SPEAKER 1: Good morning, everyone. Welcome, again, to our monthly Cardiovascular Grand Rounds series. We're actually entering our fourth year of this program and delighted that we have such an excellent turnout today, a little better than I think we have on average. And hopefully we can maintain that momentum going forward this year.

It's my pleasure today to introduce a new format for Grand Rounds for today, which is something that I think is reflective of what's happening in the cardiovascular program. And that's the notion of a heart team.

And today you're actually going to have the opportunity to have a presentation on this topic by John Muir, Cardiovascular Institute's Heart Team or Transcatheter Aortic Valve Replacement Team.

We are doing this program in collaboration. We're in partnership with the California Chapter of the American College of Cardiology. The California Chapter has actually partnered with us for the Grand Rounds series over the last few years.

But this collaboration for the presentation today is even a more profound collaboration because the slides that you'll be seeing today have also been developed in collaboration with the California Chapter of the ACC and with many experts throughout the state that has been involved with furthering our knowledge about how to manage aortic valve disease.

So without further ado, we'll start the presentation at the top given the presentation today is the update on the management of aortic valve disease and transcatheter aortic valve replacement. The team is listed on this slide.

There are other members of the team that are critical to the program-- our fantastic nursing staff in the cardiac cath lab, and technologists, the anesthesiology department that supports our cases. And I think that we could list many additional individuals here. I'm simply listing the folks that will be involved with the presentation today.

So the objectives of the talk today are to review the prevalence pathophysiology and presenting signs and symptoms of aortic stenosis, to review the role of imaging and hemodynamic assessment in the diagnosis of aortic stenosis, to assess the therapeutic options for treating aortic stenosis and the appropriate timing of the intervention, whether it's surgical aortic valve replacement, SAVR, or transcatheter aortic valve replacement, TAVR, to present a guideline in clinical trial-based approach to identifying patients who may benefit from TAVR.

And to compare the short and longer term outcomes of TAVR versus SAVR. And we'll be using that acronym, TAVR, for transcatheter, SAVR for surgery throughout this presentation. I'm now going to turn over the podium to my colleague and team member, Dr. Paul McWhirter, will run through the characteristics in key clinical features of aortic stenosis.

PAUL MCWHIRTER: Thank you, Gary. And good morning, everybody. It's great to see all the faces, so many faces, and so many from the team, actually. It's wonderful to see you all. So we're going to talk about characteristics and key clinical features today of aortic stenosis.

And really, I think one of the most fascinating things is how prevalent this disease is, particularly in our country and in industrialized nations and countries where we are allowed to age gracefully and to an older age.

And you'll see here that 7% of the population over 65-- that's 1 out of 14 of us-- potentially has aortic stenosis. Now this can be various degrees of it, but ultimately aortic stenosis is a progressive disease. We'll see that in a minute. And ultimately all of these patients could have aortic stenosis that advances to the point where they need a treatment option.

So the most common aortic stenosis for us, of course, is the aortic stenosis of the elderly. That's age-related or calcific aortic stenosis there. You can see it on the screen at the end.

And probably less common is congenital abnormality-- bicuspid aortic stenosis. This is about 1 out of 100. This is one of the most common heart congenital abnormalities. And rheumatic fever, in our country actually, thankfully, is a declining disease. But we get rheumatic fever patients that come in from our population that comes in from other parts of the world. And in our poor populations, this is still an issue.

So how does this pathology manifest? Well, the aortic valve is gradually restricted by this disease. So instead of opening quite widely, you can see in this slide that the aortic valve is a tricuspid valve that looks like a Mercedes sign. When it's young and youthful, it opens almost completely in that opening.

And as it ages, it starts to decrease in its opening orifice size. This increases the pressure gradient across the bow. So the left ventricle has to start developing higher pressures. And the pressure has to, of course, exceed the resistance to injection so that you have flow across the valve.

The left ventricle response to this by becoming hypertrophied. So it thickens. It recruits and increases the size of its muscle fibers. And its contractility. And this increases the ventricular mass. And remember a thick, thick tire or rubber will have a higher wall tension. That's how it lowers wall tension. It [INAUDIBLE] here.

But as the ventricle starts to dilate and increase its mass, the wall tension increases. And this leads to increase in oxygen requirement and development of symptoms. There are multiple approaches to the assessment of aortic stenosis. Many of these are historical.

Before we had excellent echo machines. We have the cardiac cath laboratory. And we would measure directly with catheters across the valve, measuring the pressures on both the ventricular side and the aortic side of the valve.

And there were many different calculations that we could perform. As we developed the echo machine, it took over because of its portability. It's very good low cost for use. [INAUDIBLE], its excellent correlations with the cath lab, which were R-values greater than 9.5 for most of these.

And then these other studies, particularly CT and magnetic resonance, are higher-cost studies that give us down-the-road assessments, some of them even much better than echo for the aortic valve in different aspects.

This is a classification system of aortic stenosis. And I think the most important thing about this classification system is the stage A. So many of these patients who you have maybe a bicuspid aortic valve that's functional or sclerosis, which means some thickening of the valve, but [INAUDIBLE] valve is opening well.

We now recognize that these are patients that are at risk and that these are patients who should be following in the echo lab and clinically with the physical exam for progression of disease. So here we have, then, state B, which is progression of that. Again, you wouldn't notice unless you did serial echocardiograms.

Stage C, we're talking about symptomatic patients now-- I'm sorry-- asymptomatic patients who have echo criteria for valve replacement. And stage D is severely symptomatic patients with severe aortic stenosis.

So all these stages are very helpful. But remember to look for patients at the early stages. And then follow them. So let's talk a little bit about the evaluation.

We usually capture these patients because of symptoms, right? They present to the clinic because they've got shortness of breath, or have angina, fatigue. They might have some sort of passing out spells. They might have new atrial fibrillation or irregular rhythms.

And we see them in the clinic. And this is oftentimes how they present. The problem with these patients is aortic stenosis progresses slowly. So over time, we adapt as human beings. We think oh, I'm getting more short of breath just because I'm getting older. Or I just can't exercise like I used to because I'm older.

And we've adapted to the aortic stenosis. And actually if you push these people a little bit more on the treadmill, they become very, very systematic. The takeaway point is many of these patients that say they're asymptomatic really are not.

This is one of the key features of aortic stenosis that Braunwald brought to light by early data. This is in the 60s actually that they published this. But you can see that once you start getting angina, syncope, or heart failure particularly, these patients die very, very quickly.

In two years, 50% of them will be gone. So it's very important, particularly when they start getting symptoms or if they present, come to the clinic like that, that you get right on this.

The second thing after their physical presentation is the exam. And the exam-- probably this is one of the most provocative of our heart exams because you can hear it right away. You have a blowing systolic crescendo-decrescendo murmur.

[BLOWING NOISES]

And it's best heard over the aortic valve, which is the right upper sternal border. It sometimes radiates to the neck in the carotid because it's a pencil point little jet that can shoot up that way. When the peak is early, goes so--

[BLOWING NOISES]

When the peak is early, usually the aortic stenosis is not quite as bad. But when it's late--

[BLOWING NOISES]

That's a bad aortic stenosis. That means that the ventricle is pushing very hard to eject the blood for a long period of time. And as the S2 gets soft, that value instead of opening broadly, it's just moving just a little bit. It just stops clocking. So very important signs of this.

And then the last is remember the rest of the exam. So the pulses become delayed. So if you take the wrist pulse and the apical pulse, you'll get a very significant difference that you can appreciate on that.

By the time you feel the apex to the time you feel the radial pulse. And it gets soft because it can't generate a very high peak pressure. So that's called parvus and tardus.

The echo machine, again, it's our most valuable tool, really, for initially following and discovering aortic stenosis. It's inexpensive, it's portable, and it's very accurate.

Aortic sclerosis-- we talk about jets. When they are over 2.5, you might wonder what a normal is, which is about 1.6 or 1.7. You have mild-- and the most important on the slide is that we characterize severe aortic stenosis as jets over four meters per second, mean gradients over 40.

The mean gradient and the jet velocity correlate very closely, by the way. And that means aortic valve areas of one-- these are calculated, some of these. So as you get more calculations, you get less accurate. So using the jet oftentimes is the best way to look at it. So I'm going to turn it over now to Dr. Finch for CT.

[APPLAUSE]

IRA FINCH: Paul, how do you it down? Are you hitting it the forward button? This one. Everybody being evaluated for TAVR gets a CTA of the chest, abdomen, pelvis mostly for sizing.

The aortic valve is not a round or uniform structure. And the TAVR valves in certain sizes. And one of the important parts of planning is deciding, of course, which size to put in which patient. It can't be too small. It can't be too large.

And actually as this technology and this process has evolved, CT has been shown to be very valuable for sizing. And the CT measurements are compared to the echo measurements and sometimes TEE measurements in terms of trying to determine the best size for each patient.

We actually do our CTAs here on our new [INAUDIBLE] scanner. A lot of these patients are old, men who need to be hydrated in conjunction with the study. So as this slide shows, the CTA gives very important measurements about the size of the valve and the distance of the coronary arteries from the valve.

We also do a Calcium Score on the valve, which is sometimes helpful in determining whether somebody really has critical aortic stenosis or not. And then we also do a CTA of the basically the runoff, the aortoiliofemoral vessels because we try to do these procedures [INAUDIBLE]. And you have to make sure that the arteries are going to be big enough to accommodate the sheaths.

One of the real problems with this procedure is complications that can arise from delivery of the device. So you want to make sure that the arteries can accommodate the delivery system. Otherwise you do have the option of going either through the aorta or the LV. But as I said, we try to use [INAUDIBLE] access. Over time, the delivery sheets have gotten smaller. So this has become less of a problem.

So this is a slide that just shows how some of these determinations are made. And I basically made a few of my own. This is the system we use that downloads the information from the CTA and then allows you to manipulate it and analyze it, basically finding the center of the aorta and then allowing you to determine where the valve plane is and make appropriate measurements.

And once you have these measurements, you can export the pictures and evaluate them in conjunction with the other studies. The one on the lower left is showing the determination of the valve plane. And you can see part of the coronary artery. And you can measure the distance.

And then basically we go through a similar process of finding the center of the vessel for the lower extremities. And this is the left side and the right side stretched out. And then you can go through and make your measurements and assess the [INAUDIBLE]. So those are the roles of a CT in this process.

[APPLAUSE]

GARY GERSHONY: We are fortunate to have interventional radiologist at the level of caliber of Dr. Finch. He's part of our team. Some of you don't see him because he doesn't come in during the cases. But he's always involved with all of our cases and gives us extraordinary guidance so that we can be safer and more effective procedure.

Our next speaker, I'm pleased to present, is my partner Dr. Khan, who is a cardiothoracic surgeon. And he will be presenting medical management versus surgical management of severe aortic stenosis.

TANVEER KHAN: Thank you, Gary. Aortic stenosis is a mechanical problem. So clearly the medical treatment has not been shown to be effective. This is a classic study that was down just a few years ago in 2008 that showed the survival of patients with aortic stenosis there are symptomatic, asymptomatic compared to those that have been treated.

So if you look at the top line here, this is a population of patients who show their survival over 15 years. These are patients with the general population, without aortic stenosis. This graph here shows patients of symptomatic aortic stenosis and have been medically treated.

You can see that their survival, five-year survival is roughly 10%. So we saw that with the classic study. Then in 1960s, that once these patients developed symptoms, their survival is really very short.

This line here shows patients who've been treated with surgical aortic valve replacement. And you can see that their survival curve basically has returned from this very poor survival curve back to the age-matched patients. So if we can fix their valves, replace their valves, surgically or with TAVR, we can restore these patients to their otherwise natural survival curve.

This curve is very interesting actually. These are patients who were less [INAUDIBLE] aortic stenosis who are not treated with surgery or TAVR or medically treated, but they're asymptomatic. And you can see you with symptoms, the survival is clearly not as good.

However they don't have the same survival as patients who don't have aortic stenosis at all. So basically it's where the aortic stenosis without symptoms still did not survive as long as everybody else.

So the question is should we be treating these patients without symptoms because the survival curve is not as good? It's an interesting point. We found that there's a subset of patients that probably benefit from [INAUDIBLE] who don't have symptoms. And a lot of these patients, as we saw from Dr. McWhirter's discussion, actually do have symptoms if you really look carefully at their history and some additional testing.

One important part of treating this population is that a lot of these patients historically were not treated. There are a number of studies. There were five studies that were done. What I have shown here shows that greater than 30% of patients who have severe symptomatic aortic stenosis did not get aortic valve replacement.

The reason is most of these patients were considered by their primary care physicians. And [INAUDIBLE] is being too high risk for surgery. Now we have another option with TAVR. And we can treat these patients who will certainly benefit from them.

So this slide is somewhat complicated. We'll go over the general theme on how these patients are diagnosed. One of the most important aspects is this echo as was discussed earlier. The echo is really the main diagnostic modality right now for diagnosing patients with aortic stenosis.

And one of the main criteria we look at is the velocity. Is that when the velocity is more than four meters per second, and that is consistent with severe aortic stenosis. There are other criteria such as the pressure in the area.

However, these are calculated, and the velocity is a direct measurement. So that's why when you look at all the guidelines, the velocity is really the main criteria. If the velocity criteria is not met, we can look at other criteria. But the best evidence is for patients who do meet this criteria.

So patients who have greater than four meters per second have symptoms. These are patients who certainly have severe aortic stenosis. If they do not have symptoms but have a high velocity [INAUDIBLE] tests such as a treadmill test, exercise treadmill test, that can be used to reproduce symptoms or changes in blood pressure.

If they do not have a high velocity or area but have a low ejection fraction and are worrisome for aortic stenosis, these patients may not be generating the velocity because their ejection fraction is low. So they may have aortic stenosis, but if the blood isn't going fast enough through the valve because their heart function is poor.

Doing [INAUDIBLE] stress echo given dobutamine to stimulate the heart so the contractility increases. And we can generate increased [INAUDIBLE] in the setting. That's evidence of aortic stenosis as well.

If they have a normal ejection fraction, EF less than 50 nos, if they have a normal ejection fraction and they still don't generate a high velocity across the valve, but when you look at the valve on echo it looks abnormal. It's diseased. It's calcified. It's narrow.

But they're not meeting criteria. And their function is normal. So it's not that the heart can't squeeze all of that. Well, it may mean that there's just not enough volume in the heart to be going across the valve to generate this high velocity.

So you may not reach this high velocity going across the valve, which is the a criterion, either because the heart is not strong enough to squeeze the blood through to get the velocity high or there's not enough blood in the ventricles. So there's not enough flow through the valve to get to that velocity.

So a couple of reasons why we don't see enough blood in the ventricle when the ventricle is small. And in these cases, then use index. So in the small heart maybe from a small patient, so you index the area to their size.

So aortic valve index, if it's less than 0.6 centimeters squared per meter squared of the body surface area. So a smaller patient, smaller heart. So use the index to adjust for that. Or you can look at the actual volume, stroke volume index. If it's less than 35 mLs per meter squared.

So you look at the stroke volume and then their blood ejected from the heart. So here we can look at reasons why if you may not meet the main criteria, either because, again, ejection fraction's low or there's enough volume in the heart.

Another problem that Dr. McWhirter and I were discussing earlier is there could be enough volume in the heart, but if there's to be MR, it's going back up into the atrium and not going through the aortic valve. So another reason why you're not getting enough flow through.

So when we don't meet these main criteria, then we look for other reasons why these patients may not meet them. And this is very helpful in the diagnosis. Certainly if their valve area is it normal or not severe, and their velocity is low, they have moderate AS, these are patients that really should be followed.

So the recommendations-- the closer to floor the gradient and the [INAUDIBLE] and you see them basically. So if they're just under 40, you see them maybe every 6 to 12 months. If it's closer to 2, than maybe three to five years.

So basically the closer they are to severe AS, the more often that you see them. So this is another slide that looks at it a little bit different. But basically the general theme is the same. This is basically looking at diagrams showing how you approach patients with either symptomatic or asymptomatic patients with severe aortic stenosis.

Again, symptoms velocity over four, they should be treated with a valve replacement, either surgical or transcatheter. If it's less than four, then you are looking for either, again, low EF or less volume in the heart to meet the criteria for valve replacement.

If they have no symptoms-- this is important. So who are patients who really should have replacement with no symptoms? If they have critical AF. So it's not over 4. It's over 5 meters per second. So a very tight valve. These are patients who really should be considered for aortic valve replacement without any other additional findings.

Again, if it's over 4, if they don't have symptoms, then they meet the criteria in terms of the echocardiographic findings. They don't have symptoms. So we need to look for some sort of-- it's like an angina equivalent. So it's a symptom equivalent in aortic stenosis.

So what's another symptom, so to speak, [INAUDIBLE]. Well, if their injection fraction is low, this may be a sign that this aortic stenosis is severe, even though they may not have clinical manifestations that are so typical. These are patients that may be offered valve replacement.

If they don't have a low EF and you're looking for other surrogate symptoms, who are aortic stenosis because they have a velocity of 5, but they don't have angina, syncope, or heart failure, then you're looking at exercise treadmill test.

Rapid progression is one that really has the least evidence. But in some cases where there's no other reason for this. And with each serial echo, the velocity is getting worse and worse. The patients that doesn't have symptoms, but that may be considered-- but this is really where there's no other reason for this.

And the patient looks like they're on track to having severe AS and they would be an excellent candidate. But again here, down in this corner, you really need to be sure that that is the only problem the patient has.

So this diagram is really looking at how we approach patients with moderately aortic stenosis because severely we talked about a lot in how to approach these patients with a velocity over 4. And if they don't meet that criteria, how we sort out which patients actually do meet criteria without that greater than 4 meters per second and have other manifestations of severe AS and symptoms?

But moderate AS-- so it's less than 4. And the gradient is less than 40. How do we approach these patients? Well, they have symptoms. And they have moderate AS. They don't meet the velocity. They don't meet the pressure gradient.

If their EF is low, then again, [INAUDIBLE] stress test. They may meet the criteria, the velocity makes it over 4. And the area less than 1 with a [INAUDIBLE] stress test.

These are symptomatic patients, but they have moderate AS. They don't meet the criteria of the velocity. But you can use a stress test. Again, if they have a normal EF, so it's either weak heart or not enough blood in the heart is not generating the velocity, then you look for other reasons.

A valve area that's less than 1 is calculated. So it's not as strong data, but that's another reason that a patient may be offered aortic valve replacement if aortic stenosis is likely to cause the symptoms. So again, velocity is the best measure, then the gradient, then the area. So if they don't meet the velocity, they don't meet the pressure gradient, but they meet the area only, then they may be considered a good candidate for valve replacement.

So moderate aortic stenosis. If they don't meet the velocity, they don't meet the pressure, the only patients, really, that should get aortic valve replacement with mild aortic stenosis-- so that means any of these echocardiographic stress tests [INAUDIBLE], stress test criteria-- those patients who are having other cardiac surgery.

So moderate aortic stenosis, without any other positive findings, the only [INAUDIBLE] get AVR are those who are having surgery. For example, [INAUDIBLE] valve because you wouldn't want to come back and do another procedure on them because you're already there.

So this is a summary of the recommendations from the American Heart Association and the ACC. And reviewing this, I think [INAUDIBLE] important. So the class of evidence and the level of evidence.

So class I evidence-- this is recommended. So these procedures are recommended by the guidelines. Level of evidence in this range is A, B, and C. A is multiple population base studies, so multiple randomized trials. Level B is less population-based studies, so a single randomized trial or maybe several nonrandomized studies. So these are all class I.

So the recommended and level of evidence is B. So there have at least one randomized clinical trial. So AVR is recommended. So this is the most evidence for this-- high gradient with symptoms.

Also recommended as we talked about, asymptomatic with an EF less than 50%. So if they don't have symptoms, that their EF this low, that's so somewhat of a surrogate for symptoms. And we also talked about AVR's indicated for patients with severe or even moderate AS if they're having cardiac surgery.

So class IIa. What is class IIa? So class I is recommended by the AHA and ACC. Class IIa is considered reasonable. So recommended means that the benefits greatly outweigh the risk. Reasonable is the benefits do outweigh the risks.

So IIa, level of evidence B. So again, this is at least one randomized clinical trial. So it's reasonable for asymptomatic patients with severe AS and low surgical risk if their velocity is over 5, as we discussed. So asymptomatic patients but very valve.

It's also reasonable asymptomatic patients who have decreased exercise tolerance. So again, patients asymptomatic providing other evidence. So they have an exercise test that's positive.

And the low-flow/low-gradient-- again, these are the patients that we talked about. They don't meet the criteria. They have symptoms, but they don't have a high velocity. But they may have either a weak ventricle, low EF or less volume of the ventricle from a small ventricle or possibly from MR.

Now these patients are patients that level C evidence. So level C is there are no randomized clinical trials. There may be a few nonrandomized trials. But these are basically consensus expert panels that determine this level of evidence.

So these are patients where you really want to be sure that aortic stenosis is their problem. So AVR is reasonable. And symptomatic patients, low-flow/low-gradient-- if their EF is greater than 50%, they have anatomic data.

So low-flow/low-gradient-- if they don't meet the criteria by the velocity and the EF is low, that is much more likely to be a good outcome. And they'll benefit from this versus patients who have low-flow/low-gradient.

They don't have a velocity, but they have a normal ejection fraction. These are patients where you look for a small ventricle, less volume in the heart. And this is class IIa level of evidence C.

So any of these patients, again, you want to be sure because here we're looking at data where if they have symptoms, but they don't meet the criteria. And we're finding anatomic data saying that they have they have a small ventricle, and they're not generating the velocity across the valve.

Again, AVR is the reason for patients with moderate AS depending on cardiac surgery. So moderate or severe [INAUDIBLE] having surgery AVR. And again, the least evidence and the lowest class are IIb. So this may be considered. So may be considered IIb-- the actual wording is the benefits are greater than or equal to the risk.

So these patients really-- you need to be absolutely sure if this is their only problem. AVR may be considered in asymptomatic patients [INAUDIBLE] rapid disease progression. So these are patients haven't really met any of the criteria but you're worried about them because their velocity is going higher and higher, they haven't quite met the criteria yet.

So I think that going over these can be somewhat a little bit boring going over this type of data. But I think if you look at the big picture, the way I look at it, if they have symptoms, they meet the criteria with severe aortic stenosis by echo, then they need valve replacement.

If they don't meet the criteria, then you need to look for either if the EF is low or there's not enough volume in the heart to generate the velocity. If they don't have symptoms but they have echocardiographic findings, then you need to find some equivalence of symptoms, usually a low EF. I think that's the general thing. Thanks a lot.

[APPLAUSE]

GARY GERSHONY: Our next speaker is my esteemed colleague, Dr. Ramesh Verragandham, who is one of our cardiothoracic surgeons on our TAVR team.

RAMESH VEERAGANDHAM: Thanks, Gary. And I want to echo that Gershony's comments that the reason we are so successful in the [INAUDIBLE] of our program is just not the implanters but all the excellent staff we have from the cath lab to the operating room. [INAUDIBLE] and all the support staff we have. And it's great to see all of you here. Next.

So I think there's a few more slides on who are the top candidates for the surgical AVR versus the transcatheter valve implantation. But I'll go over the brief.

This is really, really interesting. It's only in 1988 when a interventional fellow from Denmark, Dr. Henning Rud Andersen, he was working in Phoenix as [INAUDIBLE] for coming into the market.

And he had a presentation at the coronary stent. But coronary stenosis, he got this very wide idea of what he labelled as the craziest idea of why can't we do this for aortic stenosis? It's the same pathology where the aortic valve is narrowed. Why don't we implant a [INAUDIBLE] is that the most stupidest idea that anyone has seen.

And no one even listened to him. So he went to the market, brought two stainless steel wires, and went to the butcher store, got the pig heart, and start mounting the pig's valve on the stainless steel [INAUDIBLE] frame.

And got some [INAUDIBLE] colleagues to help him. And the first valve had 15 pulling sutures to mount on the stent. And after 25 days, after conceptualizing his idea, he was able to implant in a pig using an abdominal approach because the size was 41 French.

41 French is probably about 15 millimeters in size, the outer diameter. The current iteration is 14 French, which is probably about 3.4 to 5 millimeters in size. And he implanted in six pigs, but no one was willing to publish that paper at the time because everyone thought this is obscene.

And then he published a paper in 1990, a [INAUDIBLE] the European Heart Journal heard the-- in 1992 but published in the European Heart Journal. And still everyone thought it was [INAUDIBLE]. It was not possible.

And the [INAUDIBLE] thing which happened at the same time is that [INAUDIBLE] could be attained with a balloon valvuloplasty balloon. So he was able to mount his valve on a [INAUDIBLE] balloon. And consequently his patient was brought by [INAUDIBLE] company. And subsequently I got [INAUDIBLE] company to have the next [INAUDIBLE] valve.

And [INAUDIBLE] I couldn't show them [INAUDIBLE]. The whole [INAUDIBLE] flight came. In 2004, when Jorgen Andersen, the dad of Henning Andersen, leaded AVR. At '92, they put the TAVR valve in him. And he said that was the most fulfilling experience of his career.

This is Alain Cribier who popularized balloon valvuloplasty for nonsurgical [INAUDIBLE] patient. And then he took Andersen's idea, mounted the valve on his thing, and then popularized-- further improved it.

And in 2002, he implanted the first [INAUDIBLE]. Just briefly, there are two FDA-approved devices. This is an older picture. Shows a balloon expandable valve made-- so originally I've talked about the stainless steel, but the current generation is cobalt-chromium mounted with-- and the leaflets are made from the same surgical valve you use, which is bovine, from the cow's pericardium.

And now this is the balloon expandable lung. For the second valve, which is in the market is CoreValve, marketed by Medtronic. It is self-expanding. And it is made from 14 of the pig's pericardium. And this is actually a pig valve mounted on [INAUDIBLE] stent.

And this valve has some advantages and disadvantages. Obviously the second valve is [INAUDIBLE] expandable, has more radial force. So a slightly higher chance of injury because you're implanting a rigid prosthesis in a very, very rigid [INAUDIBLE] valve.

On the other hand, the Medtronic value is self-expanding, so it expands with time. Each one has its own advantages and disadvantages. And the picture is not true because it shows that the annulus is completely clean.

But in a surgical valve, the main difference is in a [INAUDIBLE] AVR, we take the patient's valve out, everything out. The annulus is completely clean, and we sew a brand new valve in place. Whereas in the [INAUDIBLE], the patient's own valve is left in place and acts as an anchor in which the new transcatheter valve is implanted.

So it just shows how a Sapien valve is implanted. This is actually [INAUDIBLE] in the previous version. The current version is called S3, which has an outer skirt and [INAUDIBLE] better feeling of skirt around it. Whereas CoreValve is made in a different way with-- I have [INAUDIBLE] that you can-- it has a different anchoring mechanism in it. OK.

[APPLAUSE]

GARY GERSHONY: I'm excited now to introduce our next speaker, Dr. Neal White, who is one of the interventional cardiologists on our TAVR team. And he's going to take us through critical clinical trials supporting TAVR for many of our patients.

NEAL WHITE: Thank you. So as usual, Gary's putting pressure on me because he just told me I have five minutes. Is there a pointer here? No.

GARY GERSHONY: You can use the mouse.

NEAL WHITE: Oh, OK. Yeah, of course. So we're going to talk about some of the landmark clinical trials. As Ramesh just said, there's two valves on the market. One if marketed by Edwards, and the other one marketed by Medtronic.

So we'll just look at two of the pivotal trials that were done with each [INAUDIBLE]. The first trial we'll look at really led to the approval of the valve by the FDA. It was the PARTNER study, and it used the Sapien valve, not the Sapien XT, which Ramesh showed a picture of, and not the S3, which we now use, but the original version, which was stainless steel.

There's a balloon-expandable valve and made out of bovine pericardium. At the time this study was done, it only came in 23 and 26 millimeter sizes. You can see the size of the sheet-- 22 and 24. That's the inner diameter. The outer diameter's another three French.

So you can see why [INAUDIBLE] pictures showing us the anatomy of the iliopelvic vessels, why it's so important that we get very good pictures because when we were using a 26 millimeter valve in the beginning, we had to have 9 millimeter vessels to [INAUDIBLE].

There are two cohorts of this study. One is called the high risk cohort, and the other is the inoperable, The inoperable is the PARTNER D. That was the original study that led to approval of the valve, the original pivotal trial.

Those people, you can see on the right side here are cohort D, were the inoperable people. They were the people that no one would touch. And this actually was a superiority trial as opposed to this part of the trial which was a non-inferiority trial, which is the way many studies are done once there's already a device that's already approved.

So what you see here in this cohort B study about a little over 1,000 patients total. And if they had transfemoral access, and they were randomized to either transfemoral, TAVR, or standard medical therapy.

Standard medical therapy, as Tanveer already told you doesn't work very well, most of the people that got medical therapy had a ballooned valvuloplasty as part of their medical therapy. And then cohort B-- or cohort A. I'm sorry-- were the highest people that surgeons said, we can't operate on these people.

But they're going to have potentially a higher risk of a bad outcome. And these are the people that were randomized to either a transfemoral or a transapical approach. And then they had that approach versus surgery. So we'll show you some of the results in a second. This first PARTNER B, the inoperable people. Again, this curve paralleled the natural history that Tanveer showed you earlier.

This is the outcomes with transcatheter aortic valve replacement in those high risk, inoperable patients. It's pretty obvious that the people that were treated with the TAVR did much better compared to the outcomes here. The mortality was 80% versus 54%.

When we look at these statistics, it's almost easier [INAUDIBLE] something [INAUDIBLE] to treat. And that's this absolute reduction of 20-- where is it-- 26%. 100 divided by that's, like you see here, a number needed to treat of about four. So this was a very impressive result. And that's why the FDA approved transcatheter aortic valve replacement.

Routine hospitalizations, which are primarily for heart failure, were also reduced greatly. [INAUDIBLE] what they were in that [INAUDIBLE] that were receive standard therapy, which was medical therapy. And you can see in the blue what they were at the end of the study with people that received the transcatheter valve.

So marked reduction in repeat hospitalization. A lot of data on this slide, but the two things to point out were these were the baseline characteristics of this original cohort. And the people were old. And the people were high risk [INAUDIBLE]. You can see their STS score of 11. And so these were very sick people.

This was the partner A group of patients who were operable but albeit with a high risk. This was the noninferiority design trial. That's why the curves are parallel.

So what you're basically saying is that TAVR with a transfemoral and transapical approach was not inferior to surgical aortic valve replacement. And so that was also very impressive results also.

And the all-cause mortality in the cohort A, after five years, you can see still was very acceptable and not inferior to the surgical approach. So for that reason, we know that TAVR works well people who were inoperable. And TAVR as well for people that are high risk for surgery.

[COUGHS]

Sorry. Another couple of just--

[COUGHS]

Excuse me-- follow-ups on that. So at five years, there was similar differences in all-cause mortality, similar differences in stroke, improvement in New York Heart Association class II, a similar degree with TAVR versus SAVR, rehospitalization, and valve hemodynamics. [INAUDIBLE], I'll show you some of that in a second.

There appears to be no structural deterioration in the valve. These valves appear very durable. And so with that in mind, it appears that transcatheter approach is very well recognized.

Now paravalvular leak is something you hear us all talk about quite a bit. And part of the reason for that is that as Ramesh described, we're not sewing the valve in. We're placing it in an annulus, which is not exactly round. So you're putting a round valve in a nonround hole.

So sometimes you don't get complete sealing around the edges, and you get some degree curve out of the leak. And there's different ways to deal with that. I won't go into that. But if the paravalvular leak is worse than mild, so moderate or severe, that seems to be associated with decreased survival.

So we're always happy when the paravalvular leak is mild or [INAUDIBLE]. And for the most part, these days, it's generally trivial or none. This was the PARTNER II trial, which was done with the newer XT version of the valve, the one that's cobalt-chromium.

The characteristics of the valve are slightly different. But it does not have a sealing cuff like the S3 does. And you can see again, there were two cohorts [INAUDIBLE] in inoperable cohort and inoperable cohorts.

This inoperable cohort randomized people to a transfemoral approach with an XT valve or a transfemoral approach with a [INAUDIBLE]. Again, a noninferiority approach. There are also a number of nested registries that looked at people with small access vessels, people with a transapical approach, people with a valve-in-valve-- in other words, a deteriorated surgical valve that now needs to be approached.

A transaortic approach-- the larger 29 millimeter by transfemoral or transapical approach. I'm not going to go through all of these. And then the most important version, however, was the operable approach to the PARTNER II study. People that were candidates for transfemoral access were randomized to surgical AVR valve or transfemoral approach with a Sapien XT in a one-to-one fashion.

And people that did not have transfemoral access were randomized to transapical or transaortic, where we do a direct a small incision up here [INAUDIBLE] direct aortic puncturing. You just drop down right on top of the valve. And they were randomized to either this transpical or transaortic approach versus a surgical approach.

And in the PARTNER II trial, the one-year survival was very good, slightly better outcomes among the high risk versus the inoperable patients. The overall risk of a disabling stroke was low. This is 2.4%. This is serious strokes, just not all strokes. But serious strokes.

And there was no difference between access type between transfemoral or transapical in terms of strokes. And there was marked improvement in New York Heart Association symptoms. Just to give you an idea about the durability of the valve-- the horse pericardium valve was the one that [INAUDIBLE] started with.

The bovine pericardium is the current version that we use on the Edward Sapien valve. This is data presented by John Webb a few years ago. And he just showed that after five years, there was good durability. Of all these implants, there were only five failed implants out of 1,000.

So I think the summary from the PARTNER studies is that TAVR was superior to medical therapy. And the inoperable patients first-generation TAVR devices had similar outcomes to SAVR. And there are still concerns about the risk of stroke, vascular access, and paravalvular leaks.

But I will tell you that as the newer valves have come along, the valve delivery systems are smaller. We're down to under 6 millimeter access vessels now from where we started at nine. And so with the likelihood of vascular complications is much less. With the sealing skirt on the S3, we get much less paravalvular leaks. And the goal for the next generation of devices is to address these.

Just a couple comments on the CoreValve just to give equal opportunity. The CoreValve was the Medtronic valve. One thing to notice is that the Edwards valve had about a three-year lead time on this study. This study was presented and done about three years later.

It was a superior-- it was a study that randomized people to SAVR versus TAVR. And these are the demographics of the trial. And again, similar age, 83. A little bit lower surgical STS risk, and maybe that had to do something with the fact that the study was done a few years later. But the point of this slide is to show you that they were still very sick patients.

This was their outcome studies. So you can see 19% risk of mortality in the surgical patients. 14% risk in the TAVR-treated patients. And actually they met the superiority objective in this trial with a statistically significant superiority objective.

5% absolute risk reduction. Number needed to treat is about 20 in that regard. Stroke rates with the CoreValve. 12.6 in surgical patients. 8.8 trended-- not statistically better-- but trended to be at least as good as the surgical patients and perhaps even trended to be a little better.

That last slide looked at all strokes. And this slide looks at major strokes. So it's similar to what we saw in the PARTNER [INAUDIBLE]. All-cause mortality or stroke, again, a durable result two years. Again, red was the TAVR, and blue is the surgical approach.

A summary of presentation with regard to transaortic valve replacement, TAVR appears to be superior to SAVR with lower mortality and equal stroke risk in high risk patients. It can be more easily performed because it's done through a transfemoral approach. Patients often go home in a couple of days. And we're tending to send them home even earlier.

We get increasing results without requiring any general anesthetic. We're doing this with conscious sedation, not conscious decision like we cardiologists do in cardiac cath with PCI. We're still involve an anesthesioloigist. The

But they don't need to [INAUDIBLE] patient. And frequent talking to the patient while things are going on. [INAUDIBLE] or something else for that. But that's the next arena that we're evolving to.

And now I think Gary's going to make a few comments about the intermediate risk patients, which are the next generation of lower risk patients that we're approaching. And there's a growing importance on the emphasis of the Heart Valve Team you've seen. [INAUDIBLE] today as part of the team collaborating in this discussion.

I think that's it for me. Oh, stroke, OK. Significant-- see, what's the point here? We've already dealt with that. Oh, the need for pacemaker implantation. There's some data to suggests that it might be a little different between one valve and another. But what it really boils down to is the depth of the implant.

And pacemakers are sometimes even necessary in surgical valve patients. So that's something that we still need to think about. But it had a lower frequency of occurrences.

And then we also [INAUDIBLE] talk about the need for any antiplatelet therapy. Typically we use low-dose aspirin and Plavix for some interval of time. And I say that because sometimes that's dictated by one month, three months, six months. Sometimes the people are on antitrauma drug like Coumadin and [INAUDIBLE]. No

We might only use one antiplatelet drug-- aspirin or Plavix is dealer's choice. But you see if you use a lot of different strategies partly because there's no consensus agreement on that. Oh, this is the nice-- this I forgot. [INAUDIBLE].

Again, we see these things-- TAVR in blue, surgery in red. Overall outcomes in terms of death or major [INAUDIBLE] cardiovascular then or all strokes. But here's something very interesting. Blue is TAVR. Red is SAVR. Aortic valve area, and the aortic valve gradient.

And if you look at these people over time, the aortic valve areas are bigger with TAVR than they are with SAVR. And the gradients are lower with TAVR than they are with SAVR. Part of the reason is that we can go into all these details, but surgeons often use smaller valves. They use smaller valves just because of the way they do the implant. It's usually done a little bit higher.

And interestingly, we've come to realize that as we start to size patients per [INAUDIBLE] valve versus open valves. So it may have something to do with that. So in terms of durability, you might get a bigger valve for a longer period of time with a lower gradient with the TAVR valves. It's something to think about. That's it, Gary. I know I went over five minutes.

[APPLAUSE]

GARY GERSHONY: Thank you, Dr. White for going through complicated studies efficiently. I'm going to shorten mine so that we have a little bit of time for our panel. So I'll just run through a few slides. I'm really going to address the evolving indications for aortic valve replacement via transcatheter approaches in lower risk patients.

So the first studies that actually looked at this was a very interesting study that was performed in Nordic countries. It's called the Notion Study. It was presented at the [INAUDIBLE] meeting about a year or so ago. And it was performed at three sites in Nordic countries. It was a randomized trial of the surgery versus TAVR, surgical aortic replacement versus TAVR.

Just as an aside, in Europe they call TAVR TAVI. And what you can see here, this was an all [INAUDIBLE] trial actually. So moderate risk and low risk. And what they demonstrated in that trial was a numeric benefit to performing transcatheter approach.

This is, again, the Kaplan-Meier curve showing mortality over time. This is mortality rate versus time. And you can see there was a numeric advantage of doing transcatheter aortic valve replacement versus surgery, although it did not reach statistical significance.

More importantly, where the studies that were recently presented at the American College of Cardiology meeting just a couple of months ago in Chicago. And these were really pivotal trials, the PARTNER 2A trial, a randomized trial of a transcatheter aortic valve replacement device, primarily the Sapient XT device versus surgery in intermediate risk patients. Those are lower risk patients than we're currently doing.

Typically patients for that so-called STS score 4 to 8. And concomitantly, as part of that trial, was a substudy called the S3i, which was the intermediate risk patients that were treated specifically with the latest generation device. The one that we're currently using-- the S3 device or Sapien 3 device.

I'm not going to go through this in detail. But just to highlight again, these were two arms to the study, the PARTNER 2 study. PARTNER 2A, as I mentioned, was using what was available at the time, the Sapien XT valve.

And it was in randomized trial in intermediate risk patients of TAVR versus surgery. And it was randomized. They was 2x2 design because they randomized transfemoral, and they also randomized patients who were not candidates for a transfemoral approach and had to have transapical or transaortic.

The S3i, or Sapien 3 intermediate risk cohort in the PARTNER 2 trial, was a single-arm trial essentially. And it was meant to compare the results in patients treated with the Sapien 3, the latest version, with a so-called sealing cup against the historic outcome in the same trial against the surgical patients.

So it wasn't randomized, but it was a propensity match, a registry trial comparing the S3 against the surgical arm in the concomitantly performed PARTNER 2a study. Just to quickly go through it, you've heard already about the first two-generation devices, which we've had the most experience with-- the first-generation Sapien and Sapien XT.

And now that valve that we're using virtually exclusively for Edwards. And we also use the CoreValve from Medtronic. But with regard to this family of valves, this is the one we're using. It has a unique design with a ceiling cut, which has gone a long way towards reducing paravalvular regurgitation.

And you can also see a dramatic reduction in diameters of the delivery systems, which allows us to treat more and more patients through the preferred transfemoral approach, which is our default in which we prefer in most patients because of the lower risk.

Very briefly going through this. At 30 days, you can see that there was a significant reduction in the transfemoral patients treated with the Sapien valve. All-cause mortality of 1.1% versus 4% for surgery.

And that at one year, you continue to see this significant reduction in all-cause mortality. Importantly because of signals in the earlier trials that there may be an incremental risk of stroke it was gratifying to see in this trial that there did not appear to be a significant increase in strokes with TAVR patients as compared to the surgical patients.

So it does not appear that in the PARTNER 2 trial for intermediate risk patients that there is any added risk of stroke in transcatheter approach versus surgical approach. This is, again, the Kaplan-Meier curve showing the composite primary endpoint of all-cause mortality and all stroke.

And now out to 12 months, this is with the Sapien 3, the valve that we are currently using, comparing that against patients who underwent surgery in the concomitant PARTNER 2a trial. These were propensity matched patients.

And what you see here is that the composite endpoint of the complications that we most worry about-- death, of course, and stroke-- was both numerically and significantly reduced in the patients treated with the current version Sapien 3 valve as compared to surgery in the propensity matched group from the PARTNER 2A trial.

And this is out to 12 months. This is what was presented at the ACC meeting. And it's been published in The Lancet. Again, looking at individual critical endpoints like all-cause mortality, again, the Sapien 3 valve lowered mortality than surgery for intermediate risk patients. Similarly, when you look at stroke alone, a numerical reduction, although that did not meet statistical significance.

What about paravalvular regurgitation? This was a secondary endpoint in the trial. And what you see here is that there was an extremely small group of patients in the TAVR group, with Sapien 3 again, both at 30 days in one year. It was only roughly 1.5% of patients who had moderate or worse regurgitation, the type of regurgitation we worry about because it can affect symptoms and can affect mortality.

And the rest of the patients had either no regurgitation or only mild regurgitation. However having said that, surgery was superior in achieving no regurgitation. You can see that indicated here in blue, whereas TAVR blue, as indicated here. Green is only mild. So the combination of mild and none was very gratifying for TAVR using this latest generation valve, but surgery still had an advantage in terms of avoiding any regurgitation.

So what are the conclusions from these trials from the combination of PARTNER 2A and the S3? In intermediate-risk patients, the Sapien 3 valves specifically resulted in low one-year rates of all-cause mortality-- only 7.5%. All strokes and moderate or severe aortic regurgitation only 1.5%.

And what it further demonstrated was noninferior for the primary endpoint versus surgery. But the Sapien 3 valve was superior with TAVR where the primary endpoint of all-cause mortality, and all stroke, and that surgery, as I already mentioned, is superior in terms of eliminating or obliterating or eliminating any paravulvular regurgitation.

The time-to-event analyses also indicated that the benefits of the Sapien 3 valve occurred in the first few months, suggesting that most of the benefits that accrue to doing TAVR versus surgery are procedure-related effects, which is not surprising.

So the conclusion, then, the PARTNER 2A randomized trial and the propensity score analysis of Sapien 3 provides strong evidence that an intermediate-risk patient with severe aortic stenosis, Sapient 3 TAVR compared with surgery improves clinical outcomes. And this may be the preferred therapy.

I would hesitate to say is the preferred therapy until our regulatory agencies move forward with this indication. But we are anticipating that with the next few months, the FDA will, in fact, expand the labeling or the indication for TAVR to include intermediate risk patients.

And this study was published in *The Lancet* concomitant with the ACC meeting. I'm going to skip through these slides. And I think we've gone through much of this already. So in summary, transcatheter aortic valve replacement improves survival rates in quality of life in patients with severe aortic stenosis who've been deemed inoperable. That's indisputable.

TAVR is superior to surgically aortic valve replacement with lower mortality in equivalent stroke risk, in high risk, and possibly intermediate risk patients, although the data from PARTNER 2A and S3i strongly support that as well.

The evaluation of all patients with severe aortic stenosis should be performed-- must be performed by I would say, not should be performed but must be performed by a multidisciplinary heart team to get the most optimal results for our patients. And ongoing developments in clinical trials of newer devices have the potential to further improve patient outcomes. Thank you very much.

[APPLAUSE]