

ADVANCES IN TRANSCATHETER A O R T I C VALVE REPLACEMENT





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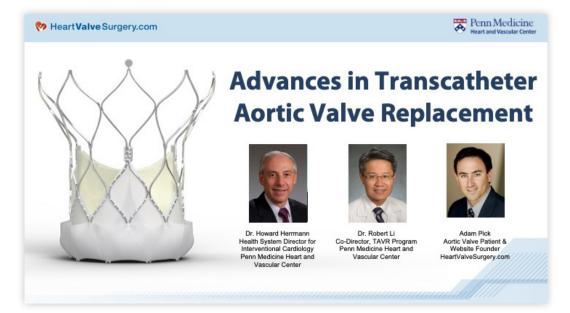
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<u>Please note: A complimentary video playback of this</u> <u>eBook is now available on YouTube at this link.</u>



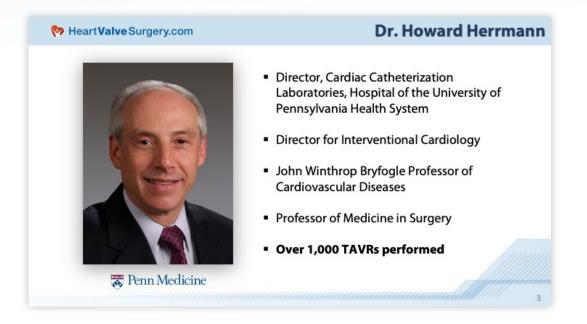
Introduction



Adam Pick: Hi everybody, my name is Adam Pick and I'd like to welcome you to the webinar titled, "Advances in Transcatheter Aortic Valve Replacement". If I have yet to meet you, I'm the patient, the aortic valve patient, that started <u>HeartValveSurgery.com</u> in 2006. The mission of our website is real simple. We want to educate and empower patients just like you. This webinar, which has had over 800 registrations from patients in countries all over the world, was designed to support that mission.



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Now, when it comes to the featured speakers of today, I'd submit to you that we just don't have experts on the webinar with us. We have an absolute dynamic duo. The first member of that dynamic duo is Dr. Howard Herrmann, who's the director of Cardiac Catheterization Laboratories at Hospital of the University of Pennsylvania Health System in Philadelphia, Pennsylvania. He's the director for interventional cardiology, John Winthrop Bryfogle professor of cardiovascular diseases, professor of medicine and surgery, and Dr. Herrmann has performed over one thousand TAVR procedures. Dr. Herrmann, thanks so much for being with us today. Here are Dr. Herrmann's disclosures.





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Dr. Herrmann: Thank you so much, Adam. It's a pleasure to be here. I don't know if I'm the Batman or Robin of this dynamic duo, but I do appreciate the introduction and I'm looking forward to sharing some of the data that we know about with all of the patients and participants on this webinar.



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Adam Pick: Getting back to that dynamic duo, here he comes, Dr. Robert Li, who is the co-director of the Transcatheter Aortic Valve Replacement Program at the Penn Presbyterian Medical Center in Philadelphia, Pennsylvania. He is the associate professor of clinical medicine, and he's been nationally recognized as one of America's top doctors. Dr. Li has performed over 1,700 TAVR procedures. Dr. Li, thanks so much for being with us today.

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Dr. Li: Really great to be here, Adam.



Penn Medicine Patient Success Stories

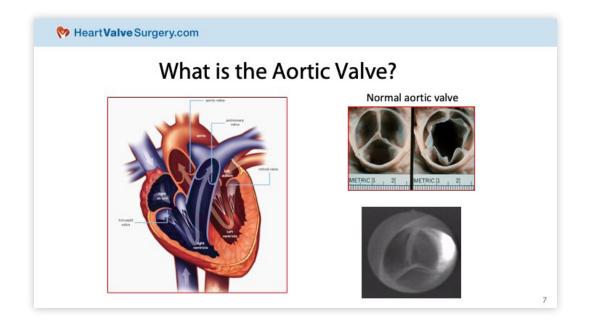


Adam Pick: I could go on about all the accolades of Dr. Herrmann and Dr. Li and the Penn Medicine team, and what I want to do is show you this. These are the smiling faces and names of patients from the heartvalvesurgery.com community who went to Penn Medicine and had successful, very successful procedures, whether it's Steven, Mark, Michael, Sean, Diane, Mowery. That said, I am honored and humbled that you are taking time away from your very busy practices at Penn Medicine to help educate our community.

Now, to kick off the webinar, I'm going to turn it over to Dr. Robert Li with a very important question for everybody on the line, which is,"What is the aortic valve?"



What Is The Aortic Valve?



Dr. Li: For my part of the talk, what I was hoping to do was to provide a brief primer on aortic valve disease and aortic stenosis. When Dr. Herrmann does his part of the talk, he'll do more of a deep dive into TAVR, the nuances of TAVR, and some of the thought processes that go into the decision. What is the aortic valve?

The aortic valve is one of four heart valves. The heart valves basically function as one-way valves to control the flow of blood both into and out of the main pumping chambers. The aortic valve is the outflow valve for the left ventricle, and essentially every single time the heart beats, in order to push the blood out to the body, all the blood has to go through the aortic valve.



The aortic valve opens up to let the blood out, and then in between heartbeats the valve closes in order to keep the blood from going back into the main pumping chamber.

On the right-hand side of the screen are pictures of what an aortic valve looks like. On the top part, you can see the aortic valve both in a closed position as well as an open position. You can see on the bottom image a moving, live aortic valve. That's what an aortic valve looks like as it's opening and closing. Some of the things I want to point out, first of all, you can see that the aortic valve has three flaps, or cusps, that open and close with every heartbeat.

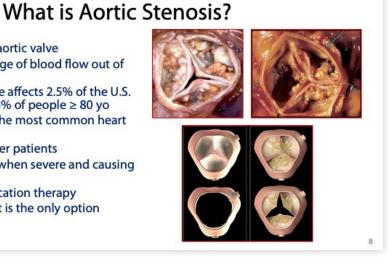
You can also see that the structure of the leaflets, or the cusps, are that the tissue is actually very thin and flexible.



What Is Aortic Stenosis?

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- Narrowing of the aortic valve
- Restriction/blockage of blood flow out of the heart
- Heart valve disease affects 2.5% of the U.S. population and 13% of people \geq 80 yo
- Aortic stenosis is the most common heart valve condition
- Usually affects older patients
- Prognosis is poor when severe and causing symptoms
- No effective medication therapy
- Valve replacement is the only option

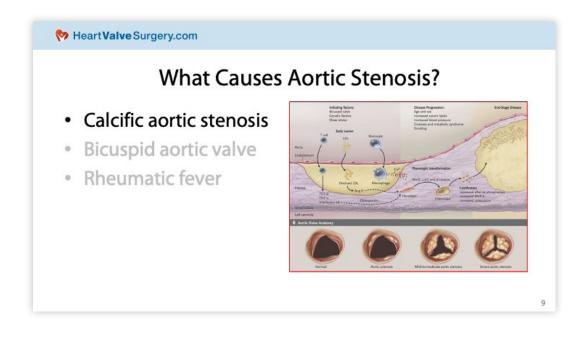


Dr. Li: What is a ortic stenosis? A ortic stenosis occurs when those thin, flexible leaflets of the aortic valve become progressively thickened and then calcified. This process of thickening and calcification results in the leaflets not being able to move well, and this results functionally in the restriction of the blood flow out of the heart, because the valve leaflets no longer open. The condition is actually pretty common.

Heart valve disease in general is actually quite common. It happens in about 2.5% of the general population in America, and it actually happens even more frequently as people get older, so that 13% of people over age 80 have valvular heart disease. Out of all the different types of valvular heart disease, aortic stenosis is the most common. It usually affects older people as they get older, but unfortunately, when it reaches its later stages, the prognosis with aortic stenosis is quite poor.

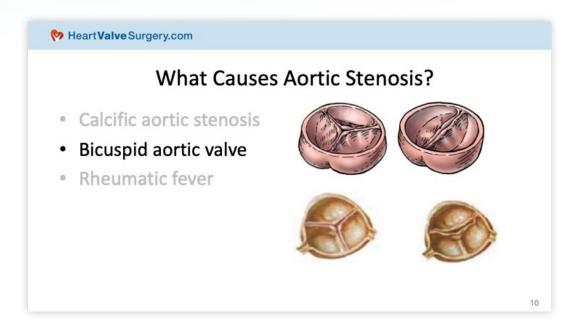


What Causes Aortic Stenosis?



Dr. Li: What causes aortic stenosis? I just want to spend a couple minutes talking briefly about this. This is a condition that – where there are different forms, so there are different mechanisms that cause the blockage to become blocked. In the United States the most common form is what we refer to as calcific, or degenerative, aortic stenosis. This is something where it's not completely understood why this process starts, but what happens is inflammation begins in the leaflets, or the flaps, of the valve. Over time, the inflammation leads to fibrosis or scarring, and then subsequently calcification. The calcification and the scarring lead to restriction in the flexibility of the leaflets.





Dr. Li: Another very common cause of aortic stenosis is related to something that we refer to as a biscuspid aortic valve. The typical aortic valve, as we saw in the previous slide, has three flaps that open and close. In about 2% of the US population, people are actually born – so this is a congenital condition, people are actually born so this is a congenital condition, people are actually born with an aortic valve that, instead of having three flaps, only has two flaps, either two symmetric appearing flaps as you can see on the top right image. Right underneath that is another type of bicuspid aortic valve where it almost looks like a three leaflet valve, but actually two of those leaflets are fused together, so it becomes functionally a valve that has only two flaps.

With bicuspid aortic valve, one of the things that happens is that the blood flow through the valve leaflets is a little bit abnormal. When people are young, the valve functions okay. It's not really blocked and it doesn't really leak in those patients. As people get older, because of the abnormal blood flow, this results in premature wear and tear and development of aortic stenosis down the road.





Dr. Li: A cause of aortic stenosis that used to be quite common but is now less common now with antibiotics being used widely for treatment of bacterial infections, is a condition called rheumatic fever. What happens with rheumatic fever is that it's actually an inflammatory autoimmune condition that results as a consequence of an infection with a bacteria called Group A strep.

Strep throat is actually a very common clinical condition that occurs with Group A strep. For some people, after they develop strep throat, in particular if they haven't been treated with antibiotics, weeks down the road they develop this condition where the body starts attacking its own tissues, including the brain, joints, its skin, but also the heart. If the valve tissue is involved in this process, the valve leaflets can become scarred, calcified and blocked.



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Aortic Stenosis Symptoms

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Symptoms of Aortic Stenosis

- · Shortness of breath
- Exertional fatigue/intolerance
- Chest pains
- · Lightheadedness/dizziness
- Passing out (syncope)
- Leg swelling

Dr. Li: Aortic stenosis is actually a condition where the progression of the problem is actually quite slow. It can actually take many years, sometimes even decades, to go from the earliest stages of aortic stenosis to the later stages of the problem. It's really only people who have later stage aortic stenosis who develop symptoms. The most common symptom is actually shortness of breath, in particular with exertion. There's a related symptom that we refer to as exertional fatigue, exertional intolerance.

This is a situation where a person doesn't, frankly, feel short of breath but they feel like when they're trying to do something, they just don't have the power or energy that they feel like they should. A lot of patients will develop chest pains when they have significant aortic stenosis. Because of the poor outflow of blood from the heart because of the blocked valve, some people become light-headed. If this is bad enough, they can, frankly, pass out. Patients have heart failures as a consequence of aortic stenosis, they can frequently develop leg swelling as well.



When to Treat Aortic Stenosis?



Dr. Li: How do we treat aortic stenosis or when do we treat it is actually the really key question. Aortic stenosis, as I said before, is a condition that can take a long time to develop. We may actually have many, many patients who have aortic stenosis and we're just monitoring them because we don't feel like it's time to provide treatment yet. These are patients who are in the earlier stages of the process. What we frequently do is we'll monitor them by following their clinical symptoms and also doing periodic echocardiograms to measure the degree of the aortic stenosis.



When aortic stenosis becomes severe, that's when we become most concerned, in particular if the aortic stenosis is severe and it's associate with symptoms or any evidence of weakening of the heart muscle because of the extra strain pushing against this blocked valve, those are clear indications to go ahead and provide treatment for aortic stenosis.

There are also some other situations where we'll recommend treatment, including patients who might be undergoing heart surgery for other reasons, people who've had a stress test where the stress test is abnormal we believe because of the aortic stenosis. Some patients will have relatively rapid progression of the severity of aortic stenosis, so that's a situation that is riskier than the usual slower progression.

Then occasionally, we'll have a patient where we'll discover their aortic stenosis and it's – and the severity of the stenosis in the valve is extreme. If the numbers that we're reporting where the severity of their stenosis is really the upper range of the possibility, that's situation that's risky and we believe treatment is often recommended in that situation.

Then finally, if there's really any evidence that the heart might be starting to feel the strain of the blocked heart valve, we'll recommend treatment. A situation that sometimes arises is that we'll do a blood test called a BNP that is abnormal, and that indicates to us that the situation is worse than we might otherwise think.



Treatment Options for Aortic Stenosis

<section-header> Nedical therapy? Balloon aortic valvuloplasty? Open surgical aortic valve replacement? Transcatheter aortic valve replacement?

Dr. Li: What are the general treatment options for aortic stenosis? Although sometimes we'll prescribe medications when people have aortic stenosis but unfortunately, there's no medical medication treatment that has yet been found that will fix the underlying problem. The underlying problem with aortic stenosis is that the valve does not open well. There's no medication that'll restore flexibility to the leaflets. There hasn't been found any medications that'll even slow or stop the progression, either. Really, there's no medication to provide fundamental treatment here.



We do prescribe diuretics frequently for symptoms, but diuretics don't change the underlying problem. In the 1980s, a procedure called balloon of the aortic valvuloplasty was developed. It's basically a procedure where we inflate a large balloon inside the aortic valve in order to try to crack open those calcific deposits on the valve. Unfortunately, the treatment did not prove to be very effective and whatever benefit was reported was short-lasting. As a primary treatment for aortic stenosis, balloon aortic valvuloplasty really is not done.

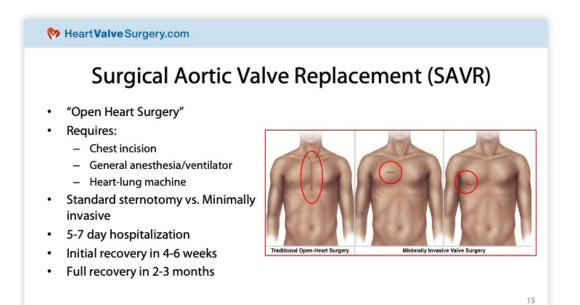
Really the only effective treatment for aortic stenosis when we believe that treatment is necessary is to somehow find a way to put a new heart valve in. Traditionally that's done with open surgical aortic valve replace. Then a newer treatment, which is really the focus of today, is a minimally invasive procedure called transcatheter aortic valve replacement.

Now, the other option is a bioprosthetic valve. These are typically made from animal, so cow or pig, sometimes human tissue. Now, compared to mechanical valves, you don't need long-term blood thinner, anticoagulation. That's good. The downside is they have a certain durability longevity to them. It depends if it's aortic versus mitral versus tricuspid, but typically, we're speaking about 15 years or so from surgery. Then you need to think lifelong what's going to be the next option, for example. Much like stenosis or regurgitation of those valves, the tissue valves can also eventually degenerate as well. Again, you need to plan in the future what's going to be the next step after we've replaced a tissue valve.

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Surgical Aortic Valve Replacement (SAVR)



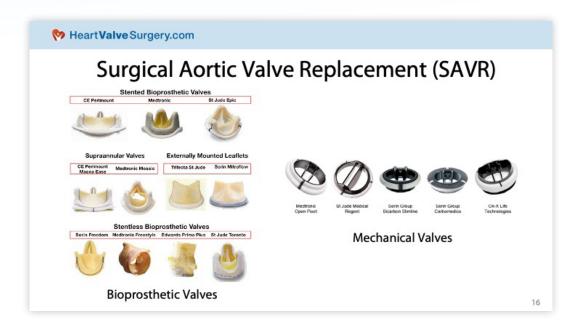
Dr. Li: Just wanted to review those two treatments a little bit. First, surgical aortic valve replacement, as the name suggests, is open heart surgery. It's what most people think of when they think of a big heart operation. It requires a chest incision. General anesthesia is always used as well as mechanical ventilation, so the breathing tube. A heart/lung machine is also required. A heart/lung machine basically takes over the work of the heart by circulating blood outside the body while the heart is being worked on.



The incision that is made with this operation varies. The traditional operation is what we refer to as a median sternotomy where the sternum or the breastbone is opened from the very top to the very bottom and the chest is fully exposed or fully open. Smaller incisions, however, are very frequently done nowadays. These are minimally invasive approaches to do the same operation with a lot – with a much smaller incision.

The hospitalization after this kind of operation is usually between five and seven days. The initial recovery at home usually takes about four to six weeks, and it's usually two to three months before patients are really back to clinically normal.



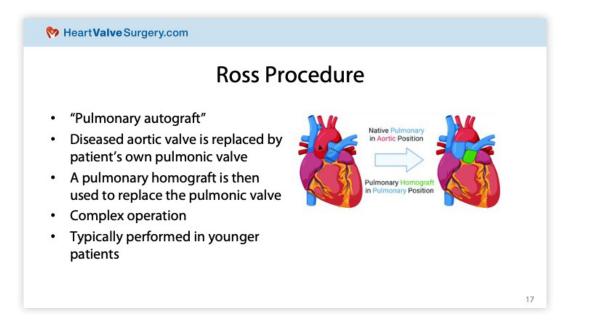


Dr. Li: One of the advantages with open heart surgery is there are really a large variety of valves that can be implanted using a surgical technique. Artificial heart valves really fall under two general categories. One are a class of valves called bioprosthetic valves where essentially the flaps are always made out of some kind of biological material. The alternative general category of valves are mechanical valves. With mechanical valves, all the parts of the valve are made out of durable materials such as carbon, metal, plastics, and fabric. Really the main advantage of mechanical valves is that the durability's extremely high. When we implant a mechanical valve, we expect it's going to last a very, very long time. The main disadvantage of mechanical valves is that they always require blood thinners with warfarin, and a lot of patients don't ant to take Coumadin/warfarin.

Prosthetic valves, on the other hand, don't require Coumadin but the main disadvantage of bioprosthetic valves is that because the flaps are made out of biological material, eventually that material will break down and wear out. The valve could become either blocked again because the leaflets become stiff, or they break down and start leaking.



Ross Procedure



Dr. Li: Another kind of open surgical aortic valve replacement isn't done nearly as much as traditional valve replacement, but this is called a Ross Procedure. I'm bringing it up because it's becoming increasingly popular. It's what we refer to as a pulmonary autograft, and what the surgeon does with this kind of operation is they take the pulmonic valve, which is structurally very similar to the aortic valve, and they take the patient's pulmonic valve and the move it from its original spot.

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They use that to replace the damaged or diseased aortic valve. In the place of the original pulmonic valve, they place another or they place an artificial heart valve we refer to as a pulmonary homograft, which is essentially a pulmonic valve from a diseased person.

Basically you have valves in two new positions. It's a technically very complicated operation to perform and really only certain specialized centers are able to do this operation. Penn is one of them; we have several surgeons who are very interested in the Ross Procedure and do it quite well. It's something that's typically reserved for younger patients because it's a difficult operation.



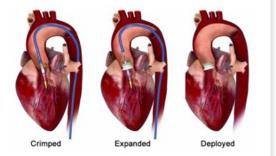
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Transcatheter Aortic Valve Replacement (TAVR)

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Transcatheter Aortic Valve Replacement (TAVR)

- Catheter-based technique
- Avoids open heart surgery
- Performed with sedation (no general anesthesia or ventilator)
- Heart-lung machine not needed
- No incisions
- Short hospitalization (1-3 days)
- Rapid recovery (1-2 weeks)

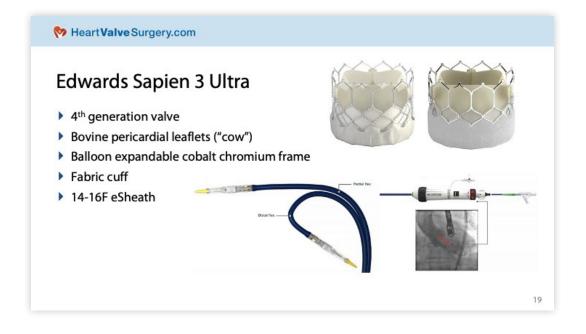


Dr. Li: Then finally there's transcatheter aortic valve replacement, which is essentially a catheter-based technique for implanting a new heart valve. Because we're delivering a valve using a catheter, it's much less invasive. It avoids open heart surgery. The procedure is, in most centers, typically done with sedation as opposed to general anesthesia, so there's no ventilator involved. Certainly a heart/lung machine is not required because the heart is never truly stopped. The hospitalization is quite short, typically one to three days. For the vast majority of patients, it's really only one or two days.

Likewise, the recovery is very quick because the TAVR procedure doesn't involve much damage to any of the tissue because there's no incision. There really is not a lot of trauma that occurs or that needs to occur. Patients are up and around pretty quickly. They're pretty much back to what they were doing before within a week or two.



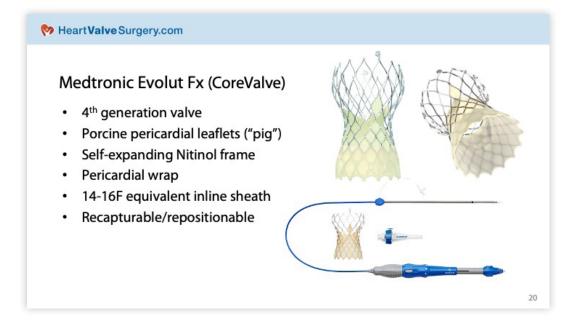
Edwards SAPIEN 3 Ultra



Dr. Li: I'm just going to briefly show the three main TAVR systems that are available in the United States. The first one is the Edwards Sapien 3 Ultra valve. This is the current version in a series of progressive improvements in this valve over the last 10 to 15 years. The structure of the valve is that the flaps of the valve are made out of a material called bovine pericardium. The leaflets are created out of the pericardial sack of cows. The leaflets are sewn onto a lattice metal frame that's made out of cobalt chromium and you can see because it's a latticework, that's what allows the valve to be pulled into a much smaller profile. The picture in the middle is an example of a Sapien valve that's been pulled and collapsed onto the delivery system. The delivery system is that blue part, and the size of the system is quite small, fortunately the 16 French, which is the equivalent of about 5 millimeters in diameter. That's why were able to insert it into an artery and pass it on to the valve, because it is so small.



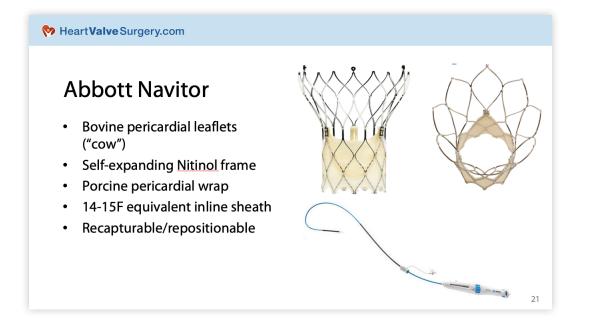
Medtronic Evolut Fx



Dr. Li: Another type of TAVR valve that's used quite frequently is called the Medtronic Evolut valve. The current version is the Fx, which like the Sapien valve, the Medtronic valve has gone through several iterations over the years. It used to be called a Core Valve, so if you see that name out there, the valve is no longer branded as Core Valve, but people still frequently refer to it as that. The structure of this valve is similar but a little bit different to the Sapien valve. The leaflets or the flaps of the valve are made out of a material called porcine pericardium, so basically tissue from a pig's heart. The frame is made out of a metal called Nitinol, nickel titanium, and nickel titanium is an interesting metal because when you create a frame – a valve frame out of it. You can actually compress it into a very small profile, but when you release it, it pops back into its previous shape. It's what we refer to as a self-expanding valve.



Abbott Navitor



Dr. Li: The third valve is the Abbott Portico valve. Actually the latest version of this valve was just FDA-approved a couple weeks ago. It's called a Navitor, so you might hear that name out there as well. Like the first two valves, the general design is pretty similar. There's a metal frame. This one is made out of Nitinol and then leaflets that are made out of pericardial material. With the Portico valve or the Navitor valve, the leaflets are made out of bovine pericardium.



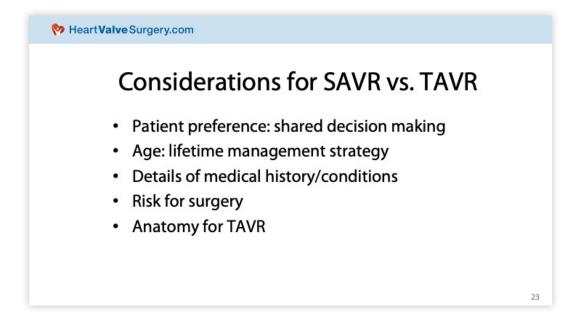
The TAVR Procedure



Dr. Li: This is just a – it's an actually very well-known animation Edwards for the steps on how the TAVR procedure is done with a Sapien valve. The first step is we take a very thin, tiny wire that we refer to as a guidewire. Then we position that across the valve. We use this wire basically as a rail to pass all of our equipment to the heart. Sometimes we'll do a valvuloplasty to prepare the stenotic valve for the implant. Then when we're actually delivering the valve, the first step is we place what's referred to as a sheath, which is – provides a doorway into the artery to allow our equipment to get into the body safely. That's the delivery system with the crimped valve. That's the silver part at the end of it that's being passed up and positioned within the valve. Then as we expand the valve, it presses up against the leaflets of the damaged valve and basically starts working as soon as it's opened up. It's a very quick process delivered in the valve.



Considerations for SAVR versus TAVR



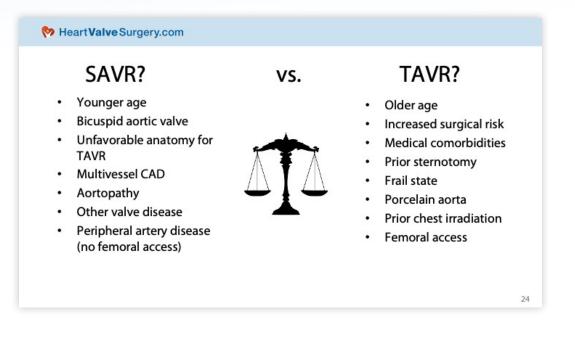
Dr. Li: We talked about surgical aortic valve replacement, and we talked about transcatheter aortic valve replacement, and although there's a lot of excitement and a lot of press with TAVR, surgical aortic valve replacement is actually still done very frequently. It's really a tremendously effective operation. The surgeons have been doing it for decades, and they've become exceptionally good at it. The results for a patient undergoing surgical aortic valve replacement are really quite extraordinary.



How do we decide what's the best choice for any individual patient? There's actually a pretty complicated process that we engage when we're evaluating somebody for aortic valve treatment.

At Penn and in many centers, it's done with what we refer to as a heart valve team. This team involves a lot of different types of doctors: cardiac surgeons, cardiologists, interventional cardiologists, frequently anesthesiologists. Anybody who would have or potentially have useful input into a patient's care are engaged and we make a decision or make a recommendation. The patient is a big part of this process as well, so we do what we refer to as shared decision where we talk to the patient in a lot of detail about what the options are. We try to get a sense of what's important to the patient. Everybody has different feelings about what they want to be done with their body, and we try to get a feeling for what would be most appropriate for them. Then ultimately, we come to a shared decision about the best way forward.





A person's age is actually – weighs heavily on our minds because somebody who's 50 with aortic stenosis is very different from somebody who's 90 with aortic stenosis, as everybody might imagine. Somebody who's 50 and in particular if they want an prosthetic valve because they're not interested in taking warfarin, because the durability of a prosthetic valve is usually somewhere in the 10-15 year range, you're basically telling this person that you're going to do a procedure where the likelihood is extremely high they will live long enough to see that valve wear out.

When that valve wears out, you have to make a decision about what is going to be the next step We try to be proactive with this thought process so you have an idea of how we're going to manage the entire course of their lives. Somebody who's 50, their valve is going to wear out if you put a bio-prostheses. Somebody who's 90, the likelihood that the valve will wear out is very low. We look at all the details of their medical history, medical conditions to really get a sense of what the risk of surgery would be for them. I know we look very closely at the anatomy of the valve because for TAVR in particular, there are a number of anatomic constraints that we have to be aware of before deciding to proceed with TAVR.



As an example, for surgical aortic valve replacement, there are certain situations where we lean more towards recommending surgery, so somebody who's younger, somebody who has bicuspid aortic valve. Most of the robust data for the effectiveness of TAVR was obtained for patients who have traditional threeleaflet valves. There's much less information on how effective TAVR is for bicuspid aortic valve, but we still do it fairly frequently. The evidence base isn't as strong for bicuspid valve in TAVR. Patients who have anatomy that isn't very good for TAVR, we obviously lean more towards surgery. If they have other cardiac conditions that may require surgical repair, those are situations where we're more often going to recommend surgery.

On the other hand, TAVR is a technique that is strongly favored if we feel that open surgery is risky, so people who are older and in particular, people who have medical conditions that we believe significantly increase their risk of doing traditional outpatient. Those are very good candidates for TAVR. There's actually a very, very large group of people who are in the middle, so people that we review and we evaluate them, and we believe yes, surgery would be very reasonable here and yes, TAVR would be very reasonable here. Obviously in this very large group of patients, it's up to them in may respects. That's what I was referring to with the shared decision process.



Penn Medicine TAVR Program

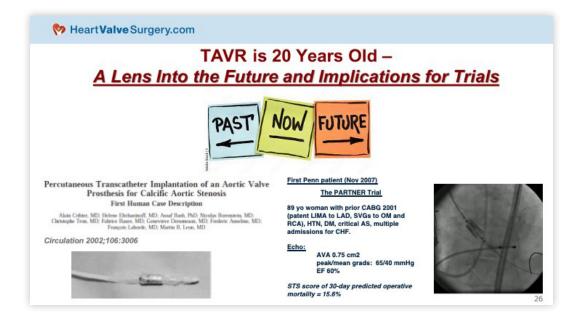


Dr. Herrmann: That was a great summary, Rob. I think everybody understands now the disease and some of the options for treating it. What I'm going to try to cover in my 15 or 20 minutes are get a little bit more deep into the weeds of the procedure, some of the complications, and some of the issues that I've been seeing in the questions and answers, because I think I'll have answers to some of those questions in the course of my slides.

I just wanted to start with this one to remind you that we think of TAVR as a form of structural heart disease. We have a lot of different options now that we didn't have 30 years ago. When I started doing interventional cardiology, really the only thing we could do was angioplasty and then stents. Now we really treat a variety of conditions within the heart, including all four of the valves. Only TAVR is currently an approved procedure.



The 20-Year History of TAVR



Dr. Herrmann: I'm going to try to take you a little bit through the past, a little bit of the present, and then where I think things are going in the future. TAVR really began back in 2002 in France, with a revolutionary attempt to treat this disease by Alain Cribier. It was brought to the US around 2005 or '6, and we performed the first one at Penn in 2007. I was here – started the program with Dr. Bavaria at that time, and I will like to also point out that this is a procedure we do with our cardiac surgical colleagues. Dr. Li and I are interventional cardiologists, but it is a team procedure. We do this as a heart team with heart surgeons, and they are an integral part of both the evaluation of patients as well as their treatment. I'll have more to say about that later on.



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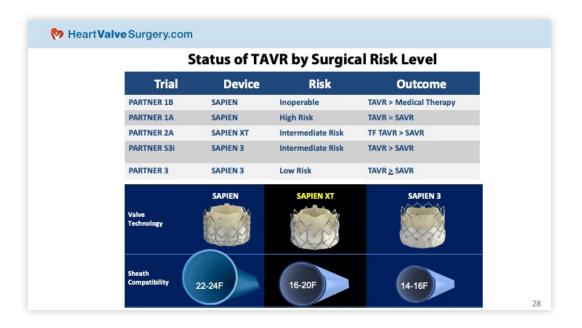
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		Low Risk (must meet ALL criteria in this column)	Intermediate Risk (any 1 criteria in	High Risk (any 1 criteria in this column)	Prohibitive Risk (any 1 criteria in this]
STSI	PROM	<4% AND	this column) 4% to 8% OR	>8% OR	column) Predicted risk with surgery of death or major morbidity	
Frait		None AND	1 index (mild) OR	2 or more indices (moderate-to- severe) OR	(all-cause) >50% at 1 y OR	
syste comp to be		None AND	1 organ system OR	No more than 2 organ systems OR	3 or more organ systems OR	
Proce	edure-	None	Possible procedure- specific impediment	Possible procedure- specific impediment	Severe procedure-specific impediment	

Dr. Herrmann: Somebody asked in the questions about risk. How do you decide who's a high-risk patient? These are some of the criteria that are used. We start with what's the risk of surgery? That's what's in that first line, the STS predicted risk of mortality at 30 days. We divide patients into a risk of less than 3 or 4%, 4 to 8%, and then high risk is more than 8%. We add to that other factors, how frail the patient is, whether they have other comorbidities, and how good a candidate they are for either surgery or TAVR. All of that goes into deciding the risk.

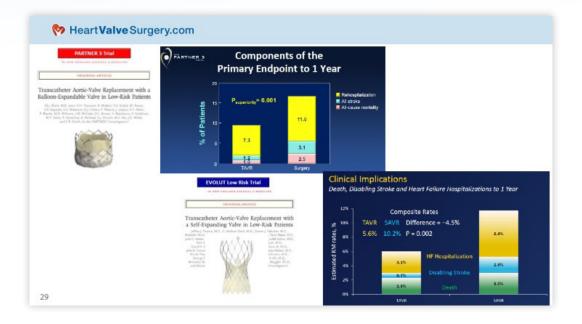


TAVR Status by Surgical Risk Level



Dr. Herrmann: When we started, we did think of TAVR as only for inoperable or high-risk patients. Through a series of very carefully done trials, what we found is that TAVR is at least as good as surgery, and in some cases better for all risk categories. We think of this, now, a little less about the risk of the patient and more about their longevity, and what procedure they want, and what we're going to do if that valve wears out. As Rob alluded to, we do have to think about the lifetime management of younger patients, less so for the 85 or 90 year old.



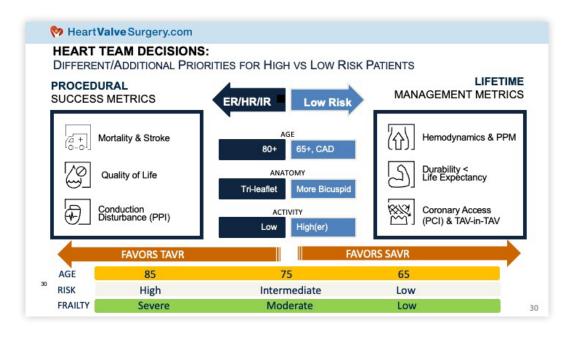


Dr. Herrmann: This is just one of the big trials or two of the big trials, one with each valve, that demonstrated that even in low-risk patients – that's what you see there in the lower bars, in the top and the bottom with the two different valves – the rates of re-hospitalization, stroke, and mortality in the short run, one year, are better with TAVR even in low-risk patients. We do have to think about what we're going to do when these valves wear out, because all bioprosthetic valves wear out after some period of time.

Whether that's 10 years, 15 years or 20 years varies by the valve and the patient. If you're 50, that is a consideration we have to think about, less so when you're over 80.



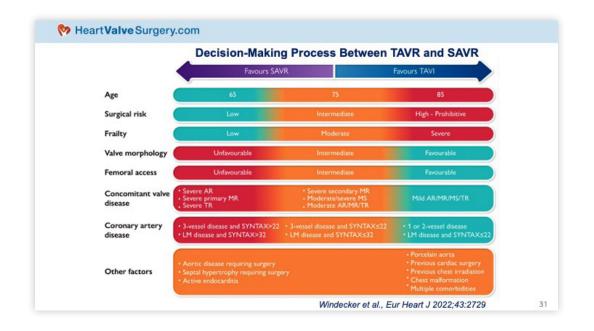
Heart Team Decision Making Process



Dr. Herrmann: That's where the heart team comes into account. That's why it's important that we have not just one doctor making these decisions for you but have a team approach. Our team includes the anesthesiologist, the imagers, the cardiac surgeon and the interventional cardiologist who are going to do the procedure. Rob and I and everybody at Penn meets once a week to go over all the patients and decide that – is it the right choice? Should they get a TAVR? Should they get surgery? What are we going to do the next time? That's what you see at the bottom there. The older patients, it favors TAVR; the younger patients, we think a little bit more about surgery as the first option.

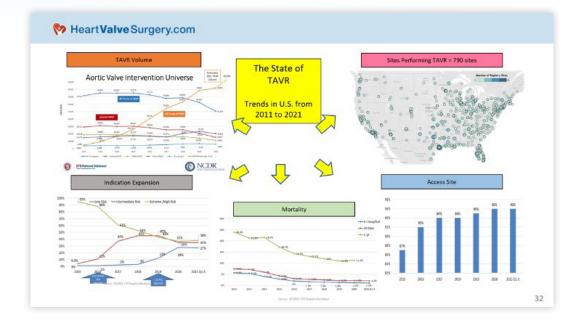


TAVR Trends: Volume, Indication, Sites & Mortality



Dr. Herrmann: This also points out that it's not just age and surgical risk, but it also depends on the morphology of the valve, other medical problems. If you need to have bypass surgery at the same time, then TAVR may not be the best option for you. If you have a leaky mitral valve, and you're a young patient who can have an operation that's more complicated, maybe surgery with treatment of both valves is the better option than just treating one of the valves. If you're 90, maybe treating the aortic valve is a good option for improving quality of life and may be less risky than open heart surgery.



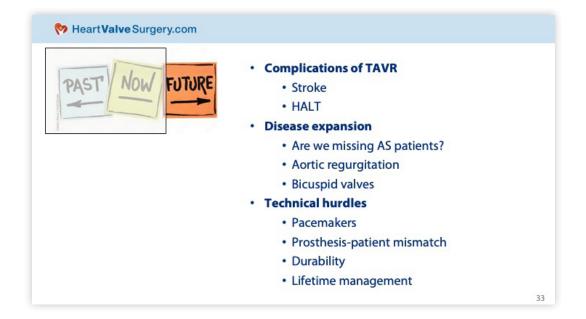


Dr. Herrmann: This is just a snapshot of where we are in the US at this point. I won't belabor this, because I want to get to your questions. This procedure, which began around 2007, got approved around 2011, has now expanded rapidly around the world. There are over 800 sites that do TAVR in the US. The mortality of the procedure has fallen to about 1%. We're doing them all now through the groin. Hardly ever do we have to use alternative access. We're treating all risk categories, about a third low risk, a third intermediate risk, and a third high risk.

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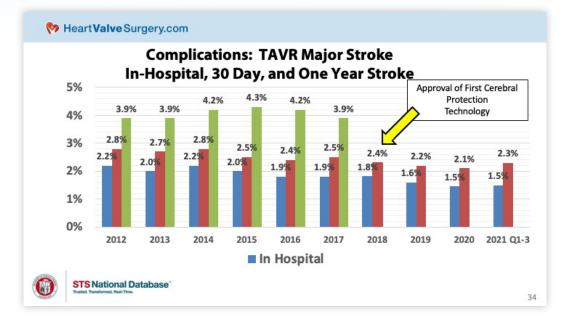


TAVR Complications



Dr. Herrmann: What are some of the future problems? This is where we talk a little bit about complications like stroke and leaflet thrombosis, some of the issues with who else is going to get this procedure, disease expansion. We'll touch on bicuspid valves. I saw a lot of questions about that. Then finally, hit the next button – technical hurdles. What are some of the complications that we have to deal with?

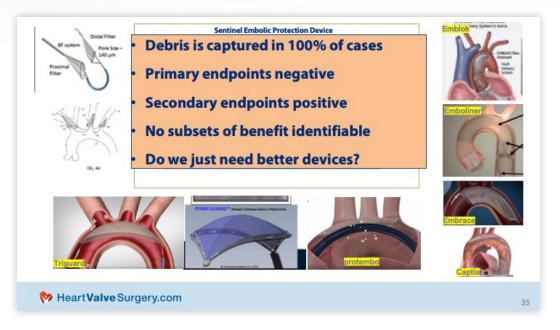




Dr. Herrmann: Stroke has been one of the major concerns everybody has. I know that some patients are more worried about stroke than dying, and we are worried about it as well. It is part and parcel of this procedure, so if you look at the in-hospital stroke rates, which are in blue, it's still between 1 and 2%.

You'll see that even after we got what are called cerebral protection devices – somebody asked about that in the questions. These are devices that help catch some of the debris from the valve as they potentially could go to the brain. We haven't made a big impact on stroke. That's not that different than the stroke rates in surgery, so I don't mean to tell you that you shouldn't have a TAVR because you're afraid of stroke. We haven't been able to lower that rate as much as we would like.





This shows you what some of those devices look like. These are the filters that we sometimes put into the brain vessels to try to capture debris and lower the rate of stroke. The trials have been not perfect to show that they work. They seem to have a slight benefit, which is what you see there in total stroke. In one study, they seem to reduce disabling stroke better. Not every trial has been that positive. Some hospitals use these devices, which are expensive and add time to the procedure, and other hospitals have made the decision that the results aren't good enough to recommend using them in all patients. At Penn, we do use these in the majority of our patients based on our feeling that they probably help. I can't fault people who don't use them because the data is just not that clear.

You'll see there are more devices coming along, different types of capture devices. One more time, you'll see that there are a lot of these coming along, and we're going to be in trials of several of these. As an investigative approach, this is an area of intense interest around the country and at Penn. We are going to be utilizing some of these devices to try to reduce that stroke rate from the 1 or 2% to an even lower number.

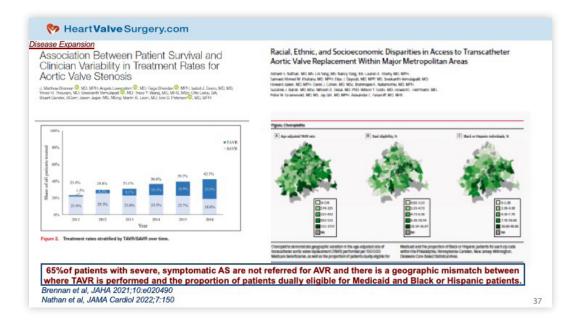




Another complication that occurs is that you can get clot, or thrombus, thickening, occurring on these leaflets. It happens with surgical valves as well, but it seems to happen a little more often with the TAVR valves. It's a complicated problem. It comes and goes. It may have something to do with valve design and shape after deployment. It doesn't correlate that much with adverse clinical outcomes, and it can be prevented with blood thinners. We do watch for this. We get echoes; that's one of the reasons patients will get an echo at 30 days after their TAVR procedure. Sometimes we follow that up with a CT scan. If we see it, in our hospital we do tend to treat it with a period of time blood thinning, six months, something like that, and it does seem to get better. It is something you should be aware of, but it's still one of those new diseases that came up ever since TAVR.



TAVR Accessibility: Disparities in Care



Dr. Herrmann: Another issue that we're very concerned about, both at Penn and nationally, is the fact that, although there are 800 sites performing TAVR, many of the disadvantaged among our society do not seem to have the same access to TAVR that they should. That we are not treating as many of the socioeconomically disadvantaged populations, African-Americans, as well as we should be. That is an area of interest, of how do we expand these new technologies to everyone and make sure that we offer it to anyone who is eligible for it?

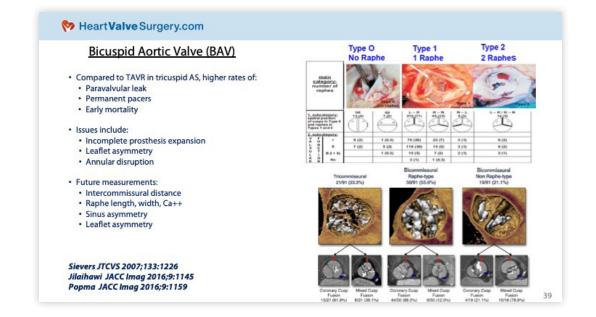




The next slide shows some of the things that are being done to improve these disparities to care, and I can – happy to talk about this a little bit at the end if people have questions about it. The point is everybody should have access, and there are enough centers around that we should be able to get almost anybody to a TAVR site.



Bicuspid Aortic Valve & TAVR



Dr. Herrmann: There were a lot of questions about bicuspid valves. Rob mentioned that this is a common problem, about 2%. These patients were excluded from most of the clinical trials. The evidence base that we have for TAVR in bicuspid valves is much smaller, a few small, couple-hundred patient series and some registry data. What we know about bicuspid valves is because they're a little bit oval and these valves are circular, they may not seal quite as well as the edges. There are more leaks at the edges; there are more patients who need permanent pacemakers. Maybe it doesn't work quite as well as surgery, although it's certainly a safer procedure for a high-risk patient.

There is some controversy in the young bicuspid aortic valve patient as to whether they should have surgery up front and reserve TAVR for when that surgical valve wears out.



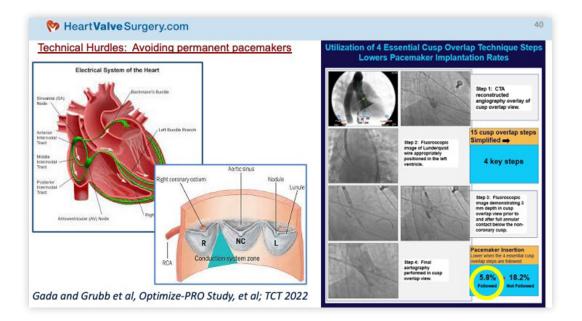
That's our general approach for patients under, say, 65 years of age or whether if they're older, they can get a TAVR, and we can still do another TAVR in that TAVR valve if it fails, but they might be subjected for the first 10 or 15 years with that TAVR valve to a slightly greater risk of a leak.

There are different types of bicuspid valves as shown on the right side and measuring them is an art in and of itself.

The point is if you have a bicuspid valve, you're not excluded from TAVR, but it is an important shared decision that you have to make with your physician about based on your age, the kind of bicuspid valve you have, and what we're going to do when that first valve wears out. It's a complex decision for bicuspid aortic valve patients, particularly the younger ones. I encourage you to have that conversation with your physicians and with surgeons who understand how to treat these patient – these kind of valves in the best possible way.



Avoiding Permanent Pacemakers

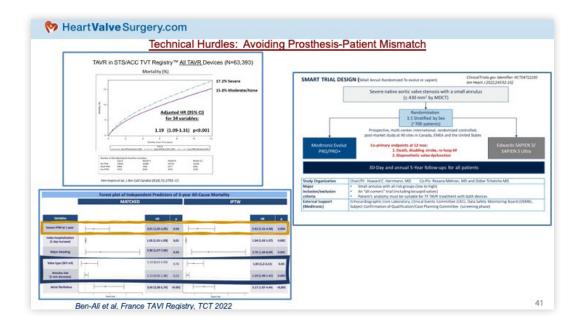


Dr. Herrmann: We also know that permanent pacemakers happen in about 5 to 10% of patients after TAVR. That has to do with the fact that the wiring of the heart, the connections between the upper and lower chambers, run very closet to the aortic valve. When we inflate the balloon or inflate the valve in that area, we put pressure on those wires and we can disrupt them. It can also happen with surgery, but it seems to happen just a little bit more often with the TAVR patients. You have to be aware of that, and we are aware of it during the procedure. We use a temporary pacemaker during the procedure and that's one of the reasons you're in the hospital afterwards, to watch for that and make sure that you don't need one.

That just shows the anatomy again. There are some techniques that we're utilizing, and everyone is, to try to lower that risk. These are technical aspects of the procedure to try to reduce that risk from 10% down as you see there in some studies to 6 or 7%.



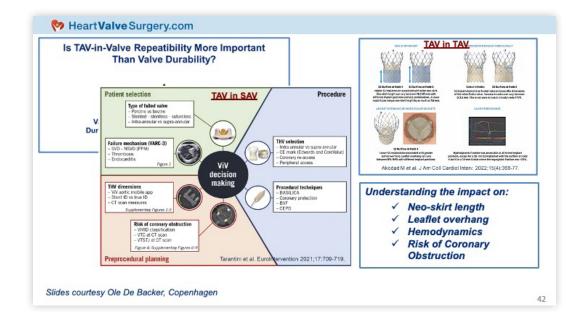
Avoiding Prosthesis-Patient Mismatch



Dr. Herrmann: There's also an issue with the size of the valve, and we know if you get too small a valve, that doesn't – that can create a bit of an obstruction. We're trading aortic stenosis, which is an obstruction to outflow from the heart, for a valve. If you get too small a valve for your body, it may also still obstruct a bit. It's important to get the largest possible valve you can and that can be done sometimes better with surgery than it is with TAVR and sometimes with different TAVR valves. Those are complex decisions we're still wrestling with and trying to understand. We actually are part of an international trial that is examining that issue in women who tend to have the smallest aortic annulai and the ones that are most at risk for this problem that's termed prostheses patient mismatch.



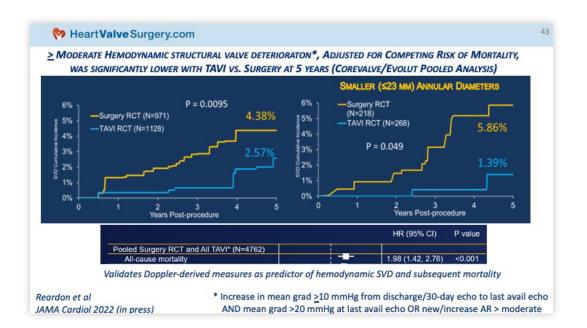
TAVR Valve-in-Valve



Dr. Herrmann: As we think about all these things, one of the most important things is durability. How long are you going to be able to live with this valve, and what are we going to do when it wears out? Those are decisions that we're thinking about more and more now, especially as we move into lower risk in younger patients. We can do TAVRs inside TAVR valves. We can do TAVRs inside surgical valves. Rarely would we ever have to do a third valve, but it's theoretically possible. Most of the time, we're talking about two valves. We're starting to think about that more in the younger patients, which kind of valve is best for the next one? Is it a surgical valve? Is it one type of TAVR valve? Where are we placing it to make sure that the risks of the second TAVR valve 15 years later will be able to not cause a problem for, say, coronary obstruction that we might have to worry about in some situations of putting two valves in together.



TAVR Mortality & Long-Term Survival



Dr. Herrmann: Finally, we have to worry about structural valve deterioration. How long are these valves going to last? In some studies – and this one is an example of that – the TAVR valves actually did better than the surgical valves at five years. Whether that's going to continue to be the trend, whether it's true of all valves, we don't really know. We think that these TAVR valves – we have good data out to about eight or nine years now showing that they're pretty robust. Say a surgical valve lasts on average 15 years, is it possible that a TAVR valve lasts on average only 12 or 13 years. We wouldn't know that yet. It's a fast-changing field. The valves keep getting better. That's the ballpark of what we're thinking about 10 to 15 years for either one. We have to think about that, what we're going to use for the second valve if you're a younger person.



Medical Insights: Aortic Stenosis Progression



Dr. Herrmann: The other couple of points I want to make is that aortic stenosis is a gradual disease. It doesn't just creep up on you and one day you have severe aortic stenosis and before that, you had no aortic stenosis. There is mild and moderate aortic stenosis, and they have some risks as well. As the valve gradually narrows, the heart has to thicken to take care of that and work harder. There is a risk of dying even as you get toward severe aortic stenosis. There has been a trend to start thinking about fixing some of these valves a little earlier, even before you have severe aortic stenosis. That is not the current paradigm that we all operate under, but there are trials going on now that are starting to think about backing that up a little bit.

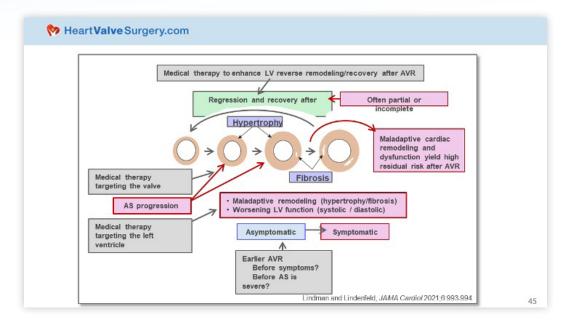


Maybe we should treat people before they're symptomatic who have severe aortic stenosis. Maybe some patients who have moderate aortic stenosis with symptoms should be treated, even though they don't have severe aortic stenosis. That's the way the future is thinking, going a little bit earlier in the disease progression.

Adam Pick: Dr. Herrmann, Real quick. I'm sure patients are wondering right now talking about taking care of the aortic stenosis earlier, you mentioned some clinical trials. Can you share by name what those may be? Patients may want to do some research on those.

Dr. Herrmann: There are several from each of the manufacturers. At Penn, we're part of the Expand trial, Expand TAVR trial, which a Medtronic trial that's looking at moderate aortic stenosis. There have been trials with the Edward valve, one called TAVR Unload, which is treating patients who have muscle dysfunction and less than severe aortic stenosis to see if that can help their heart muscle recover better. There's an Edward trial also in asymptomatic but severe aortic stenosis called Early TAVR.





Dr. Herrmann: This is just an example of showing that progression, how the heart muscle thickens over time, gradually gets fibrotic. One of the things that's very exciting, and I think will be part of the future of the treatment of aortic stenosis, is medications that might retard the progression of this disease. If you find out you have mild or moderate AS, as you see in the next slide, it's a very complicated paradigm of what causes aortic stenosis. I won't make you go through the details of this slide, but the concept is there's a lot going on as this valve gets thick and calcifies. There may be places where we can interrupt that pathway. One of the ones you may've heard of is called lipoprotein, little A, which is a form of the lipid pathway There are some medications that we already have that can interrupt that pathway. They're not yet being used for aortic stenosis, but there are going to be some trials that'll look at that in the future.



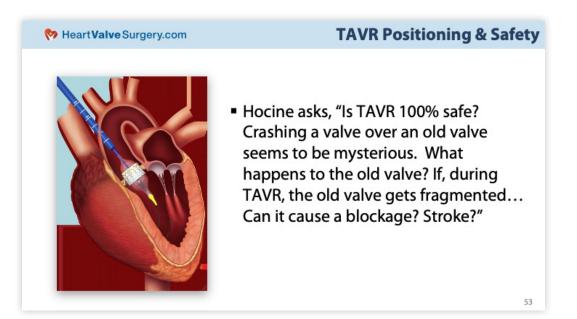
TAVR at Penn Medicine



Dr. Herrmann: I'll end here with this slide, which is just a little bit of a plug for our program here at Penn where we do about 600 cases annually We are, as you see to the right there, one of the top rated programs with a three-star rating in the US, which is not given to every program but is based on our outcomes. We still do the procedure in a very team-oriented approach. I mentioned that every procedure is done with a cardiac surgeon and an interventional cardiologist. Dr. Bavaria, Dr. Zeto, who you see pictured there with me on the front page of the New York Times a few years ago, Dr. Desai, Dr. Atlori, Dr. Ebrihim, are all surgeons at Penn who do these procedures with us. It is a team approach. We also use anesthesia on every procedure, cardiac anesthesia, to make it comfortable for patients. Even though they're not put underneath general anesthesia, they're sedated well. Most of our patients go home in the first one or two days after the procedure, which is typical nationally.



Questions & Answers - TAVR Safety



Adam Pick: Let's get right to Hocine asks, "Is TAVR 100% safe? Crashing a valve over an old valve seems to be mysterious. What happens to the old valve? If, during TAVR, the old valve gets fragmented, can it cause a blockage, stroke?"

Dr. Li: That's a really good question, and it's a question that we very, very frequently hear. As really any medical procedure or really any medical treatment has, there's always going to be some risk of a problem I think Dr. Herrmann alluded to a lot of the potential issues. Thankfully, the likelihood of a significant complication with TAVR is quite low these days. It's gotten progressively lower in terms of the complication rate from the beginning of the procedure You have to weigh the consequences or weigh the balance between the risk, which is very low, that's associated with TAVR but also the risks of not doing anything.

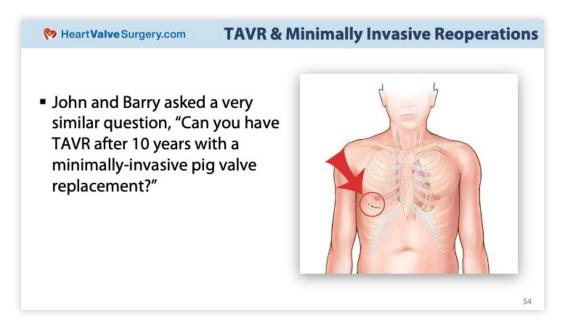




Dr. Herrmann: Right, I think that's the key point. You're balancing – you're not balancing the TAVR procedure against doing nothing; you're balancing it against doing nothing and suffering the consequences of doing nothing, which are much higher, than the risks of the TAVR procedure.



Questions & Answers: TAVR Reoperations for Minimally-Invasive SAVR

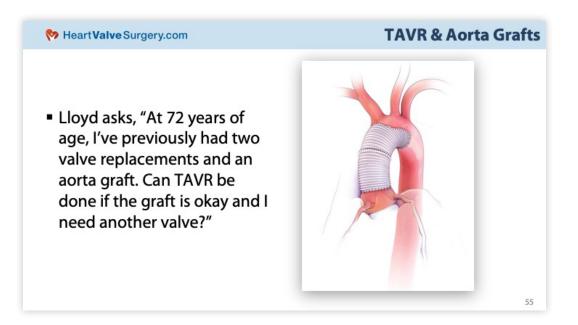


Adam Pick: Right. Let's go into the next one. We talked about bicuspid aortic valve, so I think we're going to pass on this one. Thank you for that, Dr. Herrmann. This is a – I got several of these questions from folks like John and Barry who ask, "Can you have a TAVR after ten years with a minimally invasive pig valve replacement?"

Dr. Herrmann: Yes, we call that valve-in-valve or TAVR-in-TAVR. We can put TAVR valves inside surgical valves, and that is an approved procedure, not only for the aortic valve but also we do it not infrequently in the mitral and tricuspid surgical valves as well, and the pulmonic valve. If you have a previous surgical valve in any of your four valves and it starts to degenerate, we can often put a TAVR prostheses inside it. That isn't without, though – it's not everybody. It's the majority of people, and we do have to do some careful analyses to make sure we're not going to obstruct the coronary arteries and the size of the different valves works for that, but in general, the answer is yes.



Questions & Answers: TAVR and Aortic Grafts



Adam Pick: Lloyd asks, "At 72 years of age, I've previously had two valve replacements and an aorta graft. Can TAVR be done if the graft is okay and I need another valve?"

Dr. Li: Typically, this is technically possible. We frequently will do what's referred to as a valve-in-valve procedure where we can implant a TAVR valve within a previous surgical bioprostheses. The existence or the presence of an aorta graft can sometimes make the valve delivery more complicated, but it's just about always possible. The short answer is yes, it potentially could be done.



Dr. Herrmann: It also brings up another point for patients. I know there are a lot of questions about bicuspid aortic valves, and we seem to have a lot of patients on the call who have that. We should point out that bicuspid valves are also associated with some disease of the descending aorta. That's why you often get that graft that you see there. If you're a young patient and you have an enlarged aorta along with a severely stenotic or leaking bicuspid valve, then surgery is likely the best option for you because you can treat both conditions.

What you don't want to do is have a TAVR for your bicuspid valve and then have a problem with your aorta a few years later. Now if you're older and the aorta doesn't look so bad, then that still may be the best option, to have a TAVR, but it's a more complicated disease than just the valve if you have bicuspid disease.





Adam Pick: Great, thank you so much for those insights. With that being said, we are just at the end of the hour. Before we wrap this up, I want to just – for everybody on the line, please don't hang up. I want to thank you for coming together today. Obviously with all the questions, all the registrations, and over 300 people online, this was important to you. As you know, it's important to me, so thank you on behalf of everybody for trying to live the best, healthiest lives that we can. I want to thank Dr. Herrmann and Dr. Li, the dynamic duo of TAVR. Thank you so much for your time today, your excellent presentations. They were very helpful As we wind up this webinar, I want to thank you for a very quick survey that's coming on your screen right now. As we conclude this, thank you again, Dr. Herrmann and thank you, Dr. Li.

Dr. Herrmann: Pleasure to be here.

Dr. Li:Thanks very much for the opportunity, Adam.



HeartValveSurgery.com Resources for Patients

Since 2006, <u>HeartValveSurgery.com</u> has developed several resources to help you better understand your diagnosis, your treatment options and your recovery.

Listed below, please find resources created exclusively for patients and caregivers. We hope they educate and empower you.

- <u>Adam's Free Patient eBooks</u> Download 10+ free eBooks about heart valve dis-ease and treatment options for aortic, mitral, pulmonary and tricuspid valves.
- <u>Heart Valve Learning Center</u> Visit the Heart Valve Learning Center to access over 1,000 pages of educational information about valvular disorders.
- <u>Patient Community</u> Meet people just like you in our patient community. There's nothing better than connecting and learning from patients who are sharing their stories in our community.
- <u>Surgeon Finder</u> Find and research patient-recommended heart surgeons that specialize in heart valve repair and heart valve replacement procedures.
- <u>Heart Hospitals</u> Learn about medical centers that have dedicated teams and resources that specialize in heart valve therapy.
- <u>Adam's Heart Valve Blog</u> Get the latest medical news and patient updates from our award-winning blog.
- <u>Educational Videos</u> Watch over 100 educational videos filmed by the Heart-ValveSurgery.com film crew about heart valve surgery.

