if you're CHADS2 score or CHADS2 VASc score is zero, your stroke risk is really the same as the guy sitting next to you without atrial fibrillation. And we get a little bit more granularity with these low to intermediate risk patients.

And so using the CHADS2 VASc score, we recommend no anticoagulation or just an aspirin in the lowest of the low-risk patients. And we recommend dealer's choice for a CHADS2 VASc of one. Now remember, if you're a woman, you're automatically a CHADS2 VASc of one.

So the number of patients, you know, you're just looking at the lowest risk men here. Women, at least, get bumped into this category. Two or more, we're going to recommend full oral anticoagulation.

Now what this means has changed. And that's really the point of the talk is to talk about what this means in today's world with the newer drugs. But I think this, at least, helps me see it.

What we're talking about for every 1,000 patients with nonvalvular atrial fibrillation, so patients without mechanical valves, patients without a significant rheumatic mitral valve disease. We're talking about one major bleed, intracranial bleed for 31 of events that can be prevented. OK. We way overestimate the risk of bleeding and falls in this patient population. And we way underestimate the benefits of stroke prevention.

But warfarin has its limitations. And we've all seen this. So this is a curve showing that if you don't take enough warfarin, you might as well not be on anything, because your stroke risk is high. If you take too much, then you run into the risk of bleeding. You've got to land right in this sweet spot between two and three in order to optimize your benefit and minimize your risk.

And this can be a really difficult thing to do, even with a fully compliant patient. You have frequent monitoring and dosing adjustments. You have frequent interactions with other medications, antibiotics. And then there's a lot of problems with underprescribing from physicians and under adherence from patients.

Everybody has a great aunt, or an uncle, or a grandfather, or cousin who had a really bad thing happen to them on warfarin. And they don't want to take that rat poison. OK. So what are these new drugs? OK.

So the new drugs fall in two major classes. One is the direct Xa inhibitors the other is the thrombin inhibitors. And they both target a single enzyme in the clotting cascade. The way I explain this to patients is you take your warfarin and it goes into your liver. It affects the proteins that are responsible for making the blood clot down the stream.

These newer drugs bypass that, work directly on the clotting factors. And that's one of the reasons why we get a little bit more predictable result with the dose that we give. When we give an aspirin, we don't check to see if the aspirin level is what it should be.

We know that aspirin works on platelets. These drugs are similar. We give the dose. It has an effect.

So the first of these drugs to the market was Pradaxa. So rivaroxaban followed that. Apixaban followed that. And edoxaban is at the FDA currently.

So Pradaxa has a very rapid onset. It's working within a couple hours in vitro, within eight hours in vivo. It has a half-life of 12 to 17 hours. It's cleared by the kidneys.

And so you're not going to be able to use it as reliably in patients with renal insufficiency. And you probably shouldn't use it at all in patients with renal failure. And that's going to be the same for all of these newer drugs.

It's available in two doses. This is a little bit mystifying to me, because the 150 dose was what we have from the studies. The other studies we're done with 110, but the FDA decided not to give us a 110 milligram dose. You got to go to Canada or Europe if you want that dose.

It interacts with glycoprotein inhibitors, like Multaq and rifampin. You can start Pradaxa immediately upon discontinuation of heparin. This drug and the others that have followed it have really replaced Lovenox in the outpatient setting for the anticoagulation, because it's immediate onset. And it can be stopped in a more reliable and predictable way.

It's stopped one to two days before elective surgery. We typically operate on the drug. We hold one dose. And we re-dose a couple hours after surgery for an ablation or for a pacemaker. In converting from warfarin to Pradaxa, we typically will convert when the INR is two to or less.

So what about the data? The data from Pradaxa come from the RE-LY study. So this is a non-inferiority study randomizing patients to Pradaxa versus warfarin. And we have the 150 milligram dose and the 110 milligram dose and Coumadin. And we have a non-inferior result.

So it's, at least, as good as warfarin in preventing systemic atheroembolism or stroke. Major bleeding complications are similar. There is less risk of intracranial bleeding.

So if you look at all the leading causes, there are probably a few more GI bleeds and a fewer intracranial bleeds, which are the things that I really stay awake at night worrying about. And that's going to be a class effect, I think, across the multiple drugs.

So what about side effects? So about 10% of patients taking Pradaxa will complain of dyspepsia. So if you don't warn them about it, they end up seeing a gastroenterologist and getting an endoscopy, when it was just the drug effect. So you've got to warn them about this ahead of time. This can cause heartburn.

We don't see this with any of the other novel anticoagulants. So this is unique to Pradaxa. Of course, any drug can cause allergic reactions. Bleeding risk appears to be elevated in the patients with kidney disease and in elderly patients. So I shy away from this drug in our octogenarians.

And really, ability to reverse the drug is fairly limited. The other piece that's not on here in terms of side effects is the effect on the wallet, right. So these drugs are expensive. So you know, I will often give folks a sample trial of the drug to make sure they tolerate it from a GI standpoint and to make sure that they can afford it. So I have them go to their pharmacist and find out what their take home cost will be of the medicine before you go through the trouble of switching them around.

The other thing that you have to face upfront are these lawyer commercials. OK. So everybody who you counsel that they should be on Pradaxa has heard 100 times on the radio and on television that you can sue your doctor if they put you on this dangerous blood thinner.

And so I think this is much easier to handle upfront. I say, now, I'm sure you've seen the commercials on Pradaxa. And they always nod and say yes. I say, look, all blood thinners can cause bleeding. What we're looking to do is prevent stroke.

There is a calculated risk that we're willing to take. And I'm comfortable with-- I took care of a trial lawyer in Nashville, who had made his millions suing doctors. And he was on Pradaxa. And I said, don't you feel funny advertising on this?

And he said, he said, I've reviewed the data. I'm perfectly comfortable taking the drug. He said, don't get me wrong, I'll still sue them. So, you know, you just have to recognize that this is out there.

And if you confront it upfront and say, I'm aware that you've been exposed to this. I'm aware that this is out there. We're making a calculated decision here. And I'm comfortable with it if you are. It's a much easier conversation, then to find out six months later that they're not taking it, because they heard a commercial on the way home.

So rivaroxaban was a second drug to market. It's a Xa inhibitor, half-life of five to 13 hours, 1/3 renally cleared, 1/3 metabolized in the liver, 2/3 rather metabolized in the liver. The nice thing about rivaroxaban is it doesn't cause dyspepsia. And it's a once a day dosing. OK.

So for patients that you're worried about being able to remember take a pill twice a day, this is nice. Now if they forget to take a pill twice a day, they probably are likely to forget to take it once a day. So I mean, you know, missing a dose of rivaroxaban, there is some concern that you could have a rebound effect. You need compliance with any of these medications.

But we have pretty good data for post-op DVT, PE, ACS, as well as a atrial fibrillation. So the ROCKET AF study is the study most commonly quoted for rivaroxaban. This is again a non-inferiority study comparing it to warfarin. And again, in terms of stroke risk and bleeding risk, it was comparable to warfarin. Again, it had reduced intracranial bleeding, probably at the expense of GI bleeding. And it's pretty well-tolerated, less intracranial bleeding, less fatal bleeding.

There is not a good reversal agent for this drug either. And that is something that we have to counsel our patients about. The thing that I tell my patients is all of these studies were done with these drugs. And the fact that there isn't an antidote for the medicine was part of the study. And I think we overestimate how effectively we can reverse things like Coumadin.

I mean, if someone comes in with an intracranial bleed in their eye and their INR is five, giving them plasma and giving them vitamin K really doesn't get you as much benefit as you'd like to see. So I don't worry as much about the reversibility piece. But again, I think it's part of how we counsel our patients.

So the third guy on the market is apixaban. OK. So I think there are some very interesting data about apixaban. And apixaban took a really long time to get through the FDA for reasons that aren't entirely clear to me. But they did something kind of clever when they were doing their studies.

One is they compared it to aspirin. OK. So clearly apixaban of him is better than aspirin in terms of stroke prevention. And that's not a big surprise. But the piece of data that they garnered from this study is that it's comparable to aspirin in terms of bleeding risk. OK.

So it's very rare for me to have someone refuse to take an aspirin, because of concern of bleeding. And every once in a while you run into someone that just can't take an aspirin for allergies or other things. But when I'm counseling patients, if bleeding risk is a real concern, this is as safe as an aspirin in terms of bleeding risk.

Now you have to be careful they don't have them on aspirin and apixaban together, unless they have indications for both. But atrial fibrillation by itself should not require both aspirin and oral anticoagulants. This is just another graphic depiction showing that there was no significant bleeding risk as compared to aspirin.

Now what about compared to warfarin? So Aristotle is the study that was done comparing apixaban to warfarin. And it reduces systemic stroke and embolism by 21%, reduces major bleeding risk. And this is something new, OK, reduced mortality.

So this is the first of the drugs to show a mortality benefit as compared to warfarin, OK. And, this is important, I believe. And really the drugs very well-tolerated. So it rarely caused patients to have to discontinue it. And it doesn't have the GI upset. It will still affect your wallet the same way productively.

And then the last guy on the market or the next guy-- because I shouldn't say last-- edoxaban. OK. This is currently at the FDA. Their data was presented to the FDA in January. This was compared to warfarin.

They looked at both a 60 milligram dose and a 30 milligram dose. They use the low-dose in patients with reduced creatinine clearance and low body weight or that were on drugs that would interact. I'm not sure who's using quinidine anymore, but there it is.

And a edoxaban, as well, was non-inferior to warfarin in prevention of stroke and systemic embolism. It's a once-a-day drug. It was associated with lower rates of bleeding and all death from cardiovascular cause, again, more GI bleeding.

So there is some trade-off here. And this seems to be, as I said, a class effect. We may have some more GI bleeding as related to intracranial bleeding. I don't know how much of that is from esophagitis and gastritis from the drug complicated by subsequent bleeding or what the mechanism is here. I don't think that's really well understood.

I think probably disappointing for the folks that did this study is that really the 30 milligram dose doesn't cut it. OK. So even in the older patients reduced GFR, warfarin was better, likely due to low drug concentrations. I don't think that's a big surprise. But I think they had hoped that this would provide them with an indication for the higher risk patients.

So if you take all comers in the big studies that have been done across the board, there seems to be a favorability of the novel oral anticoagulants over warfarin. So is this enough data for me to take every patient in my practice and push them towards taking one of the newer drugs? I don't think so.

I think if you've demonstrated that you can take warfarin safely, you haven't had any problems on it. I'm not going through the Coumadin looking to change everybody. Having said that, with this data in hand, it's uncommon for me to initiate anticoagulation with warfarin, unless we don't think they're going to be able to afford the drug, their kidneys don't work well, or they've got significant valvular disease, where we just don't have data to guide us.

In looking at end points-- I think I've already hit this home-- you know, reduction in hemorrhagic stroke, probably an overall trend towards reduction in all cause mortality. You have to be careful about meta-analysis data. Reduction intracranial hemorrhage, probably a little bit of an uptake in GI bleeding. But given a choice between these two, I'll take the GI bleeding over the intracranial bleeding. This is something we can typically manage.

So here is my sort of summary slide. So this is the money slide. OK. So if we look at the new drugs and we compare them to each other, probably the best effect in terms of stroke reduction is with the dabigatran and apixaban. OK. The best reduction in ischemic stroke is with dabigatran.

Bleeding risk is lowest with a apixaban and edoxaban. And mortality is better with apixaban. OK. Now it's probably worth saying all of this data is generated by the companies making these drugs, you know. So we don't have any NIH funded studies to guide us in this regard, but its a lot of patients, a lot of patients, a lot of patient years. Its a lot of data.

So when I'm faced with a patient in the clinic and I'm trying to decide what to use, I think across the board apixaban is probably the best drug I have in hand, all told. Having said that, I'm not sure that the difference is that significant. I think, especially, in the bleeding, the patients that you're worried about bleeding falls things like that.

For the non-compliant patient, once-a-day dosing, rivaroxaban and edoxaban. OK. The best data for recurrent TIA is with Pradaxa. The other studies haven't looked at this.

Chronic renal failure, valvular heart disease, you're stuck with warfarin. OK. So I don't think-- that drugs not going to go away. And there's not going to be a study looking at the novel oral anticoagulants in patients with mechanical valves, in pregnant patients, in patients with chronic renal failure. It's just too high-risk for the companies to small of a patient population. We're going to continue to use warfarin in these folks.

So what about no drugs, right? So I think Dr. Gandhi touched on this a little bit. But one of the things we're really excited about is, well, if I can treat someone's SVT and get him away from having to take a drug, what about treating someone's atrial fibrillation in a way that mitigates their stroke risk? So these are all different devices that have been designed to prevent stroke in patients with atrial fibrillation.

These are left atrial appendage closure devices. This is a clip that goes on at the time of surgery to clamp the appendage closed. This is the watchman device, which is an endocardial plug. This will probably be the first to market and has the best data so far.

This a plug made by a competing company. This is a device called the lariat device. This is a device that's placed-- this is really clever. So you put a catheter in the heart from below.

You poke across the atrial septum. You put a catheter with a magnet on it in the appendage, and then you go into the pericardium by sticking it under the breast bone. And you put this snare over a wire using that magnet. And you cinch the appendage close, all similar ways to get to the same end point.

The idea is that appendage thrombus is what causes stroke in patients with a atrial fibrillation. And if you remove the source, you should remove the stroke risk. We are just getting to the point where we have some real data to guide us in this avenue. So this isn't an echo image of a left atrial appendage at the time of surgical ablation.

So one of the things that I do is I work with a surgeon to do surgical ablation followed by catheter ablation in the patients with really persistent and difficult atrial fibrillation. And part of that surgery involves clipping the appendage at the time of surgery, using this clip. So this is the appendage beforehand. It looks sort of like a chicken wing.

One of the very interesting things is the shape of the appendage it turns out probably has something to do with your stroke risk. But after surgery, that appendage is closed and sealed. It's also electrically isolated, which means that you can't have PACs or tachycardia coming out of the appendage to initiate a atrial fibrillation. So it probably has both stroke reduction benefit, as well as an antiarrhythmic benefit.

Here's the lariat device. This is contrast in the left atrial appendage. This is the loop going over top of the appendage and cinching it shut. Now in our initial experience with this device, we had a patient who died about a month later from pneumonia, so unrelated. But he had an autopsy done and this is the inside of his left atrium.

And you can see that's where the appendage was. And it's nice and smooth. So this is a bad outcome for the patient, obviously. But this is a very nice anatomical closure of the left atrial appendage. This approach is still in the process of collecting data. It's clearly safe, and it's effective at closing the appendage.

We just don't have long-term follow-up data to tell us which patients should have this done. The data we do have with regards to left atrial appendage closure comes from the watchman studies. So this is PROTECT AF. This was a randomized study, thousands of patients comparing warfarin to appendage closure.

And this is the plug or the watchman device. It's placed through the groin, across the atrial septum. And it's seated in the left atrial appendage. They look by ultrasound after a month to make sure that it's sealed.

And if it's sealed, those patients came off Coumadin. And majority of the patients were able to come off Coumadin. And there is a trend towards better mortality in the watchman group. These two curves will continue to diverge, because most of this early on is because of complications from the procedure.

So when you're poking people's hearts in deploying devices like these on anticoagulanted patients, you run the risk of perforation and bleeding and those things, groin complications. Once you get out from the procedure related complications, these curves diverge nicely. I think this is going to be a really exciting therapy for patients with a atrial fibrillation who don't want to take chronic anticoagulation.

This is at the FDA and should be available in the next six months. Of course, I've been saying that for three years. We will-- more to come on this, but I think we'll have this clinically available in the next six months.

So in summary, the novel orally anticoagulants, as a group, have a favorable balance between efficacy for stroke prevention and bleeding risk. And most of that advocacy seems to come because of decreased bleeding intracranially. And there, at least, as effective as warfarin in preventing stroke. And we have some data that would suggest that mortality is better on a apixaban.

The two big downsides, as I see it, are cost to the patient and reversibility. So if you fall and hit your head or you're in a car accident, I don't have an anecdote to give you in the emergency room to thicken your blood. This is coming. The reversibility is something that's being worked on, but it's not currently available.

In summary, regarding atrial fibrillation and stroke, keep in mind AFib is associated with stroke. And that's the same in a patient whose paroxysmal as in a patient who's persistent. And about 75% to 80% of AF episodes are subclinical.

So the patient tells you I only have AFib once a year may believe that. But I'm a skeptic when it comes to that. Warfarin from is no longer the only option in treating patients and preventing stroke. The new oral anticoagulants are, at least, as effective as warfarin.

And in many patient demographics, we'll replace warfarin him as first line therapy. It's important to be familiar with the side effects, and the drawbacks, and the cost of these drugs. And left atrial occlusion, left atrial appendage occlusion, is going to be a great option for patients who can't take anticoagulation and maybe will be a great option for patients who don't want to take oral anticoagulation. So with that, I will stop and answer any questions.