TRACY WANG: I am very excited to welcome all of you to this symposium tonight. I'm not going to spend too much time on the introduction here. We have a fantastic agenda out with experts both medically and surgically on valvular heart disease. Each of these speakers will keep their comments to about 10 minutes, and then we will have a Q&A session for a few minutes after that.

Without further ado, I am going to introduce Dr. Maurice Sarano. I've known Dr. Sarano now for a couple of years. He is a professor of medicine at Mayo Clinic, and he directs the valvular heart disease clinic at Mayo Clinic.

And he is research really focuses on innovative treatments of valvular heart disease. So Maurice is going to get us started on our TAVR versus SAVR versus valve in valve in young patients showing us some data on valve survival, patient survival, as well as the eventual need for anticoagulation. So, Maurice, why don't you get us started.

MAURICE SARANO: The discussion constantly for the aortic valve is what are we going to do? What are we going to choose for the patient, mechanical bioprosthesis and now bioprosthesis by implantation of a TAVR? And evidently, as physicians, we're concerned about thrombosis and bleeding of patients with mechanical prostheses and structural valve degeneration of biological prostheses.

And the guidelines have been very limited in what they're saying. If you're less than 50 years, put a mechanical valve. If you're more than 70, put a biological valve. In between, we don't know really, but we give you some elements of preference. And so the complexity that we face is that we have to advise patients based on the multiplicity of factors, so we have to do, in our brain, a multifactorial analysis and projecting how the patient is going to be 5, 10, 15 years later.

And so with that and the immediate fear of the thrombosis and anticoagulation, the mechanical prostheses has gone from 25% of the market in 2006 to 15% only in 2010, and the decline continues. And it's understandable because this is a distribution of age of aortic stenosis, and you realize that the mean age is 75, median 77. Only 10% are younger than 60, and 15% are between 60 and 70.

So there is a justification of age, but some would like everybody to have a tissue valve possibly by TAVR. And the current fashionable statement is use only bioprosthesis. We can do valve in valve in the future, and you don't have to worry about structural valve degeneration.

In that discussion, the issue is what are the facts, and do we have randomized trials to guide us? There are a few, but they are quite old. This is the Scottish trial that was done and published years ago, and the mechanical versus tissue valve at the time, surgical valve, was not different in terms of survival. But survival with intact prostheses was way better with mechanical than tissue.

And then they did a reanalysis going up to 20 years, and although there was a little trend for better survival with the mechanical valve, over the 20 years, there was no significant difference. But, again, there was a confirmation with a very large difference. The mechanical valve having a more survival without prosthetic dysfunction than the porcine bioprostheses.

The other clinical trial was in the US, the Veterans trial, and in their first publication in 1993, there was no difference in survival after AVR between biological, and tissue valve, and mechanical valves. And that was the same for mitral valve replacement, but then when they republished when they did a second publication at 15 years of follow up, then you can see that the surprise was that the people with aortic valve replacement live longer than the people with a biological valve prosthesis, mechanical versus biological. And this was a surprise finding.

And you see what is interesting is the third randomized trial was very small. You see the small number of patients, but although it was non-significant, the mechanical valves were better than the bioprosthetic valves. There was a trend for a better outcome, so we haven't resolved. But there is an alarm ringing saying, oh, mechanical may be better for these patients.

So do we have observational cohorts telling us something about this difference? In *Controversies,* my former colleagues Rakesh Sari and Hartzell Schaff sort of show the experience at Mayo Clinic showing that people who were younger than 70, the mechanical valves has a much better survival. Even when you do a matching, there is a better survival with mechanical valve than with bioprosthetic valve.

But this is one institution, and then there was a series of publication from much larger samples. Here is the example. The experience of New York state that showed no difference in survival between mechanical and bioprostheses, but there was the usual similar stroke rate, higher reoperation rate in bioprostheses, and a higher bleeding with mechanical valve.

This was not really conclusive in the 50 to 69 years, but then there was this study coming from all California residents co-organized by Goldstone. And what they saw is that there was a trend for benefit for the mechanical valve with less complication, less mortality, particularly significant in the 45 to 54 year of age but with a trend in people who are between 55 and 64. Here what is very interesting is that the age where it becomes equal is around 60 to 65, close to 65. But below, the mechanical as a benefit as compared to the biological valve.

So here, we have the similar signal than the Veterans trial of a benefit for mechanical valves, and then there was this study from Europe. And this study from Europe was striking. This was not just the community. It was all of Sweden showing that the patients operating in Sweden for AVR between 50 and 69 had a significant difference in survival with a better survival with mechanical valve than biological.

And what is interesting is that when you analyze, you do a propensity score matching, you see that the biological valve have a risk increased by 30%. And whatever adjustments you do in the whole cohort, you see it's all around 30% increased risk, so what we have learned from these cohorts is that not all studies are positive. But there is a consistent trend for better survival with mechanical prostheses in that age range of 50 to 70 years old.

What about hemodynamic deterioration? Here is an old slide of different types of prostheses showing that over time, there is a structural valve degeneration that goes at different speed between different studies performed, but there is a sort of precipitous decline after a few years of these patients. Now more recently, there has been this study done in Quebec showing that after surgery for aortic valve replacement, there is quite a bit of mortality. Half of the patients are dead at 10 years, and there is a small percentage of people dying from structural valve degeneration.

But what is interesting is that to consider all structural valve degeneration-- this is not time. This is different subgroups, and you see the deterioration of hemodynamics dynamics in this subgroup of clinically relevant structural valve disease. But the important fact is that there is a clinically relevant symptomatic degeneration at 6.6% and 30% more subclinical.

So this is an interesting fact, and this fact was confirmed in a study from the same group but looking at time where there is accumulation of degeneration. And overall, their percentage of prosthetic valve degeneration reached 30% in that study with different type of degeneration over time. And what is important is that when you have a valve degeneration, it impacts mortality. You multiply mortality by two, so it's a high-risk element.

More recently, there is a paper on TAVR versus surgical biological valve, and this was kind of interesting in looking at the rate of degeneration per year. So the percentage is a rate of structural degeneration per year. And the older version of the Sapien XT valve showed a high rate of degeneration, and this rate was much higher than the surgical. So TAVR versus surgical was a much higher rate, significant rate.

But you see the Sapien 3 here, the rate of structural degeneration with bioprostheses valve failure is double. And when you do an analysis by weighing these, you see that it's significant. So there is a slight difference in the rate of degeneration, more in the patients with TAVR than structural valve disease-- than surgical valve implantation. And so this has to act long term to impact the outcome of these patient.

So what are the facts? Recent data suggests a high frequency of a hemodynamic deterioration over time, particularly with TAVR and increasing precipitously over time. So we have seen these things, these elements of the literature that are going against the grain of what you hear everyday from some surgeons.

And, really, the clinician need to consider facts and not advertisements in advising patients regarding prostheses type. We need to minimize bleeding through improved anticoagulation, and we need to obtain new data on structural valve disease in clinical practice to make our own clinical decision-making with individual patients. Thank you very much for your attention.

TRACY WANG: Great. Well, we do have a couple of questions coming in through the Q&A. The first question, which I think is a fantastic question is what potentially confounding variables may have weighed in the initial mechanical versus bioprosthetic valve decision in these retrospectively studied cohorts? Maurice, I think you had presented some great data from different parts of the US and actually also different parts of the world. What do you think is your response to something like this?

MAURICE SARANO: Yeah, it is. That's a very good point because people will may have some comorbidity that weighed on the valve implantation, so it is very difficult to include all the factors in the adjustment. And that's a good point, and this is why we need to see more studies done on the comparison of mechanical and biological valves to see if this trend goes in the same direction.

So the Goldstone California study shows a little difference. The Swedish study shows a bigger difference. The New York state shows no real difference in term of survival, and we have to integrate all that to say, OK, what is the average effect? And when you look at the experience of Mayo too, you can see that this is not the story that we heard that biological valve-- that we perceive because we don't give anticoagulation is better. I think that there is more, and the outcome of patients with a mechanical valve, in our experience, has been pretty good, in particular with the most recent valves.

TRACY WANG: And while I'm-- I'm also going to ask Marc and Mo to weigh in on this question. And while they're answering, I'm going to ask the audience if you used your chat function, it'd be great to sort of secure what your-- going to kind of poll you guys a little bit. In this day and age, if we had a healthy patient, relatively low surgical risk or bleeding risk I should say, let's say between the age of 50 and 70 years old, can we random-- can we do an RCT, a randomized clinical trial, randomizing to a tissue valve versus a mechanical valve?

I mean, what-- I know Marc and Mo, do you have any opinions on this? And the audience, if you'd like, go into the chat function. Give us a yes or no. Do you have equipoise, or would you be willing to randomize someone to a tissue versus biomechanic-- tissue versus a metallic valve?

MAURICE SARANO: I think it would be tough. I'm going to go and then let the others speak. I think it would be tough. You see, the Veterans trial was 15 years to give you an answer. That's the major point, and then everybody says, oh, but your comparison is from 15 years ago.

It's not valid today. Now we use anti-calcification and this and that. And so it's a more difficult study to do now, and so maybe what should be done should be an analysis of what happens in routine practice and compare what we have. But I'll let the other speaker tell what they think.

TRACY WANG: Mark, do you want to weigh in?

MARC GERDISCH: Well, briefly, I will cover some of it, of course, when I speak, but I would agree with Maurice. I think that the most interesting data at this point, because everything's moving so quickly, is, too, I think if we could understand the algorithm that's being applied, if we could gather data on how patients are moving through any given system, and then develop some kind of cohesive vision of how we manage this type of disease in the United States, I think that would be spectacular because we're better at getting that information from places that do have more cohesive programs, that they harvest their data easily. He talked about the Swedish data.

I'm going to talk about the Finnish data. And we have less good high quality data from these kind of 30,000 foot views that have multiple institutions and enrolling their data some well and some not so well. So if we could really refine that, understanding what the algorithm is in the country, I think that would be really helpful.

TRACY WANG: Mo, do you have anything to add to that?

MOHANAKRISHNAN SATHYAMOORTHY: Yeah, Maurice is always illuminating talk, and I think if I could just draw everyone's attention to Maurice's comments and slide discussing the PARTNER 2 data and the difference that's already being witnessed at a five-year sampling time between transcatheter implants and surgical-- sorry-- tissue bioprosthetic surgical implants. This should be alarming. It should really fundamentally ask the question biomechanically, what's the difference?

From a biomaterials perspective, what's the difference? What's happening in terms of accelerated decay? If it's being seen at five years, it should really start influencing the way we think about patient selection. So in this gray zone of 50 to 70, the concept of a transcatheter valve as this data is emerging gives me fear because we're almost looking at repeat interventions, and I think Marc going to get into this in terms of the risk of valve in valve operations, et cetera. And I can't wait to see this data, but that's the one point I would make is that should really draw attention to age and valve type selection.

TRACY WANG: Yeah, and a couple of audience members responded through the Q&A function to say that they would have a hard time with that trial, so I think that answers that question here. Here's another question for you, Maurice. Was the valve deterioration at five years any better with Sapien 3 compared with previous Sapien versions? Any information on self expanding valves? I know this is kind of getting into some of the later talks, but maybe you could just do a quick answer there.

MAURICE SARANO: Yes, absolutely. The Sapien 3 has better result than the XT previous version, and it's difficult to understand exactly why there is that improvement. Maybe it's the treatment of the tissue. The explanation in the papers, they say, oh, there are bigger valves. We don't need to do a reinflation of balloon, and we don't affect the tissue of the valve because we have a better sizing.

Maybe it's true, or maybe the crimping of the valve is something that explains some of the alteration. Is it benign to crimp the valve and then to inflate it? I don't know. Long term, do we affect the tissue? It's very difficult to know the cause.

Yes, the Sapien 3 was much better than the Sapien XT, but there was a trend for a slight difference with the surgically implanted valve where the valve was not crimped when it was implanted. And it's from the same company, so the tissues should be the same. So that little trend is worrying me, and it's within five years. So it's not when things accelerate, and so it's something-- and it's in people who are 80 years old so the older population with a lot of mortality. So we may not see the people reaching the end point of five years because of that age factor.

But what happens at 70? What happens at 55 because few patients in those trials with a mean age of 80 were in that age range? So we have many, many questions remaining on durability before we jump to doing a TAVR to everybody and projecting a valve in valve in five years and then another one and-- there are many, many, many question, and we have to really weigh and give the options to the patients.

TRACY WANG: Well, thank you, Maurice, and I really want to thank our attendees for jumping right in and sending us questions. So keep doing that. In the interest of time, let's move on to the next speaker. And Maurice will go into the Q&A and try to address some of the questions that are still in there, so don't worry. So our next speaker is going to be Dr. Marc Gerdisch.

Marc is the chief of cardiovascular and thoracic surgery and co-director of the Heart Valve Center at Franciscan St. Francis Health in Indianapolis, and I think one of the things I've really admired about Marc is that he's been the first in so many areas. He's been the first in the US to use the Edwards Sapien XT transcatheter aortic valve. He's also one of the first to implant the On-X aortic valve. And so Marc is going to talk to us about Life in the Fast Lane, Who, What, When as it relates to SAVR, TAVR and valve in valve. And I think we'll continue the conversation we've been having so far. Marc, take us away.

MARC GERDISCH: First, my disclaimer is in the form of just liking all of this stuff. I am absolutely thrilled with the direction of heart valve disease management, and I'm involved in all of it. I still do plenty of surgical aortic valve. I do TAVRs as well and expanding practice of aortic valve repair.

So given that, we're talking about TAVR a little bit, and Maurice was the perfect setup for me because there are some things we're going to overlap on and I'm just going to add a little bit to. And we will develop a little pattern, I think, of thought. So back to transcatheter valves.

This ship has already sailed. This is the best thing that ever happened to really high-risk patients. Older folks who need an aortic valve replacement whom a lot of whom we never saw and many of whom we didn't want to operate on now have that opportunity. This has been a real blessing.

We can debate about men doing better than women, or women doing better than man, or what the implications are, but high-risk patients, older high-risk patients, this was a great, great thing to happen in medicine. We get into intermediate risk and it's still great because there are a group of patients in the intermediate risk stratification in STS that there's the saying of the eyeball test. There's the intermediate risk that you want to operate with, and there's the intermediate risk that you really don't feel like you're going to improve their life. And so this also was a real gift to us, and as a heart team, we make decisions for these patients.

And it becomes a little bit more elegant conversation. It becomes a little bit more algorithmic. It's important to remember, though, that we're starting to acquire some longer term data on the intermediate group, and we're seeing that the outcomes differ over time. So although there might be that initial bump in surgery as you get out further in time, you get out to five years, they separate. More people go back to the hospital with the transcatheter valve if they lived to be-- to have five more years.

And, in fact, they have more complications such as rehospitalization. In fact-- this is interesting-- they have a little bit more endocarditis, although it doesn't show up statistically. I'm going to get back to that in a minute. But they have more reintervention, substantially more reintervention, and this becomes important when we look at those reinterventions because they're coming back in because the valves are failing. So this isn't a group of people who have a mean age of 82, and the main reason they come back into the hospital is because the devices are failing. Now most of them get another TAVR.

But if we go back and we look at those endocarditis cases, they never got touched, so those people, the people who get endocarditis in TAVRs typically don't get treated. But folks in surgical valves that get endocarditis do get treated. In this cohort, unfortunately, three out of the four died, but the point being that we don't see much in the way of structural deterioration in five years. They're not going back to re-replace surgical valves. And I may get to a little bit about that later as far as what I think the key roles are, but the point is that we see that deterioration.

Importantly, every time there's a meta analysis whatever can be done to look at SAVR versus TAVR, once you get out past two years and certainly once you get past three years, you start to see this. For everything the trend goes positive toward surgical valves. Now that doesn't mean that everybody is supposed to get a surgical valve. It just means that we have to understand what it is in the context of the human being that we're seeing, their longevity, and what the implications are for them, and the effect on their lives.

Low risk, we talked about this briefly. This is actually an important study. We want to know what's going to happen to patients at low risk because we have patients at low risk sometimes that we want to offer a transcatheter valve to. STS risk is not the be all and end all.

That said, it's important to recognize that this is the forward facing part of this study for the general population, that there's a randomization of 1,000 patients. Although the truth is if you look at the forward facing version that we received as physicians, there were over 1,500 patients that were enrolled, but a third of them are excluded. So what's going on here? Why are a third of them out of the study?

It's because they either have a small annulus, or a big annulus, their bicuspid. They have AI. They have severe left ventricular dysfunction. They have a lot of calcification near the aortic valvular complex and the alveolar outflow tract. These are all things that are not a problem in surgery whether they are low risk or high risk.

And, in fact, so if you look at this, a highly selected group of patients that were perfect for transfemoral TAVR with a mean age of 74 did better on the short end. There's no difference in all-cause mortality at one year. We're seeing some changes in valve function over time, but there's nothing dramatic.

It is important that there's some AI in 30% of those TAVRs, and I don't think that AI is a big deal when it's mild. But I do think that AI is a signal that the valve is not perfectly deployed, that it is not round, and we know that a round TAVR doesn't last as long as a not round TAVR. So 2/3 of the patients that were excluded were bicuspids, so you can see why these aren't great for TAVR.

We do do TAVR in bicuspids, and they do OK most of the time. Most of the time isn't good enough in surgery and aortic valve replaced in the [INAUDIBLE] patient. So when we're dealing with this, we cut the valve out. We put a new valve in.

Furthermore, for those bicuspid patients, it's very important that we be cognizant of their aorta. So the younger the patient, the more important any enlargement in the aorta becomes, especially if we think they have a long gain, as long as they're going to live a long time because we will address that aorta at smaller and smaller dimensions based on their longevity. And we actually have an app for that. This is a great app that the guys in Montreal developed for us. It has everybody's guidelines, so we can always have a cogent discussion with the patient.

What if the test group were minimally invasive parasternal surgical aortic valve replacements? If we selected patients with good annual dimensions so that's solid the size or even really big, they can have all of the AI you want. They can have bicuspid valves. They just have to have good femoral access for perclose femoral cannulation. Aorta is in a good position.

What if we get to choose? Well, I suspect then that SAVR is going to look better than TAVR because even those bicuspid valves are going to have to be randomized. So the reality of it is there's an application for all these devices, and we have to look at who the human being is and what the consequences are.

We can do this through a small incision. We can do it through a little incision without touching the sternum. And the patient has a rapid recovery, and it affects their lives very little. So earlier, we talked about the Swedish data. Here's the Finnish data mechanical versus biologic prostheses 50 to 70 years of age.

And people always say to me, well, you know, that's the Finnish data. In Finland, they have great health care. They can manage I&Rs. So we can see that that's true, right, because their mortality is better with mechanical valves. They're reoperations, of course, are better with mechanical valves. They're much less.

Their bleeding is the same. Why is that? It's because they have a lot of home I&R monitoring. They monitor their anticoagulation perhaps better than we do as an entire nation. Stroke incidence is the same. It's always the same, so when people say, well, stroke incidence is higher from mechanical valves, that's not true. A mechanical valve that's anticoagulated or a tissue valve, they carry the same stroke incidence overall.

So long term, you know, again, as I said, if you look at that and you say, well, that's the Finnish experience-- they have things well controlled. I think this paper is very important. Diaz, they took all of the relevant good studies so all the matched studies and the one randomized controlled study that was fairly recent, which was mentioned earlier, [INAUDIBLE], and they showed that, in fact, mechanical valves in 50 to 70 years of old age were associated with a longer long-term survival. Now people are still going to say it's inconvenient. You got to be on anticoagulation.

Maybe there are lifestyle issues. We're still going to talk about that, but the reality of it is that there are several studies demonstrating early, mid, and long-term survival benefit with mechanical valves versus biologic valves. There are several studies demonstrating no difference in survival, but there are none that show that biologic valves have a survival advantage. That is not something you can offer in the conversation.

But like politics, medicine is local. Patient management will differ both in subtle and obvious ways across institutions and even within them, and this is just the truth about the Wild West of valve disease. So valve choice in a modern era, what are we accountable for? How do we generate a valid landscape?

We have to know the patient's goals. We have to provide them legitimate feedback to what their thoughts are. The person's telling you they're going to live 30 years and you know they're not or if you have to-- they have to change course in their life and they can deliver on that, then you make a deal with them. But you have to think about what their long-term survival is, what the quality of their life is, and what's the internal milieu of their body, how it will impact the valve.

And I'm going to show you some really interesting stuff about that. No patient prosthesis mismatch. This is an absolute. So if someone is in a valve center of excellence, they should never leave that institution with the wrong size valve, and it doesn't matter what kind of valve they get.

So how do we develop this framework of discussing valve durability based on what we know, what we expect in the context of that particular human being? So match the long-term performance of the device with the longevity of the person. And what do we know?

Well, I wake up on September 27 last year, I open my favorite journal, and what does it say? It says that when implanted correctly, a Sapien 3 can last 25 years, and this is absolute bologna. That headline should not be there.

What are they looking at? They're looking at a perfectly circular Sapien 3 in a biotesting device that has saline in it and just opens and closes the valve a billion times. Sure, that might work, but in a human being, it's not the same thing.

Structural valve deterioration is unavoidable, and we don't really appreciate the full prevalence of it because we lack a full definition. As Dr. Sarano showed earlier, we can look at it in subclinical framework or the clinical framework, in other words, symptomatic, but either way, that valve is changing. So as soon as a biologic valve goes in, it starts to change.

My favorite paper on this subject, Hancock II Bioprosthesis. Dr. David followed all of his patients prospectively. 1,134 patients with prospective follow up including echo. This is the best study looking at tissue valve durability. 1982 to 2004, what does he show us?

He shows us the Hancock II is a very good valve. Mean age of 67. Patients do OK. He also shows us that without doubt the most important variable is the patient's age, so age determines durability.

Why is that? It's because of the younger you are, the more vigorous your immune response is. Conclusions, Hancock II is a good valve. Patient age is the most powerful predictor of valve durability, and for him, the most important thing was that although they identified structural valve deterioration in 87 patients, only 74 reoperated because the remaining 13 were deemed inoperable.

What is driving some of that outside of the age? And the other major factor is the active milieu inside the patient. This is a great paper from [INAUDIBLE] group looking at the impact of dysmetabolic profile, and we're all familiar with this central adiposity, insulin resistance. These are patients we see all the time, and what did they see? That once there was a signal of it, once there was a signal of impact on the valve, the deterioration accelerates dramatically, and it's a function of the metabolic syndrome in the patients.

So it's that internal milieu that will accelerate the valve deterioration. So that means not only a young patient might be better with a mechanical valve, but somebody middle aged with this metabolic syndrome and coronary disease might actually do better with a mechanical valve. It's not just the younger patient that drives-- that lives longer. It's because of that prosthesis due to structural value deterioration creates excess morbidity and mortality.

My point here is that those valves start to change as soon as they're in the patient, and this is an important paper that Dr. Sarano showed earlier. There is another paper that's very similar to this, subclinical and clinical impact. Basically, what it tells you, though, is the gradient rises on these valves. The effective orifice area goes down.

So when these valves start to deteriorate, they start to tighten over time. These are, of course, mostly pericardial valves, but that patient will live with a moderately diseased valve for several years before it's time to replace it or it's time to do a valve in valve. So why do surgeons think that these valves last a long time? They get the impression that they're going to be 15, 19 years. Almost 40% of the surgeons thought that.

It's because they see these types of communiques that talk about 20-year function of these valves, durability of the valves. The reality of it is, though, that data does not include these young folks. You put young folks in there, you're not going to get the durability out of the valve.

So has anticalcification treatment changed at all? I could spend an hour just on this. I've spent a lot of time researching this or reading the papers. There is nothing clinically evident that shows us for sure that any anticalcification process is better, and, unfortunately, the Inspiris valve, which I do implant in the younger folks that demand tissue valves, doesn't have any real data other than eight sheep out to eight months where they showed, in the mitral position, the calcification was lessened in the belly but still occurred at the commissures. We'll wait to see if that translates into a better long-term effect.

Sometimes good valves go bad. A random valve can fail in a tissue valve. Sometimes a transcatheter valve will fail very early. This is a woman who only 20 months earlier had had a 20 millimeter Sapien put in.

This is the person-- this is a young man who had chronic renal failure. When he first had his valve implanted, he was in bad shape. He came back to us, and we took that out and put a mechanical valve in him. But you can see the accelerated wear on this valve from chronic renal failure just as we know it happens in surgical valves.

Dysmetabolic syndrome, 64-year-old woman, three and a half year old valve. Dysmetabolic syndrome, as I showed you earlier, affects the valve. 50-year-old man who's six years out from a Magna, now by the time we get to this valve, his left ventricle has hypertrophied. He has bad diastolic dysfunction. He's had the disease of moderate aortic stenosis for a long time.

How do we decide to go sooner on an asymptomatic patient who's suffering the consequences of a moderately stenotic valve? This lady was 82. She finally had obstruction due to pannus growth. She might be better off than the 50-year-old because she got 25 years of good valve function until we put her tissue valve in.

When we look at an On-X valve, it only sees the outflow tract. It sees pure carbon, and it comes out to the aorta. And this is an important point for this valve because it seems to be immune to pannus growth. No one wants to be anticoagulated unless it saves or extends their life, and then they're still not happy about it. But we still have to tell them the truth.

People with TAVRs, they're often anticoagulated. 30% of TAVRs are anticoagulated. Tissue in tissue aortic valves are often anticoagulated. And remember that patients that are free of atrial fibrillation at age 55, by the time they grow old, they're at a approximately 40% chance of getting atrial fibrillation and needing anticoagulation. So having a tissue valve doesn't mean you're not going to be anticoagulated.

Should bioprosthetic valves be routinely anticoagulated? Again, [INAUDIBLE] is a beautiful paper that outlines the fact that if we really are paying attention to our patients, we should be anticoagulating a lot of them because a lot of them have an indication for it. I'm going to go back to this Chang paper that Dr. Sarano mentioned before.

4,000 patients, New York database, and I think the important signal here is that stroke's the same. Reoperations more in bioprosthetics. Major bleeding is more. Now reoperations are dangerous, right? 9% mortality.

Maybe we've improved that with valve in valve. We don't know yet because we don't know how durable these are, and we know that bleeding is a problem. So if I can fix one thing on here, if I can make this go away, then mechanical valves are the clear winner. Maybe we're changing the risk of redo with valve in valve and valve fracture, which we do a lot of, and we're actually participating in a registry for that.

But what are we really after? We're after coming up with an appropriate decision for the patient that allows them to make-- I have a cogent understanding of what's going to happen to them after they have their valve replaced. It's worth noting that the On-X valve is pure carbon.

So 17 years ago, I met Jack Bokros, the guy who invented the silicon alloy pyrolytic carbon that's on every mechanical valve on the planet, and his goal, even then, was to come up with this. And he had just discovered it. He had just made On-X carbon. He had just brought it into the valve field, and you can see how much smoother it is and less likely to be thrombogenic.

The structure of the valve, this is important because, as you know, we're moving into a very exciting trial that Tracy is going to talk about. But the mechanics of the valve allow for better washing of the hinge point. The hinge point moves up and down in this socket and gives a three way purge. And the valve leaflet doesn't have to fall as far when it closes, so it requires a smaller closing volume that then the additional closing volume can be spent washing the leaflet-- or washing the hinge. Sorry.

It opens to 90 degrees and to a 90 degree angle. It's the only valve that really gives the opportunity for true laminar flow. And this is what I was telling you about before with the motion of the leaflet in the hinge point in the frame of the valve. This is a taller valve. It has a fairing that drops down into the outflow track. That's the reason that we don't see pannus growth because the pannus would have to grow down around the carbon fairing.

The housing is designed so that it sits inside the outflow track and prevents that. Like I said, that's the Achilles heel of the mechanical valve. The blood only sees the outflow track and the valve, and this is the unique property of this valve. Its laminar flow allows it to restore normal flow. Our goal in these patients, especially the younger folks, is to recouple their heart with the vasculature in a normal fashion.

Who can we do-- well, how can we do that? We do that with a homograft, or FreeStyle, an On-X. In fact, it shows the replacement flow pattern for valves is different for the various devices. Whether that's a mechanical valve, stentless valve, or stented valve, the pattern is different. And in fact, for an On-X valve, it's very much the same as a normal healthy volunteer.

So this is a normal aortic valve flow pattern. This is an On-X valve. Laminar flow, normal vertical flow into the vortices profusing the coronary arteries. We showed, of course, that with the On-X valve, we could run it at a lower dose of blood thinner. This was, of course, the pivotal study.

And the most important thing that came from the lowering the anticoagulation study was that we could move the INR point down. We found that a sweet spot for the On-X valve was a lower dose of Coumadin with an INR of 1.5 to 2, and that resulted in a 65% reduction in bleeding events. So at the end of analysis for our primary endpoints, it was significantly less for the lower anticoagulation protocol, so we changed this. We changed the ability to-- we changed the bleeding risk for the valve, and we provided patients with a durable valve that would not provide them then with that increased risk of bleeding.

In whom should we consider a mechanical valve? Those that we don't want a high likelihood of reintervention, if they're young, chronologically or physiologic age, and talking about, like I said, the dysmetabolic syndrome in a more complex scenario. Thank you very much.

TRACY WANG: Hey, Marc. That was great. Every time I listen to you talk, I get so immersed in everything you say, and I lose track of time.

MARC GERDISCH: Yeah, sorry about that.

TRACY WANG: Just a quick question here, and we'll have you answer some more of the questions online. But I thought this was an interesting one that maybe you could answer quickly. 60-year-old, decent health, TAVR feasible, good size annulus, but absolutely refuses anticoagulation. Which option would you consider-- SAVR now with a valve in valve hopefully in a decade, so I'm assuming a bioprosthetic now versus-- with a valve in valve later on or TAVR now and then surgery in a decade? What do you think?

MARC GERDISCH: Yeah, this is an interesting topic that's come up kind of recently. I think I'm solidly in the minimally invasive SAVR department. It depends a little bit on the anatomy of the aortoannular complex and making certain that we can offer them a solid valve in valve later, and that's actually an important consideration. No patient prosthesis mismatch-- the valve in valve opportunity later.

But that same 60-year-old, if it's 70 when they need another valve, then you do their valve in valve. And then they get to be 80, then your valve in valve in valve. That is doable, but it's not great. We've done TAVR in TAVR, plenty of valve in valve, and we do valve fracture for that often. So we have to talk about them about the entire continuum, but I just had that patient the other day and did a minimally invasive SAVR for him.

TRACY WANG: Well, that's good. And we just have time for that one question, and so we'll move on to the next presentation. But there is a question-- some for you to answer in the Q&A while Mo is speaking here.

Great. So thank you for that. Next, I am going to introduce Dr. Mo Sathyamoorthy, who is the professor and chair of the Department of Medicine at TCUN and UNTHSC School of Medicine, who is our thrombosis expert and is going to be talking about blood thinning in 2020 and beyond, what this means for our AVR patients as well as how do we collaborate with surgeons thinking about artificial prostheses selection? So, Mo, thank you very much.

MOHANAKRISHNAN SATHYAMOORTHY: Well, thank you again, Tracy, and for everyone organizing this in such a nice way online during the pandemic. My best wishes to everyone for safety during this very challenging year for you and yours.

Really, in a brief period of time, I'd like to get through valve selection with regards to the choice based on your assessment of present versus future thromboembolic risk, why is this platform that we're all very experienced with so helpful and why the reduced INR, and then is there any experience with DOACs. Of course, we call these DOACs now as opposed to NOACs in application to thromboembolism reduction in mechanical valve prostheses. So I think both Marc and Maurice covered this already.

We understand that the global phenomenon for valvular heart disease secondary to structural valve deterioration keeps increasing in time. That 2050 projection probably is under what we're probably going to see. Probably closer to 900, 950 million patients will need valve replacement. The geographic international distribution between mechanical versus tissue by prosthetic is quite different with data favoring tissue by a prosthetic implantation here in the United States as compared to other countries around the world.

So we understand the scope of the problem. We're all here because we're very interested in valvular heart disease. For cardiologists that are joining us this evening, for decades past, we got very interested in the physical examination, the clinical correlation of symptoms as opposed to where a valve would stand in terms of its systematic progression, and then we would engage our surgeons to a certain extent in terms of a phenotype, decision making if you will, mechanical versus prosthetic, bioprosthetic. But, typically, it would stop there. Rarely would a cardiologist be, I think, deeply engaged in a specific platform of choice, and why is that?

Well, as I mentioned, those of us that get really interested in gradients might have an interest in one particular mechanical valve platform versus the other. And for those that are really interested in post implant hemodynamics, avoidance of this very dreaded outcome of poor selection of valve phenotype can lead to PPM, patient prosthesis mismatch. So a long held belief-- and Marc just touched on this with that outstanding slide about the likelihood of tissue valve thrombosis. This is really going up, and so you can see here some four dimensional CT data published not too long ago in the *Journal* about the likelihood of formation of microthrombosis, one of the I think important determinants of short term surgical valve deterioration.

Now, again, why? So we really start with this conversation mechanical tissue gradients and avoidance of patient prosthesis mismatch. So as I mentioned, typically, we would have really been interested in just the concept of a mechanical valve, right? And so for those of us interested in gradients, we kind of chase gradients and have a conversation with our surgeons.

However, the reason why I think it's very important for us to consider really being engaged with our surgical partners now, especially with this On-X prosthesis that's available, is we, as the managing cardiologist, will have a long term longitudinal relationship with our patients and will largely be responsible for their anticoagulation for the balance of their life. So if the INR goal is typically 2.5 to 3.5, for 3 to 3.5 depending on comorbitities, et cetera, most of us would typically not have a huge role in engaging a surgeon on valve selection.

So it really doesn't make a whole lot of difference to my management, right? So I think that's one of the reasons why traditionally we may have stepped back and let our surgical partners decide which valve. We would reaccept the patient to our practice after post-operative recovery and then manage this INR because everything is about the same.

One of the reasons why we may elect tissue balance in patients is the promise of delivering them freedom from anticoagulation, but Marc just showed you even more contemporary data. This is a little bit older data, but the likelihood of a patient developing a need for long term anticoagulation is quite high, approaching 65% in the mitral position. And in the aortic position, typically 30% to 40% will require some form of systemic anticoagulation post implant through the balance of their life.

So the promise of delivering a valve replacement for management of symptomatic aortic valvular disease and stenosis with freedom from anticoagulation with a tissue bioprosthetic valve might not entirely be accurate for the patient. Why is that? And Marc touched on this as well. It's because of two underlying comorbid conditions that track with many of our patients-- atrial fibrillation and venous thromboembolism.

So what if we told you that a particular valve, and we're talking about the On-X valve was different and was very different from its other brethren in the phenotype, what would you think about this? In fact, what if we were to share with you data and evidence, as Marc did briefly, about the lower anticoagulation burden that is reflected in an INR of 1.5 to 2? I would ask all the cardiologists that are with us this evening whether we can think of any evidence-based support for a INR goal of 1.5 to 2.0 in clinical practice?

And if you think about this and reflect on it for a moment, we simply don't have that evidence for any other disease state. So if I told you we had a valve that could accomplish this? Well, this is the On-X that we're talking about this evening. The FDA allowed for the lower INR in April of 2015, 1.5 to 2.0 after the first 90 days of standard therapy. These have also then, of course, found themselves into the ACC/AHA guidelines.

Well, is there any real world data that's cohort, observational, registry type that might suggest why this is the case, why there's a lower INR that's required? So I draw you to Dr. Williams' outstanding work that really launched incredible interest in this field probably nearly a decade ago, and this was presented at the Society of Heart Valve Disease in 2011 at the annual meeting. This was a 10-year study of very poorly controlled anticoagulant patients in South Africa with a target INR set of 1.5 to 2.

This is a 906 patient year follow up. It's a really incredible accomplishment for a study. That's really good in the surgical valve field. 42% of these patients were entirely non-compliant or kind of lost to follow up. Well, if you look at the morbid events associated with the things that we really worry about, thromboembolism or valve thrombosis, the likelihood of the aortic position was exceptionally low, very low TE rate, no thrombosis of the On-X valve with a relatively low bleeding likelihood as well, so really extremely hypothesis provoking.

This was then further, I think, accentuated in a study presented a couple of years later. This was clinical event rates with the On-X mechanical valve, multi-center experienced follow up of 12 years, 691 patients, almost 3,600 patient years. Look at these events. The total TE events for the On-X valve in the aortic position, 0.6%. Major bleeds, 0.4%. If you could go into double valves, it's still incredibly low thrombosis events, so, again, very hypothesis stimulating.

So a mechanical valve that requires less anticoagulation, why? I want to quickly cover three important concepts, and Marc already shared this slide, Jack Bokros' incredibly important discovery of a material, a physics to material engineering process allows for the production of pure On-X carbon without any silica particulates that are embedded leading to a very smooth surface. This then, from an engineering perspective, allows one to take the On-X pure carbon and shape it in a way that mimics our aortic valve, the mammalian aortic valve, the human aortic valve and allows for the accomplishment of these six very important endpoints.

This then has an impact on flow characteristics in fluid dynamics and flow in terms of laminar versus turbulent flow. And as we know, the more turbulence, the more sharing of cells, the more activation of all the troublemakers in circulation that eventually leads to microthrombosis, problems with excursion, pannus development, et cetera. You can see then also that the gradients related to the On-X valve are quite low, nine millimeters mercury on average across almost all the valve sizes.

So the hypothesis generating studies that I demonstrated led to the formulation of PROACT study, and because we have a relatively small time today, I won't go through the entire construct of the trial. Suffice to say, the null hypothesis was could we identify a patient population of high risk patients status post-AVR, which was termed the high risk AVR group, and anticoagulate them to a lower INR, and then compare this to the standard therapeutic range that we've all followed for many years. And the outcome was significant.

So this was published by Dr. [INAUDIBLE] and colleagues. A number of years ago now, there was a significant reduction in bleeding, 50% reduction in bleeding, with no significant increase in the stroke rate versus the standard of care arm if you will. The sweet spot or optimal range for the On-X high-risk patients is in that 1.5 at 2.0 range, and Marc showed a really nice slide. I have a much less elegant home-brewed slide that I'm not going to share because it simply won't stand next to Marc's elegant side that he showed a few moments ago.

But just remember, the sweet spot is 1.5 to 2.0. Is there guideline support for you as a practicing cardiologist? You better bet your bottom dollar. As I noted earlier, you have guideline support to use the 1.5 to 2.0 plus 81 milligrams aspirin long term. You see in the reference range for anticoagulation of others valves. And remember, as we keep moving that curve and shift that curve in terms of the therapeutic range, the TPR for a given clinical indication, the more likelihood there is bleeding because the likelihood of exceeding that margin and getting into the INR of 4.0, 4.5, 5.0 will result in higher bleeding rates.

So in the last couple of minutes, I wish to bring back wonderful memories for everyone here, which is the coagulation cascade, something that I dream about every night because this is something I personally really enjoy and investigate in our laboratory. So if you loved this in medical school, you're just like me. You wear a bow tie, and you're not considered normal by those that are closest to you.

Hematologists, and I won't take offense to that comment because I'm being self-deprecating. Let's just simplify the cascade. Factor 10a is converted to factor-- sorry. Factor 10 to 10a, this allows for cleavage of the [INAUDIBLE] prothrombin to thrombin, which then allows fibrinogen to be converted to fibrin. And fibrin ultimately is what allows our favorite little sticky cells to do their thing on the of the von Willebrand receptor.

How do anticoagulants work? They work essentially-- all the ones that we're typically used to using, the heparin, heparinoids, and low molecular weight heparins, et cetera. By serving as a catalyst, they essentially allow AT thrombin, which is your endongenous anticoagulant, to bind with a very high affinity and [INAUDIBLE] to this five pentasaccaride sequence, which then allows for a much greater enzymatic reaction allowing for binding to factor 10a and thrombin and then release of these in circulation from the circulation through the reticuloendothelial system.

So this is what led then, of course, to colleagues developing low molecular weight heparin, a much smaller protein, six to eight kilotons in size, and then the pentasaccharide sequence, which is commercially known as fondaparinux or Arixtra. How do direct oral anticoagulants work? It skips the concept of requiring antithrombin III to bind, and it binds directly to a very specific binding pocket directly in factor 10a. It leads directly to inhibition of that without any catalytic action if you will.

With regard to INR, even in the very best warfarin clinics that are nursing and pharmacist-adjudicated, physician-supervised, the likelihood of accomplishing a therapeutic INR is only about 60%. So despite all the effort we put into this, we're really not great at maintaining patients in a therapeutic range. So this led to a very important trial, which we participated in when I was at Vanderbilt, the COAG trial.

That was the very first NIH-funded pharmacogenetics trial. 12 centers were involved in this. The question being can we by-- by stratifying the warfarin prescription based on the presence or absence of a density to VKORC1 or CYP2C9, could this have an impact on the endpoint in terms of patients' events related to the INR, thromboembolism, bleeding, et cetera? Unfortunately, this was published by Kimmel et al in the *Journal* a number of years ago. It didn't-- the null hypothesis was not satisfied, and this, once again, shows the complexity of pharmacogenetic trials.

So have DOACs been studied for management of thromboembolic risk in the aortic position? The answer is yes. Dabigatran was examined, and I think everyone here-- we can skip through this-- knows exactly how this drug works, what it is. It's a direct thrombin inhibitor that's taken in oral form, the first of its kind. Its US label is for prophylaxis of atrial fibrillation.

Now this is extended to some other applications as well in subsequent years since I made this slide, but this was the first DOAC study in the valve space. So in the RE-ALIGN trial, I'm going to kind of quickly take you through this so you can take a moment and study this slide. But ultimately, it was a fairly large trial that looked at randomizing patients either to warfarin or to dabigatran dosed between 220 and 300 milligrams PID with the typical study endpoints that we assess in these types of mechanical valve anticoagulation trials.

What was the outcome? Well, the outcome-- oh, I don't know where that side went. I think it disappeared. The outcome was not good. There was a slide that I had here that seems to have disappeared. There were excess pre-specified events in this trial that led to the data safety monitoring board prematurely or stopping the trial early, and no movement has taken in the space since, or at least until now.

And Tracy in a few moments is kind of go through this exciting important development related to a direct oral anticoagulant and the On-X valve. So in summary, this is a valve that, in our experience and our program here in Texas, has improved long term outcomes related to anticoagulation, gives you very fine gradients with very low likelihood of reoperation with minimal, if no, pannus. It has a very low adverse event rate and, as the PROACT trial demonstrated, a significant reduction in bleeding without a significant increase in thromboembolism, and it's guideline supported.

TRACY WANG: That was fantastic. Thank you very much for taking us through this. I think there was definitely interest from the attendees, especially on that South African study that showed poor anticoagulation. There was a question about whether or not this was a peer-reviewed study. It was, in fact, a peer-reviewed study and published in the official *Journal of the Valve Disease* group here.

But here are a couple of questions about anticoagulation that I'd love to get the three of your thoughts on. And, Mo, maybe you can start on this one, and then Marc, as a surgeon, you can weigh in. So is the INR goal for a composite On-X valve graft for [INAUDIBLE] the same as just AVR alone within On-X valve? Mo, any thoughts on that from a medical thrombosis standpoint?

MOHANAKRISHNAN SATHYAMOORTHY: Yeah, so I think-- Yeah, I'll just say from a risk perspective, the moment we start manipulating the aorta, the equation changes a bit. In terms of the PROACT data, this was not something that was addressed prospectively in the trial. What defined high risk? Was it a very large left atrium, low ejection fraction, presence of thrombophilia, et cetera, et cetera?

I would probably apply this data in practice more towards just the straight valve replacement patient if you will, but I'd love Marc's thoughts on that. I don't know how he manages that in his practice, so I'm curious.

TRACY WANG: Marc?

MARC GERDISCH: Yeah, so it's a super important question for a couple of reasons. One is that we didn't include them in the study, and it was more a matter of kind of a hurdle with the FDA at the time. And I think it really hurt us because we use that conduit so much, and we have not gone ahead and changed our practice for them because we don't have that FDA clearance.

That said, if we have somebody who has the conduit and develops a bleeding complication, then we go aheac and drop them down and justify it in the documentation. It's also important to note, as you're going to describe, that we made sure that in this next iteration, the next study, that we include them because in actuality-- and, Mo, I appreciate your input. In actuality, though, if we could look at the greater data on the matter, we can't find any complications with respect to thromboembolic events related specifically to those graphs.

TRACY WANG: And then here is another question, and, again, it reflects sort of this uncertainty about INR target. If you've got a valve that's got a lower flow, so maybe a low ejection fraction or LVOT issue here, would you still be comfortable using that lower INR target range in these patients? So maybe Mo and Maurice, you guys might both weigh in on this one.

MOHANAKRISHNAN SATHYAMOORTHY: Maurice.

MAURICE SARANO: I did use the low INR. All the trials of high versus low showed that you didn't increase by having low INR. You didn't increase the thromboembolic events, and you decrease the hemorrhagic complications. So my whole practice was fighting with a coagulation clinic because I was insisting on the low INR, and they were telling the patient but you're not within guidelines.

And that concept that we should increase the anticoagulation, it's going to be more effective in preventing thromboembolic complications, I think is completely wrong. And so I'm looking forward to the clinical trial that you're going to be doing to sort of change that completely to say, OK, we don't have to have an extreme anticoagulation, in particular with patients who have isolated aortic valve prosthesis, flow is a high, [INAUDIBLE] prosthesis. In the past, we mixed the Starr-Edwards prosthesis with a bileaflet, and the Starr-Edwards multiplied the risk of thromboembolic complication by five.

So, no, I'm completely-- that what I was telling my patients. If you have an INR of 2.0, you're fine with an isolated mechanical aortic valve. And I think it's even truer, as has been demonstrated, with the On-X because these people have a flow that is really-- and a material which is of high quality, so it's different. But all bileaflet prostheses, low anticoagulation is fine.

TRACY WANG: One quick final question before we move on to my talk, which is if someone has triple vessel cardiac coronary disease, does that affect your valve choice in the intermediate age group? I mean, that's someone who may potentially need PCI later, who might need a antiplatelet therapy on top of anticoagulant therapy. Mo, your thoughts there for cancer?

MOHANAKRISHNAN SATHYAMOORTHY: Yeah, this is a tough one because, really, ultimately, I think the way we view this is the way I think all four of us have talked about this type of complex decision making. This is something that's best done with your surgical partners in terms of how best to get the most facile result for the patient in one setting if it's possible. And so there's data that we have now that supports the use of an anticoagulant with, for instance, a single antiplatelet agent post-PCI, et cetera. So though the waters are less muddy than they were about five years ago, my personal preference is a integrated surgical solution when it presents itself because that's probably going to give our patients the best long term outcome from a [INAUDIBLE] perspective and, clearly, from a valve perspective. Marc?

MARC GERDISCH: Oh, thank you so much. I think this is a super important question. I think that patient is best served, quite honestly, if we're serious about the science, with an On-X valve and coronary bypass surgery because the patient then would have the benefit of low dose anticoagulation, which is probably protective in people who have extensive artherosclerotic disease.

It's not confined to their coronaries. They would have the most definitive therapy for their coronary disease. Obviously, people would make the argument that a bioprosthetic valve would serve them better because, again, like you say, eventually, they may need stents, and then you'd end up with triple therapy. But I think that's kind of a down the road kind of thought, and I think that those same patients have a shorter durability than their bioprosthetic valves. So it's a conversation to be had.

TRACY WANG: Well, that's great.

MAURICE SARANO: But the question you have--

TRACY WANG: OK, let's move on. Sorry. Go ahead, Maurice.

MAURICE SARANO: The question you had was is very critical that triple therapy is a killer. It's the only cerebral hemorrhage I've seen in young-- relatively young patients with mechanical prosthesis when they are on triple therapy, so we should resist that as much as we can because we're going to have an excess rate of hemorrhagic complication. And if we need to do a coronary intervention that you cannot foresee before you implant the valve, well, maybe not as much antiplatelet therapy and maybe a single medication.

MARC GERDISCH: Also the newer stents only require a month of antiplatelet therapy, so in the [INAUDIBLE] stents, they can stop the Plavix after a month.

TRACY WANG: Only if it's done in the elective setting. I think very little data in acute coronary setting, so we do have to be careful there. And many of the trials looking at dual antithrombotic therapy, a single antiplatelet plus an anticoagulant have mostly been done in that AFib population. They've excluded patients with mechanical valves. So, again, some caution with pulling over that literature.

Well, thanks for that Q&A session. I have to give myself some time to talk here, so just a quick introduction. I have the privilege of being the principal investigator of the PROACT 10a trial, and I hope to use the next few minutes to really convince you that this is a potential game changer in the choice of aortic valves.

So I'm a noninvasive cardiologist at Duke. Just a quick disclosure, this is a trial that is sponsored by Cryolife, and here are my other disclosures. So we've been dealing with this issue, which is people don't like anticoagulants, and we've actually seen tissue valve implants increasing over time, especially in that younger demographic between 50 and 65. And this is really reflecting that, I think, this disinclination to use anticoagulants like warfarin.

This is what's currently recommended for patients with mechanical prosthetic valves. It's the only approved anticoagulant. As you all know, this requires continuous INR monitoring and dose adjustments. It has a lot of different limitations to it. It's got a long onset of action. It hangs around for a while.

It's got a long variable half life here, so it's just a really tough drug to manage. There are numerous drug interactions. For example, someone who requires an antibiotic may sometimes need to get INR monitoring more frequently.

My patients hate the next part, which is about diet. They have to control their diet. They can't be spontaneous, and so this is something that really requires a lot of patients' time, clinicians' time, health care system resources to manage optimally. So there have been numerous alternatives to warfarin therapy that have mostly been explored in the atrial fibrillation and venous thromboembolism type of environment here.

This slide, which I am not going to go over, really just outlines the many options there. There is dabigatran that came out first. Then study data related to rivaroxaban, which has the advantage of being daily, and then apixaban, which is given twice daily, and the latest one, edoxaban, which hasn't had a whole lot of market share in the US. But many of these trials were designed as non-inferiority. Many of them proved themselves to be great alternatives to warfarin in terms of non-inferiority so no increased risk of stroke or thromboembolic outcomes with these.

And, actually, many of these have also shown a better safety profile, and to Maurice's point about intracranial hemorrhage, that's where a lot of these agents really have the most advantageous profiles in that there is a lower risk of intracranial hemorrhage with these DOACs or NOACs compared with traditional warfarin. Rather than going into all of these trials, this is a summary slide that basically puts these studies and categorizes them into the four quadrants based on the x-axis, stroke and systemic embolic risk, and on the y-axis, bleeding risk. So the most favorable drugs should be in the bottom left quadrant, the one that's highlighted in green here, where there is the fewest number of strokes and also the fewest number of bleeds.

And we find that among these, perhaps some of the better safety profiles are things like apixaban, that green dot down here, which really has a really good efficacy profile as well as a fantastic safety profile. This is one of the few that actually proved a mortality benefit, and so that's how we decided to pick this particular agent to do our CT. Now Mo alluded to this. And I almost wonder if I managed to jinx his presentation because he couldn't show the slide, but I happen to have it in my deck here.

These are the results here for the RE-ALIGN trial. I'm not going to go over it in detail, but this was a trial that was discontinued prematurely. It was discontinued about a year after the first patient was enrolled because you started seeing those curves diverge early, and the DSMB said, no, this is not something we feel good about continuing.

But I think there are a couple of key issues that might have led to these results, and I'm highlighting two of them. There are others. One is that patients were randomized immediately after valve implantation, and many of you who are surgeons in the audience know that that's also our highest risk period in terms of a thromboembolic event occurring.

The second issue is that they picked dabigatran. Now if you ask me as a medical cardiologist in terms of which DOAC or NOAC I would reach for an a AFib patient, I would say that dabigatran now is pretty low in terms of my priority in part because of the side effect profile but also because many of these patients require dose adjustment, and we saw that in the study. In the study, almost a third of patients required a dose adjustment or a discontinuation because of the characteristics of the drug itself and how the protocol was written.

So I think these are two key factors that probably led to dabigatran really being not a great option to study and the results of the RE-ALIGN trial. So I would say that we really needed to try again. We can't just say this is done. There is some great in vitro data for apixaban compared with warfarin here.

This is a porcine valve model here looking at thrombus burden buildup on these valves, and you can see that apixaban and warfarin have very similar in vitro results. And that gave us courage to think about, well, how about we try this in humans? And so after a couple years of discussion with the FDA and with our leadership committee, we decided to test the following hypothesis, which is in patients who have the On-X mechanical valve-- and as Marc pointed out, this is the valve that really has a very nice flow dynamic profile that is less thrombogenic. So we take the mechanical valve that we hope is the least thrombogenic and match that up against apixaban, which has one of the better efficacy safety profiles that I've shown you earlier.

Between these two things, can we maintain the patients safely with this valve with apixaban compared to standard warfarin? And so our trial, which is now in progress, is going to randomize 1,000 patients. This is one of the largest valve trials that we're going to be doing here. We are focusing on patients who are three months out from their surgery, so we're not looking at highest risk period.

We're trying to make sure people are safe. At least three months later, that's when we're going to randomize patients to either continuing the warfarin or going on apixaban. And you might have noticed that we're going for and INR goal of 2 to 3 here, and you might ask, well, why given that these are patients that have been safely demonstrated to do 1.5 to 2 before?

Well, this was an FDA requirement. They wanted to really do a head-to-head comparison without giving apixaban any advantage here. And so this will be a pivotal trial for DOACs in this mechanical valve setting. It is comparing apixaban head to head with warfarin at a goal of 2 to 3, and we're going to follow these patients for two years.

The inclusion criteria is-- I'll show in the next slide-- and the exclusion criteria and the endpoints are really trying to demonstrate efficacy as well as safety. So in an efficacy side, there is a head-to-head comparison. Apixaban should be non-inferior to warfarin, but we're also going to make sure that the patients we recruit into the trial are similar to the patients we are treating in real world practice. And so there is a second efficacy comparison that will compare to objective performance criteria so historical data here.

And then finally, we want to actually show that apixaban is superior to warfarin in terms of preventing bleeding because this is something that was seen in the AFib and the VTE trials as well. So the inclusion criteria is a valve implanted at least three months ago. They are able to take warfarin with that INR target of 2 to 3.

And this next criteria is something that's also a little controversial, which is in our trial, the patients either have to be taking a 75 to 100 milligrams, so in the US that's 81 milligrams daily, of aspirin because current guidelines tell us that they need to. But the guidelines may be changing, or if a patient has a contraindication, they're OK to still be included in the trial. But this is something that I wanted to highlight there as well.

And the exclusion criteria, there are a couple in there that are really designed to make sure that this is a safe trial for our patients, that we're answering the questions that we're trying to answer, and maybe for patients who have a low creatinine clearance where apixaban's dosing is a little uncertain, we've excluded those patients. And of course, patients who bled recently, these are patients we do not want in the trial as well. We also want to make sure we're able to have the warfarin be a good control arm.

So these are the patients who are going to continue doing their monthly INR testing. And as prior trials, there have been home testing. This one, we're allowing all sorts of testing as long as their INR is within range. Our primary efficacy endpoint is a familiar one. This is one that's sort of a composite of valve thrombosis, or valve-related thromboembolism, or valve thrombosis-related mortality so very hard endpoints here.

The secondary endpoints are the components of this as well as the risk of major bleeding. We want to make sure that these therapies are safe here. And this is my final slide, but this slide I'm very excited to know that we've got several sites up and running. These stars represent where these sites are across the US.

Unfortunately, this does not look anything like an electoral map that you guys have been looking at lately, but we're hoping to get good geographic representation across the US and patients who are managed both in an urban setting as well as a rural setting here as well so that we're really getting a population that is representative of our valve population. So with that, I will stop and see if we have any questions in the Q&A. It looks like-- oh, good.

I'm seeing not a question, but I'm seeing a comment that you've got a few patients with an On-X valve and you want to enroll them. Come talk to me. Email me. We'll get you in the trial. My email is Tracy.Wang@Duke.edu.

There's a question. Can we enroll outside of North America? I'd love to say yes, but we are currently limited in which countries we're able to recruit in. Again, reach out to me. We'll see what we can do here, but right now this trial is North America only.

So I'm going to say thank you to all of our phenomenal speakers. I think this is-- every time I hear these talks, I feel like I'm learning something new, and I hope you are too. So thank you very much for your time and your attention.

MAURICE SARANO: Thank you. Excellent.

MOHANAKRISHNAN SATHYAMOORTHY: Thank you.

MARC GERDISCH: Super fun. Appreciate it.