JIM HERMILLER: Well, good evening. I'm Jim Hermiller from Indianapolis. I'm a cardiologist here. And so we have a really an all-star panel. Next slide. We're going to really talk about this very important subject, and we're really going to focus in, I think, on the younger patient who by definition is lower risk, and we're going to look at the durability and differences in the prostheses as well as the procedures. Next slide.

So who do we have tonight? We've got Chris Malaisrie, who's a Professor of Cardiovascular Surgery at Northwestern University. We've got Marc Gerdisch, who's Chief of Cardiovascular Surgery at Franciscan Health here in Indianopolis. And we have Ismail El-Hamamsy who is Director of Aortic Surgery at Mount Sinai.

So we're going to go with the first audience polling question to see how people are feeling coming into this. Next slide. So the patient, a 50-year-old man with bicuspid aortic valve disease, he developed severe symptomatic aortic stenosis. He is otherwise in good health. Echo reveals normal LV function and no other valvular disease except severe AS.

Coronary angiography is normal. He's got no aortopathy. And just as a sidebar, he did have a cardiac CTA. And although he has bicuspid disease, it's not horribly calcified. There's not pillars down the LVLT and would be anatomically acceptable, I guess, for a TAVR, it would be, to say it.

So the question is, and this the polling question, which option would you choose for this patient. Ross procedure, mechanical SAVR, a TAVR, SAVR, TAVR strategy, or a biologic SAVR. So you can see up there you've got the polling questions, to be answered. So if you'd just answer, that would be great.

OK, it looks like Marc's already in the lead, where even between Ross and biologic SAVR, and I think appropriately, the TAVR, SAVR, TAVR has one vote. So that's very interesting. We'll see at the end of how this all changes. And we're going to move on to bioprostheses, long term outcomes, and Chris is going to be presenting that. so Chris, take it away.

CHRIS MALAISRIE: Well, thanks, Herms. I'm going to pull up my slides here. Well, good afternoon, everybody. I just looked through some of the attendees, and I recognized a lot of friends on. And like Herms said, let's make this as interactive as possible, and Herms, feel free to interrupt me. You won't derail me.

So I was asked to talk about bioprostheses and long term outcomes. And I want to cover three things here. The first is, how do we quantify durability for bioprostheses. The second is, I want to talk about durability, and also survival. People forget about survival after either porcine or or bovine aortic valve replacement.

And finally, I'll finish with some data on aortic valve and valve procedure, and whether or not this is the right procedure for all failed bioprosthesis valves. For starting with valve durability, we often think about structural valve degeneration, which is defined as calcification fibrosis or disruption of the valve leaflets that cause valve dysfunction.

And both valve types are equal offenders. Both the bovine pericardial valve you see on the left here, which typically calcified, failed by stenosis, and also the porcine valves which you see on the right here, which fail by disruption and aortic regurgitation.

But it's also important to remember that structural valve deterioration is not the only way that valves fail. Valves can fail for other reasons, and these are the three. So on the left here, you can see the valve here is failed by thrombosis. There's an expanded valve that I'm peeling some clot off of.

In the middle here, this is the ventricular side of an expanded aortic valve and you can see pannus that is growing onto the underside of the valve. And finally, the dreaded complication of endocarditis, these are what we typically see when we take out infected aortic bowels.

So if we remember, the SVD is only a subset of Bioprosthetic Valve Failure, or BVF for short. You've got to be careful when you see these following terms in terms of endpoints-- freedom from SVD, and also, you'll see this a lot, freedom from reoperation for SVD. These numbers can be very different depending on how they're defined.

The second thing we look at when we tried to define valve durability is whether or not the analysis is actual versus actuarial. Gary Grunkemeier wrote a lot about this back 20 years ago now. It was during a time-- I think much of the many of the older surgeons on the call remember us talking about valve durability and how to compare valve to valve.

And if you look at the left panel here, that is an actual analysis here. So the patient is alive. They can only go into one of two states. One is they die, and the other is they get SVD. So those are the only three states.

You cannot be dead with SVD. On the other hand, on the right side is an actuarial analysis, and it overcomes the problem that some patients would have gotten SVD if they had not died early.

So that's the Kaplan-Meier assumption you see there on the right-- let's see if I can put a cursor on it-- is what if you can quantify the risk of getting SVD if the patient didn't die. So you end up with this sort of virtual SVD here that never really happened, but would have happened if the patient died.

So that is the actuarial method. So necessarily, an actuarial analysis will lead you to a higher estimate of SVD than an actual analysis. So we've got to be careful when we see these following terms, if we see cumulative incidence or crude analysis, unadjusted analysis, all of these refer to an actual analysis as opposed to a Kaplan-Meier method.

Every now and then, you see a life table method. These are actuarial, because an actual analysis looks better than an actuarial analysis. So knowing those definitions, let's look at what is in the data. This is a table that we published in the [INAUDIBLE] textbook.

And valve durability is dependent on age. So bioprosthetic valves are a great option for patients who are 70 years or older. And I'll call your attention to probably the bottom to studies there. Tirone David and Bourgignon, these are probably the most often cited papers, looking at the porcine valve and the Carpentier-Edwards valve.

And if you look at the bottom row there, with greater than 70, Tirone David reported an actuary freedom from reoperation from SVD of 100% for 70 years old or greater. So they're great options for older patients. Now, the debate between which is better, porcine versus bovine, continues to rage on.

This is a recent analysis that was published in *The Annals of Thoracic Surgery,* 2020, looking at a national registry, the Sweetheart Registry. And what do people see here? So the take home point here is that survival for patients with a porcine valve is a little bit better, with a P value of 0.001%, but not a whole lot.

What I see is this, is that survival is poor after either valve that you get. And if you look at about 10 years down the line, only about 47% or 43% of patients are alive at 10 years. So the punchline is not what I necessarily see, is like, why do these patients do poorly. They're dead 10 years after getting a bioprosthetic aortic valve replacement.

Now, this probably doesn't matter much for patients who are 80 years old or greater, maybe a little bit for patients who are 70 years old or greater. The great thing about these large databases that follow about valve durability is we also get life expectancy if you get an AVR.

But if you start with this, the life expectancy in the general population, which is shown here, obviously the younger you are, the longer you live. That's what that graph shows. But then you chart also the life expectancy of a patient who gets a valve replacement.

There is a differential there for younger patients. So 60 years old or younger, you've definitely lost some survivability. So prosthetic valves do not restore life expectancy. Patients do a lot better than having a diseased valve, but you do not restore their life expectancy.

I'll finish with some words on valve in valve. These are the guidelines that are published 2017. We've got to remember that TAVI valve-in-valve is a class IIa recommendation for high risk patients, so not low risk patients or intermediate risk patients, high risk patients. Class IIa, recommendation. This is both American and European.

And not only that, valve size matters. So this is the AUC appropriate use criteria published in 2017, and you can see your favorite society at the bottom there. It's probably appropriate for patients with a larger valve size, 23 or greater, and probably a bad idea for patients who have a valve size 19 or less. And that's what the red means there.

And this is all based on gradients after valve-in-valve. And here are the presentations for both the Corevalve and Sapien valves, showing valve gradients after valve-in-valve, Mike [INAUDIBLE] on the left and Dan [INAUDIBLE] on the right. These were presented in 2015.

If you look at all comers, the average gradients after a valve-in-valve is roughly 17 millimeters of mercury. It's going to be worse for smaller surgical valve sizes, but this is the average for all comers.

Now, there's going to be data that's going to be presented at the end of the year. Alan [INAUDIBLE], Mark [INAUDIBLE] and I are going to present the PARTNER 3 aortic valve-in-valve valve study, which is about 100 patients in the PARTNER 3 trial who are at low risk. So we're looking forward to showing you that data later in the year. Please join us at TCT.

And so in conclusion, valve durability can be measured either by an actual or an actuarial analysis. You gotta be careful when you look at that end point. And also remember that SVD is not the only reason that valves fail. They can fail for other reasons, pannus, endocarditis or valve thrombosis.

Now, durability for bioprosthetic valves is good for older patients. It's poor for young patients. But I think what the most important takeaway point from those studies is that they're universally associated with a decrement in survival. Bioprosthetic valves do not restore life expectancy.

Now, I think TAVI valve-in-valve is definitely a safe option. More studies now are showing close to 0% 30-day mortality after a valve-in-valve with good patient selection. But the Achilles' heel of valve-in-valve is the valve gradients. Now, thank you very much for your attention. I'll turn it back to Herms.

JIM HERMILLER: Chris, that was fantastic. Thank you so much. Just a couple of quick questions for you. So that 50-year-old that we pulled, you had a long discussion, and that patient says, I want a bioprosthesis. What do you quote him at 50, sort of his durability of that valve. What do you tell him? I think you're going to need another valve in X. What would you say?

CHRIS MALAISRIE: Well, I'd tell that patient probably about a 10 to 15 year durability for the valve. And we put that in perspective as well. So the patient's 50, and then they're 51, and there's a chance that they're going to need another procedure. And then where from there? I mean, you get into that sort of SAVR, TAVR, whatever after that. But I'd be interested to hear what the other panelists tell their patients as well.

JIM HERMILLER: Yeah, Anybody else want to chime in there, Marc or Ismail?

MARC GERDISCH: Yeah, I think that it's really important to focus on what Chris mentioned earlier, that age is the primary driver of valve durability and changes in valve performance. And so in a 50-year-old, I think 15 years is a real stretch. In a 50-year-old, I would generally say it's an 8 to 12 year valve, and I tell them 10.

You know, I've had enough people that I've put valves in in their late 70s that are coming back out in their late 80s, 10 years out from valve, and I think the data supports that especially when we look at continuous follow up in Dr. David's studies. So I think 15 years is a stretch on a 50-year-old.

JIM HERMILLER: Let me just ask you one thing. I think changed, I think, the way surgery is done. Let's say this patient is 60, and they're going to get a bioprosthesis, and you're setting them up for a TAVR maybe at 75 within that valve.

The way you think about it today, I would guess, is much different. You need to make sure you put a big enough valve in, which you always do, but also, they've got room for valve-in-valve for their coronaries.

MARC GERDISCH: Yeah, I think that's a huge issue. And the truth is, you you know, as we always do, the truth is, if you look at the United States data, that's not what happens. Not everybody gets an appropriately sized valve.

The lack of root enlargements, and probably root replacements, although that can get a little bit of a dangerous operation, leads to scenarios where we have patients that have undersized valves, and then they're stuck with a valve that, at that point in time, when the opportunity for a valve-on-valve presents itself, they don't have room in the sinuses, and it's kind of a tragic mishap.

JIM HERMILLER: Yeah. And let me have-- one other question, Chris. So this porcine versus bovine, it is does the porcine look better because hemodynamics and less PPM? Or, well, how do you explain that? I think your point is that that's not the real message. The message is the high mortality. But if you have to try and tease that out, what do you think?

CHRIS MALAISRIE: Yeah, I don't know what to make of the survival difference, which is only about 2%. But there is definitely a difference in how they fail. And I personally prefer the bovine pericardial valves, because they fail by stenosis. But those stenoses happened late. The porcine valves tend to fail by aortic regurgitation, but sometimes, that happens early. And that's really discouraging if you have a failure within five years. But taken overall, durability is about the same for both in the aortic position.

JIM HERMILLER: OK, all right. Well, I tell you what, let's move on from that. And Marc is going to talk to us next. Can we have his slides up? We're going to talk about mechanical prostheses.

MARC GERDISCH: Thank you. Sorry about that. So thanks, Herms. And I have been singing the same tune for-- I've been in practice for 26 years. And if I look at my practice, I still implant the same number of mechanical valves as I did early in practice as a percentage of my practice.

The truth is that I love it all. I participated in it all. I believe it at all in the right patients and in the right circumstances.

But I do think that we have to purvey a certain body of information as part of any rational conversation about valve choice. And I think that some of those conversations have gotten too short, especially between cardiovascular specialists. So I honestly think that we have to get back to some very fundamental elements, some of which Chris told beautifully, so I'm not going to repeat them.

But we're also battling sound bites. We live in this age of sound bites. And we get this little bit of information. I get up in the morning, I look at my favorite two-second journal from the STS, and what do I get? When implanted correctly, a SAPIEN S3 transcatheter may last 25 years. That's not going to happen.

So what does happen when we put a value inside a human being? Tissue valves, as Chris expressed, experience an aggressive biologic assault, initiating changes in the valve from moment one. So as soon as the valve goes in, there's an immunologic response, and that valve starts to be attacked by our body next. And that just part of the game. That's how they fail.

Mechanical valves provide greater opportunity for thrombus formation, and therefore warrant continuous anticoagulation. Everybody has to be on warfarin. The risk of stroke is equal. So if you have a mechanical valve on anticoagulation, or if you have a tissue valve with or without anticoagulation, the risk of stroke is equal.

Risk of bleeding overall is higher for most mechanical valves. I am not agnostic on this because we have a randomized controlled study. And I think that the message that I would deliver here is that that randomized controlled trial, which I participated in, is one of just a few randomized controlled trials that have been positive in heart surgery. If somebody can name a few more for me, I'll be surprised.

And it's an odd thing, because when you talk to surgeons about things, they're like, well, I think it's a good idea, but I need a randomized controlled trial. Then we do one, and nothing changes. So I think it's worth focusing on the fact that there is a randomized controlled trial demonstrating the efficacy of a specific device.

We already set 50 to 70 years of age, survival advantage with a mechanical valve. And I didn't make that up. That's not me speaking; that's the data speaking. There's not a single study that shows tissue valves provide a survival advantage. There are plenty that show mechanical valves do. There are some that are equivocal.

Diaz did a beautiful meta-analysis last year, taking the best studies, taking those and had good propensity score, matched studies, and one randomized controlled trial, not going all the way back to the old randomized controlled studies, but providing a good perspective on several thousand patients and showing us the same thing that we learned before, which is that mechanical valves for patients at 50 to 70 years of age have a survival advantage.

One of the interesting things when you look at the various studies and the data is that, oddly enough-- because we think of the bicuspid young patient-- oddly enough, when you add coronary disease, there is a survival advantage for the patient. It's a greater survival advantage for the patient if you get to the aortic valve replacement with coronary bypass versus a tissue valve with coronary bypass. And we can discuss the mechanisms for that, but it's a real thing in the data.

We talked earlier about the most important paper, in my opinion, about the follow-up on valves. And the reason that I think Doctor David's paper is important is not only that it made it clear that patient age was the most powerful predictor of tissue valve durability, but he also pointed out-- which was mentioned a little bit by Chris-- that it's not the same thing. Just because you're not re-operating doesn't mean you're not dying, it doesn't mean that you're living well, and it doesn't mean you have a well-functioning valve or that you can have surgery.

What causes hemodynamic deterioration besides age? It's the condition that we see in most of our patients, which is dysmetabolic profile. And this is super important to think of in terms of a patient that you have to manage from multiple aspects for the rest of their lives. Those patients who have diabetes, central adiposity, increased inflammatory markers, have a shorter durability for their bioprosthetic valve.

So nothing changed here. Bioprosthetic valves, this is 13-point-- plus or minus five years. This is what happens to them. And the clock starts ticking as soon as the valve goes in. And indeed, whether they have clinically significant changes in the valve, or-- sorry, not clinically significant or significant changes to the valve, they're still changing.

So if you put a bioprosthetic valve in a patient, and let's say they do get out to 12 or 15 years. Still, at 10 years, they don't have a normal functioning valve. They have a valve that's moderately stenotic, and they have to live with it until it's severe.

So tissue winds on bleeding. Tissue wins on convenience. Mechanical wins on durability. Mechanical wins on consistent performance-- it doesn't change. Mechanical wins on re-operations. Mechanical wins on survival. There's wiggle room, I think, in the 65-70 year age group. And they're equal on stroke.

Now, the turning point for me is 2002, when I meet this guy, Jack Bokros. In the 1960s, he was working at General Atomic, and he invented pyrolitic carbon. And that pyrolitic carbon, it was used to make every mechanical valve that you all have ever put in or seen, up to and including the On-X carbon valve.

But the On-X valve has pure carbon. All these other valves have the original version of pyrolitic carbon, which was doped with silicon to regulate the volume distribution of the material on the valve leaflets. Dr. Bokros moved the entire game when he designed a valve that was pure carbon.

Because this is what all the other valves look like. Every other mechanical valve that you put in looks like this under an electron microscope, because it's a silicon alloy pyrolytic carbon-- so it's rough. And this is what On-X carbon looks like, the carbon that's used for the On-X valve, which is very smooth like glass, even under an electron microscope, and therefore less pro-thrombotic.

Furthermore, instead of just taking a ring, and putting a couple of leaflets in it, and sticking it on top of the rough edges of a cutout valve, he designed a valve that had a fairing that passes down into the outflow tract that hides the annulus and that provides laminar flow. This design of this demands laminar flow. And as the leaflets move, they have a shorter distance to fall, a smaller closing volume, and they're able to spend more volume washing the hinges. And the hinges work by sliding up and down in that cool groove. And as a function of that, you have a much more robust washing of the leaflets and, as I mentioned, laminar flow.

So in a healthy volunteer on the left, you have laminar flow. In an On-X valve, you have laminar flow. You can get that with a Ross. You can get that with a homograft. But you can also get it with an On-X valve.

The problem is, with mechanical valves, bleeding, because people have to be anticoagulation. And bleeding is a function only of the anticoagulant. It has nothing to do with the valve itself, right? So we just have to address the anticoagulant if we want to make progress with this.

And so we did the On-X study. We did the ProACT study, which showed that we could manage the On-X valve with an INR of 1.5 to 2. And we would have no increase in thromboembolic events, but we reduced the bleeding events by 60%. Which means we eliminated, it basically, because tissue valves have bleeding, too, right? Bleeding effects occur in people with tissue valves, other anticoagulants. They have bleeding events. And with a 60% reduction, it neutralizes it.

So what are we left with? Convenience. So can we make it more convenient? Answer this first. What's more prothrombotic, AFib or an On-X valve? AFib initiates the coagulation cascade. You've got abnormal endothelial function, a lack of nitric oxide. And down here, ARISTOTLE study right with the apixaban, 21% reduction in thromboembolism over warfarin.

So if apixaban can work as well as warfarin or better than warfarin in AFib, can it be the same with the On-X valve? And that's what we're pursuing now. We have the ProACT 10a steering committee for that. We have started enrolling.

And this trial design has already been published in the *American Heart Journal* in July of this year. And we established the need for the trial, right? Because number one, in the US, we are not good at managing Coumadin, especially compared to, for example, Nordic countries. We just do a bad job.

Furthermore, it is inconvenient, and patients want to be able to eat what they want and do what they want. So we designed this trial with, of course, clearance through the FDA. We're already enrolling. And we happen to be the highest-enrolling site already. We've got, I think, 12 programs in 11 states up and running. The goal is to enroll, randomize 1,000 patients to each limb.

The limb with warfarin will be a standard warfarin dose. This was after discussions with the FDA. So it'll be Eloqus in the On-X valve versus warfarin standard dose 2 to 3 in the On-X valve.

JIM HERMILLER: That's a great, great review. Let me just start this off. When that 50-year-old patient comes in to you, and you say, here's the data, here's survival, are you able to make that point with the majority of your patients? I mean, many of mine come in, and they've got this notion that they do not want a mechanical valve because they've heard of these disasters related to bleeding.

MARC GERDISCH: Yeah, so I think you have to just tell them the truth and let them decide. And I always-- when I talk to every patient-- are you still able to hear me?

JIM HERMILLER: Yeah, yeah.

MARC GERDISCH: I always talk to every patient, and I tell them we have every version of valve on the shelf. So I'm happy to put whatever you want. I like them all. I'll do a Taylor for you if that's what you want. It's perfectly legal and appropriate. I can do that.

But I also tell-- I explain to them the whole story. And once they understand that first of all, the fact that we're able to manage them at the lower cost of blood thinner is really interesting to them. I have patients that come to me specifically for that. I explain the science and, furthermore, just the fact that when they learn that a tissue valve does change over time, that it isn't a perfectly robustly or reliable device, that it can change over time, that, combined, with longevity data, I think, tends to sway them.

I do still have patients that I'll put a tissue valve in that are in their 50s, but it is by no means the majority of what we do. And so I would say things really haven't changed for me much in 20-something years, just by explaining the data.

JIM HERMILLER: Yeah. There's a question from the audience about, could you elaborate a bit about the combination of CABG and a mechanical valve, and, maybe, even the greater survival benefit when it's CABG on top of the ADR?

MARC GERDISCH: Right, so there's probably two reasons for that. One is that atherosclerosis and valve disease, deterioration, even bioprosthetic valves are bundled into cardiometabolic syndrome and have a relationship to that. So the person who's getting an aortic valve and has coronary disease has a higher likelihood to suffer from that type of condition that would also contribute to a more rapid demise of a bioprosthesis. So the mechanical valve, of course, isn't going to fail like a bioprosthetic valve would.

Now, add to that the fact that well-controlled warfarin is probably cardioprotective, cardiovascular protective, in those patients who have vascular burden and who are now going to be well-managed with warfarin. In fact, if you look at the tissue valves, there's a couple of different tissue valve studies that did drill down on patients who had a tissue valve and warfarin versus tissue valve and no warfarin. And the tissue valve and warfarin tended to out-survive the patients who did not have warfarin, because it's not just because of thrombosis of the valve. It's because there's some cardioprotective element to well-managed anticoagulation.

JIM HERMILLER: OK, great. I'm going to just-- one other question from the audience, and that is, how is apixaban working when there's been so much problem in the past with 10a inhibitors, 10a blockers in prior valves, prior mechanical valves?

MARC GERDISCH: So there's only one study, and it was done in Europe, and it was-- well, although all the folks participating in it were very well-intentioned and brilliant people, they approached it a little bit differently than we are. And this, of course, is why the FDA feels it appropriate for us to do this study.

First of all, we're using a apixaban, which has the best record, really, with safe management of anticoagulation. But perhaps more importantly, it's specifically just the aortic valve. It's just the On-X valve, which we've proven we can manage at a lower dose of blood thinner. An INR of 1.9, 1.8, which was the sweet spot, is barely anticoagulated. Now, it doesn't mean you can walk around not anticoagulated, but you have to have-- it just doesn't require aggressive anticoagulation.

And in that study, they started the oral anticoagulant immediately after surgery. They didn't give three months of standard warfarin therapy, which we will do in this study, just like we did in the prior ProACT study to allow some healing of the valve, to allow whatever issues might occur around the time of the operation to subside. And now you've got a clean study with patients three months, with standard therapy, switching over to a different anticoagulant.

I think it's a much cleaner study. Plus, the European study had combined aortic and mitral valves or just mitral valves. So it really is-- it's not a fair comparison.

JIM HERMILLER: Yeah, OK. Well, good. Well, that's that. And we'll come back to this, I'm sure, at the end, when we discuss this further.

And we're going to move on. And Ismail, if you want to pull up your slides, and we're going to talk about the Ross procedure.

ISMAIL EL-HAMAMSY: Well, thank you. Thanks again for CryoLife for organizing this webinar, and thank you for the two previous speakers for their fabulous presentations.

I think the good news tonight is that we're all in agreement. I can't disagree with anything that Chris said or that Marc said. If I summarize, Chris mentioned that he doesn't think a biological valve is a great idea in a non-elderly patient, and Marc suggested that mechanical valves are probably better than tissue valves. And I would agree with that as well in that patient population.

What I will tell you, however, is focus on survival, which was really the theme of tonight's talk, and I'll show you why, perhaps, the Ross really needs to be re-examined in that conversation. So my first point is that conventional aortic valve replacement in the young adults is associated with excess long-term mortality, which is really the main focus in non elderly adults. We're really interested in what happens at 10, 15, and 20 years, if not longer.

And this is one study from Sweden where they have population-wide databases. And they looked and expected and observed survival in patients undergoing aortic valve replacement with tissue or mechanical valves. And what they showed is after about seven or eight years from surgery, you can see that observed mortality is definitely higher than the expected mortality in the agent-patient matched general population.

Now when you look at these curves, you may think that this is probably driven by the older patients, except when they stratified the patients according to their age at the time of surgery, the younger patients in that cohort actually had the highest observed-to-expected ratio of death at 4.5, and patients over the age of 70 had exactly the expected survival in the general population. So bottom line, the younger the patient is at the time of surgery, it may sound counterintuitive, but the higher that excess mortality is in the long term.

So we a few years ago and looked at mechanical aortic valve replacement in young adults, looking at elective isolated mechanical AVR over 450 patients under the age of 65. And we excluded anything that we thought may impact long-term survival-- so concomitant procedures, coronary disease, et cetera. And the mean age of the patients was 53, so exactly like the patient the doctor Hermiller presented at the beginning of this presentation.

The main follow-up was nine years and was 95% complete. And if you look at survival of these patients versus the age and sex-matched general population, you can see that at 10 years, already, there's a 7% survival gap, and that continues to increase as the years go by. In fact, when we combine survival, mortality, and death in these patients undergoing isolated elective mechanical AVR, 10-year survival free from re-operation was only 82%. These are highly selected patients with no other health issues whatsoever. So in other words, in 10 years, one in five patients was dead or re-operated, and that was mainly driven by death rather than re-operation-- sobering results.

Now, as we mentioned earlier, we can now aim for lower INR targets with some valves, particularly the On-X valve. Except, if we look at the actual ProACT trial, the annualized rate of major events-- major bleeding, all thromboembolic events, or thrombosis-- in the low INR group was 4.5% patient-year. That's almost 1/2 the patients at 10 years having a major bleeding or thromboembolic event. Again, it's food for thought for these patients in the long term.

Now, what about tissue valves? Well, this is a study from the Cleveland Clinic of over 3,000 patients undergoing pericardial AVR, and their conclusion was similar. Younger patients had worse-than-expected survival that was further diminished with the insertion of a small prosthesis, so introducing the notion of patient-prosthesis mismatch, which we talked about earlier in the other talk.

And this is another study from Bourguignon from France, looking at over 2,500 patients undergoing tissue AVR. And they stratify the patients according to their age at the time of surgery, as you can see on the x-axis. And they looked at observed survival in black and expected survival in the age and sex-matched French population in gray.

And what you see, very similar to the Swedish study, is survival that is significantly lower than expected the younger the patient is. And if we take that 50-year-old patient that we talked about earlier today, we can see that we're probably amputating somewhere between 10 to 15 years of anticipated life expectancy in these patients with a tissue aortic valve replacement. Again, focusing on the long game, not only on the short game, in these younger patients.

And the final study I'll show you to support this point, and also to support Dr. Gerdisch's point about mechanical versus tissue valves is this study from *The New England Journal of Medicine* looking at California-wide data, almost 10,000 patients undergoing isolated AVR under 65 years of age, where they stratified patients according to their age. So 45 to 54 years of age, 15-year mortality was 26% to 30%-- almost 1 in 4 to 1 in 3 patients dead 15 years after surgery. Not very good results if you're talking about a 50-year-old.

And 55 to 64, again, same thing. At 15 years, 1 in 3 are dead. And notice that mechanical valves performed better than biological valves in both these patient groups.

So again, I think that conventional AVR in young patients are definitely good options in the short term, but they're far from being curative procedures. They are, at best, palliative procedures. And that's why we need to look for alternatives.

Now, why are the results not so good in the long term? I think the answer is twofold. One is hemodynamics, and two is biology.

We need to think PPM any time we're doing aortic valve replacement, particularly in younger patients. And we know that after surgery, the overall prevalence is very high. It's almost 40% to 45% of patients leaving the hospital with either moderate or severe mismatch.

Now, mismatch in older patients is not very impactful. But in patients under the age of 70, it has a direct impact on survival, as you can see on the left side of the screen here. And for those who are thinking, perhaps, doing TAVR may solve the issue of patient-prosthesis mismatch versus tissue valves, these are results from the PARTNER 3 trial in low-risk patients, and the incidence of moderate or severe mismatch was actually equivalent in both groups at 34% after TAVR and 30% after surgery.

In fact, if we look at echocardiographic outcomes at one year after that TAVR versus surgery from the PARTNER 3 trial, at one year only after the procedure, 10% of patients in the TAVR group had mean gradients over 20. In other words, 1 in 10 patients had moderate stenosis, versus 5% of the surgical valves, which is still not very good either.

And the second point, as I mentioned earlier, is biology. We need to remember that the aortic valve is a living structure. It is not just a passive, open-shut structure. And I can tell you so because I spent four years with Professor Yacoub doing my PhD a number of years ago, and the title of which was "The Living Aortic Valve."

And the aortic valve looks very much like a blood vessel. It has the endothelial cells on both sides, interstitial cells in the body of the leaflet that can contract, that can relax, that produce the extracellular matrix. But importantly, that living structure performs a lot of complex functions, which, for us clinicians, translates into a perfect laminar flow across a normal aortic valve, excellent hemodynamics at rest and with exercise, low thrombogenicity because these endothelial cells can produce nitric oxide and prevent platelet aggregation, and, obviously, resistance to infections, because they can mount an inflammatory reaction.

And when we look at late outcomes after aortic valve surgery in our patients, what determines clinically relevant endpoints, such as survival, valve-related complications, or even quality of life are all of these features that I mentioned-- the type of flow, the presence of mismatch, the need for anticoagulation, or the likelihood of having endocarditis.

So the question is, does a living aortic valve substitute with unique biological and hemodynamic features, does it translate into improvements in clinically-relevant outcomes? And let's remember that the Ross procedure is the only replacement operation that guarantees long-term viability of the aortic valve and the aortic roots. We have explants up to about 30 years after surgery showing that preserved cellular structure within the valves.

I'm sure some of you in the audience may be thinking some of these things right now. "I don't believe in the Ross procedure." Or, you may have heard that all these patients come back for reop. And certainly, now, we're hearing more and more, let's just put a large tissue valve and then come back for a valve-in-valve procedure.

And some of this may be true, but I think a lot of it may be overstated. Obviously, 10 minutes is not enough to convince you that the Ross procedure should be considered, certainly not that the guidelines should be reconsidered. This is a state-of-the-art review which was co-authored by many colleagues and written by Amine Mazine, a resident in Toronto, Professor Yacoub, Dr. David, Dr. Bonow-- a lot of very prominent aortic surgeons and valve specialists co-authored this paper, which I suggest for all of you to read if you're interested.

I'll only focus on survival here, since this is the topic, and survival is really a binary endpoint. You can't be half dead or half alive, so it's a very hard endpoint. And this is one of the few prospective randomized trials in our valvular surgery literature, where Professor Yacoub randomized patients to undergo a Ross versus a homograft replacement.

And these were, really, all comers. 8% had active endocarditis, and almost half were reoperations, with the most frequent previous surgery being a homograft root replacement. So by no means were these patients destined to a very good long-term outcome. And yet, when we looked at survival up to 13 years, it was exactly identical to the UK age and sex-matched general population, whereas the homograft group, as you can see, has a drop-off in survival, just like we see with tissue valves or with mechanical valves.

And many other studies since then have looked at long-term survival, and all of them show the same signal-- survival that is exactly identical to the age and sex-matched general population. Dr. David from Toronto, Hans Sievers from Germany, Peter Skillington from Australia, Francisco Da Costa from Brazil-- different countries, different continents, same signal. Survival restored to that of the age and sex-matched general population.

In fact, in Amine Mazine's review, you can see here all these papers are referenced mean follow-ups in the double digits, all survival at 15 and 20 years exactly identical to the general population. So I would submit to you that it is the only replacement operation that restores long-term survival following aortic valve replacement. And I'll quickly go through what the Achilles' heel of these operations are. Is it surgical risk or durability?

This is my experience with the aortic root reconstructive surgery. I started my practice in 2010. I performed nearly 500 Ross procedures and a number of valve root reconstructive procedures. But focusing on the Ross practice, the mean age was 48 years. All-comer patients, 15% redos, 6% active endocarditis. Operative mortality was only two patients-- so less than 0.5% percent. Compares very favorably to regular aortic valve replacement.

And definitely, there is a learning curve. Both mortalities occurred early on in the experience. But in the last seven years, we have had no mortalities in the experience. And you can see here, complications occur early on, but as experience progresses, the rate of complications is particularly low in these patient.

Survival is identical to the general population so far, but importantly, hemodynamics are fantastic after the Ross. The main indexed effective orifice area is 1.5. The mean gradient is 5 millimeters of mercury. And importantly, no patients had moderate or severe mismatch, including all patients that we had to reoperate on because of mismatch with a small prosthesis.

And these are gradients over time. They're mean gradients. You can see that they do not increase, as you see with tissue valves, because these valves do not degenerate.

What about durability?

This is from the review. And basically, the annualized rate of reoperation, if performed in high-volume centers is around 1% patient-year reoperation range for patients in their 40s at the time of surgery-- which really beats any other type of aortic valve replacement and compares very favorably with mechanical aortic valve replacement in terms of durability, of course.

So again, to answer the question, I think there is a need to re-examine the guidelines. We're not the only ones to say it. Dr. David mentioned that the Ross procedure is the best operation to treat AS in young and middle-aged adults. This is from the Cleveland Clinic. "Is it time to reconsider the use of the Ross?" This is Michael Borger from Leipzig. "Time to re-evaluate the guidelines."

There's certainly a lot of movement, based on the data from the last 10 years, to re-examine the Ross and its role in these patients. And I would tell you that the paradigm is really evolving from the simple question of anticoagulation versus reoperation, i.e. Mechanical versus tissue valve, to really looking at survival and quality of life in these non-elderly patients. We need to have them alive at 15 or 20 years before we even consider strokes, or anticoagulation, or any of these other points that we mentioned.

So in conclusion, I think the Ross can be performed with similar operative risk in high-volume centers. It provides excellent quality of life, better freedom from valve-related complications. I did not delve into it for the interest of time, but certainly less endocarditis and so on. Better hemodynamics with no mismatch, and restored late survival. All of these are really unique features to the Ross procedure, or aortic valve surgery in younger adults. Thanks again for the invitation, and I really look forward to a very animated discussion over the next 15 minutes.

JIM HERMILLER: Ismail, that was fantastic. Thank you. That was a very compelling data and argument about the survival. There are just a couple questions. One is, how many cardiovascular surgeons can do a good Ross procedure?

ISMAIL EL-HAMAMSY: It's a procedure-- well, it's a procedure they should be done in centers that have expertise with aortic root reconstructive surgery. It is certainly an operation that can be reproducible. It can be taught. It can be performed by surgeons, again, who have a certain facility with aortic root surgery. Chris can definitely speak to that. He started his Ross practice earlier this year and has been on a roll, really, with these cases and having very good results.

So I certainly think that if a surgeon has interest and some expertise with aortic root surgery, the Ross procedure is no different than any other complex reconstructive surgery, whether it's complex mitral valve repair, or valve-sparing surgery, et cetera. So it's teachable, and it's reproducible, and it can be done very safely. As my data really shows, we started from no experience when I started my practice, and we built it up. And the data that I showed includes our learning curve. So I really think that it can be done quite safely.

JIM HERMILLER: Yeah, and Dr. Perez-Tamayo, he-- [INAUDIBLE] a question and asked, should the Ross procedure be accompanied by an internal/external ring or an external graft?

ISMAIL EL-HAMAMSY: Yeah, these are good questions. I think the four patients who present with aortic stenosis, the annulus does not tend to dilate over time, and the match between the pulmonary and the aortic annulus is perfect, so no need for any annuloplasty. For patients that present with AI, who typically have a dilated aortic annulus, it is important to perform an extra-aortic ring annuloplasty to reduce the size of the aortic annulus so it matches that of the pulmonary and, importantly, to stabilize that annular dimension over time. And that's what we've been doing, and we've shown some pretty good data with this approach.

Now, one of the trends recently has been to put the autograft within a background graft to try to stabilize it. I personally do not think this is a good idea I think the entire premise of the operation is to preserve the normal dynamics of the aortic root. By confining the autograft within a straight or a stiff background graft, we're really preventing sinus motion, which is so important for leaflet mobility, for reducing the impedance on the ventricle. And I think these are all parts of the reasons why outcomes, particularly survival in the long term, are so much better with the Ross than with other option.

So I think blood pressure control is the best way to prevent sinus dilatation for the autograft. And we keep these patients an anti-hypertensive medication for about six to 12 months after surgery, avoiding exceeding 110 millimeters of mercury systolic pressure.

JIM HERMILLER: OK, just another question from the audience-- two of them. And really, one is choice to replace the pulmonary valve, and then, somebody anonymous asks, how about the pulmonary prosthesis durability and the issue of the pulmonary valve?

ISMAIL EL-HAMAMSY: Yeah, both very important points, because, obviously, one of the comments is replacing a single-valve disease by a double-valve disease, then. And so the choice for the pulmonary side is the pulmonary homograft. We now use de-cellularized pulmonary homografts grafts which CryoLife produces and the center-of-graft prosthesis. And we have a paper just out now in the *JCCVS* looking at durability of those in a cohort of over 500 patients from several centers showing very good results-- within the first decade, at least-- with these decentralized homografts.

And in terms of durability or need for re-operation on the right side, as I just mentioned, in these 500 patients, within the first decade, only four patients required re-intervention, and that 1% re-operation range that I showed in my slides, that really included all three interventions, both for the aortic valve or the pulmonary valve. And typically, when you look at the distribution of aortic versus pulmonary, it's about 1/2 and 1/2 which valve requires re-intervention. And nowadays, if the pulmonary homograft required reintervention, a transcatheter approach is really the favorite approach, provided there's enough distance between the left main and the pulmonary homograft to avoid left main compression.

We used to use Melody valve. Now, instead, we put a stent in, then a SAPIEN valve in there, and that provides very reliable results, at least in the handful of patients that have undergone it in our hands.

JIM HERMILLER: OK, well, that was fantastic. And I'm going to ask Marc, if you're in a debate with Ismail, what would you come back with to argue, hey, that 50-year-old, rather just put a mechanical prosthesis in there. Rather put an On-X in.

MARC GERDISCH: Well, first of all, I've known Ismail for a really long time, and I've watched him build this practice. And it's very, very hard to argue against everything that he said. I mean, it's all valid data, and he's lived this throughout his career. So kudos, of course, to Ismail for incredible practice and his ability to deliver this message.

So I think that one of the things we don't have is we don't have a good comparison of the well-performed Ross procedure versus the On-X valve managed at a lower dose of anticoagulation, I agree, you see a higher incidence of events-- which you showed. But we don't have-- you said we need life. We need to see how long people live. So we don't have a really good comparison there.

There is one study-- actually, Ismail, I don't know; you may remember it-- a German study several years ago with, actually, mechanical valves. I don't know that they were On-X, but they were well-controlled anticoagulation. And they had trouble distinguishing those otherwise young, healthy people who received a mechanical valve-- they had trouble distinguishing them from the general population.

Because one of the things we have to consider is that although you do do some sicker folks and combined procedures, et cetera, most of the Ross folk, patients, are going to be in pretty good shape. So it's a category of patient that generally does well anyway. They preserve left ventricular function, and you lower their anticoagulation. So I think those are the points that I would make.

And as he just mentioned, and you just mentioned, the pulmonic valve remains somewhat of an issue. And we've rehabbed some of those valves. And it's true, we've been able to put stents and SAPIENs into them, or I've just redone-- I've just taking their holograft out and put another one in. But those are big operations, and even the rehabbing can be pretty tricky.

And plus, an On-X valve I can do through a 3-inch incision next to the sternum, which patients love. And they're in and out of the hospital with minimal trauma. And so there's some advantage to that, too.

JIM HERMILLER: Yeah.

MARC GERDISCH: Chris, you want to weigh in on this?

CHRIS MALAISRIE: Good deal. I've been waiting for you to ask me a question.

JIM HERMILLER: Yeah, there you go.

CHRIS MALAISRIE: Thank you very much.

JIM HERMILLER: You've got it from here on out.

CHRIS MALAISRIE: Yeah, so I'll provide a testimonial for Ismail. If you're going do the Ross procedure, do it exactly the way Ismail shows you how to do it. He published a paper on how to teach the Ross procedure. At Northwestern, we had done Rosses more than a decade ago. Good survivability, but we found that 50% of them needed repos. So we stopped until I saw Ismail's technique on it. And if you do it the way Ismail does it, it's going to be great.

The problem with a Ross procedure is that we have to remember-- and this is important for the average surgeon-- the average surgeon does maybe less than five aortic replacements-- if that much-- per year. So to ask an average cardiac surgeon to do a Ross procedure is a big deal. But asking them to do an aortic valve replacement with a mechanical valve is really not a big deal at all. So we have to remember, also, whether or not the Ross procedure is going to be scalable.

There is one thing that still bothers me about the mechanical valve that I'd actually like to ask the panel. It's that patients often ask me, will I hear that mechanical valve click? And I tell the patient that it doesn't click as much as the older ones do. I could hear those click from across the room. But what do other people tell their patients about noise from a mechanical valve?

JIM HERMILLER: When it stops, worry.

ISMAIL EL-HAMAMSY: Yeah. So yeah, when you don't hear it anymore, that's a problem, right? So one of the things in On-X-- CryoLife will never say this, but the On-X valve is a little bit quieter. And the reason is because as it makes time-- there's two reasons. One is the travel distance for the leaf at the close. Because the fairing is a taller valve, because the case is taller, the travel distance is shorter. And when the valve touches down on the ring, it touches down in two places. So it tends to be a quieter valve.

Having literally put in hundreds and hundreds of them, I haven't had anybody tell me, I can't stand this. So I do tell them, though, early on, they're going to hear it pretty loud and clear. If they're slight, if they're a slight person, plan on hearing it for the rest of your life, and your kids will tell you across the room. But a little bit more robust body habitus, usually, it quiets down and becomes-- I can hear my own native vari growling at night. I should probably another echo. But if you listen hard enough, you're going to hear it. But it's not that-- it hasn't been a huge problem.

JIM HERMILLER: Yeah, particularly in Indiana, where we are, it's not. There's a lot of insulation.

ISMAIL EL-HAMAMSY: All true.

JIM HERMILLER: So just Chris, I'm going to give you the final comment. How about that? What would you do with this 50-year-old? We know what Ismail, we know what Marc would do. What would you do?

CHRIS MALAISRIE: Coming into to my clinic, I'd offer that patient a Ross procedure. But it is the patient's choice. So I'd lay it all out to him, including that crazy TAVR/SAVR/TAVR option, because someone's already discussed that option with that patient. But they should all be laid out.

But if it's a patient who says, well, what would you do, doc? I would offer a Ross procedure. I think that's a great Ross case.

JIM HERMILLER: OK, and Marc, am I wrong you'd say On-X?

MARC GERDISCH: So I would talk about everything, and I do actually discuss Ross procedures my patients, even though I don't do the operation-- at least not right now. I may just run out to Ismail and get myself a lesson. But I do tell them that I have folks, good friends, that know how to do that operation, and I'll get him to them. So it's laid out as an option.

JIM HERMILLER: Yeah. And then, Ismail, just to finish, there's one question from the audience. Not that this ever happens, but what if [INAUDIBLE] TAVR down the road? Can you do that in a Ross?

ISMAIL EL-HAMAMSY: There's no experience [INAUDIBLE] with it. And the main issue that I foresee with current technology is there's really no calcification within the pulmonary autograft on the aortic side. It's not the mode of failure. It's more if it fails, it's autograft dilatation and aortic regurgitation, but with no calcium.

So really, again, with current TAVR technology, there's not really anything that would work. But there is, as you know, evolving technology for patients with AI. And that may prove to be a potential option in the long term. Although in the majority of these patients, when they come back, we can actually perform valve-sparing root replacements, which would then preserve the whole notion of having a living valve in the aortic position while correcting the root dilatation problem.

JIM HERMILLER: OK, well, that's great. I think we've run out time. We're going to finish with that poll one more time, see if we've changed anybody's opinion. So if we could bring that up, Kristin? There you go. All right, oh, biologic SAVR really lost. The one person stuck with TAVR/SAVR/TAVR, and I think more certainly went mechanical and Ross.

So this has been a great session. I just want to thank all the speakers. This was really instructive, really entertaining, great discussion. So thank the audience, and everybody have a great night.

ISMAIL EL-HAMAMSY: Thank you very much. I really enjoyed it. Thank you, Dr. Hermiller, for running this.

JIM HERMILLER: Yeah, this is fun. This is just fun. Everybody [AUDIO OUT]