

SPEAKER 1: Good morning. Welcome to Internal Medicine Grand Rounds. Our speaker today is Dr. Frank Cuoco, assistant professor with the Division of Cardiology. Dr. Cuoco graduated from Case Western Reserve University in 1996 with an MS in biomedical engineering. He then attended medical school at Georgetown University, where he received an M.D. and MBA in 2001. He stayed on at Georgetown to complete his residency in internal medicine and a fellowship in cardiology. He then came to MUSC, where he completed a cardiac electrophysiology fellowship.

During his time at NUSC, Dr. Cuoco has focused much of his clinical work and research studies on advancing novel cardiac ablation techniques and technologies. He was most recently published for his work in force sensing catheters, in balloon catheters for atrial fibrillation ablation. Notably, Dr. Cuoco is also the only operator for left atrial appendage occlusion in South Carolina. His presentation today describes the role in which catheter ablation plays in stroke prevention for atrial fibrillation, and how this compares with current pharmacologic therapies. Please join me in welcoming Dr. Cuoco.

[APPLAUSE]

DR. CUOCO: So thank you for having me this morning. First question I got about this talk was from Teresa. She asked me if I was going to go over everybody's heads today. And I said, but that's what EP's do. Of course I want to do that. But I promise you, we're going to try and keep this pretty clinically focused. And my goal is to show you some real life, real clinical situations, and then try to apply our most recent literature and data to how we're going to manage patients with atrial fibrillation. We're going to focus not today on symptomatic benefit at all. We're not talking about patients with symptomatic a-fib, because that changes the game. What we're really going to focus on today is stroke prevention.

So here are my disclosures, we are going to talk a little bit about some non FDA approved devices and indications today. Some of these may be approved by the FDA in the very near future. So let's start with the first case, on a 65-year-old female with sick sinus syndrome and a pacemaker. Who has, what is essentially asymptomatic, [INAUDIBLE] fibrillation.

Her events are recently well weight control, she's on a beta blocker. Her overall burden of atrial fibrillation, which we can tell from the pacemaker, is 2%, so relatively small burden. Her longest episode that she's ever had is only an hour and a half. She's never needed cardioverting, most of the episodes last less than 10 minutes, as detected in the pacemaker. She's currently taking an AF for those aspirin, at the recommendation of her primary care physician. She has a remote history of peptic ulcer disease, but never required transfusion, and has not had any significant GI bleeding, or changes in her bowel habits in the last 10 years.

Her husband took Coumadin in the past, and then he had a major subdural hematoma. So she is adamant that she does not want to take rat poison.

So one of the questions that we're going to try to address with this case today. First of all, is how much AF increases the stroke risk. Does it matter that she's had a relatively low burden? Do we even need to worry about it? If she didn't have a pacemaker, we may not even know that she's having these episodes of atrial fibrillation. What's the stroke risk for this patient? Right? I think if you look carefully, you know she doesn't have diabetes, didn't have hypertension. She's a relatively young, otherwise healthy female. Does she have significant stroke risk, and should she be anti-coagulated?

If she is supposed to be anti-coagulated, what's her bleeding risk? She has a remote history of peptic ulcer disease, is this a significant bleeding risk? And she should be on aspirin, she should be on oral anti-coagulation therapy. And if on oral anti-coagulation therapy, should we be thinking about novel anti-coagulants, or Coumadin? What about catheter ablation? A lot of patients like this do get sent to me for catheter ablation, and does catheter ablation reduce the stroke risk of patients with AF. And finally, what's going to be the role for occluding, or closing the left atrial appendage in this patient?

So let's start off with the first question, is what's the stroke risk based on the burden of atrial fibrillation. Well, we don't know. We really don't know for sure whether or anti-coagulating patients with a very low burden of AF is going to have benefit. But what we do know from the search that was published in the New England Journal of Medicine that we participate in here, at NUSC, when I was actually an EP fellow is that relatively low burns of atrial fibrillation are associated with increased risk for stroke.

This was a trial where patients were given a pacemaker for a standard indication, but then monitored through their pacemaker for atrial fibrillation. Now, these patients never had a history of atrial fibrillation, they just had to be age 75 or greater, and have at least one risk factor for stroke with atrial fibrillation, like hypertension.

And what we found from this trial, is that just one six minute episode of an atrial arrhythmia, with a rate greater than 190 in this case, with the find in the study, one six minute episode was associated with a greater than twofold risk of a ischemic stroke.

As I mentioned before, none of that-- no one knows for sure that anti-coagulating these patients will reduce that risk, or have significant benefit over the perceived risks. However, we do know that just a little bit of atrial fibrillation does increase the stroke risk. So just because patients have relatively small burns of AF, or have only had one or two episodes AF, that doesn't mean they can't have a stroke.

The problem is, we're going to talk about in a little bit, is that not all AF related stroke is mechanical. It's not necessarily just about status. There are other factors at play when patients have atrial fibrillation relation, such as endothelial dysfunction and inflammatory changes that promote clot formation and stroke. We'll talk about that a little more when we talk about the left atrial appendage.

So now, the most recent guidelines are actually taking us away from our standard risk factor scoring of a CHADS2 score, and ask us to look at more factors at play, such as the CHADSVASC. And as you notice, this case that I gave you, basically gave us a patient with a CHADS2 score of zero, someone who typically might not anti-coagulate. But as you see here, in addition to the standard risk factors for stroke with atrial fibrillation, including heart failure, hypertension, diabetes, age grade greater than 75, and prior stroke, you also now have factors such as female sex, age 65 to 74, and vascular disease or coronary disease as significant risk factors for stroke and atrial fibrillation.

So now you take the same patient that I gave you that had a CHADS2 score of zero, and if you look, she has a CHADS2VASC score of two. What does that matter? As you see here, when you start looking at patients stroke risk, you start to look at with a CHADS2VASC score of two, an adjusted stroke rate per year of about 2% or more. And remember, that's an annualized stroke risk. So that means over the next 10 years, she's got a 20%, or 22% in this case, for stroke. So that's not insignificant in an otherwise healthy female. You're going to expect her hopefully, to be around a lot longer. And her stroke risk over that next 10 years is not insignificant.

And for most patients, as we're going to see later, for bleeding. The lowest risk patients for stroke are also relatively low risk for bleeding, so there's the risk benefit matter in this patient. If you look at bleeding rates per year, when you start to have low risk scores-- they haven't done this for CHADS2VASC yet. But you see here that your major bleeding event rates per year go way, way, way down when you have low risk. When we have multiple risk factors, then those co-morbidities increase the risk of bleeding.

So these are basically the way the new guidelines look for considering anti-coagulation with atrial fibrillation. And that's basically if you have a CHADS2 score of two or more, then you definitely going to anti-coagulant. If you're aged 75, and there's no contraindications, you should anticoagulant. If you have at least two other risk factors, such as we discussed before, like you have this aged greater than at least 65, female sex, vascular disease, and or one of these others. Again, anticoagulant. Remember, prior stroke, always anticoagulant. And actually, I never stop any anti-coagulation in those patients, because they're at the highest risk, even if they've had successful catheter [INAUDIBLE].

However, once you get down to this one that's a CHADS2VASC score of one, you can make it sort of dealer's choice. That's truly the situation where we would say yes. You can discuss what the risks and benefits are with your patient. If your CHADS2VASC score is zero, then it's really nothing. Those patients really probably shouldn't be anti-coagulated, they don't have a statistically significant benefit. Because they're bleeding risks outweigh the benefit, because they're stroke risk per year gets less than 1%.

Now, you notice here how aspirin is sort of in parentheses here. These are the European guidelines, and even in the US guidelines, they're-- pretty much aspirin has fallen out of favor for stroke prevention in atrial fibrillation. There's never been a single randomized controlled trial that shows that aspirin reduces stroke rates in AF. They had to pool all the data together from all the AF trials to even show what barely met statistical significance, in terms of a 20% reduction of stroke, just to give you a ballpark figure. Coumadin gave you about a 65-ish reduction of stroke rate across all studies.

So we're barely met statistical savings, and it was small. And remember, most of the patients that you're using aspirin on with a CHADS2 score in those ranges, they have hypertension or diabetes. So they have risk for atherosclerotic and atheroembolic disease as well. And that may be where aspirin really helps, in terms of stroke prevention with AF. Just because it's mitigating their atheroembolic stroke risk, not necessarily their AF related. Atheroembolic stroke.

So what about aspirin versus in this case, novel anti-coagulants. This was one of the first studies that really looked at patients who couldn't take Coumadin This was the Averroes trial, there was about 5,000 patients or so-- sorry, 4,000 patients or so. It compared patients who couldn't take Coumadin to aspirin-- randomizing into aspirin versus Apixiban at the usual standard dosing of 5 milligrams twice daily.

And what you see here, is that the picks have been significantly increased, or decreased the stroke risk in these patients. But notably, what was really interesting, was that it didn't statistically significantly increase the risk of bleeding. So basically now, you have these patients-- you realize two things. One is obviously aspirin is not very effective at reducing stroke risk in these patients. But even more so, is that aspirin is not completely benign. It's got a similar bleeding risk as ELIQUIS. So when you look at this, again, you look at major bleeding. So major bleeding slightly higher, but not statistically significantly so. Fatal bleeding the same, intracranial bleeding, the same. Discontinuation rates due to bleeding, similar between Apixiban and aspirin.

So what I would urge you to say, well, obviously cost is an issue here. And that in access to the medication becomes an issue. But if you're looking at actual benefit, aspirin has little in the way of benefit, and probably similar in the way of risk as many of our newer agents. And I would strongly urge you that if you're really thinking about putting someone on aspirin to reduce stroke risk for AF, you should at least consider a novel anticoagulant.

Now, when you look at comparing, for example, in this case, and again, I'm using Apixiban as an example here. We have data with all of them, but I didn't have time to go through every trial. But I wanted to use Abixiban, because it was the only one that's been randomized against aspirin. From Aristotle, you compare stroke and systemic embolism between Apixiban and Coumadin again. You had a statistically significant reduction in the pondering outcome, the study of 21% overall risk reduction between them. And again, safety, better with the novel anticoagulants. But when you look at bleeding breakdown between intracranial bleeding, GI bleeding, fatal bleeding, all similar. Clinically relevant, non-major bleeding, also statistically significantly lower with the novel anticoagulants.

And then this was the only drug that actually reached statistical significance, in terms of mortality reduction compared to Coumadin. So again, if you're talking to patients about what novel-- what anticoagulant do they want to go on? Do they want to be on Coumadin? This woman didn't want to be on Coumadin, remember. She had a bad experience with her husband. You can tell her, look. I know I understand you had issues, he had an issue with intracranial bleeding.

Some of these novel agents, all of them actually, but rivaroxaban, dabigatran, all of them have shown decreased risks of intracranial bleeding, which tends to be the most severe. That was true across all aspect.

But what about if you have really good Coumadin control? So here, we have four tiles of Coumadin control. And you see here on the left, we have-- these are the patients that have the worst Coumadin control, these are the patients that have the best, in terms of Coumadin control. This was efficacy and stroke risk. Over to the right here, is safety. So worst Coumadin control, best Coumadin control. The dark, light gray line, here is Coumadin. The dark gray line is Apixaban. What you can see here, is obviously the worst Coumadin control where your INR is only in range about 25% to 50% of the time. Then you see here that clearly Apixaban is better, in terms of stroke prevention.

When you get down to where your Coumadin-- where your INRs are therapeutic 80 plus percent of the time. Then you see here that the curves are pretty similar. But when it comes to safety, when obviously there's poor control over your INR, safety is much better with Apixaban. But even when there's excellent control, you still get this safety benefit with the novel anticoagulants. So you may say, well, efficacy is similar, but there still is better safety profile when you go in with the novel anti-coagulants compared to Coumadin. Even in the best of INR scenarios.

And just to give you an idea, women in clinic, even here at [INAUDIBLE] Academic Medical Center, you're looking at maybe 60%, 65%. The best randomized controlled clinical trials had 65% time in therapeutic range. That's what that TTR is, time in therapeutic range. So to think that your patients are spending 90% of the time in the therapeutic range, you're sadly mistaken. That's just not happening.

What about catheter ablation? Does catheter ablation work? Well, we don't really have any randomized control prospective data to tell you yes, you should stop Coumadin, or whatever anti-coagulant, after successful catheter ablation. Meaning you've monitored the patient, they're not having atrial fibrillation post-ablation. What we do have is a pretty large retrospective series. We are working on this prospective data, but unfortunately, it's very difficult to enroll in these clinical trials. I'd be happy to address that question at some point, but it is difficult.

But we have here is over 3,000 patients who had atrial fibrillation, about 2,600 of which went off their anti-coagulation. About 550 remained on anti-coagulation in retrospect. And we see here that the event rates after AF ablation are very, very low. This is basically meaning that this is a reverse log curve, so as you move down the curve, there's more events. You see here they're very, very low. So the patients who are even off their oral anti-coagulation, are having similar rates of embolic events, or stroke afterwards. And you see it really in the low risk groups, you're looking at one thromboembolic event each group. So this, you can't really get a lot of statistical data on this. Obviously, nothing's going to be significant when you have these low numbers. But what you can tell patients, or what I tell patients is, is that thromboembolic risk after a successful ablation, where patients have been monitored is really, really relatively low, at least in the data series that we have.

The problem though, with atrial fibrillation ablation is that there is recurrence. And even though we think that we made sure they're AF, because when they came in for follow up, their EKG shows normal sinus rhythm. The patient's not reporting any symptoms of arrhythmia, and even maybe a 30 day monitor showed no evidence of recurrence.

As you look, and you go out a year after ablation, two years after ablation, you see this attrition rate where patients have occurrence of atrial fibrillation. Remember, AF is not a static disease state. SVT, WPW, for example, that's a static substrate. You have an accessory pathway, it doesn't change over time. When we go in and we ablate that accessory pathway, it's gone. It's not going to grow back, per se. It's not like the patient's going to develop new accessory pathways over the next 10 years.

The problem is, is that atrial fibrillation is what a lot more-- I talk to my primary care, when I talk to my patients, when I talk to my referring physicians, even when I talk to the intervention list, and I'm trying to explain why patients have AF. And they're like, I thought you fixed that. Well, maybe we fixed it temporarily, but just like I thought you fixed that patient's right coronary by stenting it. That patient still went out and ate McDonald's, and didn't take their blood pressure medicines, and didn't take control of their diabetes, and they developed a worsening coronary disease.

The substrate in AF is dynamic and it changes over time. And just because you've gotten the triggers, or substrate in your initial catheter ablation procedure, those triggers and substrate can change over time. That's why you see this recurrence rate of atrial fibrillation.

So what I tell everybody, when they're thinking about getting AF ablation, whether they're symptomatic or not, I tell them count on at least two. This is not something that you're going to always get with one. If you look at-- this is some of the data from the best centers in Europe. Relatively small groups, but these are all paroxysm patients, by the way, these are not even persistent patients that have much higher recurrence rates.

But if you look, there's 160 patients. Only about 45% of patients were successfully ablated at five years with no recurrence rate with one single ablation procedure. When you start looking at second procedures, the success rates start to go up to around 75%. And when you have a third procedure, which is a smaller number of patients, you can get that success rate at five years up to around 80%. So even in the most straightforward paroxysm patients, you're still going to look at 20% of patients having recurrence, and maybe needing some medical care. And certainly, not sure what we know about their stroke risk.

So what about AF ablation on stroke risk? This was actually some recent data that was published just last year on heart rhythm. And I think the pictures show it better. And they did is they broke out patients by CHADS2 scores. So in black here, their CHADS2 score is low risk, zero to one. In gray, it's two to three. And in blue it's greater than or equal to four, so very high rates. And what they did was they took three groups of patients with atrial fibrillation. They took a group of AF patients that never were ablated, they took a group of AF patients that were ablated, and then they took a group of patients that had no known history of atrial fibrillation. So they are three core. So that a true control, no history of AFIB, they had AF, and that they're AF with ablation.

And what you see here, is if you look at patients who had atrial fibrillation, but never were ablated, and compared them to the group of patients that never had atrial fibrillation, you see all these patients had a higher risk for stroke, about almost at least a two-fold increase risk for stroke. No matter what your CHADS2 score. When you look at patients who had atrial fibrilla--

So basically, as you see here, independent of what your CHADS2 score was, as soon as you have AF, you have an increased risk for stroke compared to patients who don't. Now, if you looked at the group that actually had AF and had a successful ablation, and compared those to those-- no AF groups. Not the patients that had AF and didn't have an ablation, but no AF group, that risk seems normalize. It's not statistically lower, but it's normalized.

And again, that was true across all categories. When you look at different age groups too, same thing. When you compare AF ablation versus no known atrial fibrillation.

So what we talk about with patients is, I can't tell them in a prospective fashion that if I take 1,000 patients with AF and successfully ablate them, and another 1,000 patients with AF and successfully ablate them and compare outcomes between those I stop anti-coagulations, I don't stop anti-coagulations, I can't tell you.

Honestly, what the right thing is to do which group will do better? What I can tell you, is that if you undergo a successful catheter ablation, and you have a relatively low risk for stroke, or have even had a prior stroke, then your stroke risk is probably mitigated to some degree. And whether or not it's statistically significantly better to stop the oral anti-coagulant, again, we don't have that data.

But we weigh the risks and benefits in each patient. And I do think we have some data to at least support us testing this hypothesis, because this data that I'm showing you here, is consistent across lots of groups of patients from multiple centers, multiple countries. The stroke risk seems to be lower, or at least mitigated.

What about left atrial appendage occlusion? So now, we're going to talk a little bit about the left atrial appendage and its role in stroke and atrial fibrillation, why perhaps-- we're going to think about going after this intensive reducing stroke. The left atrial appendage is a gestational remnant of the fetal left atrium that's typically thumb sized, from the patients with AF, it can be quite variable. And we've learned this, in terms of figuring out how to close it. There's multiple different shapes, and they all get funky names. There's the chicken wing, and the cauliflower, there's lots of different ones. And different ones are difficult to plug, difficult to close.

Does it really do anything? Well, it may have some roles in hemodynamic regulation. It does control the release of [INAUDIBLE] peptide. Which, by the way, if you ever take a history on a patient with AF, and they tell you, yeah, I went into AF, and God. I was peeing all day. All right? That's physiologic. Because when the left atrium stretches, and the left atrial appendage stretches, and the patient goes into AF, it releases [INAUDIBLE] peptide.

The heart thinks, OK. I got too much fluid on board, I got too much pressure. So it sends a signal, patients pee. So I can tell you, they always know, patients always say, yeah, I know when I went into AF, because I had to go pee. So it is true, it is physiologic. There also may have some roles in left atrial pressure and volume relationships.

You can see here, these are just even two different examples, this would be a chicken wing, this is kind of a cauliflower appearance appendage, very, very different shapes and sizes. And some of them can be very, very large, and some can be very, very small. Both of which can present challenges in terms of surgically dealing with them.

Well, why is there thrombus formation in left atrial appendage? Interestingly enough, going back to third year medical, or first year medical school, all the elements of Virchow's Triad. Hypercoagulability exists in the setting of atrial fibrillation. Obviously, there's the classic hemodynamic stasis that we all know about. But there's also changes in hypercoagulability due to platelet dysfunction, changes in beta thromboglobulins, D-dimers, fibrinogen and prothrombin fragments are all elevated in these states. Also, there's endothelial dysfunction in patients with atrial fibrillation and inflammatory changes that occur at the endothelial level that promote thrombus formation.

Which again, is why patients who are even adequately anticoagulated can have strokes. And other reasons why I tell patients who have very high risk for recurring stroke with AF, that even if you're not having atrial fibrillation, there's risk for stroke. Because the mechanical is not everything.

One of the reasons that this can also happen, is if you think about-- this as a left atrial appendage in a patient who never had atrial fibrillation. This is a left atrial appendage in someone who did, and what you can see is that there are changes. Actually one in the size and dilatation, but there's loss of the fine branching structure of patients with atrial fibrillation.

And this promotes more stasis and error for clot formation in the left atrial appendage. And remember, you're not always talking about a big bad clot sitting in the left atrial appendage that's going to cause your stroke. It's these little small ones that sit in here that break off, and can cause a pretty serious and devastating ischemic event. So this is one of the other reasons these changes occur when the patient's in atrial fibrillation, typically in persistent AF.

What about the left atrial appendage? It is clinically recognized as the primary source of cardioembolic thrombus. Basically, in patients who don't have rheumatic heart disease and atrial fibrillation, over 90% of the clots that have been found in these patients are always located in the appendage. That doesn't mean that you can't get a clot somewhere else, what it can tell you is that when you are looking for a clot, typically this is where you find it.

Now, when you start going to patients with dramatic atrial fibrillation, they get markedly dilated left atria, and they have tremendous amounts of stasis in the atrium, particularly due to mitrostenosis. Notice So there you can see clots in much different patient populations. And again, that's why when you hear about the concept of valvular atrial fibrillation versus non-valvular atrial fibrillation, what we're really talking about here is rheumatic AF versus non-rheumatic AF, because the clot formation is so much more prominent in rheumatic AF, and it can be so variable in terms of its location. You can see right atrial [INAUDIBLE].

So why do we always chase this down? Well, in spot studies, they did TEE's on 786 patients. And what they found in terms of increased predictors of thrombo-embolic events was that just the thrombus detected in the left atrial appendage will probably be greater than twofold risk for stroke. Then spontaneous echo contrast, even a very high risk, and then reduced peak flow velocity. Often you'll see as when we're doing TEE's in patients with atrial fibrillation, we will measure the flow velocity on the left atrial appendage, because it's been associated with increased risk for clot formation and stroke.

These are obviously some pictures, so I think some of you have probably seen this before. This is not the way you want to find the thrombus, this is post-mortum with a big thrombus in the left atrial appendage. You see here with the mitral valve cut away. Here's a CT scan, you see the left atrial appendage here. Left atrium here, with a dense, dark, lots of contrast here where thrombus is formed. And then on TEE, this might be what it looks like here as well, where you see this dark thrombus here in the left atrium.

Caveats. The problem is fixing the left atrial appendage, it sounds great. Let's just close up this left atrial appendage, we can reduce stroke rates by 90%. That's where 90% of the clots are, we should be good to go, right? But the problem is etiology of stroke is multifactorial. As we talked about, it's not just stasis. Finding a thrombus in the left atrial appendage does not prove it's the source of emboli. And as we mentioned before, it's small thrombi that can cause these strokes as well. So just maybe you don't even not necessarily see them, doesn't mean they're not there.

And the concept of excluding the left atrial appendage from the circulation needs to be studied. When it has been studied, we're going to talk a little bit about it. We're going to talk about transcatheter techniques.

So initially the first device that was developed is the PLAATO device, and that has since developed into the WATCHMAN device. There is also an Amplatzer Cardiac Plug device that has been sort of modeled after the same devices that we use to close atrial septal defects and painted frame, you know, valves. These are typically the left atrial appendage occluders that we have. We also have the ability to close to the left atrial appendage epicardially, which I'll show you in a little bit. That's where we're actually sort of mimicking a surgical closure of a left atrial appendage. These are all percutaneous.

But really, most of the data in this arena is surrounding this WATCHMAN device, and it is going back to FDA panel next week. It was originally approved at 13-1, but the FDA decided to wait and make a decision. They wanted more data from false studies, which I'm going to show you here in a minute. And it will go back to panel this month. And when it goes back to panel, if it's voted again in such a positive fashion, then approval will probably come in the next six weeks to six months. Which means this will probably hit the market like I said, by early January 2015. And we at MUSC will be one of the initial sites that is offering this, and probably one of three sites in the southeast that's been offered this technology. That's why I think it's important for you guys to know about it.

The WATCHMAN device is self-expanding-- widens in all frame, with fixation barbs. It's got a permeable polyester fabric that covers it. It's available in multiple sizes, it's delivered percutaneously transeptally through the left atrium, and then implanted with a catheter and deployed in the left atrial appendage. You can see sort of the demographic here, and this is sort of what it looks like here with a CAT scan where it's occluded.

Most of the left atrial appendage, if you notice here, if you're careful, this is actually the left upper pulmonary vein here. You see this ridge here, we call this the Coumadin ridge. And there is a small remnant of the left atrial appendage here. And yes, can clots form there? Yes they can, and we've seen it. And that's why again, stroke risk are not zero, necessarily. Oh, I missed a slide here, I apologize.

The main trial is the is the protect trial, and I accidentally deleted that slide, I apologize. That randomized patient, I'll explain to you how the trial was done. It randomized patients in 2-1 fashion between the WATCHMAN device and Coumadin. Mind you, none of these devices have been studied against novel anticoagulants yet, because these were all started with--

And what they did was, is that they kept these patients anti-coagulated for about six weeks and then left them on anti-platelet therapy for about six months, the ones who got the left atrial appendage occlusion. And the primary outcomes were obviously reduction in stroke and systemic embolism, and then safety endpoints, in terms of bleeding. And then obviously, it was power to look at things such as mortality.

The other study that I'm going to combine data with, because this is what everyone's been looking at, is the PREVAIL study. The PREVAIL study was a follow up study that the FDA asked Boston Scientific to do, looking at the safety and efficacy of implants of this device. So the initial data, as you're going to see with PROTECT was quite good. That is, it was at least as good as Coumadin, if not better, in terms of efficacy of reducing stroke.

The problem is there were a whole bunch of tampanods early on when they put this thing in. The left atrial appendage is a pliable thing, these fixation barbs are sharp, and you can just slide open that appendage. And initially, they saw what are relatively high rates of significant complications in implant, almost 10%. And that scared them. But then when you saw that 10%, I should say probably about 7%. But what scared them-- so that scared them. But what they saw was as you move further along the timeline, those event rates drop down to about 3%, which was much more tolerable.

But the problem is that was because these were very experienced centers, with slick operators who knew how to do this thing. And they said, well, if we're going to introduce this mainstream, we got to know that not every operator is going to have this really high rate of complication when they first start. Because otherwise, we're going to be hurting a whole lot of people to get good outcomes later.

So what they did was, they did a prospective randomized multi-center study to see that they could actually do this safely. It was a similar design to the PROTECT trial. But what they did was they took these operators ahead of time, and they trained them. They brought them to centers, they showed them how to do this, they gave them animal models, and they said, look. These are the trip, and they had experienced operators going over the tips and techniques that not only successfully implanted efficaciously, get the thing deployed, but to reduce complications. And so I'm going to include all the data from these.

What you see here, is that there were already over 2400 patients enrolled in the US with these trials, PROTECT AF was 800, PREVAIL was 460, and these CAP registries were basically continued access protocols available to these PROTECT investigators. So you see where there's already been 18-- almost 1900 WATCHMAN devices implanted, with a total number of patient reaching almost 6000.

What you can see is in terms of the patients who are implanted, you say, well, maybe they were implanted in a bunch of low risk patients who didn't really need this thing, and that's why the thing did OK. Well, that wasn't the case. If you look at CHADS₂VASC scores, basically, almost all the patients had a CHADS₂VASC score of at least two. And no one who shouldn't have been anti-coagulated, no one who shouldn't get this device got the device. So their CHADS₂VASC are zero. So I think that was pretty well enrolled.

If you look at the primary efficacy over-- this is the five year data from PROTECT AF, the original trial. You can see here that there was a 39% relative risk reduction that barely just missed its statistical significance. It met non-inferiority, it almost met superiority, in terms of its statistical significance. And it's really kind of interesting, because I've watched-- this slide has changed over the last two years that I've dealt with this. Because intermittently when they keep breaking up the data, so at two years it wasn't quite significant, at three years it was significant, four years it was significant, and now, at five years, it barely falls out of statistical significance. The point is is that really, it's at least as good, and it probably is better at stroke reduction.

And if you look at all strokes, so all strokes is about similar-- this is data pooled across all the WATCHMAN studies, ischemic stroke, about similar. Hemorrhagic stroke, just like with the novel anticoagulants, and as you can imagine why. Because these patients aren't on oral anti-coagulation anymore. That's where it strongly favors WATCHMAN. But remember that these hemorrhagic strokes are the most fatal, that's why. Because you're going to see here, there's probably a trend towards improved mortality with WATCHMAN. Again, didn't quite meet statistical significance, 0.063, but in literally last year, it had been at 0.849.

But you are looking at mortality ratios again, about a 30% reduction in mortality. Again, all related due to bleeding, and a lot of which is driven by reductions and hemorrhagic stroke. All caused death. Again, across all studies, 0.07 almost statistically significant reduction in mortality. Cardiovascular unexplained death did favor WATCHMAN in these studies.

So what about safety? I alluded to this earlier. So initially, about 5% of patients had paracardial tamponade with the PROTECT data. This is from the original study. 15 of which were treated percutaneously. Seven patients actually had to go to open heart surgery. They all had extended hospitalizations, but no one died. And again, as I noted to you before, in the first half of the cohort it was about 6% weight of tamponade it's dropped to under 4% in the second half of the PROTECT AF core.

So again, that's why PREVAIL was done. If you look here, initially, so these were the event rates with implants. Almost 10% in the first half of PROTECT AF. But then, when you look across experienced operators who PROTECT AF, and the continued access protocol, and then PREVAIL. Which reminds you were new operators, who had never before implanted this device. You see here now, the overall event rates in implants drop-- so this is really what the FDA wanted to see. They wanted to see that you can train doctors to do this stuff.

If you look at bleeding events, and you pool the data across here, what happens to bleeding events over time? Obviously, there's a market reduction between WATCHMAN here in blue, and Coumadin in terms of overall bleeding events. And this is remember, is freedom from major bleeding event, usually down the curve there's been more episodes of significant bleeding. So you're looking at a 70% reduction, which clearly means statistical significance.

If you look at major bleeding rates over seven to after seven days, and you look has bled scores. Which is risk scores, or what's your risk for bleeding. Again, market reductions in all of these groups compared to WATCHMAN.

What about patients who couldn't take anti-coagulation? If you look at patients who couldn't take anti-coagulation, there's a small group of patients studied in the ASAP trial that was published last year in Jack. And these patients, as I mentioned before in PROTECT, all the patients took anti-coagulation for at least six weeks, and then anti-platelet therapy for six months. None of the patients in this study could be on Coumadin. And what you saw here was, again, a 77% reduction of ischemic stroke. Because these patients weren't on Coumadin, they weren't able to safely be implanted without significant increases in complication rates and thrombotic rates by early implant. And you did still see a marked reduction in ischemic stroke, obviously. Because remember, none of these patients were on Coumadin. So the WATCHMAN device patients obviously clearly did better in that case.

So quickly, before I move on to the second case, I just want to throw on a little plot twist on that first case. This patient, you convinced him to start oral anti-coagulation with a novel anticoagulant. After much prodding, I think you could make that argument. She had a CHADS2VASC score of two, she had very minimal risk of bleeding. We knew she was having continued AF, she was relatively asymptomatic. So we wanted to anti-coagulate her. Well, one year later, she presents with acute coronary syndrome, left heart catch there's a 90% prox RCA and she's going to get PCI.

And of course, now you're stuck, right? Because now your interventionist wants to put in a stent, patient's already on Eloquist, or Apixaban, or rivaroxaban or whatever you want. Now, we're only looking at triple therapy. What does that mean?

As you can see here, this is data pooled up, looking at patients who are on triple therapy. Use as a hazard ratio we just compared to aspirin alone as your control, 81 milligrams. You start to see as you add [INAUDIBLE] or Coumadin, the bleeding risk goes up. You start adding aspirin and Coumadin together, you start to look at a hazard ratio of at least two, so two-fold increased risk for stroke. But now, you add plavix plus aspirin yielding a four-fold increased risk for stroke. We're changing mortality-- sorry, a four-fold increased risk for bleeding.

We're changing mortality when you're on triple therapy. But obviously, bleeding is a serious, serious problem. And you have to look at the has bled scores I think, to help-- at least, we do when we're talking about what type of step we want to put in, and how long do we want these patients on triple therapy. This is similar to a CHADS2 score, you just look at what these are. And you give certain points for abnormal renal or liver function, high blood pressure, stroke, bleeding, Lable INR's. Whether they're elderly, or whether they're on alcohol, or drugs, the increased bleeding risk. And you can get a maximum of nine points.

And as long as you have a has bled score of three or greater, you are at significant increased risk. I'm not going to go over this in detail, but what we can see is as you start to look at high risk has bled scores, we really push bare metal stents. Only because we don't want to have these patients on long term triple therapy, because their risk for bleeding will go up significantly.

When you have low or intermediate risk, you may consider drug alluding stents. And typically, what people will do is they will peel off the aspirin as soon as possible. Because multiple studies have suggested that the additional aspirin is what is really kicking over the increased bleeding risk. And that the benefits of, for example, clopidogrel or plavix in terms of stent thrombosis is better than aspirin plus a vitamin K antagonist.

Actually, all the data I've shown you so far is with Coumadin. What do we know about novel anticoagulants? Well, very little. In terms of addition, we do know that rivaroxaban really may have shown some benefit, in terms of treatment of acute coronary syndrome. But the bleeding risk remarkably markedly higher. So we are not using rivroxaban for acute coronary syndrome.

What about Apixaban? Apixaban was studied in the APPRAISE trial, which is another acute coronary syndrome trial. But the problem was, is it was given in a lower dose. It was given in 2.5 milligram dosing. So what we know though, is that there is still an increased risk of bleeding when you add Apixaban to dual anti-platelet therapy. The hazard ratio is about 2.6. But again, you can't directly compare that with Coumadin. So we can't say this is a two point, this is less than threefold increased risk for bleeding. Because again, this was a lower dose. We do know obviously, that adding novel anticoagulants does increase your bleeding risk significantly, and probably on a similar level [INAUDIBLE].

So that case is done. I'm going to quickly talk about a couple of more things and then leave some time for questions. I'll move quickly through this, but this is another sort of more complex patient. 75 male, Jehovah's Witness, longstanding history of persistent AF, history of two prior strokes, has also diabetes, hypertension, has had multiple GI bleeds, his hemoglobin's been less than seven.

He's a Jehovah's Witness, remember? He doesn't want blood transfusions. And he had an LA thrombus on a recent CT scan, what are you going to do for this patient? Can you use oral anti-coagulation? Do you want to ablate this patient at all? Can you ablate this patient? Is it going to do anything, does it have any chance of working? And what about the role of closing the left atrial appendage?

What I can tell you is is oral anti-coagulation an option? It might be. It might be transiently while you're trying to clear a thrombus so you can do things, because that's actually was a real patient. Now these symptoms must begin.

What about ablation? Well, when you look at paroxysmal versus persistent atrial fibrillation, look at these attrition rates. So this is the attrition rate over for paroxysmal atrial fibrillation. So you're looking at around eight years, you start to look about half the patients have a fib again. If you look out six to eight years in patients with persistent a-fib, who undergo a catheter ablation, you're looking at maybe 25% of them that will actually maintain sinus driven that far out.

In this guy who's had AF for 10 years, it really doesn't benefit. Can you stop oral anti-coagulation in patients with prior strokes? The answer is, there's been very limited data. We're looking at a total of maybe 300 patients. The event rates have been very low, just like I showed you before. So maybe it's safe, but there's no prospective data there. And I can tell you, I rarely, rarely, rarely stop patients of oral anti-coagulation have had a prior stroke, even if they undergo a successful ablation. If I really have to, this is the paper I use as a reference. Because at least then, we did show that there were no thromboembolia.

What about what can we do for this patient, in terms of closing the appendage? I don't have any time to go over the surgical thing. All I can tell you is that the surgical data, you know when surgeons close the left atrial appendage in the OR? There's nothing prospective for that. It's all retrospective. What they've shown is that patients who were undergoing valve surgery and had their left atrial appendage closed had about a sevenfold reduction in late embolism. So that somehow got extrapolated into the guidelines for cardiac surgery, that you could close everybody's left atrial appendage at the time of mitral valve surgery.

It probably doesn't hurt them, but whether or not it helps them, is another story. And I can help address questions, if you guys have specific questions about surgical closure for that atrial appendage. But I can tell you a lot of times it's incomplete, and we really have no perspective.

What we do have, is another percutaneous technique, which is this LARIAT device. It's FDA approved. And how did it get FDA approved without any prospective data? Because it's just the suture delivery system. And they got FDA approved as a suture, they didn't get FDA approved as a left atrial appendage [INAUDIBLE], but that proved as a way to appose tissue using a stitch. It is a slick device, I've done at least two dozen here. And I actually have two more on Thursday. But we really do reserve them for the sickest of the sick. In patients who need it, this is how it's done.

This is an epicardial sheath put in, like you would put in a pair of cardiosyntethis sheath. And it sits in the epicardial space, we come up and go transeptal, just like we do for any other catheter ablation in the left atrium. And through this catheter we put a wire, and on the tip of this wire there's a magnet. We also can use this balloon catheter that goes over this wire, which has a radial pick markers [AUDIO OUT] and see that [AUDIO OUT] on TV as well. I'll show you that in a minute.

Through this epicardial sheath, we put another wire that has a magnet on it. And these two magnets touch, they are actually very strong. And you could pull this wire through the appendage if you aren't careful. And over this wire, this now serves as a rail, and you can deliver this lasso device. What they call, in this case, the LARIAT.

And you slide it up over the left atrial appendage, you use that balloon as a marker to mark that you're all away on the appendage. And then you cinch down this snare. On the snare, there's a pre-tied suture with a knot. And you push that knot down using the special device. You actually first, you detach these magnets. And again, you have to be care-- [AUDIO OUT]

So then you can deploy the stitch, slide the lasso down, and then you just cut this stitch. And then you might say, well, fine. What happens to this? Well, the body absorbs it, kind of like your appendix. Just goes away, and it's pretty amazing. Let me show you what it looks like.

This it looks like from inside the chute dye. You saw there, the appendage flash. I can show that again. This is again, us putting that magnet in the appendage. You see a TV probe there, watch these wires, watch these magnets. See? See how they grab each other? They just really snap and grab each other, they ploy right out of your hand, they're so strong.

And then from here, you can see how we had to carefully sort of slide this way up over the appendage. You see we use that marker there to mark the [INAUDIBLE] appendage. You can see as we cinch that down, you get right to the [INAUDIBLE]. We usually puff a little dye, pull those magnets apart, deploy, and then here, we'll puff dye. And I don't know if you can see that, see now that appendage is gone. If you go back, I'll play again to see if you can see-- see that? That's what the appendage looked like before.

And again, on TEE, this is what it looks like beforehand. This is the left atrial appendage, this is our balloon sitting in the left atrial appendage. You can see it rounded here. This is after we've closed the left atrial appendage acutely. This is flow in the left atrial appendage. You notice there's no flow going back through what was the appendage. Before, there's flow just flowing between the two. No flow here.

And then this is at three months of follow up. You can see here, see how the appendage is completely absorbed, there's nothing left. Its smooth and there's no flow. So this thing really works. The problem is is that there's no data for it. It's all retrospective data, this was a non-randomized single center trial, again, 90 patients. This was published back in 2012. They confirmed that they closed it. CHADS2 scores was at least greater than one. I can tell you now, anecdotally I don't do CHADS2 scores of one of this.

Successful ligation in 96% of patients, but there was a 3% complication rate, mostly related to paracardial access and paracardial pain. There are no patients who died, there are reported cases of perforations. Most of the time, you're looking at a 95% to 98% long term closure of the left atrial appendage with minimally leak. The problem is is that you can have what looks like this over time, with the left atrial appendage gone, but you can also have this, which is a stump thrombus.

And just like I showed you the stump with the WATCHMAN, which can also occur, you can get these stump thrombi. There is slow flow a lot of times in these patients with persistent a-fib. Remember, they're not on/or anti-coagulation. So we don't know what the real incidence of this is, and we don't know what the real clinical significance of that is. And that's why we need prospective data with this device.

Complications include chest pain, about 25%. But we usually leave a drain in, we've been pulling that drain sooner and sooner since it causes so much pain.

The problem is too, in the studies that they've done, over half the patients remain on long term anti-coagulation. There are certain anatomical limitations, you can't do this if the patient's had prior CABG or adhesions for pericarditis because you can't get in the epicardial space. Remember, we're just doing this with a dry stick. I actually use a micro puncture needle to get in the space. If the left atrial appendage is located behind the pulmonary artery, I'll show you a picture of that. But the patient has persistent LA thrombus, which is why this patient, I had to temporarily anti-coagulate for about a month just to get his appendage to clear, which we were able to do. He's actually done quite well.

So if you look here, this is a CT scan that we get beforehand to look at the patient's anatomy. You can see how it rotates around. See here, this is the pulmonary artery, and this is the appendage sitting behind it. There's no way to get at this appendage, because I'm coming from this angle here, and then I have to swing around the pulmonary artery. There's no way to get that. Typically speaking, the appendage will hang out in front of the pulmonary artery over here, and you'll be able to see it.

Here's a CAT scan too. Again, seeing this is the pulmonary artery. Remember, I'm coming up from this direction, and I'd have to come all the way around to get that. This is why we need to get CAT scans of all the patients before we do the procedure. We don't want to find that while we're in there that we're not going to be able to get to it.

So this is my final slide. In terms of perspectives, oral anti-coagulation use is obviously still the mainstay of our therapy, but it is limited by multiple factors. Bleeding, perceived risk for bleeding, cost, being a big one, especially with the novel anticoagulants. Patient preference, discontinuation [AUDIO OUT]. The left atrial appendage is highly associated with stroke and non-valvular AF. There's no doubt about it that patients with low flows in their appendage, and clots detected in the appendage are markedly increased risk for stroke. And left atrial appendage occlusion is potentially efficacious, safe, and feasible. The WATCHMAN devices, and actually the implants cardiacs are both approved in Europe for patients who can't, or relatively either absolutely out of relative contra-indication.

The indication they're going to go for in the US is actually an alternative to Coumadin. The WATCHMAN is the best study device date, recent data shows both non-inferiority and basically, trends towards improved mortality and relatively acceptable safety profiles. And as I mentioned, FDA approval hopefully will be coming shortly.

The percutaneous closure with the LARIAT device is something we are doing here in very limited, in select patient groups. No randomized data exists. So we really only do this in the patients who just can't take anti-coagulation, or are at very, very high risk with prior strokes. It is FDA approved, but again, I stress that it's only for the highest risk patients. I've gotten patients with CHADS2VASC scores of one. And I tell them, this is not the device for you. You don't need this. And remember, there are some anatomic limitations as well.

We definitely need more randomized controlled trials for future devices, comparing them to the novel anticoagulants. Remember, not all anticoagulants have shown better safety than Coumadin. So if the novel anticoagulants are much safer, and these devices are not quite as safe, then we may need to look at that risk profile over time. So with that, I'd be happy to answer any questions.

[APPLAUSE]