CHRIS MALAISRIE: Welcome to the great debate on aortic valve prosthesis, sponsored by CryoLife. I'm Chris Malaisrie, and I'll be the moderator for this exciting live webinar for the next hour. A little bit about me, I'm an attending cardiac surgeon in Chicago and professor of surgery in the Division of Cardiac Surgery at Northwestern University and Northwestern Medicine.

Within the Bluhm Cardiovascular Institute, I co-direct the Marfan Clinic, Bicuspid Aortic Valve Clinic, and Thoracic Aortic Surgery Program. My academic focus is clinical research in novel valve therapies, including transcatheter and minimally invasive valve surgery and valve repair.

As you're aware, aortic valve replacement is going through a paradigm shift. Innovation in the type of intervention in valve prosthesis has opened up new opportunities for patients and clinicians. When it comes to prosthesis choice for long-term outcomes in otherwise healthy patients who have expected survival of 20 years or more, durability and anti-thrombotic therapy become the crux of the discussion.

Today's live webinar brings experts in the field of valvular heart disease and anti-thrombotic therapy, Maurice Sarano, John Alexander, and Vinod Thourani, to discuss and debate how well a patient live their long lives with aortic valve prosthesis options of today and possibilities of the future.

Let's jump in to our exciting agenda. We have three topics that will be presented today, starting with Vinod Thourani, who will talk about TAVR as an approach for AVR and discuss his thoughts on long-term outcomes and durability of transcatheter valves. Following Dr. Thourani, Maurice Sarano will discuss long-term outcomes of bioprosthetic valves in surgical AVR patients.

Finally, John Alexander will share his thoughts on the role of anti-thrombotic therapy in both SAVR and TAVR patients, and present to you the intent and designs of the exciting new study, the PROACT Xa trial that just started.

All right, so let's get started with the polling. First question for Ms. Moore-- she's a 62-year-old female, low risk symptomatic patient with severe aortic stenosis, who needs an aortic valve replacement. Ms. Moore has no severe comorbidities or bleeding risk factors. Her parents are still alive in their mid and late 80s. And her maternal grandparents lived well into their 90s.

Please indicate your preferred procedure for AVR and valve type that you would select for Ms. Moore. Number 1, surgical AVR with bioprosthetic valve; number 2, surgical AVR with mechanical valve, not an On-X valve; number 3, surgical AVR with a mechanical valve that is an On-X valve; and number 4, transcatheter aortic valve replacements. So let's go to that polling.

I think we have all the answers. So let's look at the results. So for option 1, 35% picked bio AVR. 13% picked mechanical AVR that is not an On-X. 43% picked AVR with an On-X valve. And lastly, only 9% picks TAVR. So we'll keep tabs of this and remind people at the end.

Now the second question, a little bit different now, same choices. Mr. Jones is 55 five years old. He's a high-level exec in a waste management company. He's considering options for severe symptomatic bicuspid aortic stenosis.

He does have a past medical history, though. He has diabetes. He's on insulin. He's got coronary heart disease and has had stents placed already. And his creatinine is 2.1, all of this indicates an STS score that would predict intermediate risk patient.

So we'll bring up the polling questions. And again, the options remain surgical AVR with a biovalve, surgical AVR with a mechanical valve, not On-X, surgical AVR with a mechanical valve that is On-X, and TAVI. All right, I think we have all the answers here. Let's look at these results.

For surgical AVR with bio, 25% picked this option. Mechanical AVR that is not On-X, 13%. Mechanical AVR that is On-X is 47%. And TAVI was 15%. We'll keep these results in mind, and let's go to our talk.

So first, I'd like to introduce our first speaker, Vinod Thourani. Dr. Thourani is an attending cardiac surgeon in Atlanta. He's the chief of cardiovascular surgery at Piedmont Healthcare and the Marcus Heart Valve Center. He is president of both the Southern Thoracic Surgical Association and Heart Valve Society.

He serves on national boards of the STS, is on the board of ISMICS, and is on the surgeon's council of the ACC and the AHA. He's authored over 400 articles in all prestigious medical journals. I think he's most well known for his leadership in the TAVI trials, particularly PARTNER trials, over the past decade.

Today, Vinod will share his thoughts on the latest data on effectiveness and durability of TAVR valves and long-term outcomes with these valves. With that, I'll switch the screen over to Dr. Thourani.

VINOD THOURANI: Great. Thanks so much, Chris. It's an honor and pleasure to be here with you today. A very exciting topic, I think. I'm going to go ahead and share my screen. And we'll get going. OK, can you see that OK?

CHRIS MALAISRIE: Looks good.

VINOD THOURANI: OK, great. These are my disclosures for this event. So what is a current TAVR status? If you look at where TAVR has been over the last decade or so, you can see that the first TAVR was in 2002. And in 2010, you had TAVR in prohibitive surgical risk patients, and PARTNER B allowed TAVR to come in.

And then you see over the time period of a decade now, from 2010 to 2020, we've gone from prohibitive risk to high risk to intermediate risk, and then, finally, to low risk surgical patients. You can see on the top are the PARTNER studies-- all randomized trials, except the very first one, with prohibitive risk patients. And on the bottom, you can see all those by the CoreValve or the Medtronic system.

And these have all led to multiple*New England Journal of Medicine* articles that have now led TAVR to be applicable or given a choice to cardiologists and surgeons for all risk categories.

And you can see here, if you just look at the most recent trials, the low-risk TAVR trials, you can see the PARTNER and the Evolut low-risk trials. You can see their average age is 73, almost 73 and 74 across the board. Their average STS score is low, at 1.9.

Their composite one-year outcomes show, you can see is lower with TAVR in PARTNER 3 and also in the Evolut. They were different composite endpoints, yet you can't compare the two trials here. But you can see that compared to surgery, they were lower. You can see, again, one-year results. You see mortality lower for TAVR in both trials.

So was stroke rate, at least in the PARTNER study, but not in the Evolut study. And you can see the difference in atrial fibrillation also. However, you can see pacemaker rate was higher in both the PARTNER 3 TAVR and also the Evolut low risk trials, compared to surgical patients.

And most recently-- this is unpublished data. This was presented at the virtual ACC. This is the first time that we're getting a look at two-year PARTNER 3 outcomes for these patients. And what you're seeing is that the primary endpoint, which is death, stroke, or rehospitalization, you can see that it was higher for surgery than it was for TAVR in two years, for 11% versus 17%.

However, when you look at the death and disabling stroke, you can see that one year, TAVR was 1% versus 3.1% for surgery. But as you can see from year 1 to year 2, there was an increase in stroke, death, or disabling stroke up to 3%. And so at this point, at two years, there's no difference between surgery and transcatheter valve therapies.

And so there was between one and two years, there were seven deaths in TAVR, and there were three deaths in the SAVR group. And there were six strokes in TAVR and one stroke in the surgery group. So this is the first glimpse of what we're looking at for low-risk patients.

And it's very important to remember that in the low-risk trials, things like, for instance, bicuspid valves, which you're seeing at type 0 in the second bar over and then you're seeing type 1 and type 2, these were not patients that we put into the low risk trial.

So I think it's very important. These were straightforward trileaflet valves of patients in their 70s. And in your cases that you presented, Chris, were in their 50s and 60s. And those patients were not part of this study of the lower extremities.

So we can't really extrapolate the low risk trials to those patients that you just presented because they weren't bicuspid and they were much lower than the average age that we were looking at. So we as a community have to be careful in how we interpret this data, the low risk trial data.

And again, this was a patient that has severe bicuspid disease. And you can see on the right side how it goes into the LVOT onto the anterior leaflet of the mitral valve. And these are not patients that are part of low risk trials, and we have to be very cognizant of that.

I do want to give you a glimpse of what's happening in the world when it comes to transcatheter valve therapy. This is as of February 2020. One of my roles now is the co-chair of the TBT database for the country. And so we get access to this. You can see that over almost-- this is now almost 700 patients-- 700 sites now can do transcatheter valve therapy.

And as you can see that over 52,000 patients in the first three quarters of 2019 had TAVR. There's the growth has expanded greatly, but not in valve in valve patients. And when you look at the world of aortic stenosis, you can see the rise in red of TAVR. So you can see in 2018 in the United States, we did almost 60,000 TAVRs, and we surpassed that in 2019. I'm just showing you the first three quarters.

Meanwhile, in blue, you can see the number of isolated AVRs has gone down. And AVR/CABG has gone down just slightly, and AVR/MVR has stayed about the same, too. So you can see the difference in what's happening in the United States for these patients.

So when we look at durability, the first time that durability became a concern was a EuroPCR presentation by Danny Dvir, where you can see after year 4, there was a severe drop down, a drop often in patients. And the thought of degeneration in TAVR valves was very rampant.

However, this was never published. And quite honestly, the two institutions are represented on this slide that actually did the data that it was represented from. And you can see these graphs do not look anything similar to what you just saw in the previous slide.

And so I think that the definitions that were used were very different than what we're used to. Anybody with a mean gram of 20 was considered structural valve deterioration. I think if TAVR or SAVR was looked at that category, we'd all be in trouble, relatively speaking. So really, the freedom, how we define freedom from-- or reinvention versus echo-based really makes a big difference in how we define durability.

So what data do we have? First of all, we don't have great surgical data. I'm not going to show you that. My talk was more on TAVR, so I'm going to concentrate on that. But quite honestly, we don't have great surgical data that's from a core lab and that's adjudicated. The best data that we currently have is from our randomized trials.

Here is the PARTNER 1A, which is the high risk patients. We followed those patients for five years. You can see here in gray, in red, TAVR and SAVR are almost on top of each other, and they're indistinguishable.

So really, when it comes to mean gradients-- this was Core Lab adjudicated-- real good echoes from sites. And you can see that mean gradients in valve areas were similar between the two. And so therefore, the valve performance for TAVR and surgery was sustained up to five years.

Similarly, remember the average age of these patients were in their 80s. When we looked at this, though, in a different way, just the TAVR patients, you can see that from 0, from right after the procedure, the mean gradient was right above 9.

In over five years, it went to just above 10. So there was not much deterioration when you look at mean gradients. And the same for the aortic valve area, there's not much degradation in the aortic valve area-- mind you, in elderly high risk patients.

Now if we start to look in a less risky group, this is the PARTNER 2, so these are now the intermediate risk patients. This is data we presented at TCT last year. And what you're able to see, that TAVR had a slightly higher aortic valve area compared to surgery.

But for the most part, both of them are doing really well up to five years. Again, this is an 80-year-old patient population. And when you look at the mean aortic valve gradients, again, both of them, surgery and TAVR, are equivalent out to five years in intermediate risk patients-- mind you, patients in their low 80 years of age.

Well, this is again some of the data that we presented. What were some of the reasons for reintervention? In the TAVR group, there were 21 patients. And in the surgery group, there were five patients. Stenosis was the most common reason. Regurgitation was the other most common reason that TAVR valves needed something done for them.

You can see for surgery, 80% of the patients had endocarditis and they needed something done. Well, how were they treated? You can see that the most of the TAVR patients were treated with repeat TAVR. And they had a very low mortality of about 5%. The surgery patients, all of them had to undergo surgery again. And they had a 60% mortality.

Remember, we're talking about patients in their 80s. And having redo surgery at that time or surgery at that time for endocarditis led to a higher mortality. When we look at freedom from aortic valve reintervention up to five years-- this is aortic valve reintervention-- you can see that this is significant, but they're both somewhere between 97% to 99% from freedom of aortic valve reintervention in both groups.

Also, if you look at the CoreValve trial-- this was for the intermediate risk patients in CoreValve SURTAVI trial-- what you're able to see in this case is that the TAVR outperformed surgery with the self-expanding valve, compared to tissue valves. This is almost none of these patients had mechanical valves. They all had tissue valves.

And we all know that the gradients in the valve varies from mechanical valves is much better than it is for tissue valves, depending on what size valves you put in. And when you do head-to-head durability of TAVR or SAVR, this is a notion trial. This is a low risk trial from Europe.

And when they looked at six-year outcomes, you can see 5% valve failure on the y-axis. You can see this roughly is about 7.5% versus in the TAVR group and 6.7% in the surgery group. Again, Core Lab adjudicated. They found no major difference between it.

What are some of the hypothesis for potential structure valve deterioration that we've seen? It is potentially leaflet thrombus. We know that TAVR has a higher leaflet thrombus rate compared to surgery. And is it one of these aspects that is leading to some other issues for durability or concern for durability for TAVR valves.

So when we just talked about the durability portion, more extensive testing is required than surgical valves currently. To date, no significant deterioration of aortic valve area or mean gradients up to five years. We need to follow these patients for longer. Low rates of reinvention for SVD through five years for TAVR, SAPIEN valve and SAPIEN XT.

The SVD for TAVR in low-risk patients remains undetermined at this point. I was showing you two-year data that Mike Mack presented. And we have to follow that very carefully. And of course, 10 years planned follow-up for both the CoreValve and the SAPIEN 3 valve for a low-risk and intermediate risk is being planned.

So bioprosthetic valves, tissue valve, SAVR or TAVR, are both associated with SVD. For this talk, since I was asked to talk about TAVR, I did not talk about the surgery component. It may take years until we have a large head-to-head comparison. Surgical or transcatheter strategy suggests that the one approach is better than the other using similar SVD definitions. That, to me, is the key part that we need to stay ahead of.

Most implanted tissue valve, SAVR or TAVR, can be safely treated by a less invasive approach, which is to have a valve in valve if they do not have PPM. And then there are hypothetical reasons for reduced durability of implants, including HALT. I think that what we have to really keep in mind is that the low-risk trials, the TAVR SAVR trials so far, there are a lot of patients who are not applicable for those.

We have to make sure that we're making very rational decisions on how long we think these patients are going to live. And of course, that does include mechanical valves in that entire discussion. Chris, thank you very much for the invitation to give this talk.

CHRIS MALAISRIE: Well, thanks, Vinod. And I'll get my screen back up. Thanks for that great talk. And I think you showed some pretty convincing data. That durability for TAVR is pretty good, valve areas and mean gradients. And I think most people, if not all people, will agree that TAVR, in 30 days outcomes, is probably as safe, if not safer, than SAVR.

But what struck me most is that data for durability is only five years. So I think most of us are looking forward to seeing five to 10 years, which I think you, Dr. Thourani, are definitely planning on doing for the low-risk trial.

VINOD THOURANI: Absolutely, yep, and in intermediate risk patients also.

CHRIS MALAISRIE: Well, our second speaker this evening is Maurice Sarano. Dr. Sarano is a cardiologist in Rochester, Minnesota and professor of medicine at the Mayo Clinic, serving as the director of the Valvular Heart Disease Clinic and consultant in the Cardiovascular Diseases and International Medicine.

He has been involved in several international committees, such as the International Academy of Cardiology, French Society of Cardiology, and the European Heart Association, in addition to the AHA and ACC.

Throughout his career, Dr. Sarano has authored over 330 patients. And to me, he is most well-known for his seminal work in mitrial regurgitation, which forms the basis for guideline recommendations for how we manage valvular heart disease today.

Today, Dr. Sarano will discuss long-term outcomes of bioprosthetic valves after surgical aortic valve replacement. With that, I'll switch the screen over to Dr. Sarano.

MAURICE SARANO: Thank you, Chris. It's a pleasure to be here. And following the talk of Vinod, we're going to talk about bioprostheses, but all the time, when you look at one type, you have to compare it to the other in saying which one is best. And when you do a valve replacement, you're not sort of doing an appendectomy where you remove the problem, you leave something in.

And you can have major complication-- thromboembolism mostly for mechanical prostheses and structural degeneration for biological prostheses over time. And the decision is quite difficult. And this is the sort of synopsis guideline on what to do for the type of prostheses. And you see that this is motherhood and apple pie, older than 75. So age is the main factor, and then a list of things here that we're going to integrate.

But it is clearly difficult in the important age range of 50 to 70 years and disputed in that range. And the complexity of that decision in advising patients is based on the fact that we have a multiplicity of factors. And we have to sort of do a multivariate analysis in our mind to say, OK, what's going to happen to the patient?

And then we have to project how the patient is going to be in five, 10 years. Is he going to have a cancer? Is he going to be on dialysis? Is the subject going to be at risk for falls? And so you have to integrate all that and the durability of the patient to advise. And there is a fashion towards bioprostheses so that when you're looking 2006, already 75% of the aortic valve replacement were made of bioprostheses. And in 2010, it was 85%.

And when we look at the age of the patient with aortic stenosis with 10% of less than 60 and 15% between 60 and 70, you understand that there is often a preference for bioprosthesis and we see over the years, the increase in the percentage of bioprosthesis, which is considerable now.

So the important thing in that decision, besides the fashionable aspect, besides the reassuring fact that we're not giving immediate anticoagulation for a long time, what are the facts when we compare the results of mechanical and bioprosthestic valves? Are they a randomized trial? Yes, absolutely. This is the Edinburgh trial that was published in '91.

And you can see that at the time, there was a little trend for mechanical procedures to have a better survival, and you have a clear difference in terms of people alive with an intact prosthesis, which is much better for the mechanical valve versus the biological valves. Evidently, they had more bleeding with that.

And then they did the second publication that they did with the 20 years followup. And at 20 years, there was still no difference in survival, a little bit better for the mechanical valve over the bioprostheses, and still that big difference in alive with an intact prosthesis, which is much better for a mechanical valve than with a porcine valve.

The other clinical trial that was done was published in '93 in *The New England Journal of Medicine* was the Veterans Administration trial, comparing, again, biological and mechanical prostheses. And there was a slight advantage for the mechanical prostheses, as you can see, but it was not significant for AVR or for MVR.

Years later, they published in 2000 the 15-year followup. And as you can see, what was surprising is that over time, for AVR, the survival was better with a mechanical valve than with the biological valve. And the degree of reoperation was much lower for mechanical valve than biological valve.

So two large trials relatively old now. And there is that small trial done in Italy in two centers of mechanical versus biological. And you can see that here, there is no significant difference. The p-value is 0.2. But the mechanical valves trend towards a better survival than the biological valve.

So there is, in the clinical trials, a trend for difference whereas the survival is a little bit better with mechanical than with biological valves. So if we look further, as compared to these mostly old trials, we can look at observational cohorts and saying, OK, what is the outcome of biological valve versus mechanical?

And I have to show that controversy in circulation of my former colleagues. And looking at the Mayo data, the survival for people who had AVR in patients younger than 70, the survival was really different. And when you did an adjustment so you had the propensity score to match the patient, you still see that mechanical valves have a better survival than biological valve.

This is a one-center thing, but recently, more data have come up to our attention. A study done in New York State on the patients operated over the state, 50 to 69-year-old, there is no difference in survival between bioprostheses and mechanical, no significant difference. But you see that the trend for mechanical is that for a slight benefit. The curve for mechanical is slightly above the bioprosthetic in term of survival.

And this is a matched population. The issue in those comparison is how do you match your population, how many variables you get in, how do you know in those registries that are statewide, what is the granular description for these patients in terms of status. But this is a match population.

And they saw same rate of stroke. Again, multiple times, it was shown that the rate of stroke is the same in mechanical and bioprosthetic valve, more reoperation for bioprostheses, more bleeding for mechanical valves.

Another study was done now in California, published in *The New England Journal of Medicine* by Goldstone. And here, in terms of survival, you see that there is a significant difference in the younger age group for mechanical valve, a trend for a better outcome for mechanical valve in the 55 to 64-year-old.

But what is the most interesting is the sort of spline curve of benefit of the risk ratio of biological over mechanical, which is higher than 1 for people above 60 and changes around 64. The equipoise point is around 63, 64 for these two.

But in this case, the range of uncertainty was kind of relatively big. For the mitral valve replacement, there was a benefit for mechanical in the younger group and in the older group. And again, here with a narrower range, you see that the benefit of mechanical persists up to 70, 72, where it crosses the line. And here there was a benefit for a biological valve.

So these two papers are statewide analysis. And they somewhat contradict each other in terms of benefit of mechanical valve, although there was a trend, even in New York state.

But here is a paper that is very interesting, studying all of Sweden results. So this group looked at the entire Sweden experience of people 50 to 69 years old, the group which is the most difficult to make a decision. They matched those groups. They matched those patients, again, around 1,100 in each group. And at 10 and 15 years, the survival is better in people who have a mechanical valve than biological valve.

And in this, if you look at the propensity match patient, the hazard ratio is around 1.34, 34% more mortality in biological valve. And when you look at the entire population that they had over this time, the hazard ratio is around 1.31, 1.32 when it is adjusted. So the same result in the entire series that is really suggesting that there is a survival benefit in the mechanical valves versus the biological valve in that specific range of 50 to 70 years of age.

So while studies are not all positive, the consistent trend is for a better survival with mechanical prostheses. We like biological prostheses, but maybe the result is better, the survival is better with mechanical prostheses.

Another point-- and that's going to be the last-- is the hemodynamic deterioration. Years ago, Dr. Rahimtoola showed the deterioration of hemodynamics and the structural failure of prostheses, porcine valves, mitral porcine. And the pericardial valve was new at the time. And you could see in those valves that there was a sort of precipitous decline before and around 10 years of follow-up.

Interestingly, studies that are more recent showed the deterioration starting before 10 years and then the precipitous drop in the persistent valve. And those two studies are giving almost an identical curve of occurrence of deterioration. And the issue of the hemodynamic deterioration, structural deterioration is of considerable importance.

In this paper published recently in *JACC* you see that in one center, the survival at 10 years was 48%. So half of the patients are dead by 10 years. And within the 10 years, very few of them are reoperated. They get to be very old. And there is a great hesitancy in doing something if there is a deterioration.

What is very interesting to look at is the clinical and subclinical. The clinical abnormalities, structural valve deterioration were around 6%. But the subclinical is quite high, 30%, with, it's indicated here, a gradient that is higher than the good valves and the valve area that is smaller and more aortic regurgitation at 10 years than the people who have the good valve at 10 years. So clearly, there is an abnormality here, even in the subclinical structural valve.

And this is not the progression like aortic stenosis-- slow progression over time. When the degeneration begins, it will progress precipitously and will lead to an abnormality that will become clinical relatively soon. And that's where it's difficult to address.

Another study from the same center, but presented in a different way, in looking at all of their bioprostheses, is showing that the number with hemodynamic, not structural valve degeneration only, but hemodynamic abnormality, high gradient to structural valve degeneration, and you see the main thing that you have to see is that it's a relatively large percentage of patients who have structural abnormality.

And they will occur in a progressively increasing way over the longer term. More and more patients as a percentage of the patients at risk are affected by that. So this is one center. This is a relatively small number. But it is raising really the question about the rate of deterioration of bioprostheses before the 10 years and immediately following the 10 years mark.

So when you look and you have hemodynamic valve deterioration and you do a time dependent analysis for survival, you realize that the risk is more than double of mortality. So it's a very important finding. It's not the benign finding. It's a very important finding. And it will affect the survival of patients. And we have all seen this patient with degenerated by a prostheses who present, are inoperable, cannot be touched in any way, and do not make it very far.

So what are the facts here? Recent data suggest a relatively high frequency of hemodynamic deterioration of bioprostheses increasing precipitously over time between the five and 10 years, and after the 10 years, increasing even more. So what's the way forward in my point of view?

First, clinicians need to consider these facts in advising patients regarding the type of prostheses that they're going to be choosing. The second point is that the advantage of the mechanical prostheses in terms of survival could be quite improved if we had improved anticoagulation. And that's a crucial aspect.

And we need to obtain new data in routine clinical practice regarding structural valve degeneration, because we lack large and diversified data on this aspect to enlighten the decision and the advice that we're going to give to the patient. Thank you so much for your attention.

CHRIS MALAISRIE: Thank you very much for your talk.

MAURICE SARANO: Thank you.

CHRIS MALAISRIE: And it strikes me from your talk that TAVR and bioprosthetic AVR are actually in the same boat, and that maybe clinicians are asking the wrong question first, meaning AVR versus TAVI. And maybe the right question to ask is mechanical versus tissue. And your data from the talk projects survival out to the 10, 20-year range. And I think that deserves some attention.

So next, we'll go to Dr. Alexander, our final speaker this evening. Dr. Alexander is a cardiologist in Durham, North Carolina. He's a professor of medicine in the Division of Cardiology at Duke University, where he serves as the vice chief for clinical research and the director of cardiovascular research at the famed DCRI.

Dr. Alexander has published extensively on the translation of novel therapeutic concepts in both acute coronary syndromes and chronic coronary artery disease, and on novel methodological approaches to clinical research. To me, he's most well known for his leading role in anti-thrombotic agents. He now serves as the principal investigator for the PROACT Xa trial.

As our last and final speaker this evening, Dr. Alexander will discuss the role of anti-thrombotic therapy in all AVR patients and give us insight into the currently enrolling PROACT Xa trial. With that, I'll switch the screen over to Dr. Alexander.

JOHN ALEXANDER: Great. Thank you, Chris. And it's my pleasure to be here. And I'm going to try to share my screen successfully, hopefully.

There you go. So it's my real pleasure to be here. And Chris, I want to thank you and CryoLife for organizing this virtual meeting. We thought we were going to be doing this in person, but COVID has gotten in the way. These are my disclosures. And I have research support, as you've heard, and serve as a consultant to CryoLife.

So we've been talking about aortic valve replacement and options. And as you're all aware, there are transcatheter options. And we talk about them as though they're all the same, but the valves are actually different from each other.

There are a number of bioprosthetic valve options, some examples shown on this slide. And then there are a number of mechanical valve options. And across these three broad categories, there are differences in the valves. And those might be important for concomitant anti-thrombotic therapy.

Now also here, I've shown that for transcatheter valves, the typical anti-thrombotic regimen-- again, what I'm more interested in-- has been aspirin and clopidogrel. Bioprosthetic valves, it's typically aspirin and often with a vitamin K antagonist maybe for some period of time-- three or six months. And then for mechanical valves, typically low dose aspirin plus a vitamin K antagonist.

Now it's really important for all of you to realize where these anti-thrombotic regimens come from. For the FDA, for a sponsor to get a new device approved by the FDA, they have to provide a reasonable assurance of the device's safety and effectiveness. And prosthetic valves are all developed with some anti-thrombotic regimen.

Now where this anti-thrombotic regimen comes from varies. Sometimes it's a guess. Sometimes it's an extrapolation of what's worked in other settings or with other valves. And sometimes it's based on historical experience with other valves. And it's really this valve plus the anti-thrombotic symbiotic regimen, which has to have a reasonable assurance of safety and effectiveness.

And I've recently had conversations with the FDA, and they point out that there's typically no systematic evaluation of, nor any requirement for, identification of an optimal anti-thrombotic regimen, for either safety or effectiveness. The valve plus the anti-thrombotic regimen just have to have a reasonable assurance of safety and effectiveness.

But as you've already heard, anti-thrombotic options are a major factor in surgeon and patient valve choice, particularly with regard to patients and physicians wanting to avoid lifelong requirements for vitamin K antagonists, most commonly warfarin.

And this has driven data you've already seen. A part of what has driven a move toward tissue valves from mechanical valves has been the desire of patients and clinicians to avoid warfarin. And this is data from young patients, 50 to 65, reflecting a general move toward tissue valves.

The next two slides show what's in the current guideline recommendations for people with TAVR and bioprosthetic surgical aortic valves on this slide. For TAVR, it's clopidogrel may be reasonable for the first six months after TAVR, in addition to lifelong aspirin.

Level of evidence C-- that's expert opinion based on what was used in the TAVR trials. And then anticoagulation with a vitamin K antagonist to achieve an INR of 2.5 may be reasonable. And this is based on observational non-randomized data.

For surgical AVR, low dose aspirin is reasonable lifelong. Level of evidence, B. And again, anticoagulation with a vitamin K antagonist to achieve an INR of 2.5 is reasonable for three to six months in patients at low risk for bleeding, again, based on non-randomized data.

And as somebody who studies anti-thrombotic regimens for a living, I'm struck by the relatively low quality of evidence we have to guide anti-thrombotic regimens after TAVR and bioprosthetic SAVR.

Now there are obviously questions that remain regarding this. And these are data from the GALILEO CT study and clinical outcomes trial that were presented last year. GALILEO and about 1,600 patients undergoing TAVR compared a rivaroxaban anticoagulant regimen to a dual antiplatelet regimen.

And what they showed on CT scan-- here are images of leaflet thickening and thrombosis-- is that rivaroxaban resulted in less reduction in leaflet motion compared to antiplatelet therapy and less leaflet thickening compared to antiplatelet therapy. This benefit on valve thickening and mobility, however, did not translate into an improvement in outcomes.

And there was actually numerically more adverse outcomes in the rivaroxaban group and the antiplatelet group, such that the trial was stopped early. This primary outcome was death or thromboembolic events, so clinically important events. Now this is just a first randomized trial trying to improve on post-TAVR anti-thrombotic therapy, and we need more.

So I now want to turn it to surgical mechanical prosthetic valves, anticoagulation with a vitamin K antagonist and INR monitoring as recommended, lifelong, and to achieve an INR of 2.5 in patients with mechanical by leaflet or current generation single tilting disk AVRs and no risk factors for thromboembolism.

For older valves and patients at high risk for thromboembolism, a higher INR is recommended. And a lower INR of 1.5 to 2 may be reasonable in patients with the mechanical On-X AVR and no thromboembolic risk factors. And I'm going to show you some data based on which that recommendation is made.

Aspirin is recommended in combination with oral anticoagulation, and direct oral anticoagulants with direct thrombin inhibitors or factor X inhibitors should not be used in patients with mechanical valves, mostly because of a lack of data in these patients to date.

So as I mentioned, it may be that not all mechanical valves are the same, maybe that not all bioprosthetic valves are the same and maybe that not all TAVR valves are the same. The On-X mechanical aortic valve got its original PMA in 2001 and has over 200,000 implants worldwide.

It's made of paralytic carbon on a graphite substrate that makes it very smooth and potentially less thrombogenic. It has an orifice inflow area with a flared inlet. And its leaflets form a nominal 90 degree angle relative to the orifice plane. Again, things that may make it less thrombogenic. And it's had multiple studies evaluating its safety and efficacy with standard VK anti-coagulation. That is an INR 2 to 3.

But John Puskas and Cryolife and others performed the PROACT trial. This was a multi-arm trial that looked at a low risk AVR cohort and randomized patients to either clopidogrel and aspirin or warfarin with an INR of 2 to 3, a high risk AVR cohort that randomized patients to warfarin an INR of 2 to 3 plus aspirin, or lower INR warfarin INR 1.5 to 2, and then a mitral valve cohort that I'm not going to talk about today but that has just recently completed enrollment and is in follow up.

And these are the main outcome data from the high risk AVR cohort that randomized patients to two different target INRs and the low risk AVR cohort that randomized patients to warfarin or clopidogrel. Starting on this side, you can see there was a reduction in the primary endpoint that included thromboembolic events and bleeding, with a lower INR compared to a higher INR.

This was driven predominantly by a large reduction in bleeding with a lower INR. And there was really no difference, there was a numerical increase but no statistical difference and low rates of events with either INR target with warfarin. Correspond that or compare that to the clopidogrel data. There was a big increase in primary outcome events, same primary outcome with clopidogrel compared to warfarin.

This was almost all driven by an increase in-- it was actually driven by an increase in thromboembolic events. That were more with clopidogrel plus aspirin than warfarin plus aspirin. And there were more bleeding events with clopidogrel plus aspirin than with warfarin plus aspirin. Very low rates of thromboembolic events here with warfarin in this trial.

Now there's been, over the last 10 years, there's been a number of new oral anticoagulants. It's hard to call them new anymore. You're all familiar with them. Dabigatran is a direct thrombin inhibitor. And then rivaroxaban, apixaban, and edoxaban are all factor 10 inhibitors.

And these drugs have really replaced warfarin in patients with atrial fibrillation and in patients with venous thromboembolic disease. And there's been a lot of interest in whether they can replace warfarin for patients with mechanical valves.

One important study that cast a lot of doubt on this prospect was the RE-ALIGN trial. RE-ALIGN studied the direct thrombin inhibitor dabigatran in patients with either mitral or aortic valve mechanical aortic valve replacements and included any mechanical valve type.

They randomized patients both early after surgery, within three months, or late after surgery. And they randomized them to warfarin generally with an INR of 2 to 3, or three different doses of dabigatran-- 150, 220, or 300 milligrams twice a day.

For those not familiar with dabigatran, this lowest dose, 150 milligrams twice a day is the high dose that's used in patients with atrial fibrillation. And then they followed patients for 12 weeks.

Unfortunately, RE-ALIGN was stopped early. There was a large proportion of patients who didn't reach target plasma levels of dabigatran, which was actually the primary endpoint of the trial. But maybe more importantly, there was a stroke rate of 5% over 12 weeks in the dabigatran arm compared to zero in the warfarin arm, and a bleeding rate which was all driven by pericardial bleeding in the early enrolled cohort of 4% in the dabigatran patients compared to 2% in the warfarin patients. So dabigatran was not effective and was associated with risk.

So some key lessons learned from RE-ALIGN-- patients with mechanical valves are different from those in atrial fibrillation or venous thromboembolism. And we need to study anticoagulants in this setting. Early enrollment meant post-op may have impacted bleeding and possibly valve thrombosis and stroke. But very importantly, mechanical valves might not all be the same. The On-X valve versus the St. Jude valve, which is the predominant valve in RE-ALIGN. And then aortic and mitral valve positions might matter as well.

And then finally, dabigatran may not be the best NOAC. It's a factor II or thrombin inhibitor and not a factor X inhibitor. Factor X inhibitors will prevent thrombin generation and not just thrombin activity. And dabigatran has relatively poor bioavailability which leads to a lot of fluctuation in drug levels.

And then also importantly, preclinical studies are not predictive of drug efficacy and safety in patients. Dabigatran looked really good in animal models.

So there's obviously interest in studying the other NOACs. And they have been studied in preclinical data. This is a study of apixaban in an aortic heterotopic valve model in pigs. And what you can see is that compared to control, that is no anti-coagulation, apixaban in a dose related fashion prevents thrombus formation as well as warfarin does, again with a INR in the 2.5 to 4.5 range, a little higher in pigs than in humans. And this is very encouraging for apixaban. However, as I mentioned, we saw similar data with dabigatran in the same model before RE-ALIGN.

And so based on this, we've been working with Cryolife over the last two plus years. It's taken a long time to design the PROACT Xa trial. This is a trial that's just started in patients with an On-X valve in the aortic position placed more than three months prior to randomization. We're going to enroll 1,000 patients, randomize them to one to one to apixaban at its standard 5 milligrams twice a day dose. There's a dose reduction in selected patients, almost none of whom will be in this trial because they aren't getting mechanical valves or to continue warfarin with a goal INR, a target INR of 2 to 3.

We chose this higher INR rather than the 1.5 to 2 because it is the gold standard. And we don't want to handicap the warfarin arm if we're comparing it to apixaban. We plan a two-year follow up with more than 800 patient years in each arm. The primary endpoint is a compositive valve thrombosis or valve related thromboembolism. And secondary endpoints include components of that endpoint and major bleeding.

And we have two co-primary analyses, a non-inferiority analysis to warfarin to establish that apixaban is as good as warfarin with a non-inferiority margin of 1.7% per patient year. And then that apixaban has a primary outcome that's below the objective performance criteria for mechanical valves of 3.4% per year.

So very excited to give you a quick status update. This is a little bit dated now. The first patient was enrolled in PROACT Xa on May 7, a little less than a month ago, in Little Rock, Arkansas by Thomas Rayburn is the PI. The rest of the team is shown here in their COVID masks and here without their COVID masks.

There are now three sites that are open for enrollment and four patients who are enrolled. And over the next six months, we're really excited about getting another 50 or so sites activated in the United States and Canada, and getting patients into the trial.

Really importantly, this study can be done almost entirely remotely. Patients can be consented remotely. Drug is being shipped directly to patients at their homes. And then most of the rest of the trial is aligned with standard of care clinical care. Much of the follow up can be done by telephone if patients are not having serious clinical events. They would obviously need care for those.

And so, if you have patients or if you're interested in PROACT, you can reach out to me or you can reach out to the folks at Cryolife. And we'll figure out a way to get your patients into the PROACT Xa trial. Thank you very much. I'll stop there and look forward to some discussion.

CHRIS MALAISRIE: Thanks, John. Thanks for the great talk. And I'm struck still in 2020 that clinicians aren't aware of the low INR indication for On-X valves. And what you showed there were the American guidelines. But the European guidelines did not make mention of the On-X valve, which I find interesting.

But you showed some very convincing data to support the low INR goal. And so much so that you went ahead and designed the PROACT X trial. I think it's going to be really, really exciting.

And I see everyone's on the panel here. And I'm pretty sure everyone sees the case one again. So while we re-poll this question, I want to start this discussion with Dr. Sarano.

MAURICE SARANO: Yes, sir.

CHRIS MALAISRIE: This is a 62-year-old, senile calcifis AS, so not bicuspid, low risk for AVR now. So how do we work through a case like this if this case comes to clinic?

MAURICE SARANO: We're in the early 60s. The patient has a probability of longevity which is high. And here there is a trend for advantage in using mechanical valve. Now if this person is very active, like I had a patient like this who likes to ski and takes risk, then maybe they do not want the anticoagulation and will move to have a bioprosthesis.

But to me, it is the first step is to consider a mechanical valve. A lot of patients ask about the TAVR and considering when they need to be replaced valve in valve. I am a little worried about the durability of the TAVR. The signal is that second phase, two to five years, increased mortality. And I don't think I would offer TAVR to this patient. And maybe the others have opinions.

CHRIS MALAISRIE: While people think of their comments, let's go ahead and show those answers here. Do Vinod and John have any remarks? Do people see the results of the polling?

JOHN ALEXANDER: I mean, Chris, what I would say is, I mean, Maurice nicely alluded to how antithrombotic therapy factors into these decisions. And I think we know less about the optimal anti-thrombotic therapy for each of these valves. And aspirin plus clopidogrel doesn't really have a lower bleeding rate than low dose aspirin plus warfarin.

And so if this patient also would be very easy to manage on warfarin. They don't have the comorbidities that make INR control difficult. So I think there's a lot of unknowns in the anti-thrombotic therapy thing that people just assume that warfarin is worse.

VINOD THOURANI: So, Chris, I just want make a comment on this a little bit you know as surgeons I think it's difficult a little bit because the patients come to our office saying we want a TAVR. So they're coming from their non-- they're coming from their cardiologist, let's just be fair here. They're coming from their cardiologist to us, going to the valve team, going we want a TAVR. And we have to sometimes talk them out of it.

And so if the valve team saw them as first line of defense, we could equally talk to them about mechanical, tissue. And then we could talk about tissue, you talk about TAVR and SAVR. But that's not how it's being presented.

It is coming from the non-interventional cardiologist or the internist saying, go get the TAVR [INAUDIBLE] you go home the next day and you'll be able to play golf in three days. So we're being approached in the valves in a uphill battle. We can talk about it on a webinar, but reality is that that's what they're coming to. And we have to talk them out of it, which is not easy.

So I think that we, as a mindset, have to talk to people more about mechanical valves. And somehow or another, we have to have our general cardiologist and their internists not telling the patients to come in for a TAVR at 50 years old or 60 years old or 70 years old. So we're really-- it's an uphill battle, I have to be honest with you, in the trenches.

MAURICE SARANO: Absolutely. And it is very difficult because people come with that idea that they want a small opening. So I think that surgeons have to make an effort to have the minimally invasive approach. I know that if you are minimally invasive, it's a little bit of something uncertain.

But the idea of a small opening the extremely appealing to patients. And it's very understandable. It's unstoppable. So if we don't offer the minimally invasive surgical AVR, they want to go to a TAVR.

VINOD THOURANI: Yeah. We have to work on that group of patients-- I mean that group of physicians so that the patients don't see it from the get go and then we're working backwards.

CHRIS MALAISRIE: Yeah. I think so. Patient preference is a class one recommendation. But the heart team consultation is also a class one recommendation.

JOHN ALEXANDER: I mean, Chris, it strikes me that it's awfully shortsighted. I mean, these are people who are going to be having this valve, as Maurice said, for 20 years. And the week of the surgery is a very small part of that lifelong question.

VINOD THOURANI: You're right. We're seeing a lot more time talking about the lifelong management of aortic stenosis. And that needs to be really highlighted, in my opinion.

CHRIS MALAISRIE: So I think that those thoughts really come to bear with Mr. Jones. So he's 55. He's got AS from bicuspid aortic valve now. But he is intermediate risk for AVR. So let's start this discussion with Vinod, Dr. Thourani. How does a clinician think through this particular case?

VINOD THOURANI: Yeah, he's a-- and I imagine his aorta is clean, right? He doesn't have any aorta that's bigger than 45 millimeters. Right, Chris?

CHRIS MALAISRIE: For this, no aortic aneurysm

VINOD THOURANI: Yeah, look. I mean, at this age of 55, my recommendation is going to be a mechanical valve for this patient. He's an executive. So he's not, you know, climbing rocks or cutting down trees every day in the middle of forest and things like that. And he should have an expectancy of living for, hopefully, 30 more years.

I know his creatinine is the only thing that kind of worries you a little bit. But a 55-year-old bicuspid valve disease would most definitely head into a surgical pathway for the most part. And on top of that, at this point, I would recommend a mechanical valve for this patient. I think that's relatively straightforward in my mind anyway. He'd have to refuse the mechanical valve, obviously.

CHRIS MALAISRIE: We're cueing the re-poll again. I suspect it's going to be even less than 2% from the previous question. What are the other thoughts from the other panelists?

MAURICE SARANO: The difficulty is that creatinine, as Vinod said. Because there is a fear that if there is hemodynamic instability that he may go to dialysis. And that would be a difficult situation. So the only hesitation is around that aspect, not the chronic anticoagulation treatment which is not a problem with renal failure. But more of, OK, you do the surgery. There is a more dynamic instability. So it depends on how the ventricle is, the cardiac output, if we have a good chance of having no deterioration immediately after surgery, and to have no deterioration of the renal function, no hesitation for mechanical valve.

CHRIS MALAISRIE: John, probably the same for you.

JOHN ALEXANDER: I was going to ask, is the risk of TAVR with necessary CT and coronary angiogram and then is the risk of TAVR really that much less to the kidney. And I think that's a risk factor either way. But he's young, I would lean toward mechanical valve with him.

CHRIS MALAISRIE: Well, let's see let's see the answers to the re-poll. It's funny how we went up with TAVR on that, from 2% to 3%. But still most people would answer mechanical valve AVR. I think that difference is statistically not significant.

We're a little bit past the hour. We got permission from Cryolife to go over a little bit. And I think the panelists have a little bit of time. And before we get to a couple questions from the audience, I wanted to ask Dr. Alexander, I think, the most important question from these group of talks is that if your trial, the PROACT Xa trial demonstrates safety and efficacy for apixaban for the On-X valve, how will that change the answers to these questions that we just asked? Will it be a game changer?

JOHN ALEXANDER: Yeah, so I think it will take the warfarin question off the table. And I think that-- I mean, in my experience and I think this is echoed in the experience of others, that warfarin is a real impediment to getting people to think about mechanical valves. Because it's a lifelong need for a drug that is difficult to manage and therefore requires monitoring.

Chris, I have almost no doubt that apixaban will be safer on bleeding than warfarin within an INR of 2 to 3. It has been in every study. And valves don't bleed. It's three months out from surgery. It's not the valve that bleeds. It's the patient that bleeds.

And these are lower risk patients and in atrial fibrillation. And in that trial, in Aristotle, apixaban had a 30% lower rate of bleeding. So the real question, the huge question that we're going to answer with PROACT is will apixaban prevent valve thrombosis and valve related thromboemboli.

And I think if it does, I mean it's a twice a day easy to take medicine with no side effects other than bleeding. And there's less of that than warfarin. And it will be generic. By the end of PROACT it will be generic and therefore cheap as well. I think it will be a game changer.

Now, the next questions, obviously, are the other factor X inhibitors also effective and what about for other valves, what about for other kinds of mechanical valves. And I think those are all things that would need to be studied separately. I mean, there is enough differences between the valves and there's enough difference between the anti-coagulants that these would really need to be studied. But yes, I think it would be a game changer.

VINOD THOURANI: I don't think we can extrapolate one drug in one device to another drug in another device. I think that's a really important comment, John.

JOHN ALEXANDER: Yeah. I know. And it's actually interesting how much it's been done. I mean, we talk about dual antiplatelet therapy as though it's all the same. We talk about anticoagulation as though it's all the same. And we talk about mechanical valves and bioprosthetic valves as though they're all the same.

VINOD THOURANI: Just like we talk about the low risk TAVR trials and we put every patient into that low risk TAVR trial.

MAURICE SARANO: Question for you, John.. For all the people who have prostheses and have mechanical valve and need to take Coumadin, the anticoagulation clinics tend to push higher the INR. You know, I have trouble because I push my patient to be closer to 2 than closer to 2.5 or 3.

And so, that idea that if we increase the dose and we increase the anticoagulation, we increase the efficacy is a little not there for me. What do you think about that?

JOHN ALEXANDER: Well, I think that's correct. I mean, two things. One, with warfarin, we're not that good at being precise. And as patients get sicker, have more liver disease, have more renal failure, have more heart failure and therefore liver congestion, it gets harder to manage the INR. And if you try to tailor it to the lower end of 2 to 3, you just end up spending more time out of range, low.

But I also think it's interesting. If you look at the PROACT data, for example, the rate of bleeding was cut almost in half by targeting a lower INR. And there was almost no difference in thromboembolic events, which were very low anyway. And so this is all with the On-X valve.

And so, we've had interesting discussions. I mean, I the clopidogrel data from PROACT very compelling. With no anticoagulant, you get thromboembolism. So you need some.

MAURICE SARANO: You need some anticoagulation, no doubt. How much?

JOHN ALEXANDER: Butt a low level, a low level looks pretty good. Yeah. And so I think we could go lower. You know, we've gotten a lot of questions about in PROACT Xa, why did we choose 2 to 3. And I could talk a lot about that. We had a lot of discussions with FDA about that. That's the control arm. But I think there's pretty good data that lower would be OK. And I'm hoping-- I'm optimistic apixaban will be OK. We obviously have to wait for the data.

CHRIS MALAISRIE: Well, I promised the audience we're going to get to audience questions. But it looks like we may have just time for one. And I think this one comes from Portland. If the DOACs are going to be effective for mechanical valve, why have we not seen that to be effective in preventing HALT in TAVI valves?

JOHN ALEXANDER: So I'll start. So there haven't been a lot-- there been some studies looking at treatment of HALT. And the Galileo study was the biggest study that I'm aware of that has looked at systematic use of rivaroxaban versus antiplatelet therapy alone at preventing HALT.

And it's interesting that there was some-- there was statistically significant less HALT with rivaroxaban in TAVI and Galileo. It didn't result in a reduction in clinical events. And that disconnect, I think, is not well understood why that is.

It may be that the thrombus that occurs on the valve has less of a thromboembolic effect and more of a valve degenerative effect and that rivaroxaban has some efficacy at preventing that. I think we're still learning.

There's also pretty good data that oral anticoagulants, including the NOACs, it's not randomized data, will help HALT resolve and lead to earlier resolution of HALT. So I would say the question is still open. And we don't know.

And then, a comment to something Vinod said at a meeting we were at together. We talk as though these bioprosthetic valves are all the same, and that TAVI and SAVR are the same. And the blood flow in the aortic root where HALT occurs is so different depending on numerous factors, including valve type, size of the aorta, et cetera. And the role of all of that in HALT, Vinod, I'd love if maybe you comment on that.

VINOD THOURANI: Yeah. I mean I think we're looking at this. Lakshmi Prasad Dasi at Georgia Tech and I are looking at this. And we're submitting some NIH grants based on this. And I think you're absolutely right. It'd be quite interesting, you know, Chris, as we're talking about this, I think it'd be very interesting to look at the differences between TAVR, SAVR, and mechanical.

And right now we were just doing TAVR and SAVR, tissue SAVR. It'd be really nice to add mechanical into this because I think that's a really important adjunct. I'll call Dr. Dasi on the way home after this webinar about this. But I think we need to add a third arm to our study that we've submitted to the NIH. You're right, John.

CHRIS MALAISRIE: Well, any closing comments, Dr. Sarano?

MAURICE SARANO: No. I think it's we have to keep our mind open. I think that whether the On-X will be transformative of the mechanical valve, but we have to keep our mind open. And then we have to remember that we have now much more solution. We are doing double the number of valve replacement that we're doing in the past.

We were undertreating severely aortic valve disease. And now we are better. Not perfect. And we need to move to have all that panel of treatment that we can give to patients with valve disease.

CHRIS MALAISRIE: Well, great discussion tonight. I'd like to thank all the speakers, Vinod, Maurice, John for their time and their excellent presentations. I'd like to thank the attendees. I was following it. And we're up to about 227 attendees from multiple countries today. Thank you for taking the time to join us on this webinar and for staying engaged and participating in today's discussion.

VINOD THOURANI: Thanks, Chris, for the invitation.

MAURICE SARANO: Thank you.