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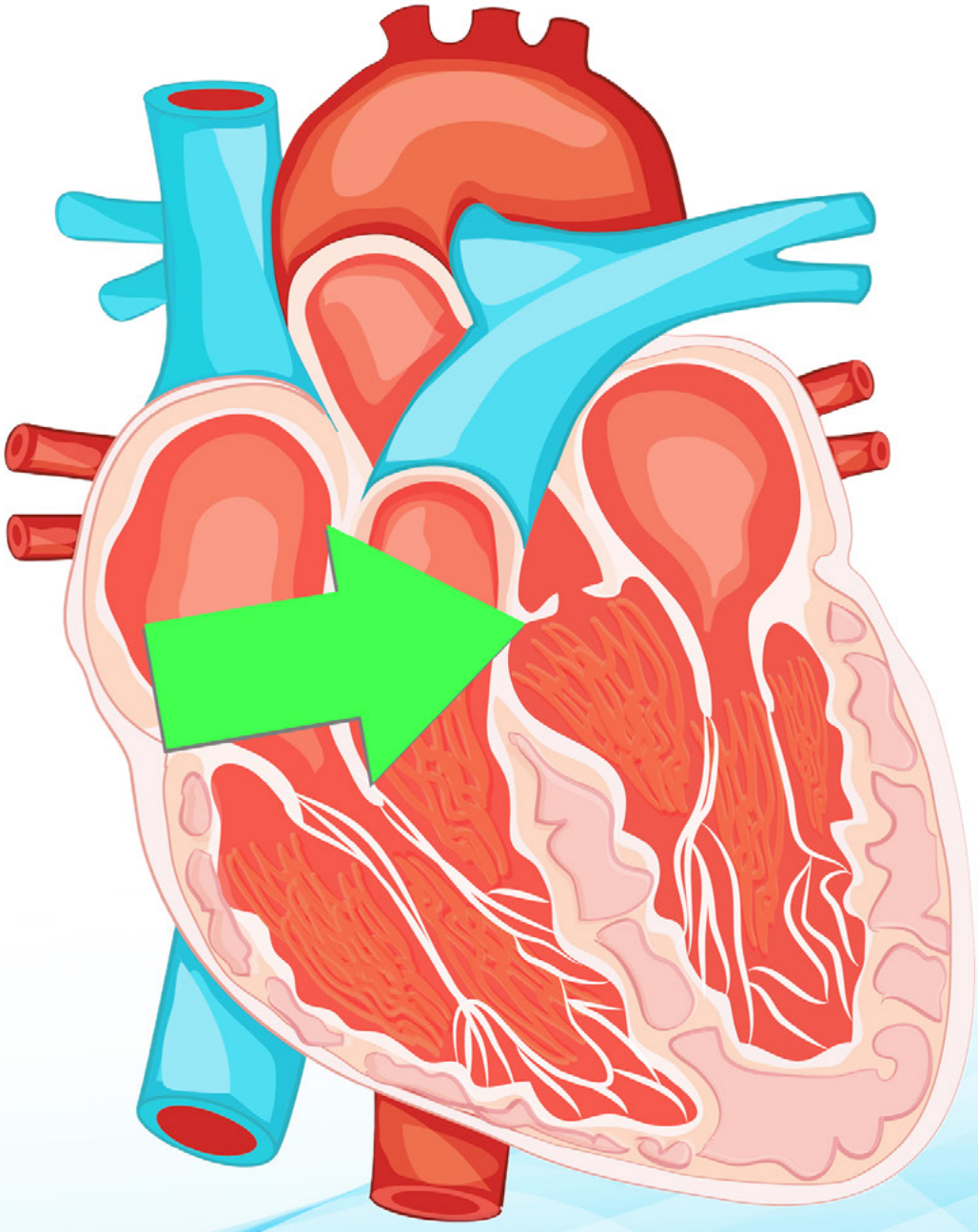
ADVANCES IN CONGENITAL

AORTIC VALVE DISEASE THERAPY



Penn Medicine

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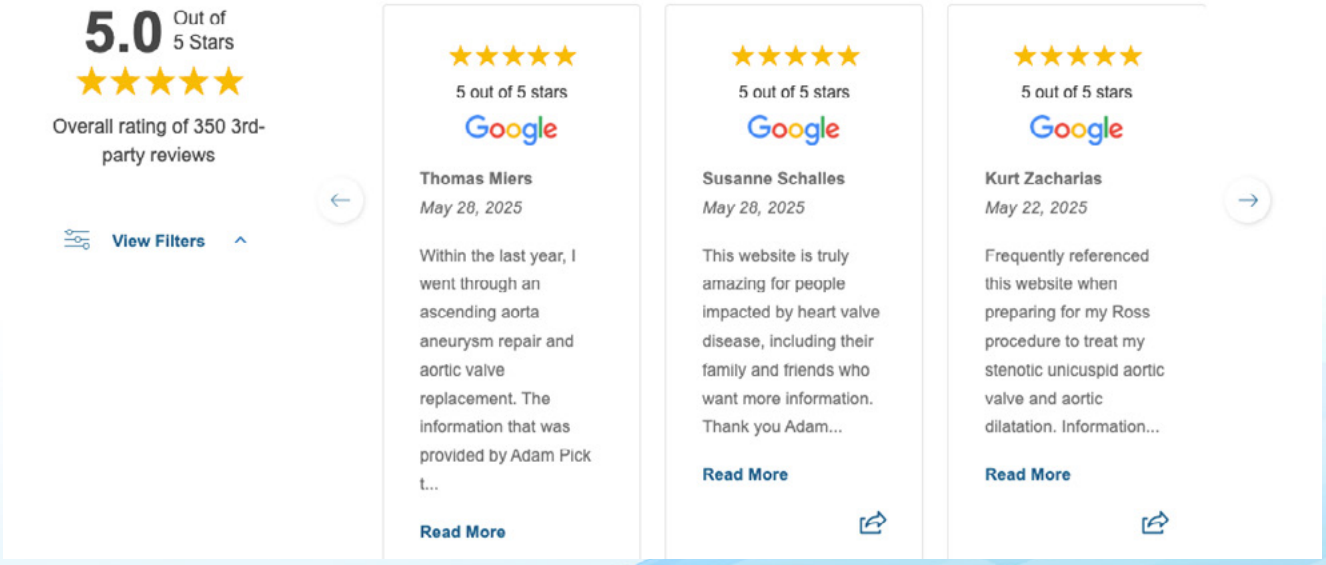

Authors

Dr. Nimesh Desai

Cardiac Surgeon
Penn Medicine
(888) 640-6922
Learn More.

Dr. Allison Tsao

Interventional Cardiologist
Penn Medicine
(215) 445-3533
Learn More.

Adam Pick

Patient, Author & Website Founder
HeartValveSurgery.com
(888) 725-4311
Learn More.

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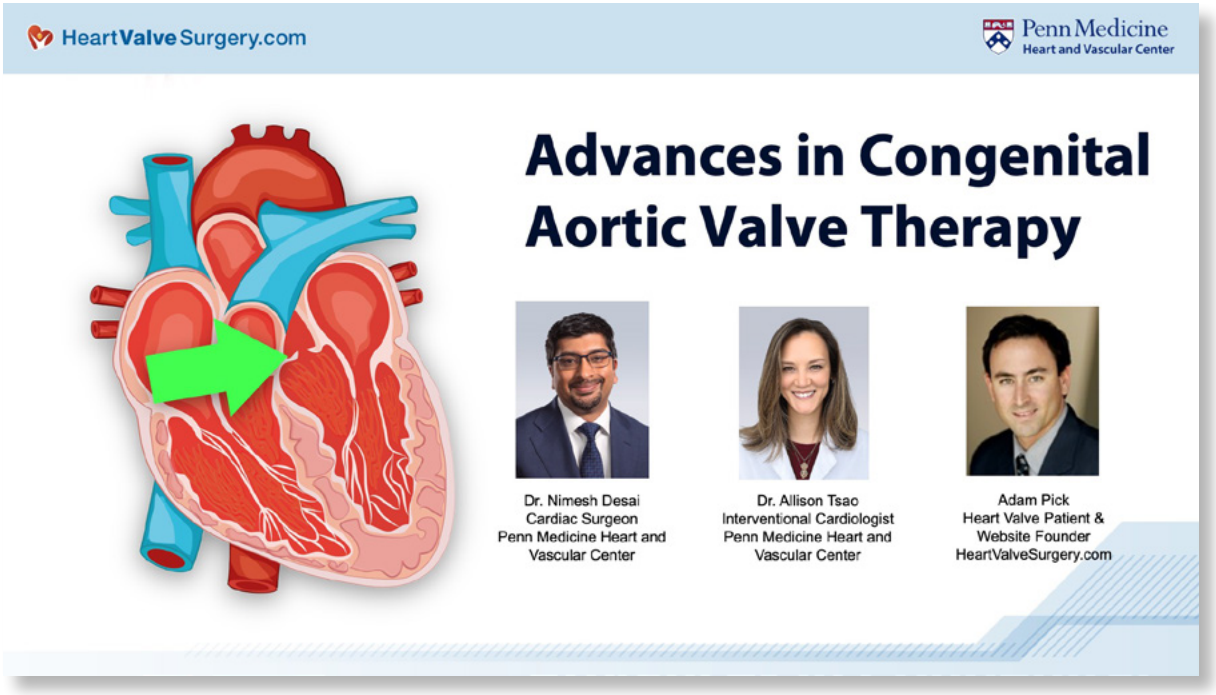
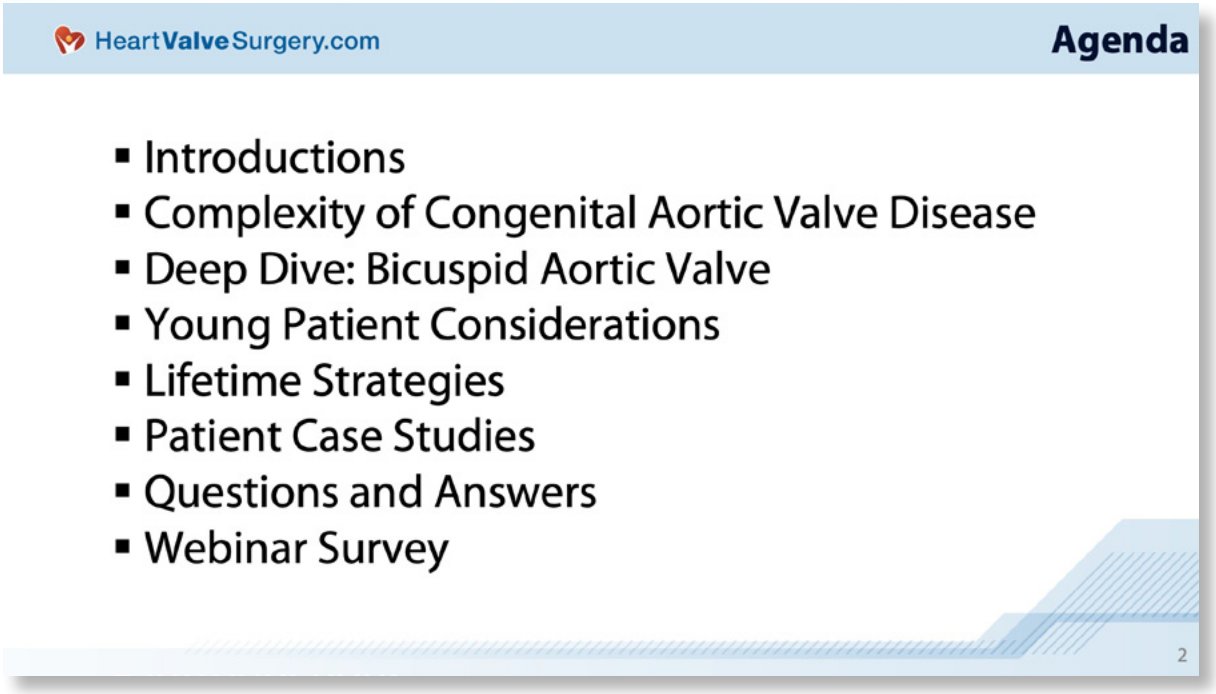
Introduction



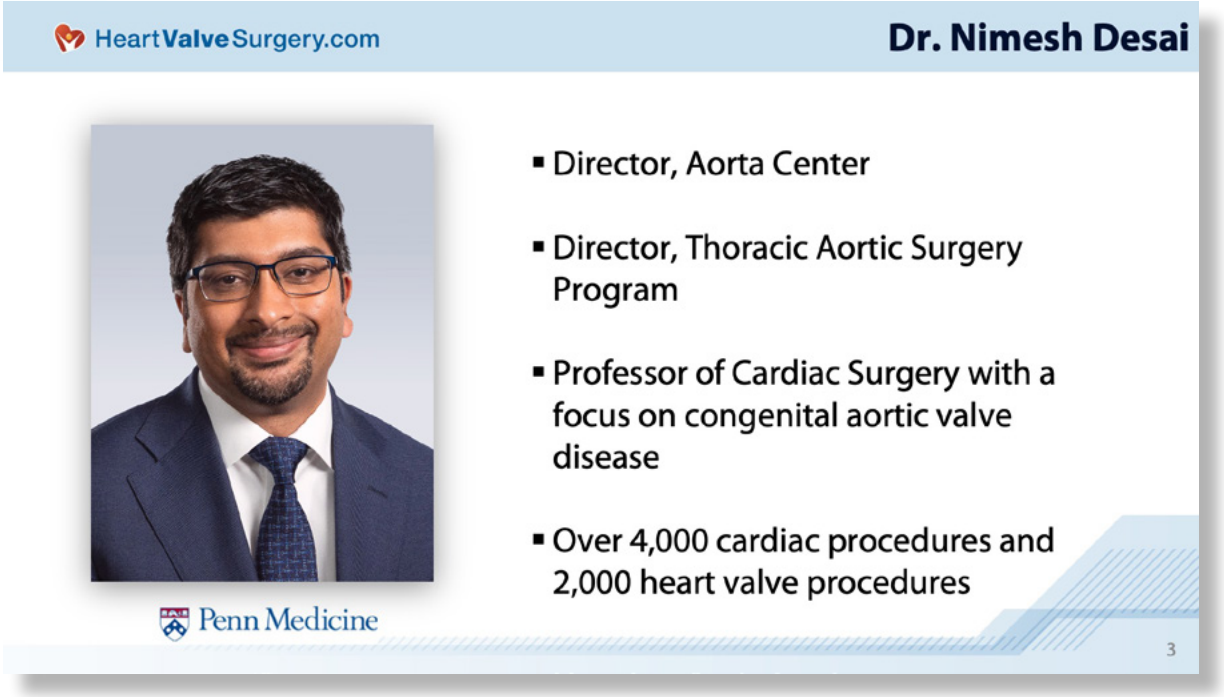
Adam Pick: Hi, everybody. My name is Adam Pick, and I'd like to welcome you to the webinar titled, "Advances in Congenital Aortic Valve Disease Therapy". If I've yet to meet you, I'm the patient who started HeartValveSurgery.com all the way back in 2006. The mission of our website is really simple. We want to educate and empower patients just like you. This webinar, which has had over 600 registrations from people in countries all over the world, was designed to support that mission.

Now, throughout the webinar, you're going to be in what's known as "listen-only" mode, but I encourage you to submit your questions, because we're going to try to get them answered during the Q&A session of the webinar.



Now, let's take a look at the agenda for today. I'm going to introduce our featured speakers. We're going to talk about the complexity of this disease. We're going to do a really interesting dive into aortic bicuspid valves. We're going to look at the considerations for young patients and lifetime management strategies of the disease. One of my favorite parts is the patient case studies. Then we are going to do a Q&A session. Lastly, I'm going to ask you to complete a quick five-question survey.

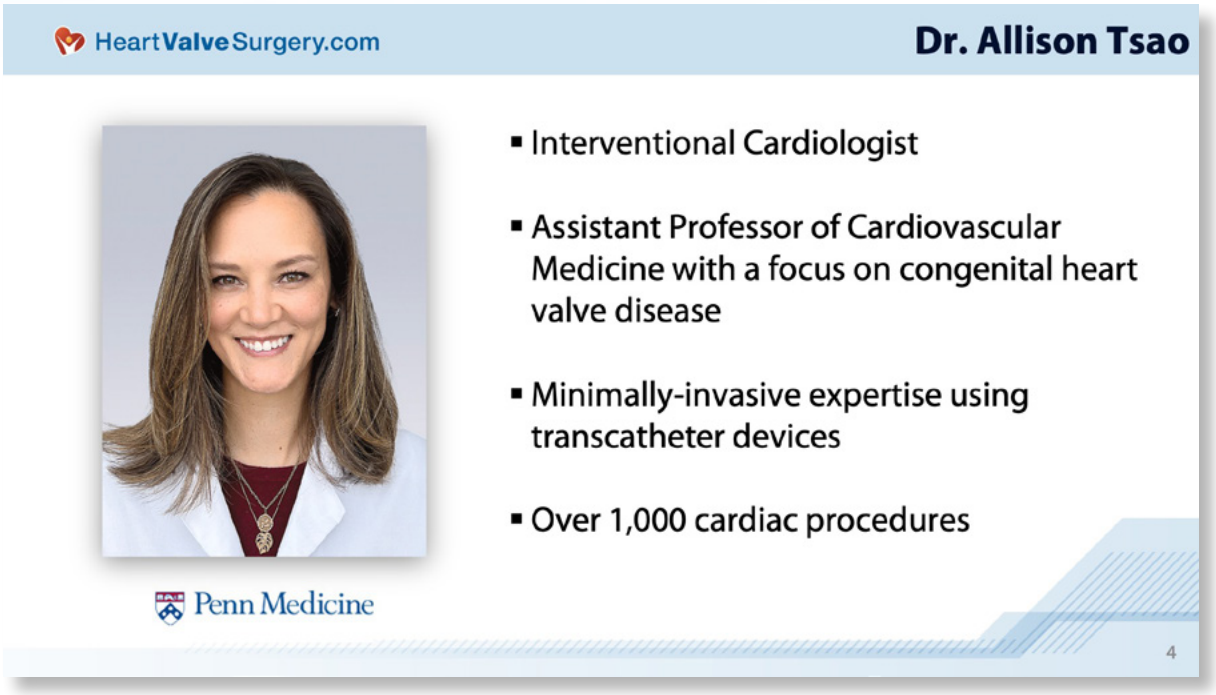
Now, when it comes to the featured speakers for today, I'd submit to you that we have a "Dynamic Duo" of heart valve therapy. We not only have a cardiac surgeon, but we also have an interventional cardiologist that have come together to co-manage patients just like you. So who are they?



Dr. Nimesh Desai is a director of both the Aorta Center and the Thoracic Aortic Surgery Program at Penn Medicine in Philadelphia, Pennsylvania. He's also a professor of cardiac surgery with a focus on congenital aortic valve disease. During his extraordinary career, Dr. Desai hasn't performed just one, or two, or 3,000 procedures; he's performed over 4,000 cardiac procedures with more than 2,000 involving a repair or a replacement of a heart valve.

Dr. Desai, you and I have known each other for a long time. Thanks so much for being with us today.

Dr. Nimesh Desai: Yeah, thank you, Adam. It's been a pleasure to be here and be with the whole heartvalvesurgery.com community.



Adam Pick: Let's move on to the second half of the dynamic duo, and that is Dr. Allison Tsao, who is an interventional cardiologist at Penn Medicine. She's also an assistant professor of cardiovascular medicine with a focus congenital heart valve disease. What Dr. Tsao specializes in is the use of minimally invasive catheters for the treatment of repairing or replacing heart valves. During her career, she has performed over 1,000 cardiac procedures.

Dr. Tsao, thanks for being here today.

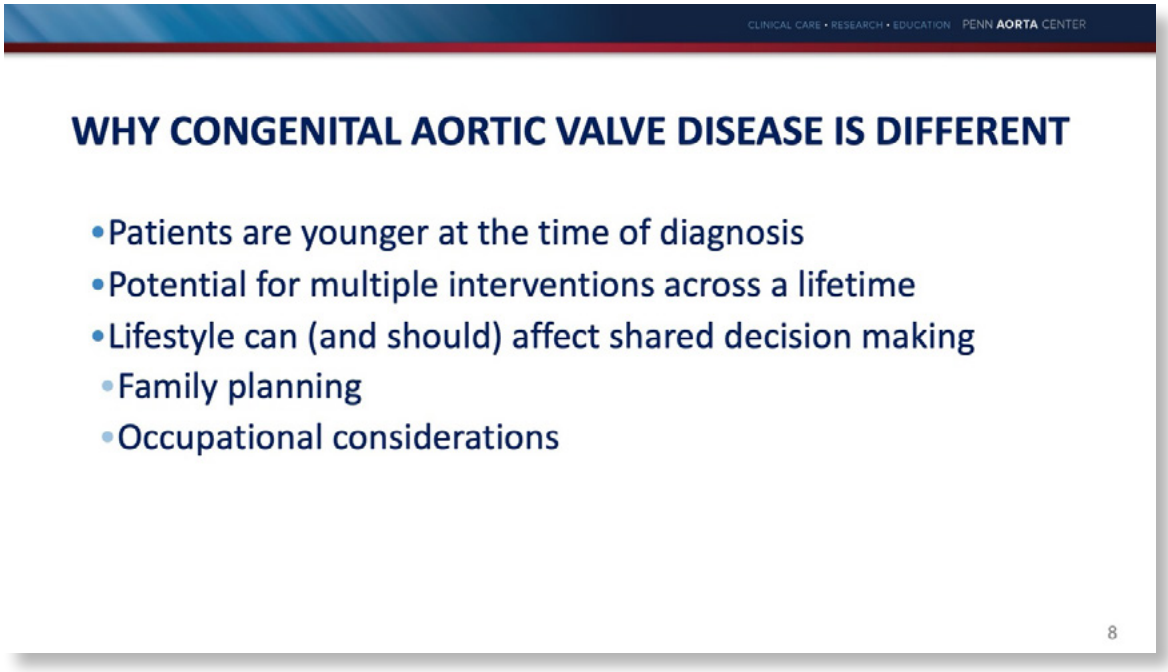
Dr. Allison Tsao: I'm so happy to be here. Thanks for including me.

Penn Medicine Patient Success Stories

Adam Pick: I could go on and on about the accolades and achievements of Dr. Desai and Dr. Tsao. Instead, what I want to do is I just want to very quickly show you some of the success stories, the faces, the smiles, and the people of the folks from the HeartValveSurgery.com community who've had very positive, excellent outcomes at Penn Medicine, whether it's Michael King or Diane Mowery or Sean Murphy, or Gerald Shaffer, or Eillen Garton.

It is a gift that we have these incredible physicians on the line with us today, and I'd like to say on behalf of four community, thanks for being here and welcome, Dr. Nimesh Desai and Dr. Allison Tsao.

Why Is Congenital Aortic Valve Disease Different?



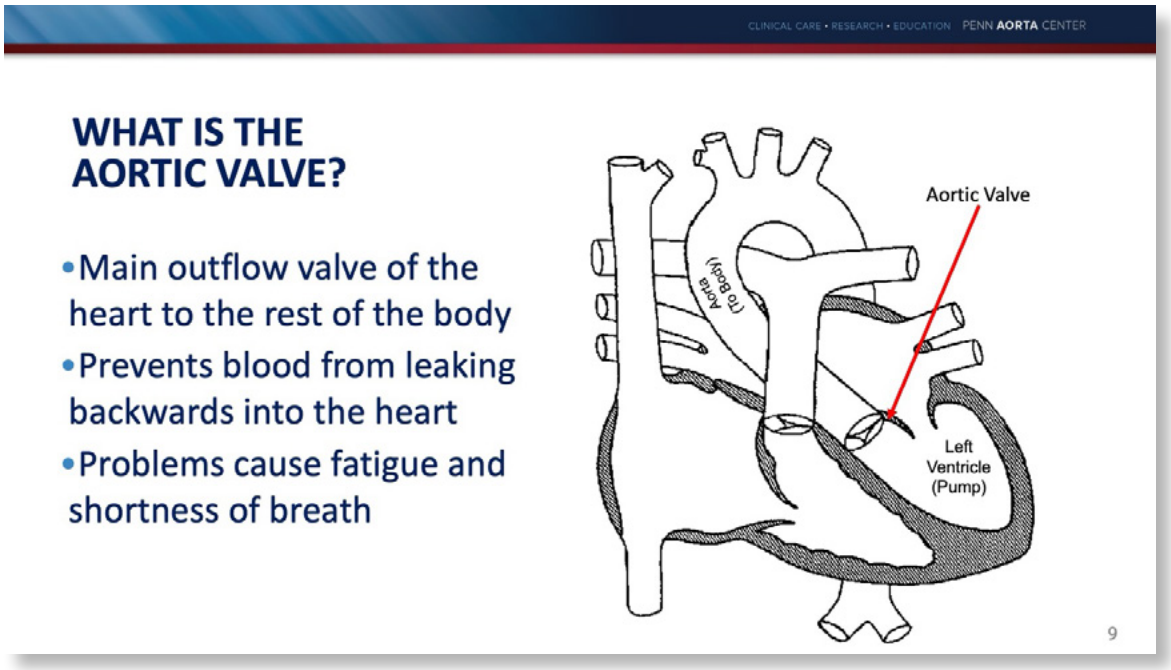
Dr. Allison Tsao: Thank you so much. It's such a pleasure to be here. I'm really excited to have this opportunity to discuss congenital aortic valve disease and some differences there in how we approach it in the younger patient but also to be doing this in collaboration with my close partner and friend, Dr. Desai. Hopefully, we'll be able to relay some of our thought process in how we co-manage and approach patients like you or family members that you know.

So why should we think of aortic congenital valve disease as something slightly different than maybe acquired or degenerative valve disease in an older patient? The important thing here is that you or a loved one might be diagnosed at a much younger time in your life. That might influence what surgical repair or replacement is approached for you, but also there's going to be the potential for multiple interventions across the lifetime. This is not going to be a single repair, replacement and done. We're going to have to be really thoughtful about what's the best option now and what your best option might be in the future and what potentials are still on the table for you in the future.

With that, we are here to help you with your life. I always tell people that, "We're not here to change anything. We're here to help you live your best life and make sure your cardiovascular system can keep up with you." In that aspect, your lifestyle can and really should affect the decisions that are made and should be part of a shared decision-making process.

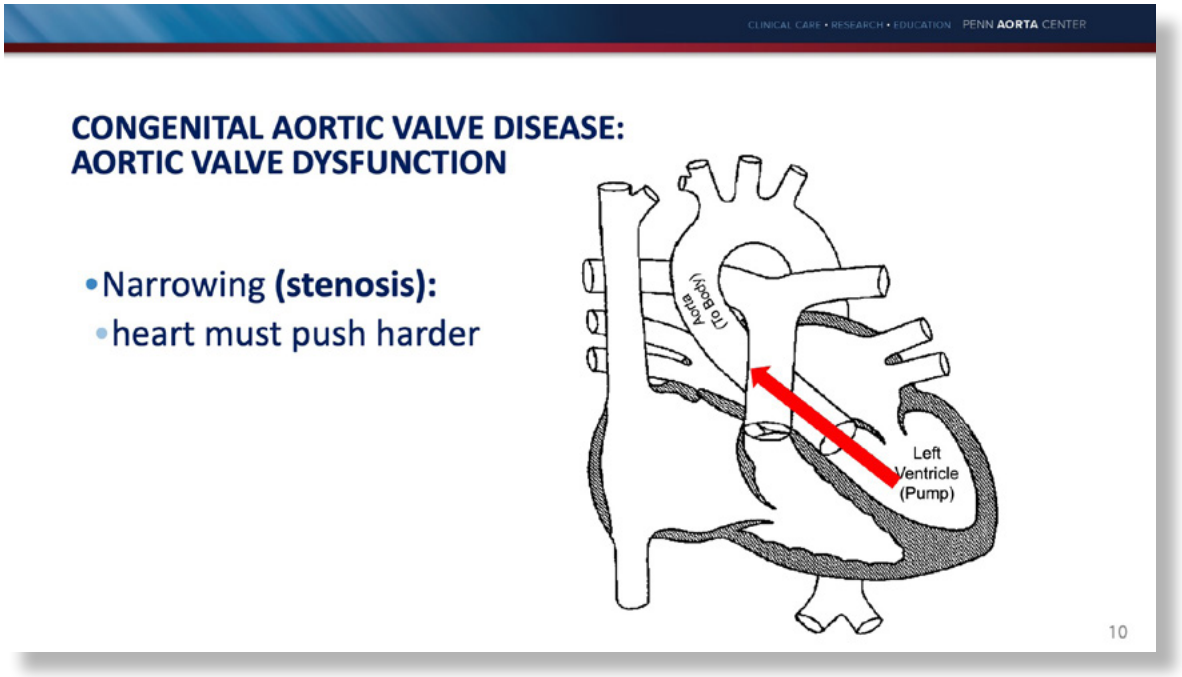
Some important points that we'll highlight in the next hour will be considerations for family planning, occupational or lifestyle activities that are going to be important to you that should go into how we approach options for you, whether that's recovery period, medications that will be important, and timing.

The Aortic Valve

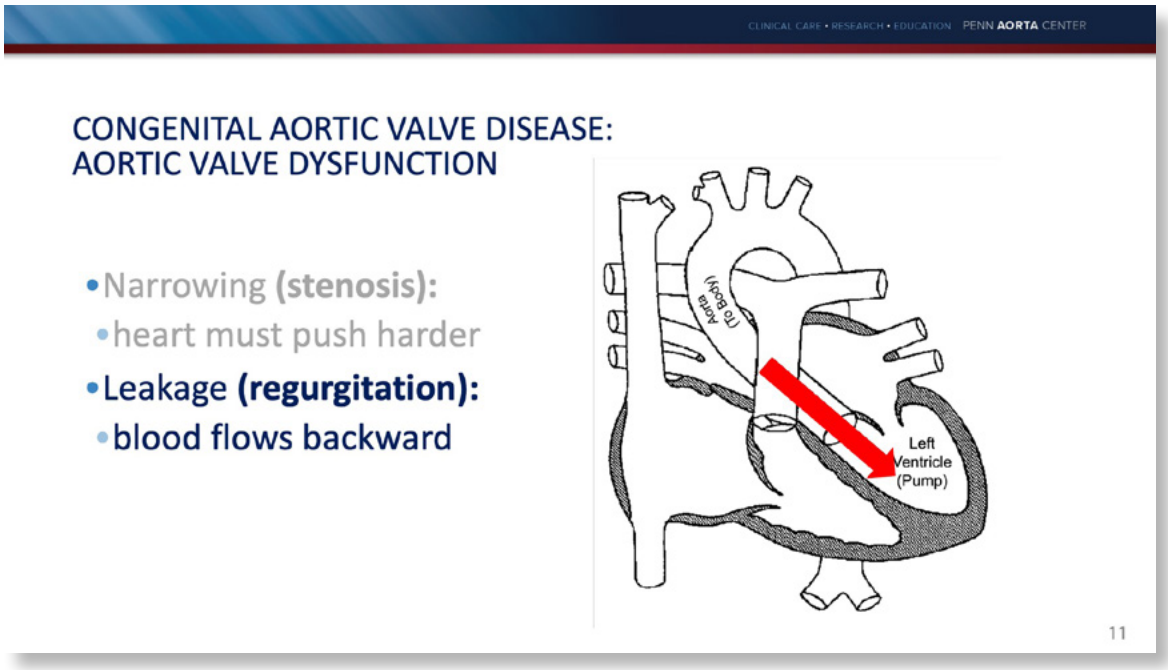


Dr. Allison Tsao: So this is a very well-educated community, so this is slightly redundant, but what is the aortic valve? This is the main outflow valve from the heart to the rest of the body. It is the throughput to have all of the oxygenated blood go to your organs for you to do what you want to do. It prevents blood from leaking backwards into the heart, and when we have issues with it, whether it becomes too tight or too loose, we can – patients can develop symptoms with fatigue, shortness of breath, or inability to do what they want to be doing.

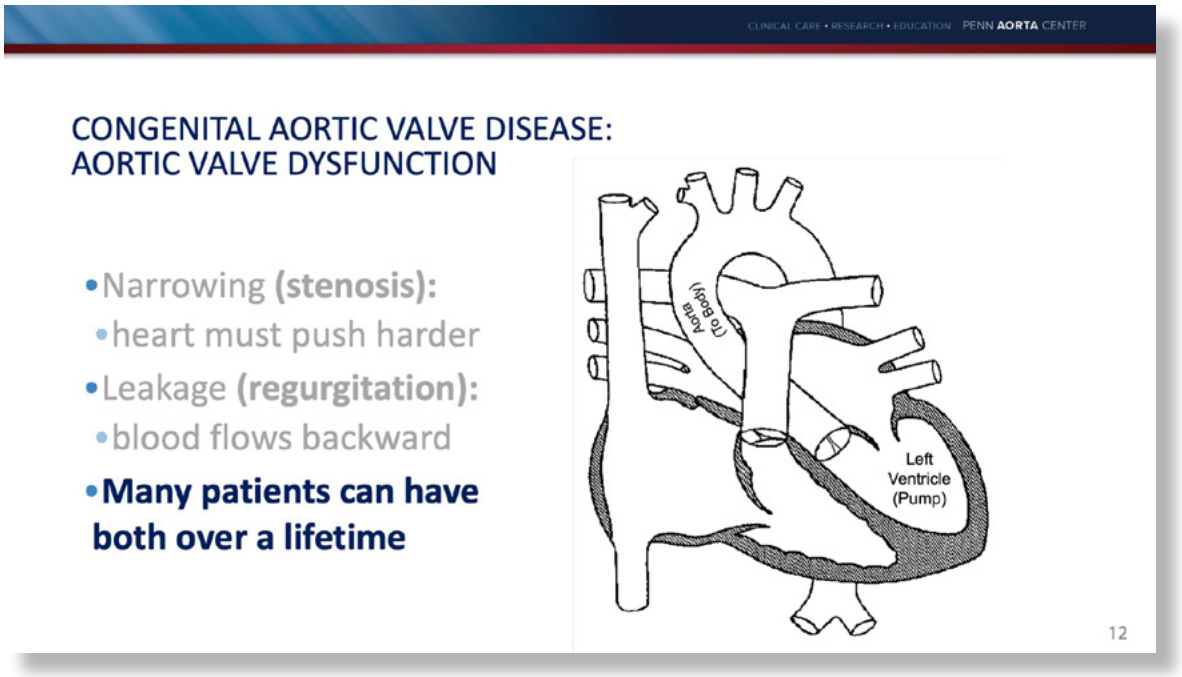
Aortic Valve Dysfunction



Dr. Allison Tsao: So patients can develop narrowing, or stenosis, of the aortic valve, and that means the heart has to push harder in order to get more blood out with each heartbeat.

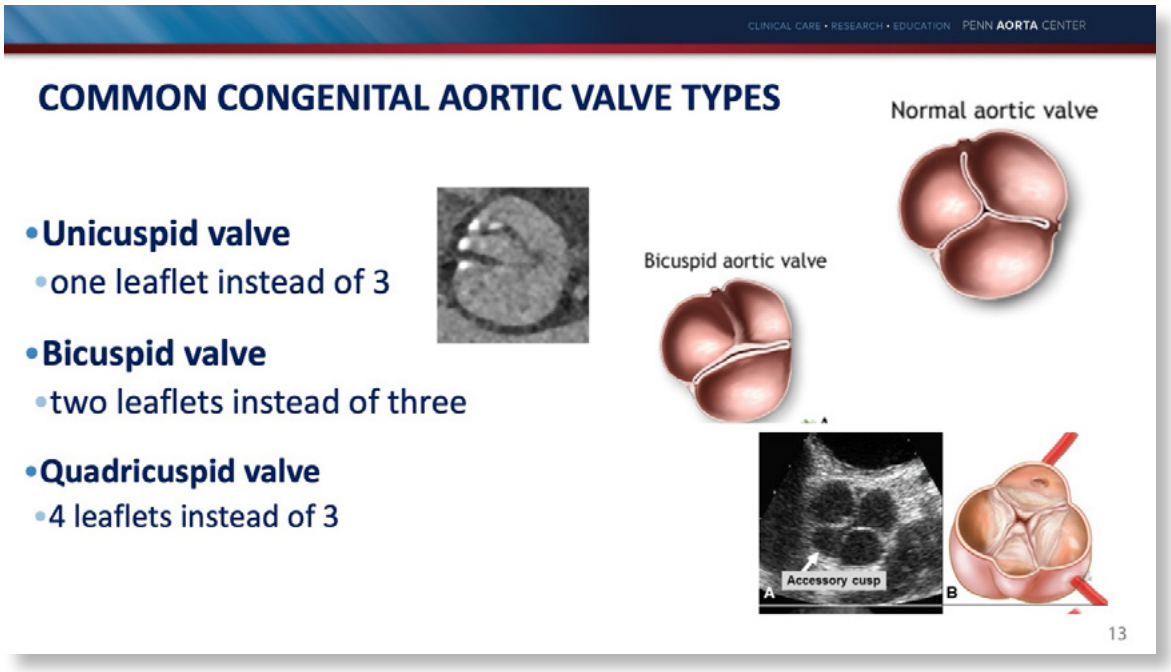


The next issue is you can develop regurgitation. If you hit the forward button again, next slide, you'll see that when it becomes regurgitant, that valve is not competent or the leaflets don't come together, and the blood can flow backwards. Again, this is inefficient blood flow through a system that's designed to have one-way blood flow.



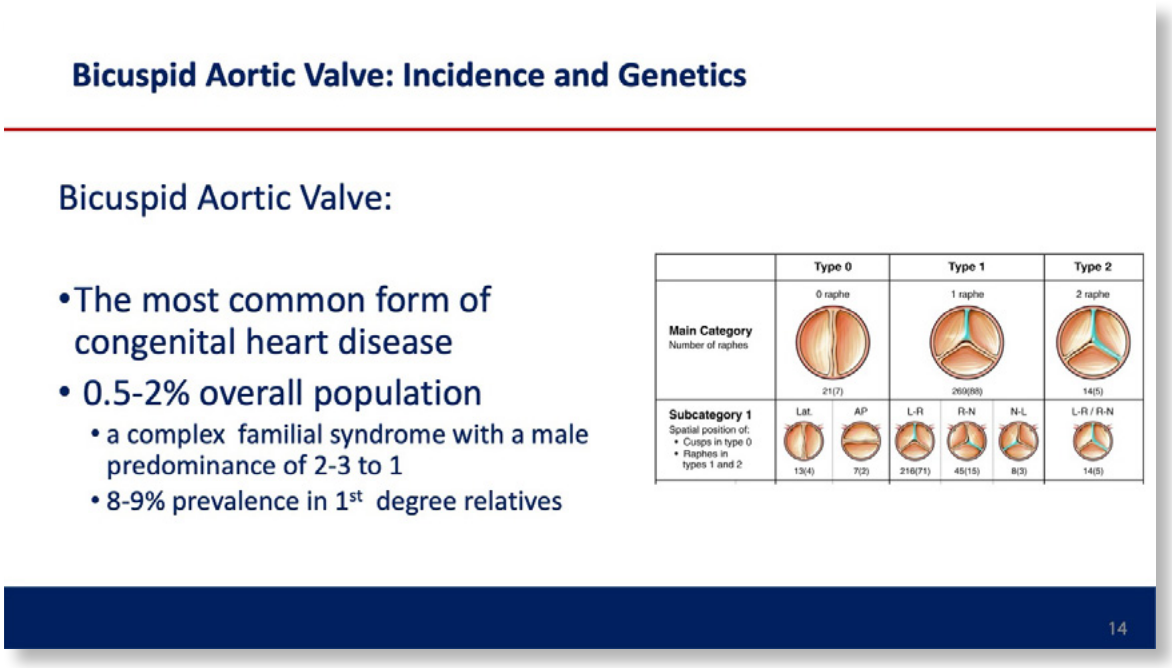
Importantly, especially in the setting of congenital aortic valve disease and thinking about care over a lifetime, many patients can develop both at different periods of their life, and it might be influenced by prior interventions that they've had in the past.

Common Congenital Aortic Valve Diseases



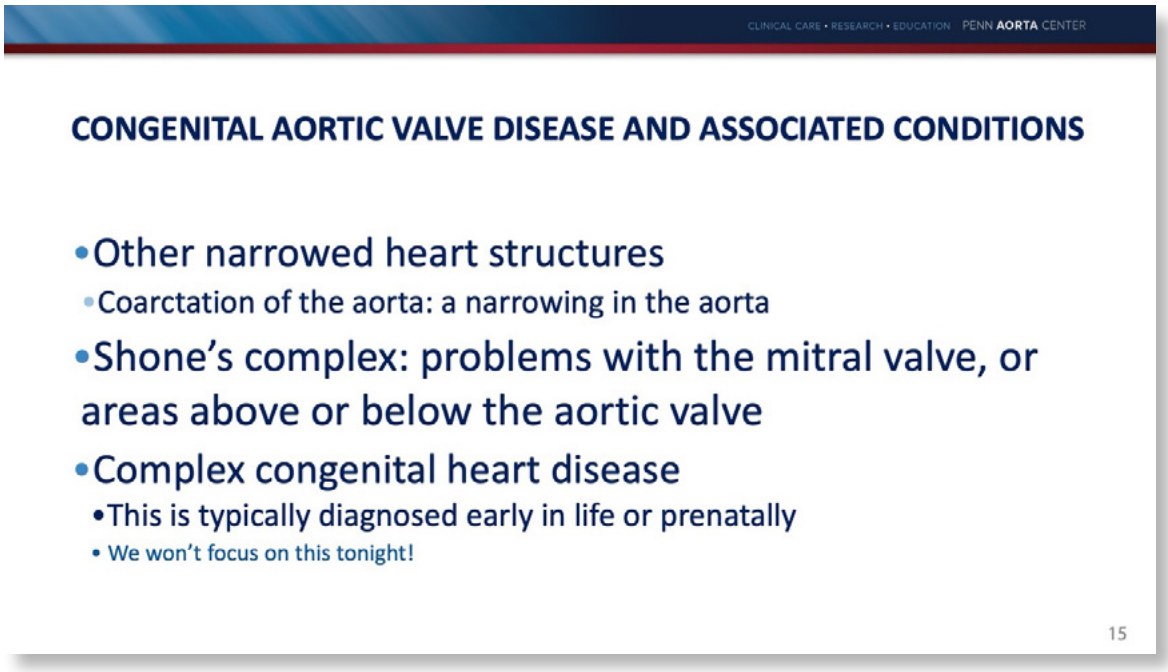
Dr. Allison Tsao: Anormal aortic valve should have three leaflets, a tri-leaflet or tricuspid. Sometimes that language gets used very interchangeably. In the top right-hand corner, you see a normal aortic valve with three leaflets that should open and give you a nice, efficient, round orifice. Dr. Desai knows I love physics. We like things that are round in the body. Gives you good forward flow. When we think about congenital aortic valve disease, almost anything can happen. The most common ones that we'll talk about will be a unicuspid aortic valve, which we see here. It almost looks like kind of a C-shape with an oval opening; a bicuspid aortic valve with two leaflets, and symmetry might vary in that, again, with an oval orifice; or even a quadracuspid aortic valve, four leaflets. Again, you can probably find a case report with different numbers and different leaflets, but just know that there can be an entire spectrum of congenital aortic valve disease when we think about this.

Bicuspid Aortic Valves



Dr. Allison Tsao: Bicuspid aortic valve, we'll focus a lot on that here. Know that we use that interchangeably when we think about congenital aortic valve disease in general. It is the most common form of congenital aortic valve disease in the general population. Depending on what population we're looking at, that can be 0.5 to 2% of the population. The important thing to remember with the aortic valve is we talk about the valve, but this is really a complex syndrome that can run through a family. It affects more than the aortic valve. It's really thinking about the entire aorta or that entire blood vessel through the body. It is more prominent in men with a 2 to 3% predominance to women, but men and women can develop bicuspid aortic valves for congenital aortic valve disease. An important thing to remember for everybody on the call is when you have congenital aortic valve disease, it's much more common in first degree relatives. So part of this collaborative approach in approaching a patient with congenital valve disease is making sure we're not only caring for you but caring for your family and making sure you're educated and knowing where your loved one should also get care or be screened for this.

Associated Cardiac Conditions

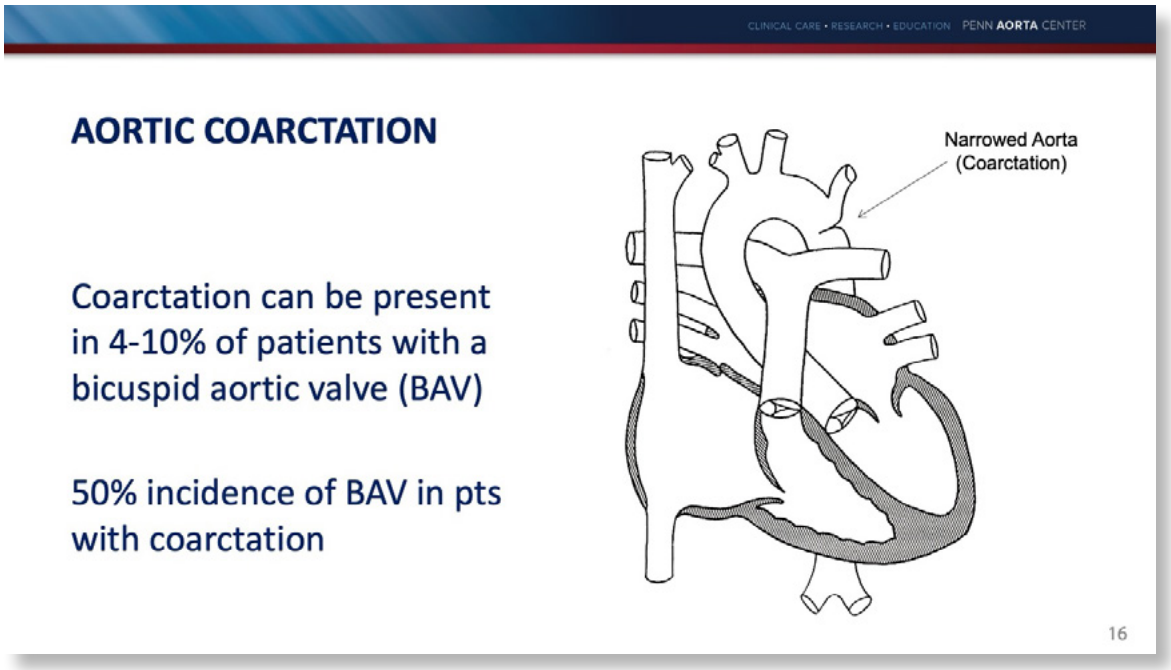


Dr. Allison Tsao: One thing that we also like to think about in this total approach to a patient is that congenital aortic valve disease can be associated with other narrowed heart structures. This can be coarctation of the aorta. This might be a new word, but this is narrowing of the aorta itself.

Shone's complex, this is a complex series of narrowing of various structures. So once the aortic valve is abnormal, know that other parts of the heart might also be narrowed. That can involve the mitral valve, a different left-sided heart valve, and also areas above and below the aortic valve. I have some schematics or some pictures to show you guys soon.

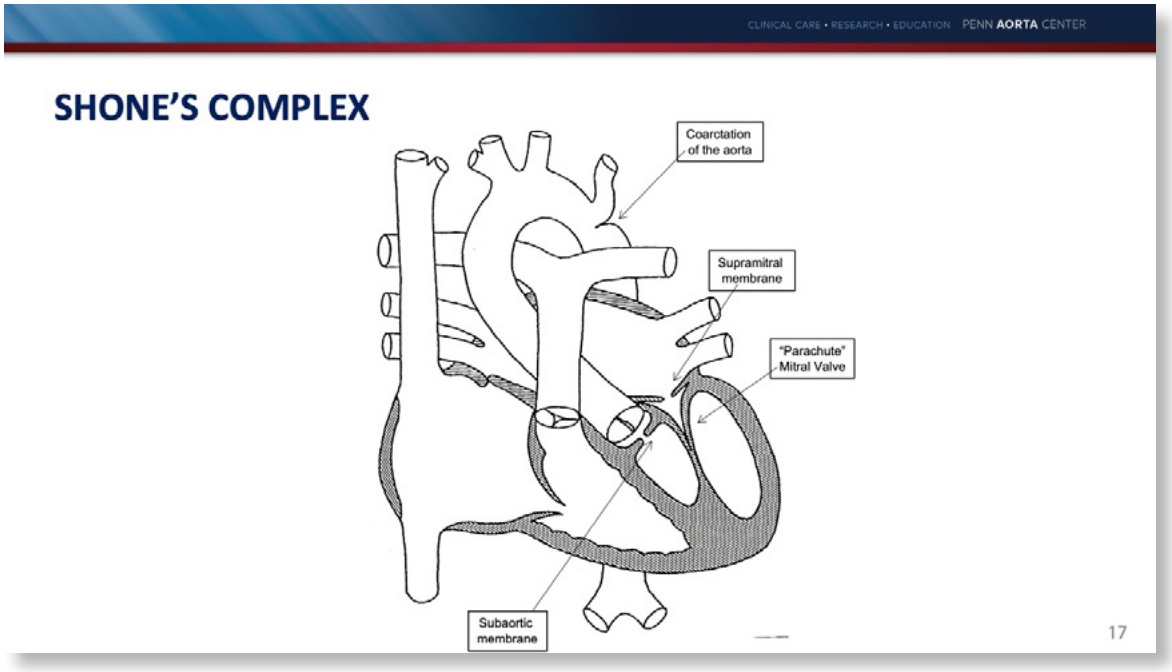
One thing that I'm not going to talk about specifically is complex congenital heart disease. There is an increased incidence of congenital aortic valve disease in a patient with complex congenital heart disease. This is typically diagnosed early in life or prenatally, and we're not going to focus on this tonight. If those questions come up, I'm happy to relay and communicate afterwards.

Aortic Coarctation



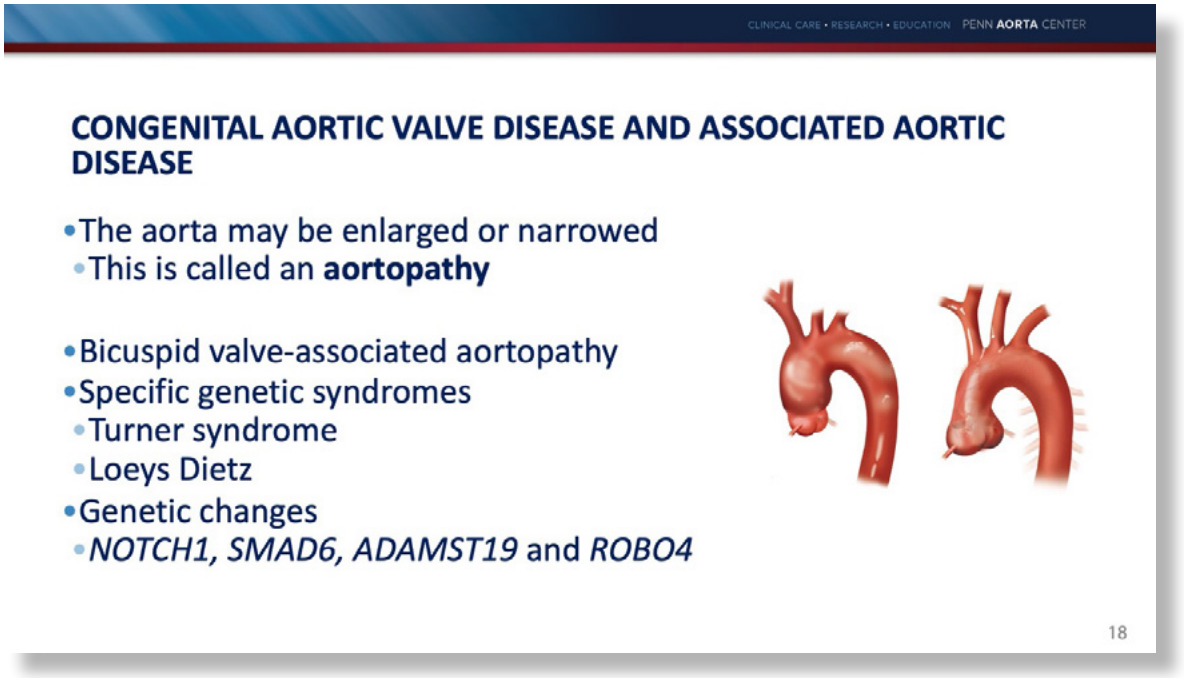
Dr. Allison Tsao: Aortic coarctation, this is the simple cartoon of this, but coarctation of the aorta, that narrowing that we see on the right-hand side, can be present in 4 to 10% of patients if you have a bicuspid aortic valve. So if you have a bicuspid valve, maybe up to a 10% chance that your aorta is narrowed. We need to remember that when we meet patients, patients like you or your loved ones, and make sure that we have appropriate imaging for that. Now, another thing to remember is the flipside. If you have a coarctation of the aorta, maybe that's your first diagnosis. There's a 50% chance that you have a bicuspid aortic valve or some congenital abnormality in your aortic valve. This is important because a patient might be diagnosed very early on with coarctation and nobody will think about their valve. We want to meet those patients. We want to make sure they've had a screening echo and we know the anatomy for their valve.

Shone's Complex



Dr. Allison Tsao: This is just a quick cartoon of Shone's complex. Just know that once one thing is narrowed like a bicuspid valve, you could have coarctation, narrowing of your mitral valve, whether above or below it, and also narrowing in the area immediately below your aortic valve. Things to just be aware of. This is why Dr. Desai and I like to see patients in collaboration, so we never forget we're looking at the whole heart beyond just one valve.

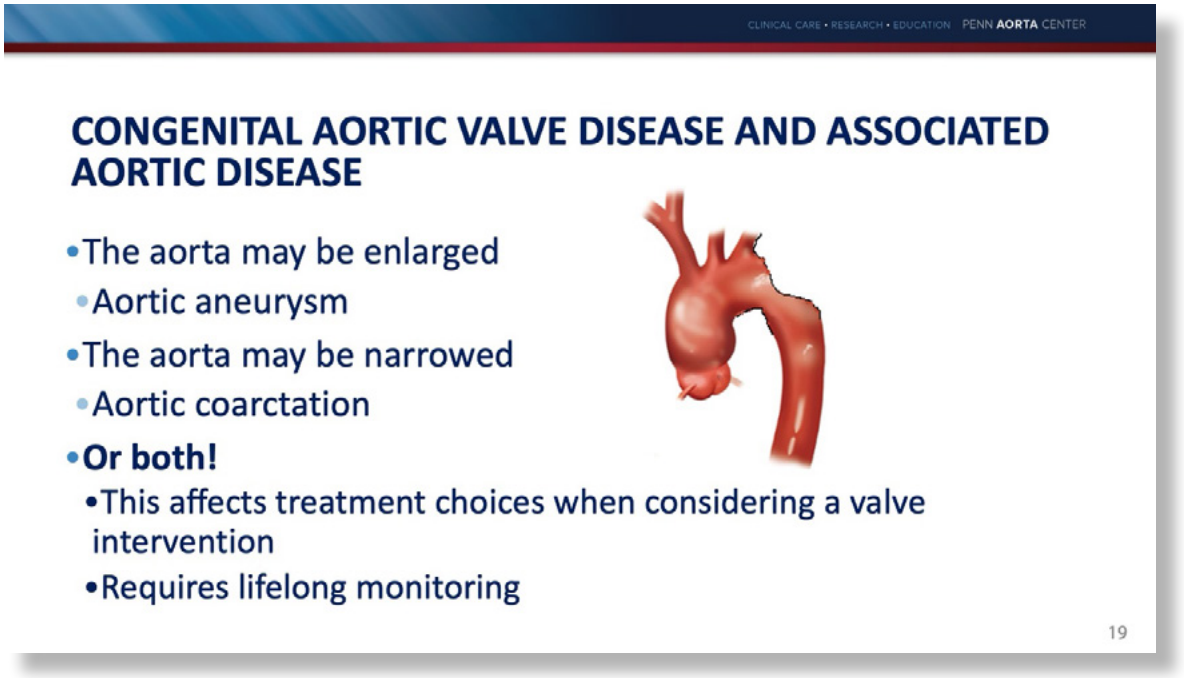
Aortopathy



Dr. Allison Tsao: Now, when you have congenital aortic disease, we talked about coarctation. Another important part is there's an entire aortopathy, and I think Dr. Desai has been in webinars before that have discussed the aortic valve is actually from the aorta.

Embryologically, that's how the heart forms. When the aortic valve is abnormal, we need to think about that entire blood vessel. Bicuspid valve associated aortopathy is a very interesting topic to talk about. We need to remember that there are other specific genetic syndromes that go along with this that go beyond just a bicuspid valve. These are things like Turner's syndrome or Loeys Dietz syndrome. There are genetic syndroms that exist that have a higher incidence of bicuspid valve and aortic disease. We like to see these patients.

Again, we collaborate and make sure we're managing the totality of their heart and genetic disease as a team. There are also specific genetic changes that might not be linked to larger genetic syndromes that I've listed here. We'll evaluate patients when we meet them in clinic in collaboration with our aortic geneticist to make sure we're screening and then – a patient for these changes and then we can expand that screening to their family members as appropriate.



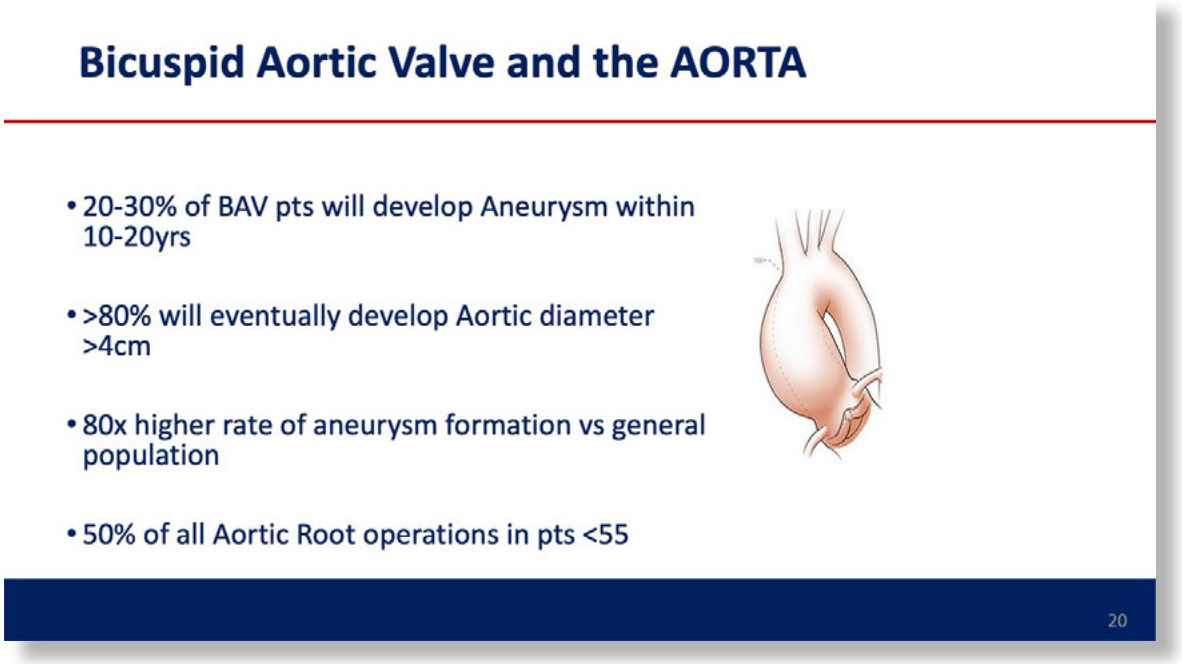
In summary, we need to think about that entire aorta, whether it's enlarged with aortic aneurysms, whether it's narrowed with an aortic coarctation. Once that congenital aortic valve disease has been diagnosed, we're thinking about the entire cardiovascular system and the presence of these is going to influence what treatments we might decide to pursue for a patient; also the order which we might approach those interventions. Once we "fix" a valve, or a narrowing, or an aneurysm, we know that this is going to require lifelong monitoring, ideally in a collaborative congenital aortic valve disease and aorta center.

Patient Question: What Is An Interventional Cardiologist?

Adam Pick: Dr. Tsao, we have a question that came in from Rick Hollen. He asks a question, “Can you explain exactly what an interventional cardiologist is?”

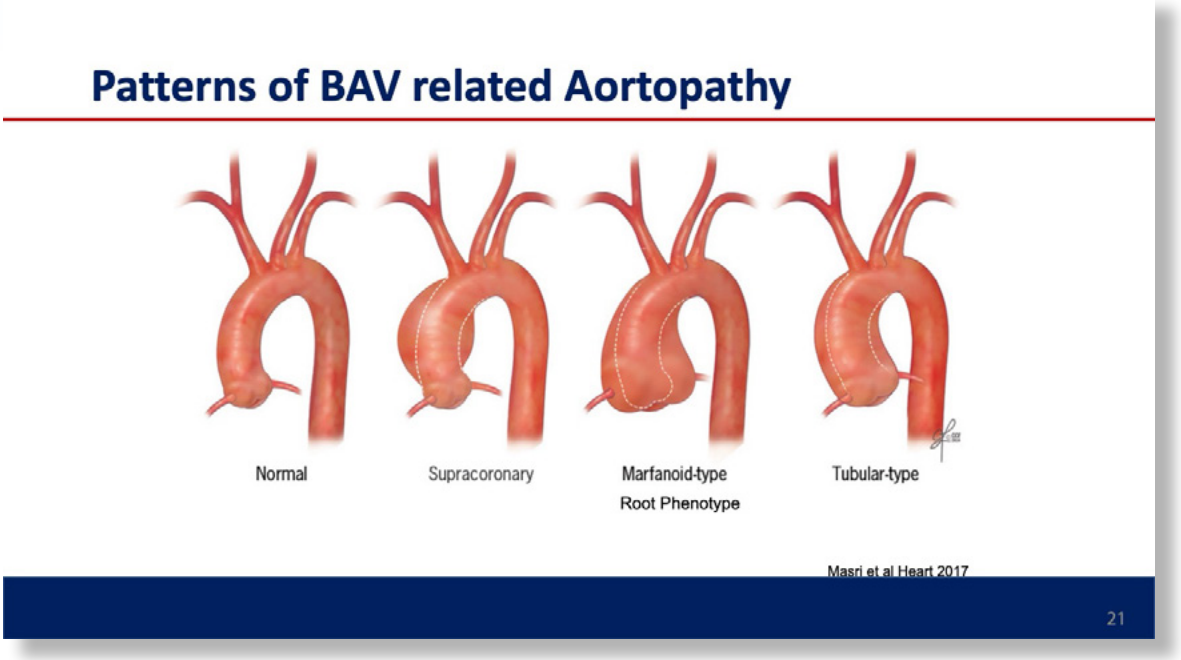
Dr. Allison Tsao: So I am a cardiologist. I see patients in clinic, but I spend the majority of my time in the cath lab, and I do interventions in the heart. I might put in stents into blocked blood vessels. I might put minimally invasive valves in collaboration with Dr. Desai. Sometimes I close connections in hearts. If your heart has a hole in in that should not be there, I’m somebody who might put a device in to close that. I am largely procedurally-based, but when you meet an interventional cardiologist, you leave with a fancy band-aid. I don’t do any cutting. Dr. Desai and I collaborate closely on some hybrid procedures as well, which we’ll get into.

Bicuspid Aortic Valve and the Aorta



Dr. Nimesh Desai: The bicuspid aortic valve and the aorta are really one structure at its essence, that when the aorta forms when you're an embryo, the elements of it that form the aorta also form the aortic valve. That's why these two things are intrinsically related.

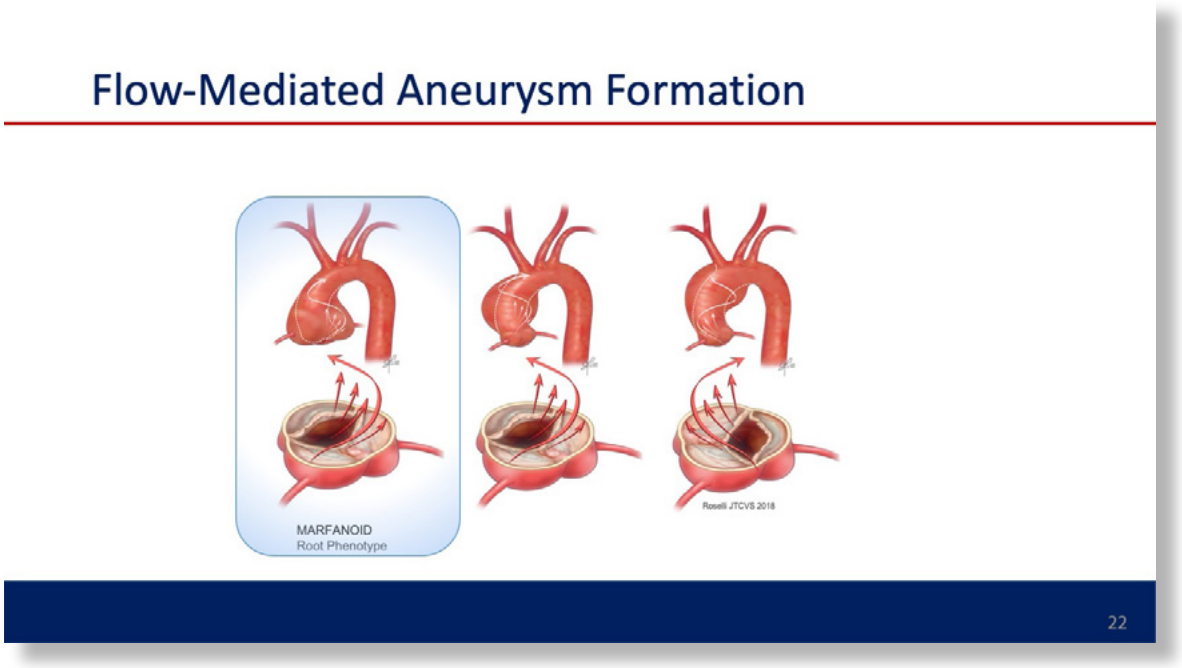
Aneurysms, or enlarged aortas, happen in about 20 to 30% of bicuspid valve patients at the time of their diagnosis within 10 to 20 years. We know that aneurysms are pretty frequent in bicuspid valve patients. In fact, if you watch aortas of bicuspid valve patients over a longitudinal period of time, almost 80% will develop an aorta that is larger than 4 centimeters, which would be considered a small aneurysm or out of the range of what is a typically sized aorta. That's an 80 times higher rate of aneurysm formation than the general population. Bicuspid valves and aneurysms go hand in hand together. Interestingly, if you look at people who need aortic aneurysm operations, especially in the younger patients, almost half of them are actually patients with bicuspid aortic valves.



One of the questions we often get asked is, "Why do people develop bicuspid valves and what kind of different patterns are there – aneurysms, rather, with bicuspid valves?" What kind of patterns are out there that would lead us to either intervene or not intervene on the aorta at different time points? The first picture we have is a pretty normal-sized and normal-looking aorta. Then we have different patterns of aortic aneurysms that can form. The most common pattern is the second pattern, what says super coronary there, and that is where the aorta is enlarged above the aortic valve. It doesn't actually involve the aortic valve or what we call the aortic root where the aorta joins the heart.

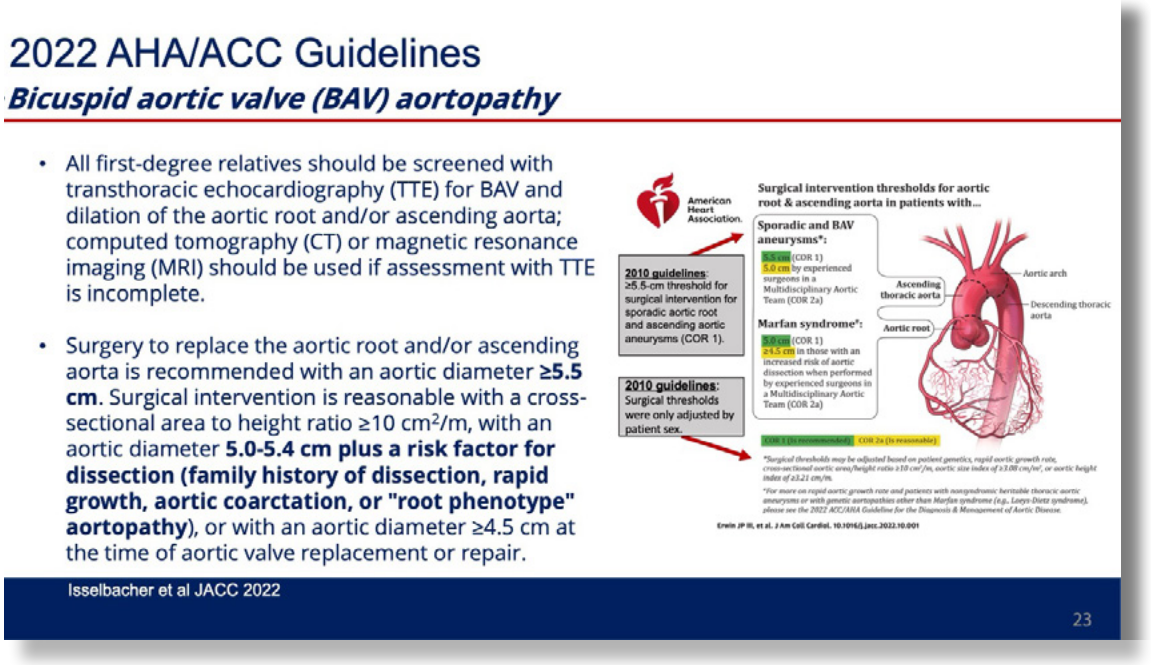
The next one is where the root itself is dilated. The actual part where the aortic valve and the aorta join into the heart is enlarged. That kind, we actually are a little bit more aggressive about operating on to prevent things like a rupture or a tear in the aorta. This is the kind we're usually more likely to intervene on earlier or at a smaller size. Then finally, there's the one in the format where all of the aorta is enlarged. That's actually a fairly common variant as well.

Flow Mediated Aneurysm Formation



Dr. Nimesh Desai: How your valve is shaped also influences whether or not you develop an aneurysm and what kind of aneurysm you end up with. These are different patterns of flow coming out of different shaped bicuspid valves. As Dr. Tsao showed earlier, there are so many different variations in bicuspid valve that people often use the term bicuspid valve, but I'll tell you, having taken out or cut out probably two or three valves in them over the years, every bicuspid valve looks different. Some look almost like a three-leaflet valve and some look almost like two perfectly identical leaflets. It's a big variation in what is a bicuspid valve. The shape of that valve can actually fairly significantly influence whether or not you get an aneurysm and what part of the aorta that aneurysm ends up in.

AHA/ACC Guidelines for Timing Interventions

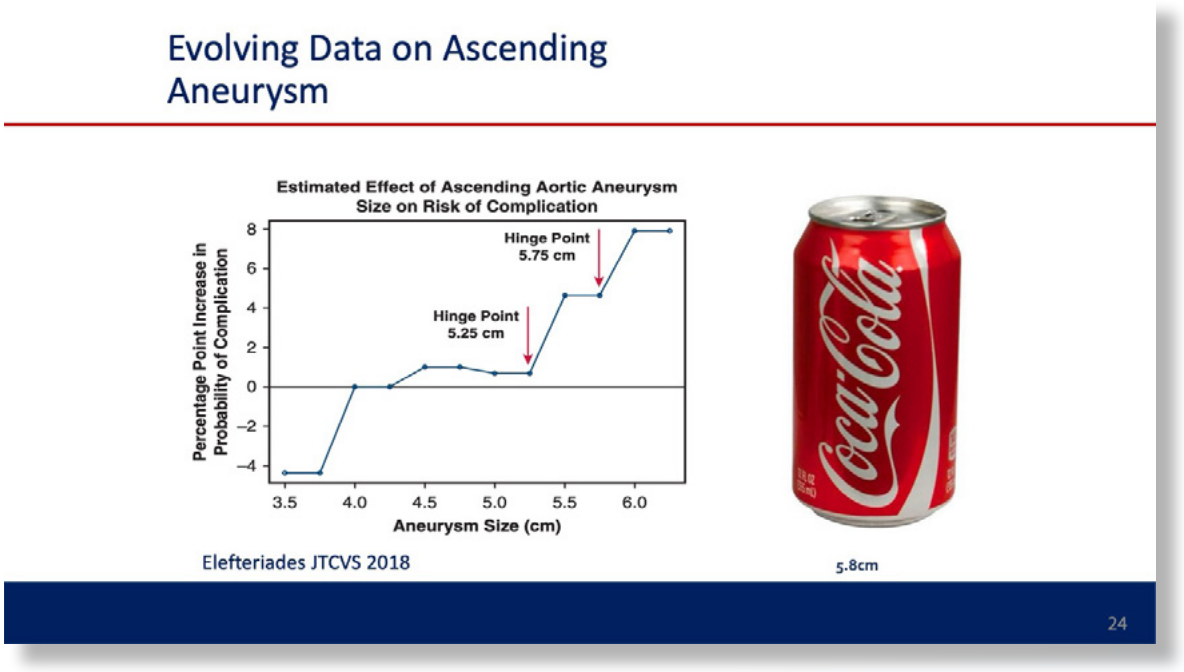


Dr. Nimesh Desai: There's been a lot of questions about when should we intervene on the aorta in a patient with a bicuspid valve. I know there's a ton of words on this slide, and I just wanted to stick the current American Heart Association guidelines in here about when we're intervening on aortas, aortic aneurysms in general and when we're intervening on aortic aneurysms associated with bicuspid aortic valve.

So the first thing that is important – and this gets back to this idea that Dr. Tsao was talking about, that bicuspid valves do tend to run in families, to some extent – that if you have a bicuspid valve, we do recommend that family – first-degree relatives of someone who has a bicuspid valve should also be screened for bicuspid valve and aneurysm also. Interestingly, one person in the family might have a bicuspid valve with stenosis and no aneurysm and another member of the family might have an

aneurysm and a bicuspid valve that's leaking. So the type of – the actual pattern of bicuspid valve and aneurysm aren't always the same within a family, even though the bicuspid valve runs in that family to some extent.

Typically, we will almost always intervene on a bicuspid valve aneurysm at 5.5 centimeters; in most patients these days, closer to 5 centimeters because our surgeries have gotten a lot safer and we know that there is a risk of aortic dissection or a tear in the aorta or something leaking from your aorta when you get above 5 centimeters. That's typically what we're looking at today, somewhere between 5 and 5.5 centimeters depending on different risk factors related to the individual patient in front of us.



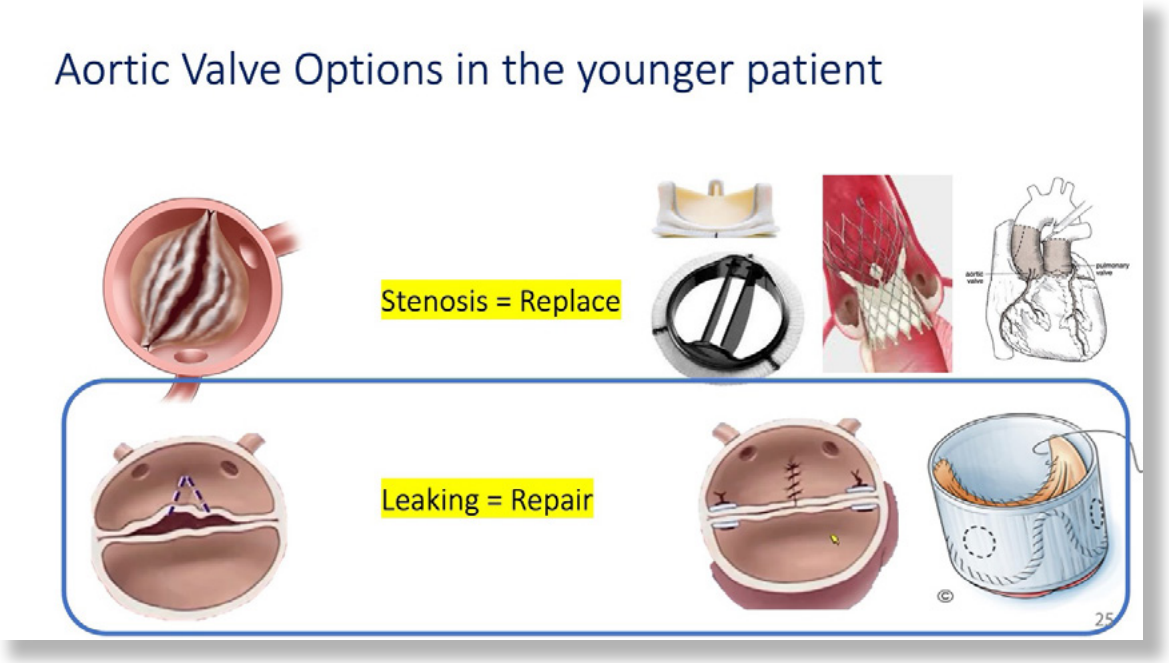
This is where the – this is the underlying data where this comes form. For those of you who have had an aneurysm and have been followed for a long time, you've actually gone through a couple of different cycles of guidelines where

the numbers changed where it was 5.5; then it went down to 5; then it was 5.2 and all over the place. This is actually why our numbers are changing. It's because we're learning more and more about the natural history of this disease. Originally, we knew that there was a point between 5 and 6 centimeters of the total diameter of the aorta where we started to see an increase in complications related to that aneurysm. So 5.5 was a pretty reasonable number to just take in between those two, between 5 and 6. Now that we have much better CT scans and much more granular data about when things are happening to these aortas, we know that the risk starts to increase at 5.2, 5.25, pretty significantly. Then it goes up a lot more at 5.75. We'll almost never wait until a patient gets above 5.5 these days simply because we know there's a risk of rupture or tearing of their aorta.

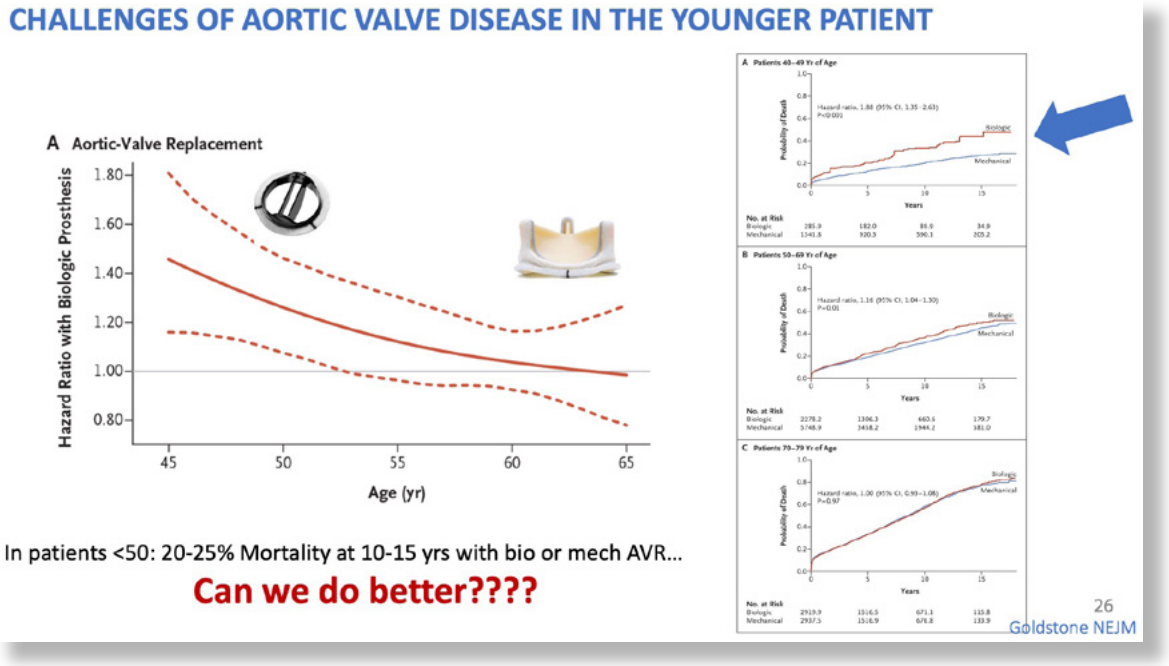
For most patients between 5 and 5.2, it's a conversation about what the right time is. A lot of different factors can weigh into when we'll actually recommend surgery. It has to do with when the patient wants to fit it into their lifetime as well.

Just to put these numbers in context, so 5.5 centimeters being our upper cutoff for the aorta, a Coke can is about 5.8 centimeters in diameter. That's a good reference for how big the aorta actually can get. The other thing to think about is what a normal sized aorta is, and I didn't put it on the slide, but it's actually about the side of the inside of a toilet paper roll, so somewhere around 2 to 3 centimeters would be typical.

Aortic Valve Replacement Options & Research



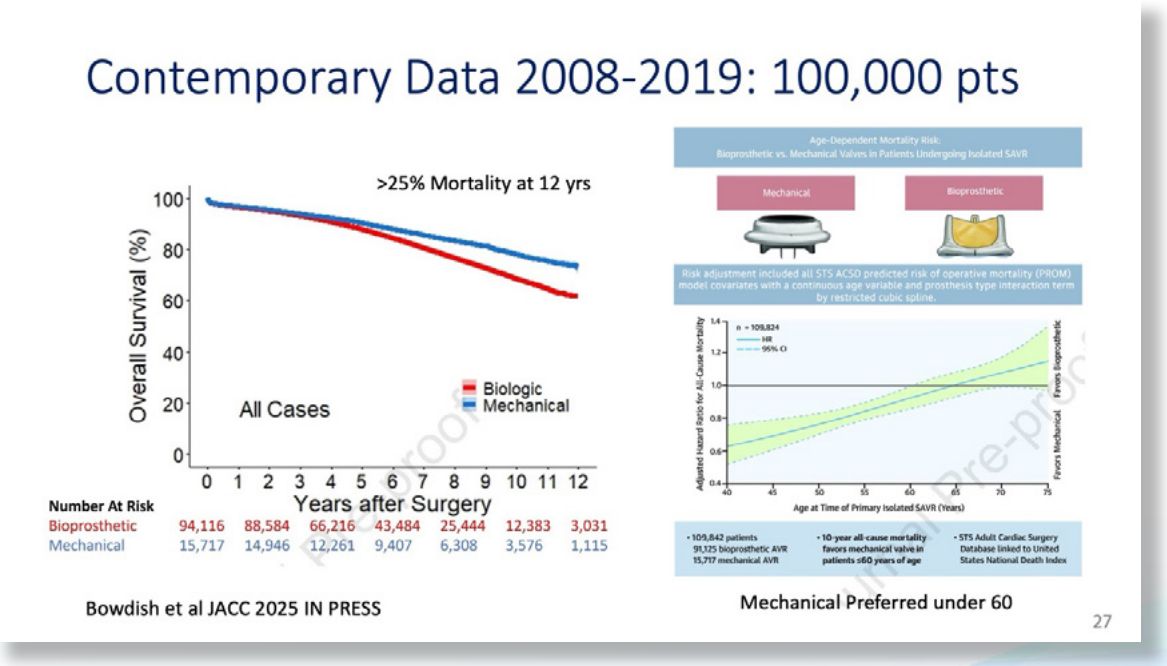
Dr. Nimesh Desai: When it comes to dealing with an aortic valve, as we mentioned earlier, could be either leaking or could be narrowed or stenotic. We have a lot of different options. These days in the younger patient where we know there is – they have many years ahead of them, we want to think about a lifetime strategy to take care of their valve. Typically, we start off with a paradigm where we want to repair. In the stenosis patient, we have to replace the valve and there's a lot of different options. We'll talk about leaking valves and repairing them first.



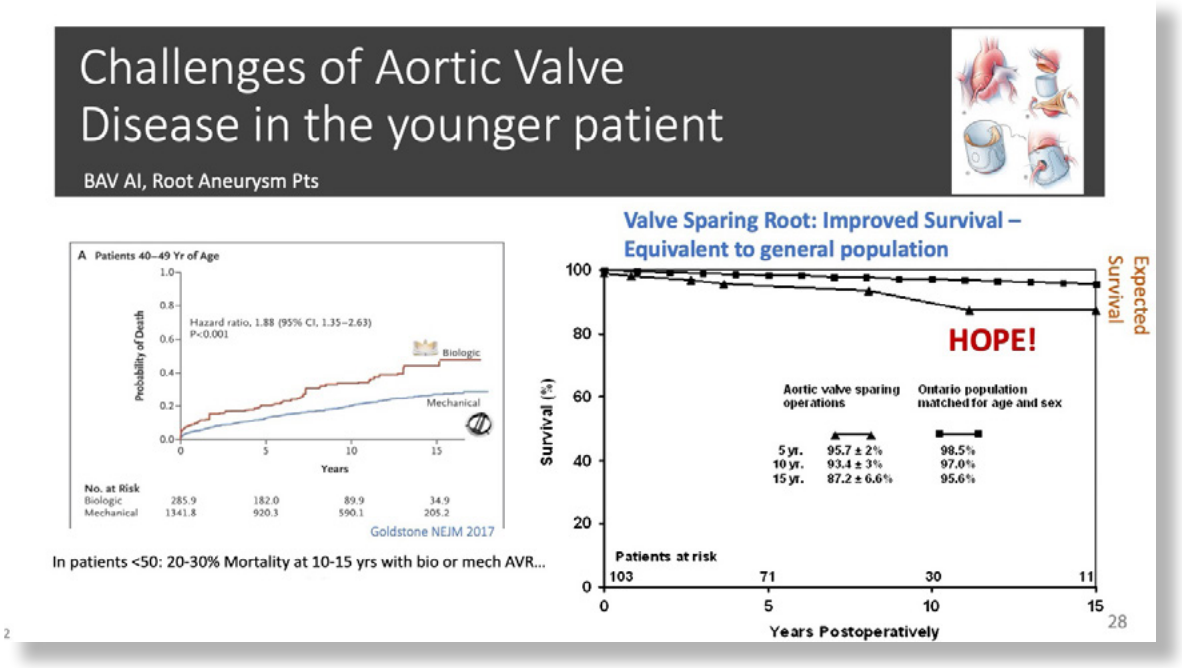
So the first thing I want to bring up is this idea of the different prosthetics. We already had a question earlier about durability of valves and there are a lot of different options to use to replace the aortic valve in terms of prosthetics, but they fall into two main categories of artificial devices that we can put in. One is a mechanical valve. People often say it's a metal valve; it's actually made out of carbon. It's almost like glass, the carbon that's in there. That's the first picture with those two metal discs that open and close; not metal. Even I said it; there you go. Those two carbon discs that open and close.

The other option is a biologic valve, a tissue valve, that's either a valve fashioned out of the tissue of an animal into a valve or is the animal's valve itself, and it could be a cow; it could be a pig. In some places, it could even be a kangaroo or a horse, so there's all kinds of material you can use to make valves out of.

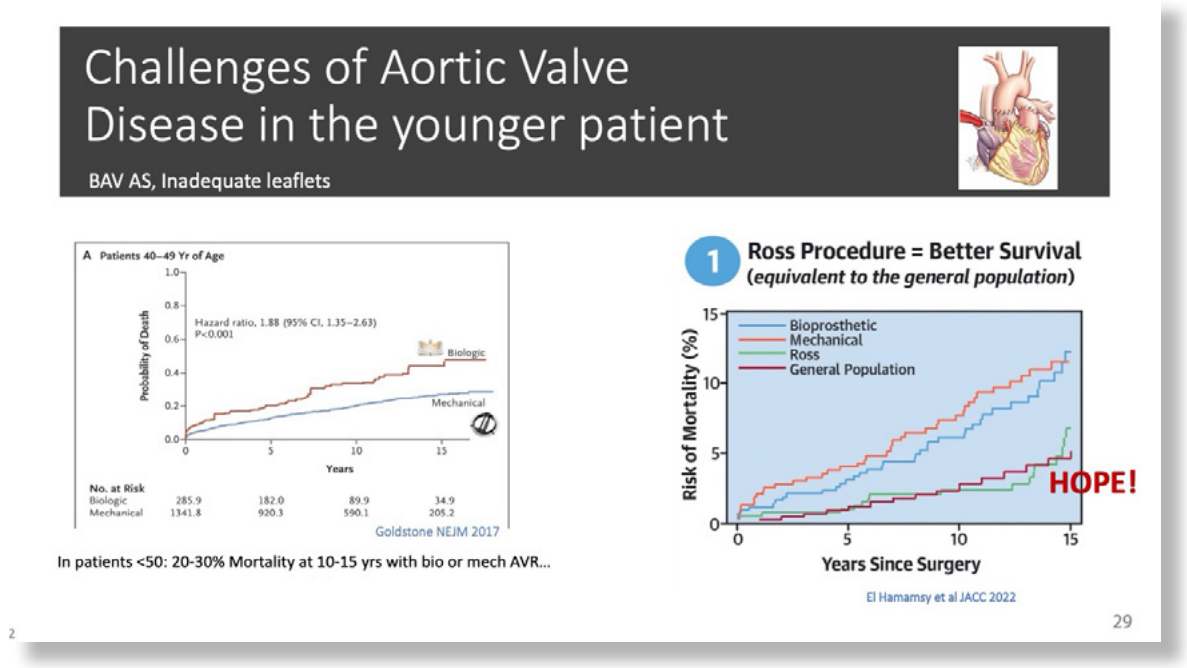
One of the things in the younger patient that we worry about is the consequences of replacing the valve early on and what that does to their longevity over the long term. There's a lot of studies that show that if you get a mechanical or a biologic valve earlier in life that there may be a cost to pay for it later in life. Those studies are very confounded, but I think there is a signal, at least, that when you can do a more biologic solution or a more reparative solution that more naturally mimics that human anatomy, we may be able to prolong life more.



This is some contemporary data that shows the same thing, that we see that over the long run, even in younger patients, that if you replace the valve with a mechanical or a biologic prothesis, there may be a little bit of a price to pay in terms of longevity. We're still learning why that is, and sometimes it's – a lot of it has to do with patient selection and think surgeons generally are pretty good at picking the right thing to do in the right person at the right time. So this data is a little bit difficult to interpret, but it does really lead us to think about are there ways to give people better valves than what we're doing today.

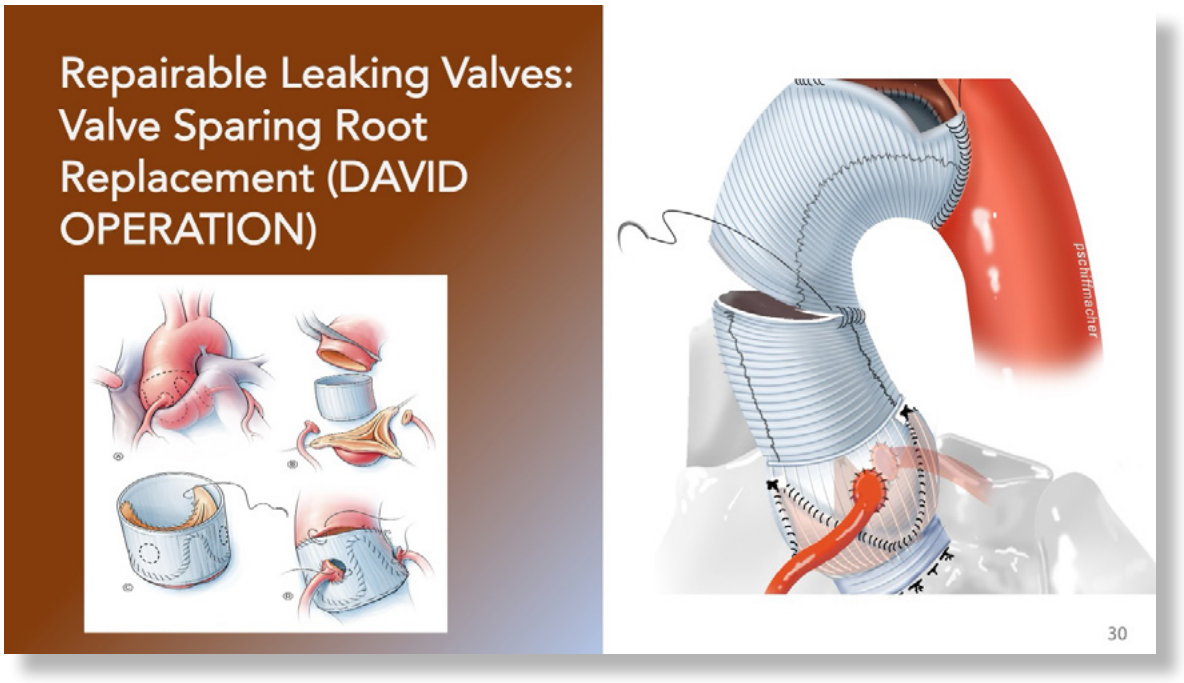


Here's some data that is starting to show that there are some options that can improve or get people back to their original longevity. This is data looking at valve-sparing roots, which I'm going to talk about a little bit later, where we actually repair a bicuspid valve or a three-leaflet valve that's leaking instead of replacing it; we repair it so you end up with your own valve.

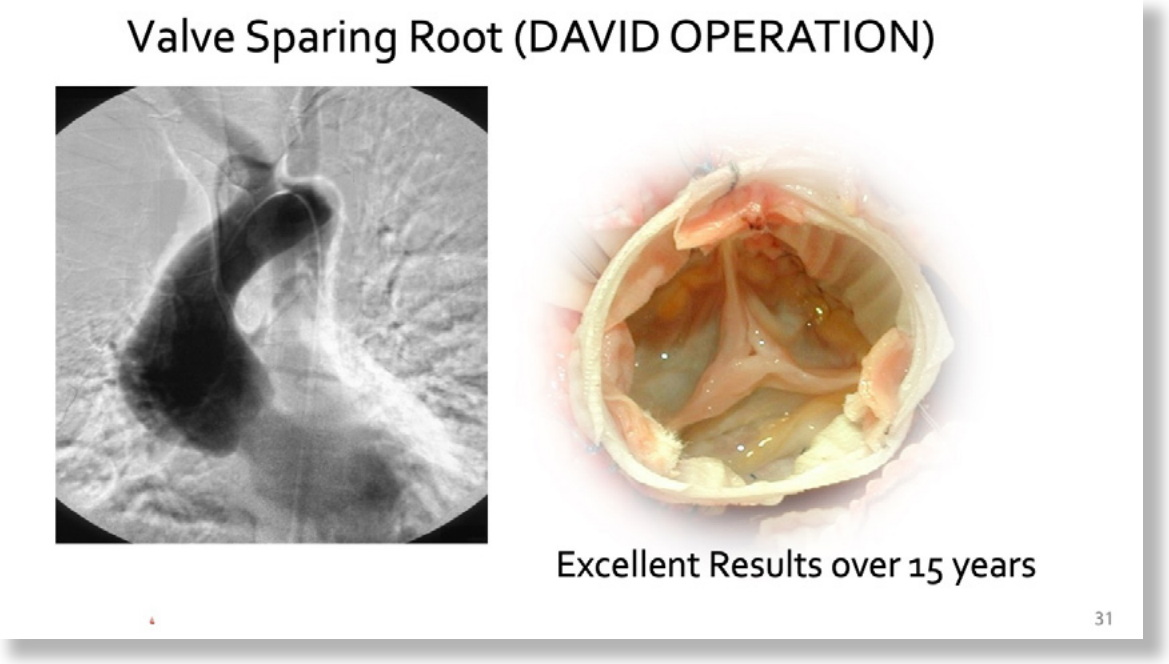


The other hot topic in aortic valve replacement today is doing the Ross operation. It's a pretty strong signal that a Ross operation really can return a person to their normal life expectancy, at least as far as we can study this out to 10, 15, maybe even 20 years.

Valve-Sparing Root Replacement (The David Procedure)

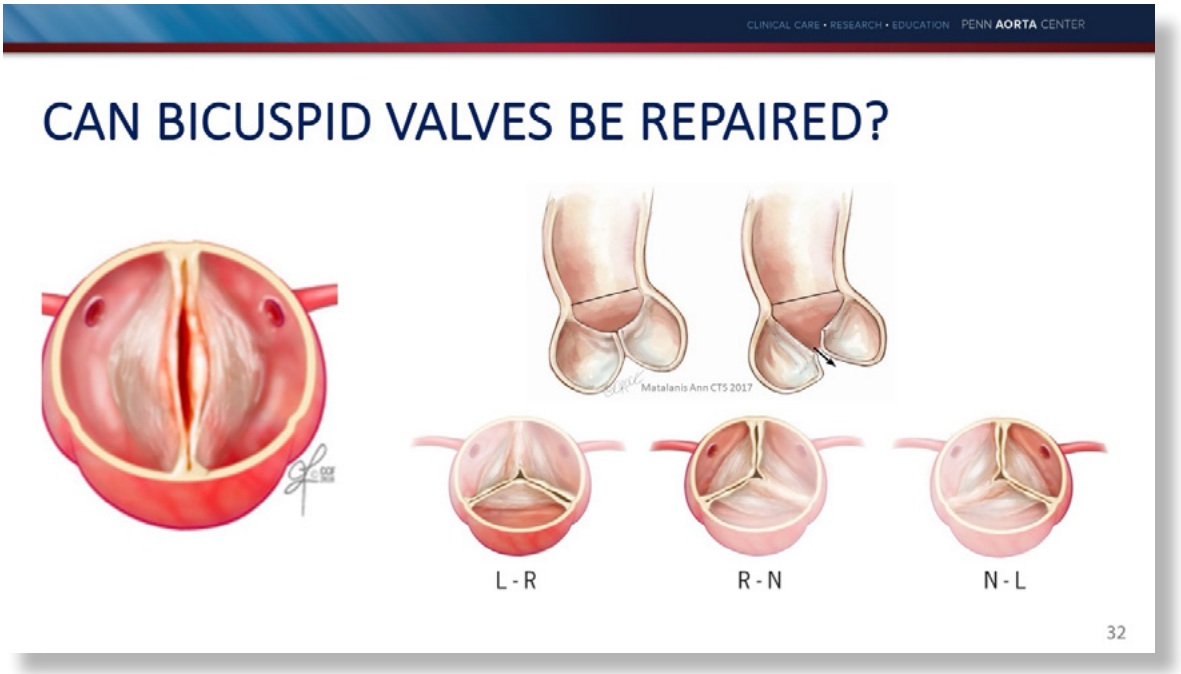


Dr. Nimesh Desai: So let's talk about these leaking valves and repairing them. So the primary way that we repair most leaking valves these days, because they're usually associated with aneurysms, is something called a David operation or a valve-sparing root replacement. What that is is a technique to treat the aneurysm and the valve problems at the same time. We essentially cut the whole aorta out and then implant their aortic valve inside this Dacron tube so that their own valve is still working, opening and closing, but if it's been spread apart by the aneurysm and is leaking because of that, we can cinch it all back down again and have a functioning aortic valve. Also, if there's an associated aneurysm, this completely takes care of that.



Here's an example. Promise not to show anything bloody or gory but here's an example of a patient who had a leaking valve from a big aneurysm. You can imagine the aneurysm pulled the valve apart, but the actual leaflets, those doors that open and close in the valve, completely normal. We don't need to get rid of the valve; we can just get rid of the entire aorta and bring all the geometry back to its normal position again. Then you have a completely normal functioning valve.

Can Bicuspid Aortic Valves Be Repaired?

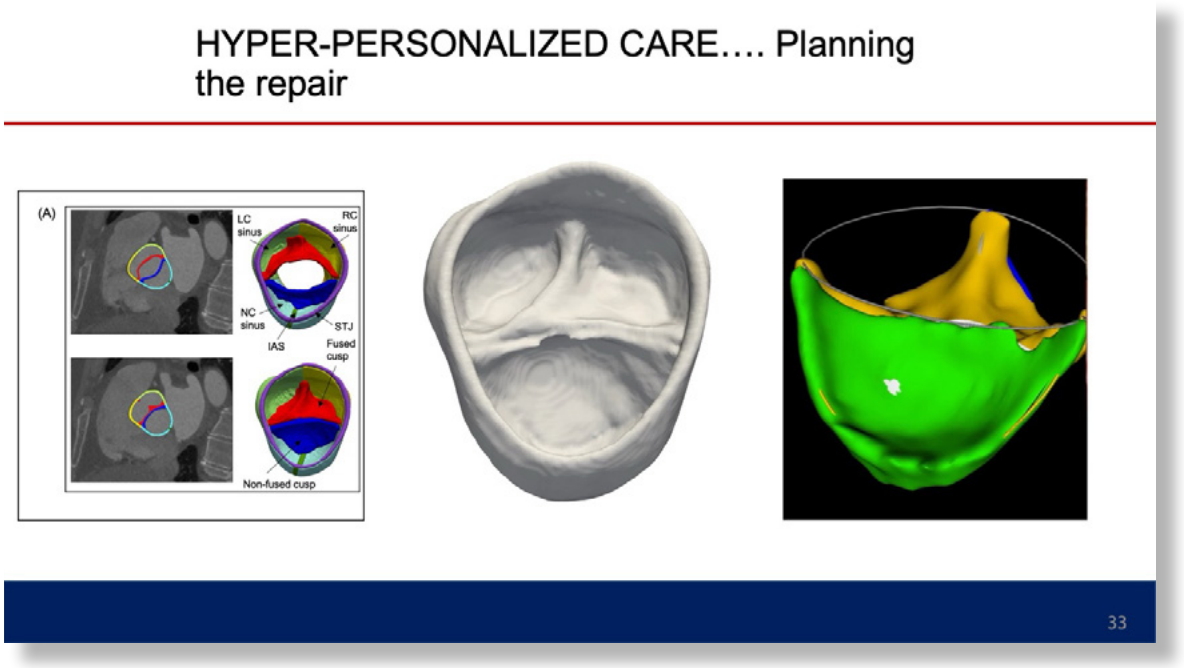


Dr. Nimesh Desai: Tthe next question is, "If that's a three-leaflet valve, we can return someone back to perfect anatomy?" Can we do this with bicuspid valves as well? My perspective is that there's one type of bicuspid valve that we often see in people, never needs to have surgery, never needs an intervention, and that is the picture, the red picture that you see on the left, which is what we call a 180-180 or a true bicuspid valve. When people say the word bicuspid valve, they often think that this is what they look like. This is actually really rare for bicuspid valves. I tend to call it a true bicuspid valve. This valve can last a person's lifetime and never need an intervention because it's very evenly put together and symmetrical. It doesn't have uneven loading on the leaflets that

eventually cause them to stretch and start leaking like you see in the next picture there, or eventually from all of the stress placed on them become calcified and stenotic. So these are just different reasons why all this happens.

This is more typically the kind of bicuspid valves we see where they're more asymmetrical. It's often two leaflets that are partially conjoined and then one normal-looking leaflet. Again, the closer your anatomy is to the first picture or the closer we can get your anatomy to the first picture, the 180-180 symmetrical valve, the more likely that valve is to last a lifetime.

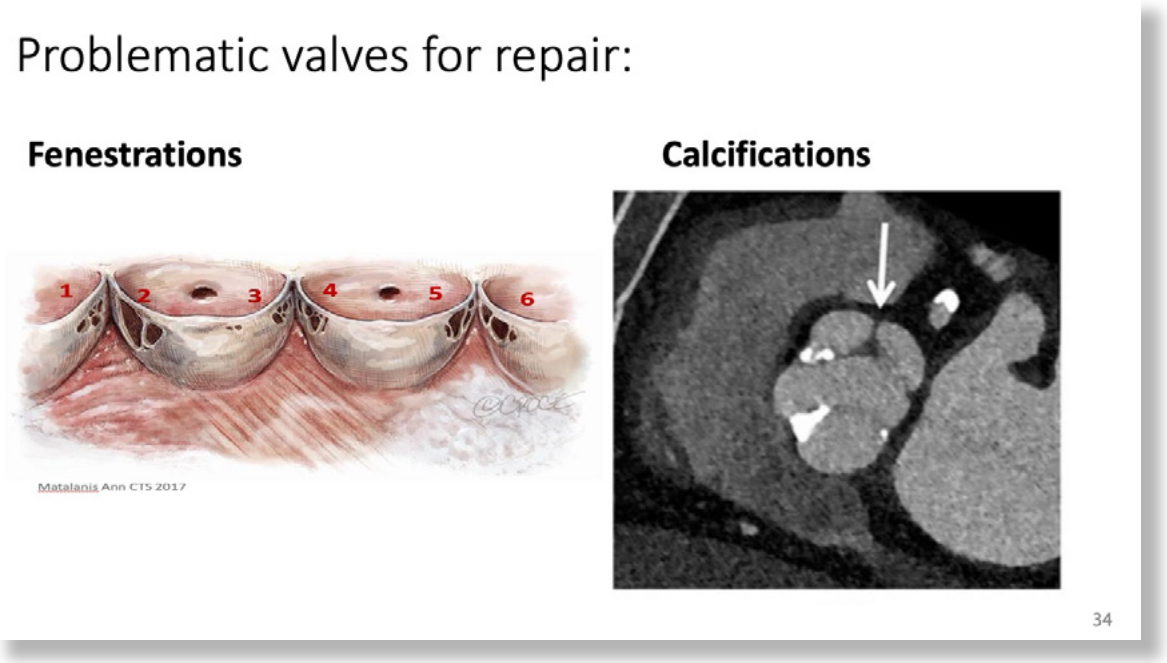
New Technology for Aortic Valve Repair Simulation



Dr. Nimesh Desai: We have a lot of cool tools we're using these days to actually take data from people's CT scans. This is an actual patient's valve. If it's leaking, we can try to figure out what's wrong with it using this kind of information. This is a special CT and some imaging scientists that did this for us. Adam, if you can click on the next picture there, what you're going to see there is we're actually simulating a repair. We're going to take the components of this valve, break them down into mathematical chunks by our scientists and actually do a repair on the valve by raising the height – you would do this by putting a little stitch in there to close that area up to see if we can actually get that valve to work again.

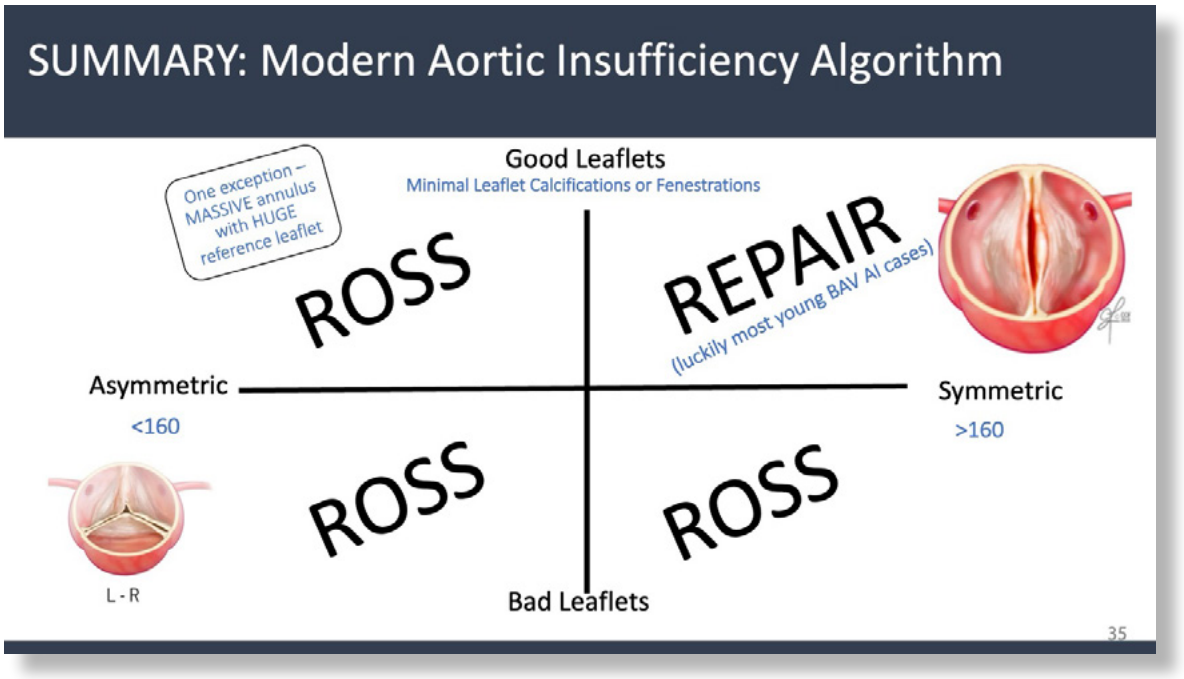
So advanced imaging and things like that are really evolving in this area. We're trying to take it away from being just purely an art where the surgeon gets in there and looks at it and has to figure out how to "Picasso" the valve back together again to stop it from leaking and actually coming in with a plan of knowing if I increase the height of these two leaflets by 2 millimeters, you're going to have a perfect valve again. So that's where we're going with this stuff.

Problematic Valves Are Not Repairable



Dr. Nimesh Desai: There are some valves you can't repair. When you have a valve that looks like this, even if you can put it all back together again – see all those holes, the little fenestrations there? We call them fenestrations, the French word finetra for window, but a valve that looks like that might be repairable but it doesn't really have good stuff to stay good for the long term. These we usually need to replace. If your valve has a lot of calcification, those bright white things that you see on the CT scan picture on the right, calcifications – if your valve looks like that, even if it's only leaking and doesn't have stenosis, it's still one we probably need to cut out and replace with something.

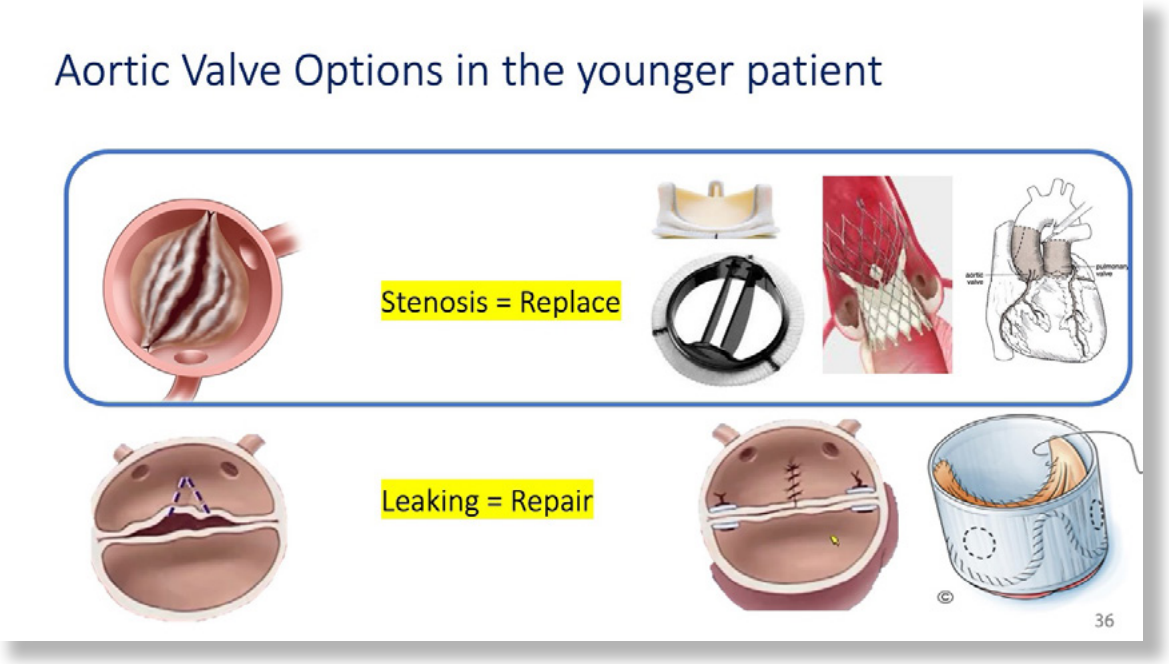
Bicuspid Aortic Valve Treatment Matrix



Dr. Nimesh Desai: So this is a way that I tend to think about what to do with valves, bicuspid valves, in young people. If they have good leaflets and they're symmetric, you repair it. If they don't, then typically you're replacing it in an older patient or doing the Ross in a younger patient.

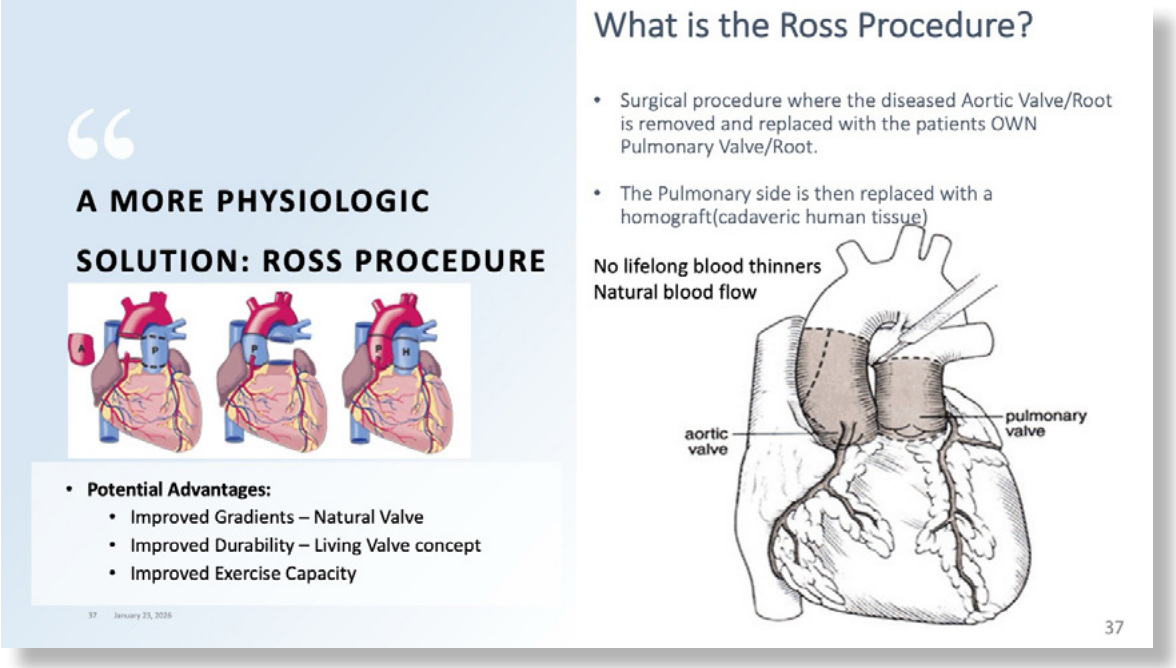
So the next thing we're going to talk about is what we do when we do replacements.

Aortic Valve Options In Young Patients

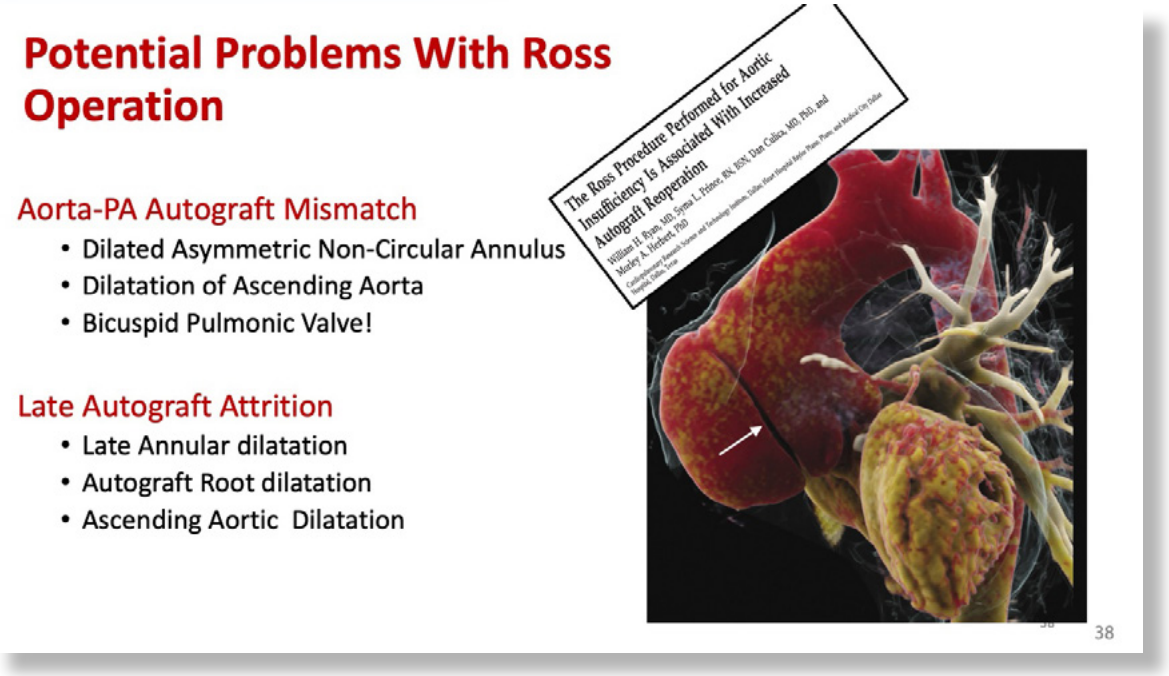


Dr. Nimesh Desai: So when we talk about different replacement devices – we talked a little bit about the mechanical valves and the tissue valves. Transcatheter valves are also a very hot option, especially in the older patient. In the younger patient, we use them sparingly, although there are situations that we do use it, and I'll talk about a couple of those in a sec. Then the Ross operation.

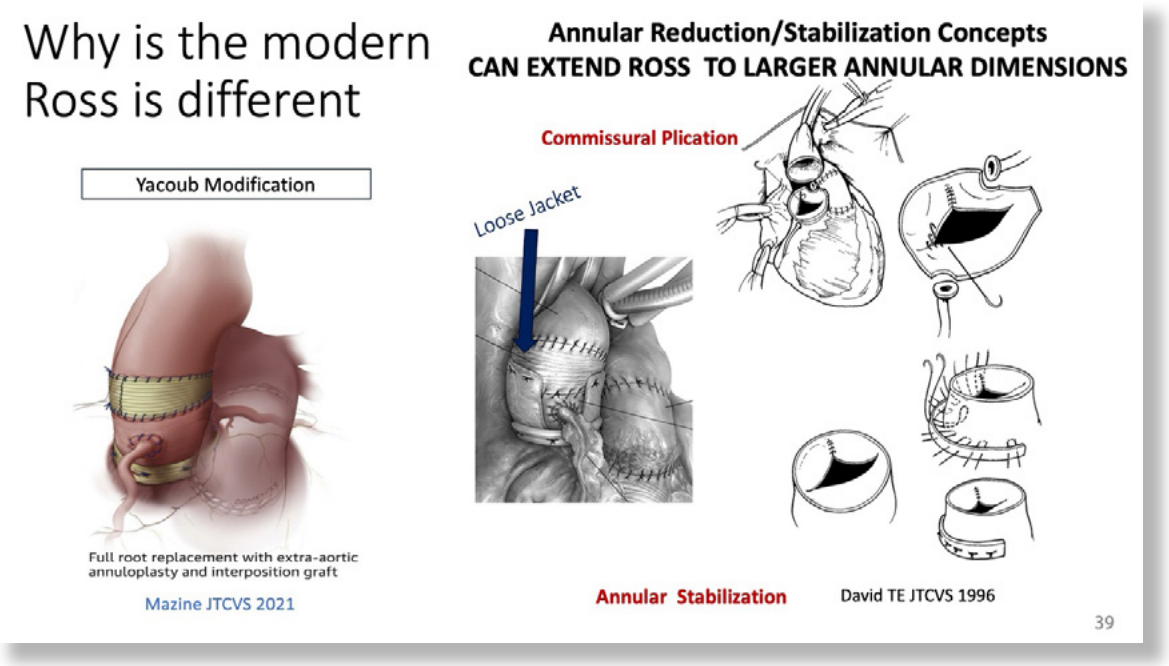
The Ross Procedure Explained



Dr. Nimesh Desai: So the Ross operation, we basically swap the pulmonary valve, which is usually a nice, three-leaflet valve, into the aortic position and then that leaves us with a problem because you don't have a pulmonary valve anymore. We use what we call a homograft or a human cadaveric tissue from a donor. That tissue has been cryo-preserved so it's been preserved in a very cold solution; it's been frozen down to a very low temperature. That takes away the immunogenicity. It's not treated like a transplant organ at all; it doesn't have that reaction in the body.



There's been problems with the Ross, and that's why you'll often hear different positive, extremely strongly positive or extremely negative opinions about the procedure. Really, historically there was a lack of understanding of what to do about – with the pulmonary autograft, the part you move from the good valve, you move over. The reason there was a problem is you're taking a valve that was used to a pressure of about 30 on the pulmonic side and putting it in a spot where the pressure is 120. That can really stretch it out or damage it. There's a whole bunch of things that we've done now to try to prevent that from happening.



We will either wrap the entire thing in a Dacron graft or stabilize. Dacron is just a fancy polyester. We'll either replace part of the aorta; we'll put a little stabilization band at the bottom. We'll take the person's native aorta and wrap it around the Ross. There's all those different things we do now to actually prevent that from happening. That was the main failure rate of the Ross or failure mode of the Ross.

The other thing that has been problematic is what to do with the human cadaveric pulmonic valve. Sometimes people do tend to calcify those. The newer generation of those are de-cellularized, so the actual cellular material of the donor has been washed away and we think they're actually quite resistant to that now as well.

Patient Question: Ross Procedure Surgeon Expertise

Adam Pick: Dr. Desai, , we have a question specific. I'm going to go back to the Ross procedure slide, because this is a great one. As you may know, I'm a Ross procedure patient. I had a Ross done back in 2005; I'm 20 years out. I've had no re-intervention, no re-operation. When you talk about those studies and the success of how this procedure can help somebody, I'm definitely a good case study and have been very thankful. On the flipside, we have some new patients that are considering the Ross. Here's one from Austin Stillman. He says, "Hello, my name is Austin. I'm 30 with a congenital aortic stenosis and bicuspid aortic valve looking at getting a Ross procedure this year. My question is this. When evaluating surgeons, what is the minimum number of adult Ross procedures you believe a surgeon should have performed to consider them as a viable surgeon for this complex operation?"

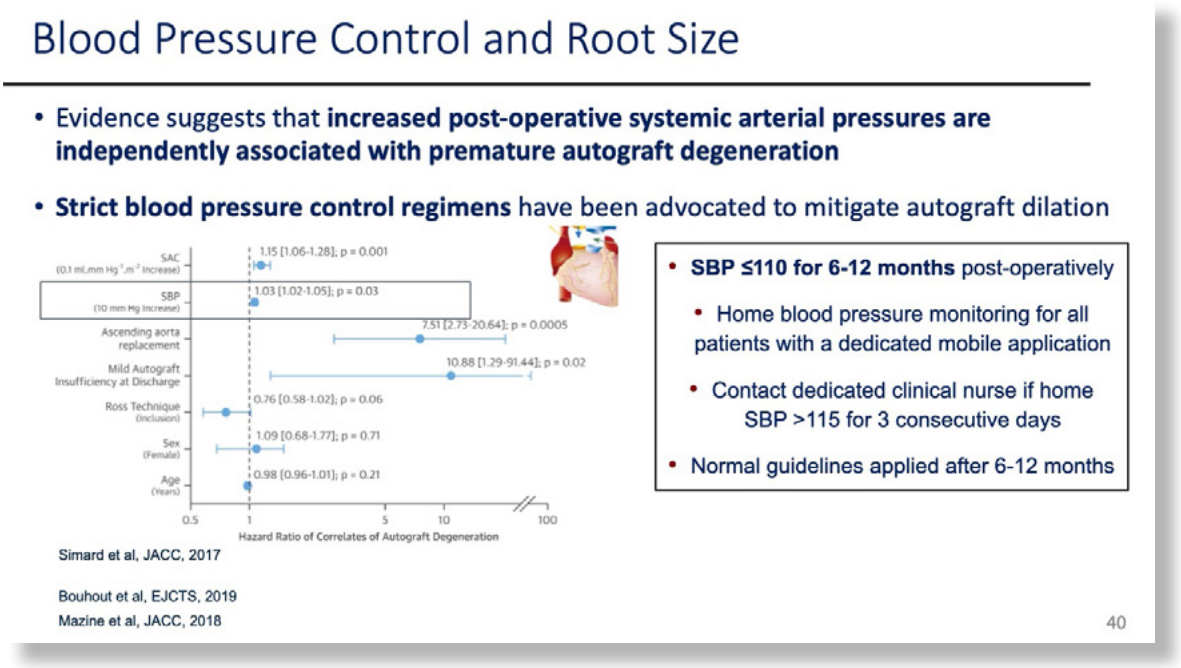
Dr. Nimesh Desai: That's a very good question. In a lot of ways, the adult Ross is also a little bit different than the Ross that we do on young children just in terms of the concept of what you're trying to do in that operation. In the young child, you still know they're going to need surgery one day, but for a fully grown person, whether they're 18 years old or 45 years old or 50 years old, there's certain elements of doing the Ross, which I'll get into a little later in the presentation, but in terms of the actual volume, we actually have some pretty good data, and it's published data, that says about 30 is a good number. I also think that's 30 within a reasonable period of time, not 30 over ten years, hopefully, but you really want to go to a busy Ross program, one that does

Ross Procedures on a weekly or at least several a month basis because it is a technically challenging procedure. You also want to be in the hands of a surgeon that is a very, very accomplished root surgeon because it is generally done as a root replacement procedure, and it is orders of magnitude more complex than just straightforward root operations with prosthetic devices.

So I think the key is to go to someone who clearly has had a large number of cases under their belt. I really do think that is at least 30 within a two or three-year time range, which isn't even a lot for here.

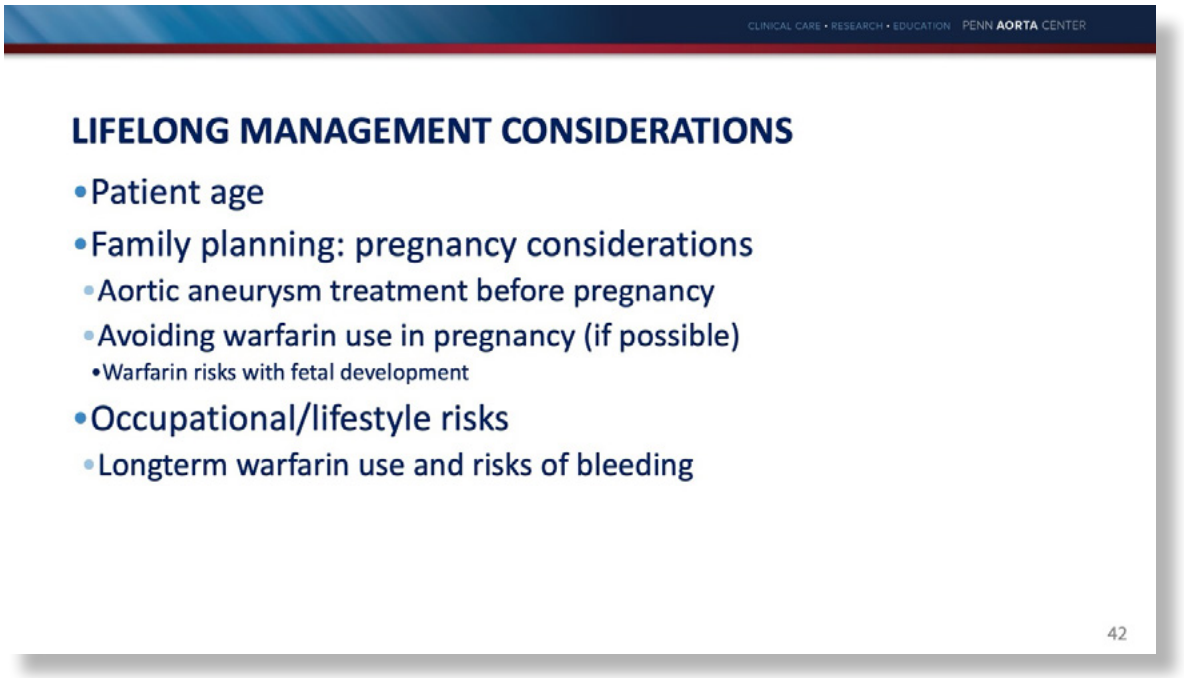
Adam Pick: Great, I hope that helped you, Austin. Let's continue on.

Blood Pressure Considerations



Dr. Nimesh Desai: The other thing that's really important here, as I said, we're trying to bring a low pressure valve into a high pressure situation. We try to lower that pressure as much as we can. In the old days, we used to let people's blood pressure run pretty high after cardiac surgery. Wen we do a Ross operation, we are on top of that blood pressure, and it is going to be 100, 105 or so for the first three to six months, even up to a year after the procedure. That just gives that pulmonic autograft, the good valve, time to get used to being in the higher pressure environment. That valve is your own tissue; it's a living conduit. It will basically become the aortic valve in the aorta if you let it season up slowly.

Lifetime Considerations for Congenital Aortic Valve Defects



Dr. Allison Tsao: I think now we might go into a little bit more of how we incorporate all of that data that you went through and all just the advances we've seen in aortic valve replacements and talk about next steps and how we approach this in our collaborative practice.

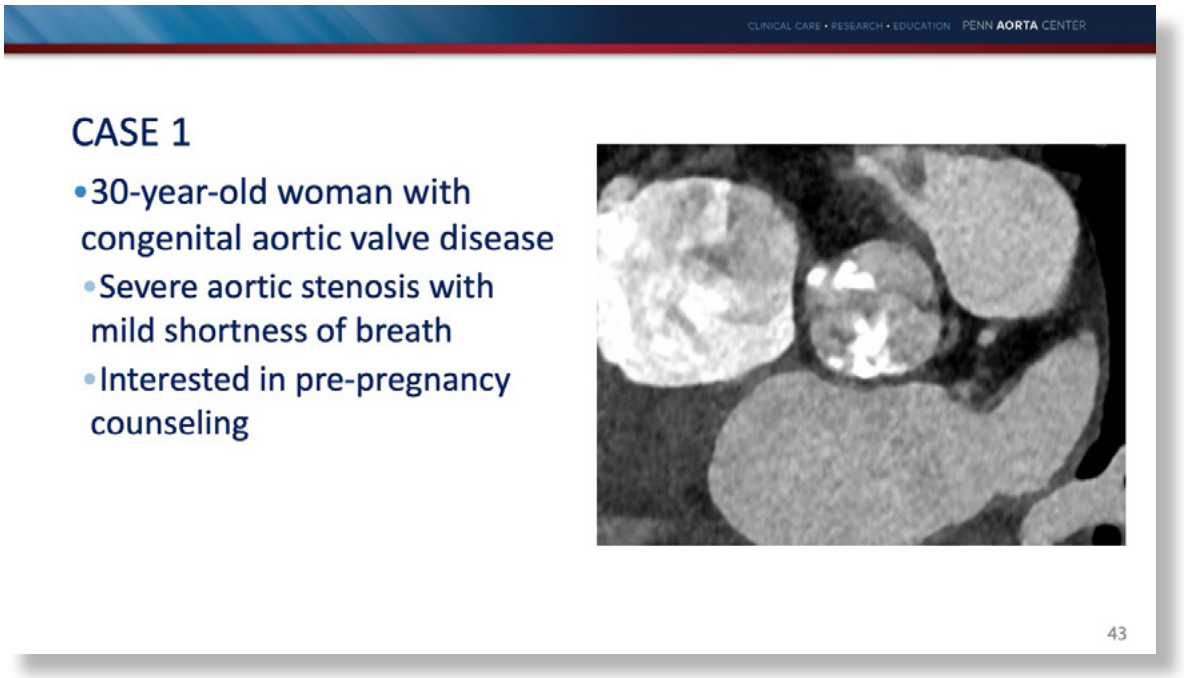
Dr. Desai and I see patients together in clinic when evaluating patients with congenital aortic valve disease. We're going to talk about some of the patients that we've actually seen together.

Some of the lifetime management considerations that I briefly touched on at the beginning that are going to come into the next few slides are going to be

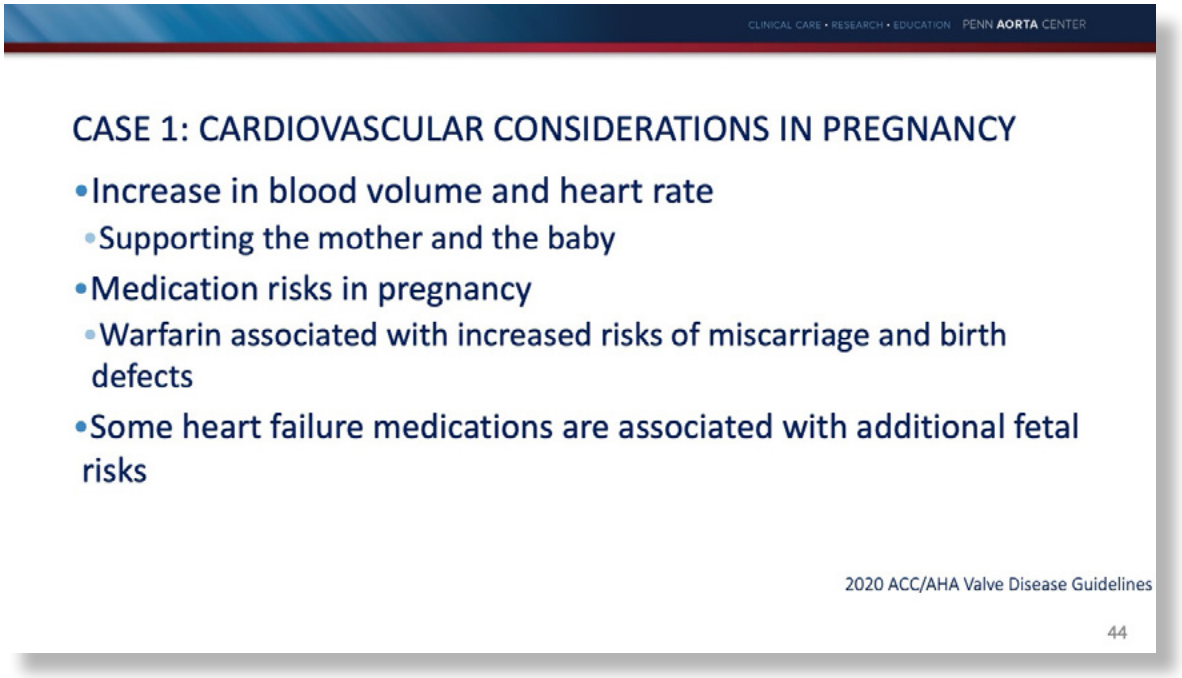
incorporating patient age and how family planning or pregnancy considerations are going to come into play with that. Now, each one of these topics could be an hour-long talk, so this will be – just we'll broach on it, and it's really for you to be educated and know the questions, maybe help you ask the questions that you need to ask for your providers. I think that's the most important part.

Aortic aneurysms and the presence and need for intervention prior to pregnancy, there's a lot of data on this. We're not going to dive into this, but know that that's going to be a component. Dr. Desai showed us some data on mechanical aortic valves as well as a durable approach to a patient with aortic stenosis at a young age just because of valve durability. That means the use of a blood thinner and commonly, we use warfarin for that. That is a medication that will have major implications with pregnancy planning. Then finally thinking about occupational or lifestyle risks specifically for long-term warfarin use or even recovery time. We are very cognizant when we are taking care of young patients. You have a job; you have kids; you have life to live. What is the recovery time to help you get back on your feet?

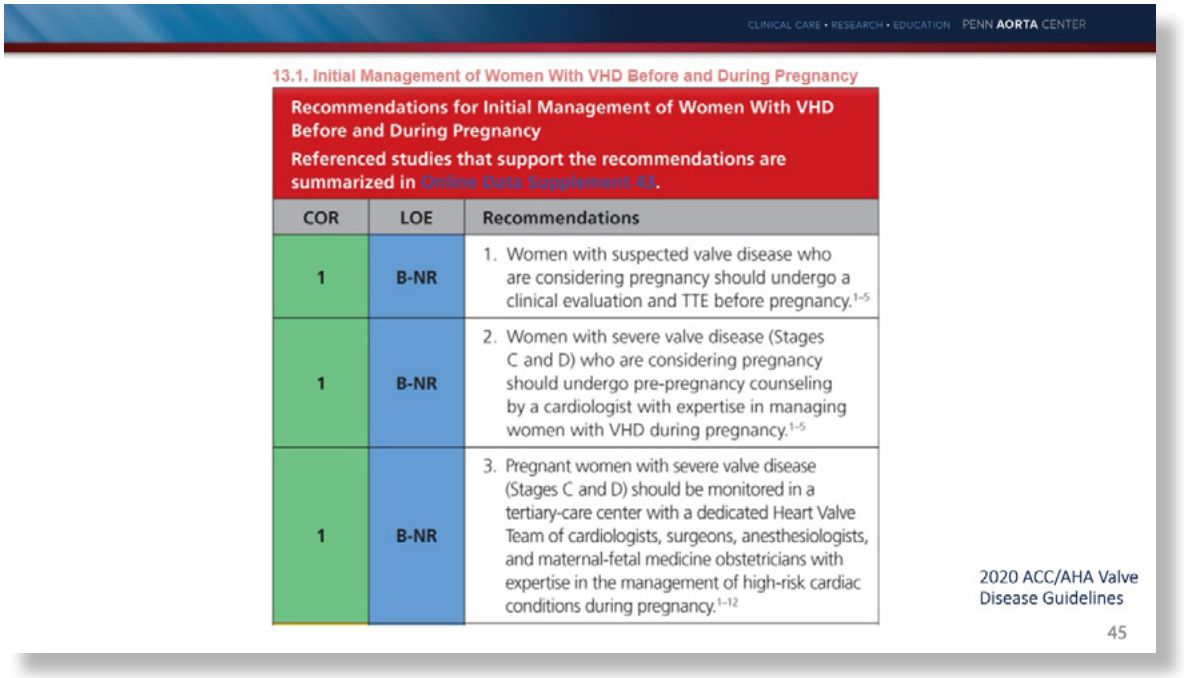
Patient Case Study #1: Pre-Pregnant 30-Year-Old Woman



Dr. Allison Tsao: Let's dive into a few cases, if that's okay. Dr. Desai, I'm going to put you on the spot as we talk about some of these. The first case is a woman who came to see me. She's 30 years old. She has congenital aortic valve disease. It's been known; she has a murmur. She's had echoes. We've followed her regularly. She has severe aortic stenosis and she's recently developed shortness of breath, so symptomatic aortic stenosis but still doing well, working regularly. She's interested in pre-pregnancy counseling.



Considerations that I have as a non-interventional cardiologist but just a cardiologist seeing somebody in clinic as an adult congenital heart disease specialist, I know that pregnancy is going to put a fair amount of stress on her heart and that valve. Your blood volume needs to increase in order to support yourself and also the baby's blood volume and growth. Then the risks of pregnancy, I touched on warfarin, and its risks for potential birth defects or increased risk of miscarriage during a pregnancy. We're going to do this to help her live longer and carry a healthy pregnancy. We want to minimize those risks. Also some heart failure medications or medications that are required when the heart starts to struggle can be associated with birth defects as all. Those are considerations we have.



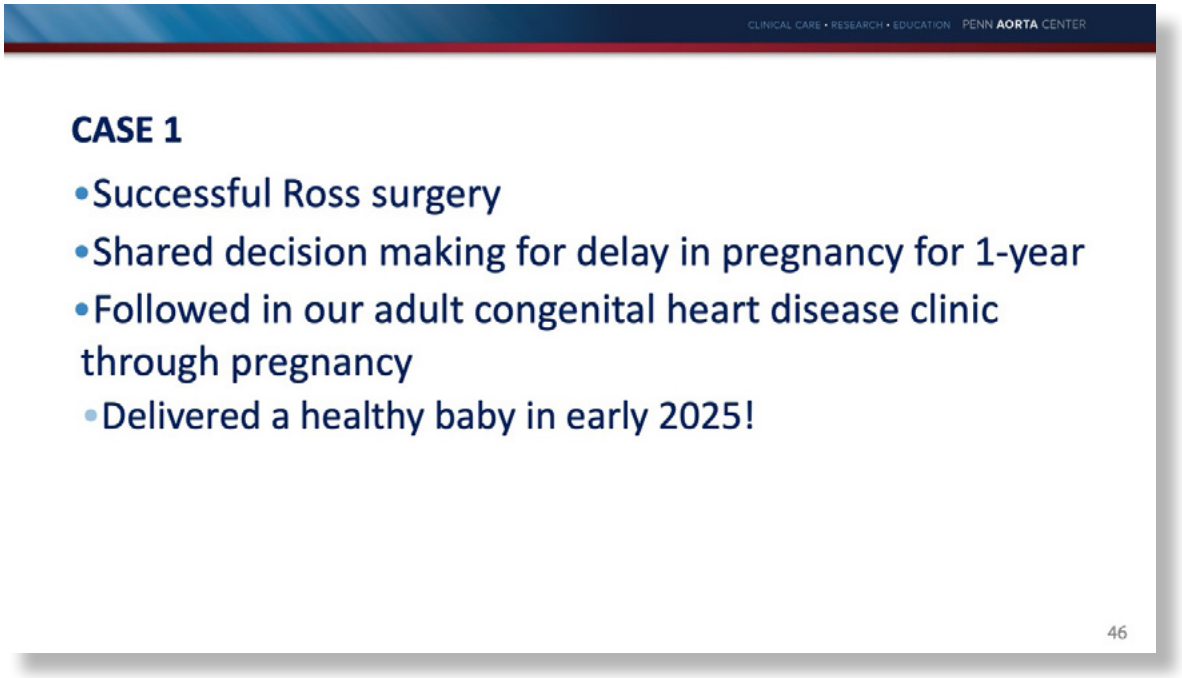
We'll touch on guidelines. We have the American College of Cardiology and the American Heart Association has guidelines that if there is a woman or patient who has valve disease and is considering pregnancy, they should be evaluated at a heart valve center. I won't go into the nitty-gritty details of all these words, but know that you should be seen at a valve center that is comfortable managing women through pregnancy and have all of the resources available. That's going to be clinical cardiologists, advanced imagers, maternal fetal medicine specialists, cardiac surgeons, interventional cardiologists so we can make sure all of the options are available for you either in pre-pregnancy screening or managing you through a pregnancy that we might not have had

pre-pregnancy screening for. We are committed to manage you through that time period.

Dr. Desai, this woman, she's 30 years old. She has severe symptomatic aortic stenosis. I need her valve fixed to get her safely through a pregnancy. With her young age, you showed us some good data about a mechanical valve and that might be the most durable, but I have real concerns about warfarin use for her. What are the options that you would offer her based on all the other data that you've presented to us?

Dr. Nimesh Desai: Yeah, so I think she still has all three options potentially in play. A tissue valve in someone this age, particularly when they're going to go through a pregnancy and go through a high output state is something that's not a permanent solution. It could be something that could get her through the next 10 or 12 years, hopefully, and then she would probably have to have another procedure and likely have to have another open valve replacement at some point later in life. That's one potential option. Sometimes people have made that decision and then actually had a mechanical valve when that valve fails, so that's a potential option.

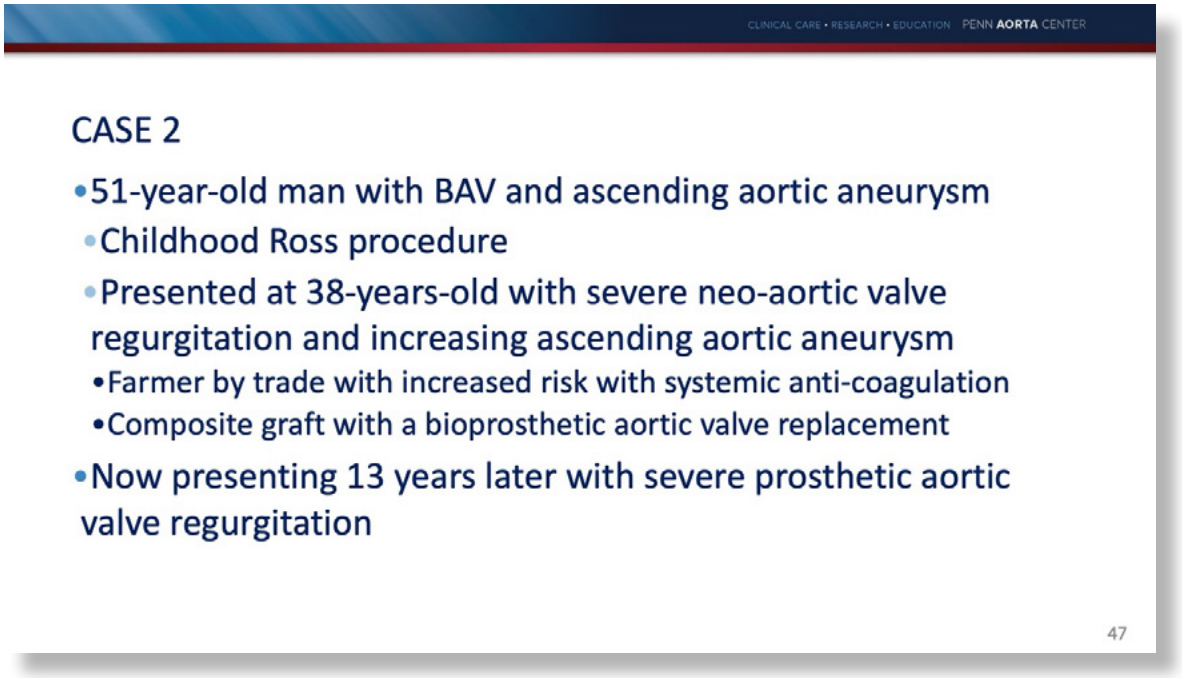
Mechanical valves can also be supportive through pregnancy. We have patients I know you certainly have taken care of that can be treated but that is a – I always felt that's a bit of a risky strategy, but it's doable. I think that's more for people who already have a mechanical valve in place in that situation. Then finally, the Ross procedure where you may have the durability of a mechanical valve or maybe even better than a mechanical valve but don't have the anticoagulation issues.



Dr. Allison Tsao: Thank you. So she did undergo a successful Ross surgery with Dr. Desai with shared decision-making and this goes to an earlier question. Surgical number is so important for a Ross but also being in a system of care that's designed to support you post-surgical period and life-long. Dr. Desai talked about blood pressure control. We're really strict. While we were following her, we've delayed moving forward with pregnancy to a year before we pursued that. Then she's been followed in our adult congenital heart disease clinic through that. Next slide.

She delivered a healthy baby boy in early 2025, so really that's the biggest success. She'd going well. We have systems in place to monitor the patient throughout pregnancy at all stages. Again, having a system in place through your valve center that can support you in all of your life decisions is the most important part.

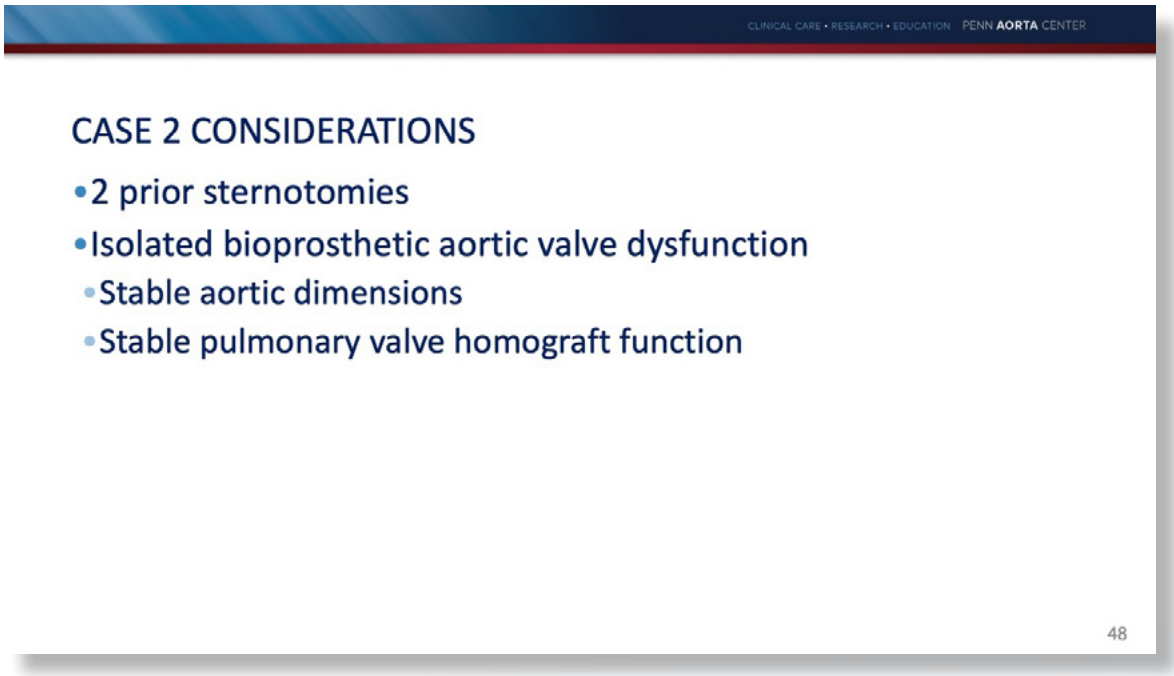
Patient Case Study #2: Active 51-Year-Old Man



Dr. Allison Tsao: This next case that we'll talk about is a 51 year old man that Dr. Desai and I have both taken care of. He had a childhood Ross procedure, so he was much younger, and we know he needed to be hooked in with lifelong care. at 38 years old, he was Dr. Desai's patient and he had neo-aortic valve regurgitation, so that autograft in the aortic position did develop some leaking. That goes into that. At the same time, he had an increasing ascending aortic aneurysm. Again, he had congenital aortic valve disease with an ascending aortic

aneurysm, so we need to think about that beyond just the root. I think he had some complexity and had aortic root dilation as well.

He was a farmer by trade, so even though he was 38, his ability to recover and work with heavy machinery and be on a systemic blood thinner was a real consideration. Even though there was a conversation about durability, his desire to avoid warfarin was really important. He ended up with a bioprosthetic composite grafted replacement, the details of which Dr. Desai's laughing at for how I said that. He had that aortic surgery. His pulmonary autograft was working very well at that time. He's now coming in 13 years later with severe prosthetic aortic valve regurgitation.

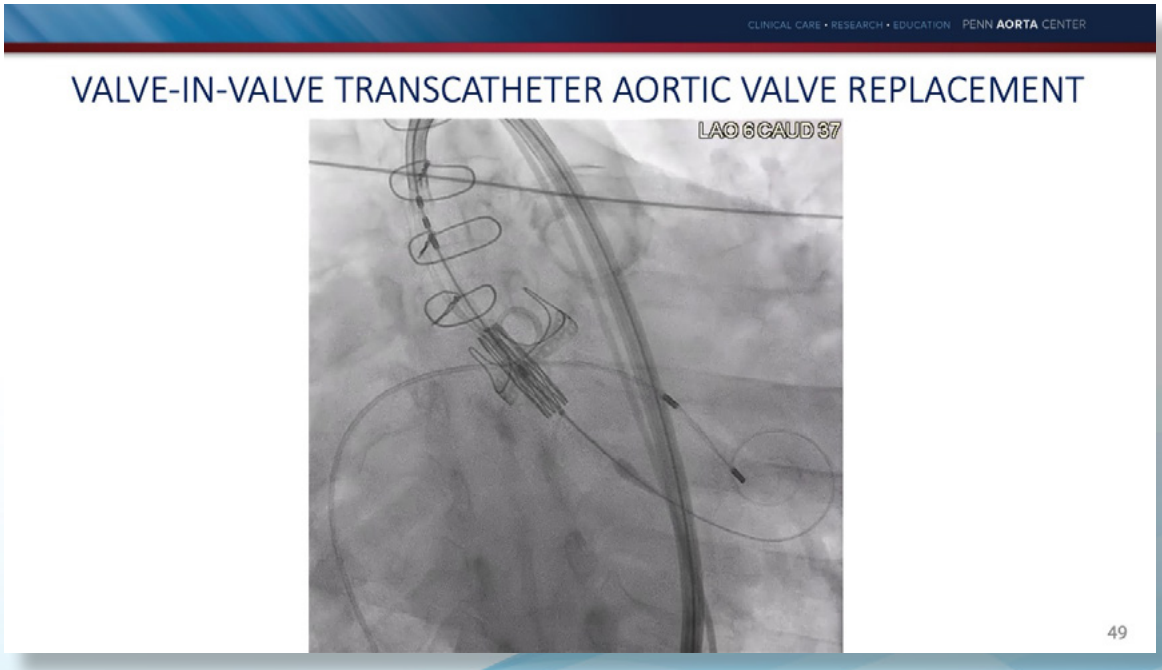


Dr. Desai, this was a patient that we co-managed. He's had two prior sternotomies. He now has isolated bioprosthetic aortic valve dysfunction, stable aortic dimensions. He's had his prior graft. Importantly, a valve I love and is near and dear to my heart; his pulmonary autograft was working very well. He did not have any indication with calcification to intervene on the pulmonary side at

that point in time. What are some of the discussion points we had and how we approached this patient?

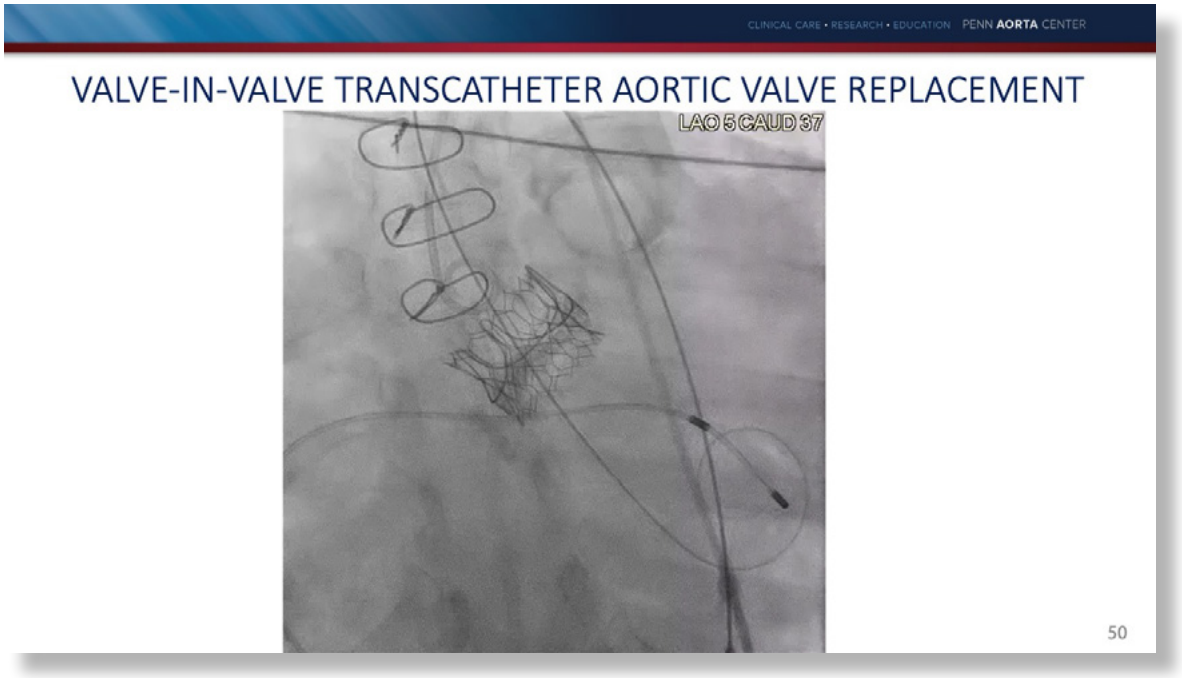
Dr. Nimesh Desai: Yeah, and this is where the decision-making gets really complicated. He's still young. He's had two sternotomies, two big operations, too. My own feeling having talked to him was he really wanted to keep working at a high level now. This was not the time for him to go through another open procedure. We start thinking about – we go back in and replace everything with a tissue valve again; we already tried that. We got 13 years out of it, not bad, but we would've loved a little bit more. He still wasn't someone who wanted to or was willing to have a mechanical valve.

So we chose instead to go with the minimally invasive option to extend the life of the root that he has in there right now knowing that unless there's a really dramatic change in technology in the next 10 or 15 years, he'll probably still need to have another sternotomy to take all of this out and put another new valve inside. Right now, he wants to keep working. The best thing for him was to not go through another big open operation.



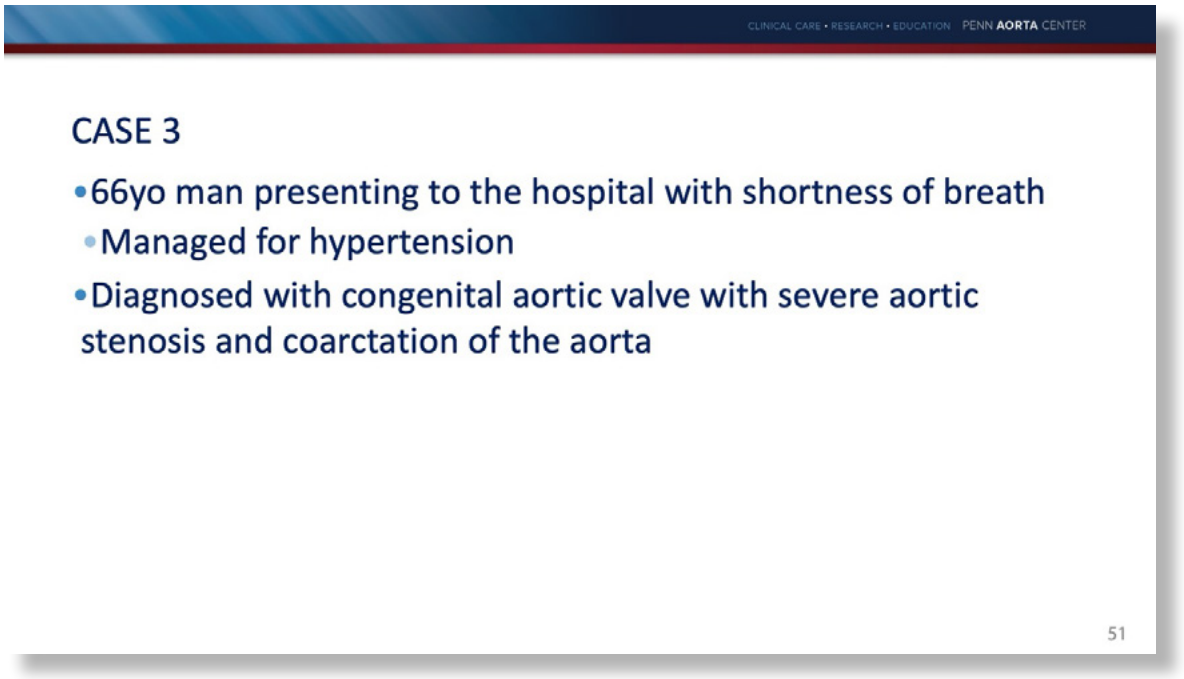
Dr. Allison Tsao: This was a combined procedure. This was a transcatheter aortic valve replacement commonly called the TAVR that Dr. Desai and I did together. This is a balloon expandable valve that's going up inside his surgical valve that's already there. He started with a severely leaky valve or aortic regurgitation. That new valve is being deployed in there. We see a lot of stuff on this slide. There's equipment that we go through the blood vessels in the leg that go up to the heart to get there. That's why you end up with some fancy band-aids from the leg but no open sternotomy.

I can tell looking at this that he does have a prior Ross. We see some calcification up at the top not where our valve is going up but in the other spot. The important fact that his pulmonary valve was working very well at the time was crucial in that decision-making. So going back to the patient's question about failure rates, had his pulmonary valve been dysfunctional at that point in time, too, I think our conversation might have been different. Although we do have transcatheter therapies for the pulmonary valve as well, which Dr. Desai and I also do, we're not going to focus on that in this aortic-centric conversation now but really exciting work that we're doing there, too.



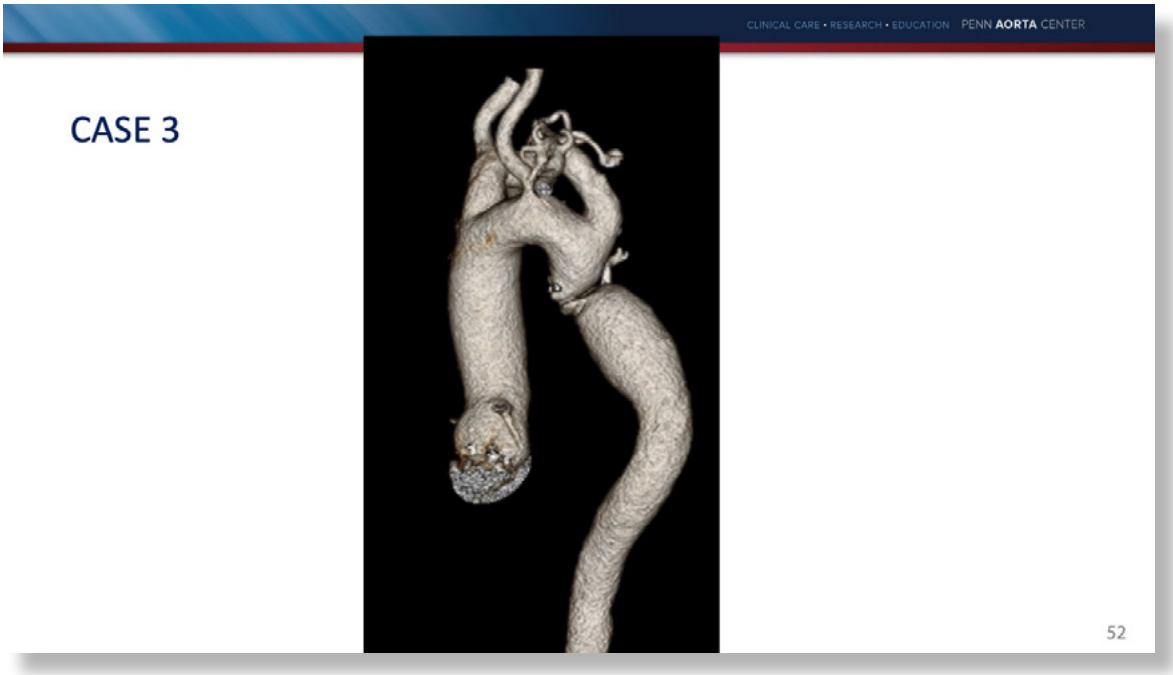
This is the subsequent picture. We're injecting contrast material under x-ray and we show that there's no more leakiness. All that contrast material is staying above the level of the valve, and it's no longer going backwards into the heart, so this was a great result. Patient was able to be discharged the next day and get back to work in about one to two weeks.

Patient Case Study #3: Symptomatic 66-Year-Old Man



Dr. Allison Tsao: All right, our third case, I think this is it, a fun one to talk about, really collaborative practice management. This is a 66 year old man, so not as young even though we're going to talk about congenital aortic valve disease. He's been managed for a long time for hypertension, high blood pressure. He's coming to the hospital with severe shortness of breath. During that hospitalization, he was diagnosed with congenital aortic valve disease and

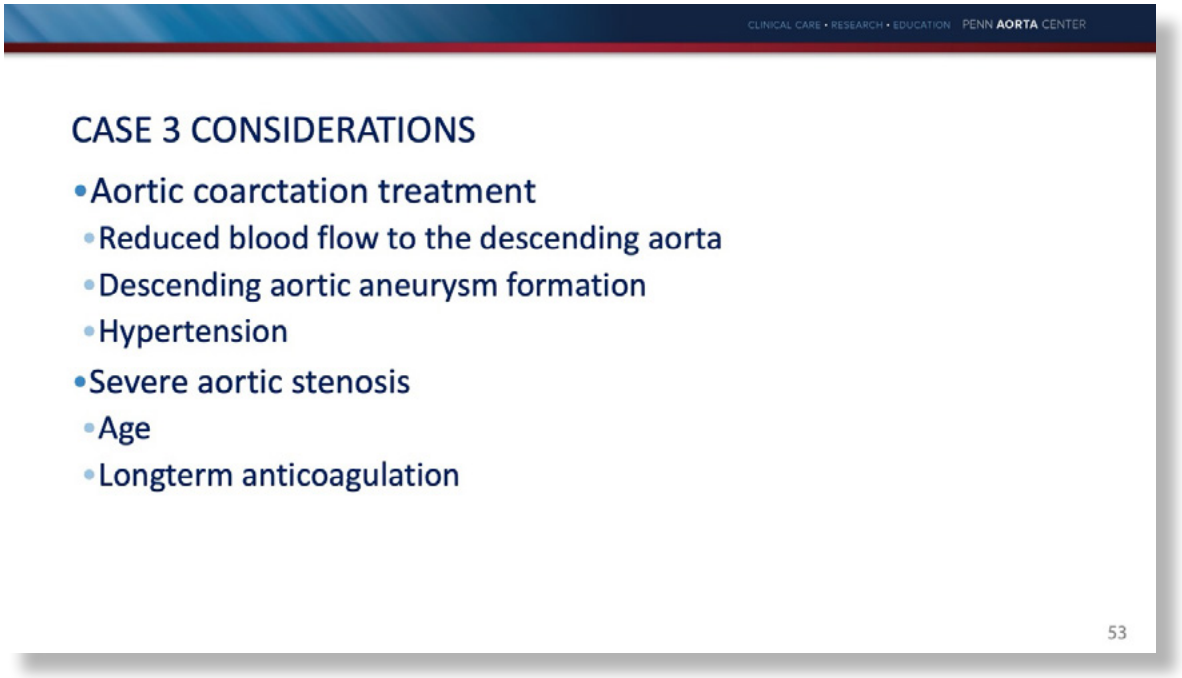
severe aortic stenosis, maybe bicuspid, maybe unicuspid, very hard to tell with non-invasive imaging, and coarctation of the aorta, so this was that important part where we want to think about the entire aorta and make sure we're imaging that. With his history of high blood pressure, we need to think about that.



This is a picture of his aorta and that tight narrowing that we see. I usually describe the aorta as a bit of a candy cane and then the narrowing after it starts to bend down, right there, perfect. That is a coarctation. What happens with that is the blood flow is diminished to the organs below the diaphragm, everting past that. We think about the kidneys, the belly, liver. Blood flow is reduced. What happens is those organs want a lot more blood, so your blood pressure through hormones and other things start to go really high.

When we're thinking about fixing an aortic valve, again, we'll go back to what Dr. Desai was talking about, we really care about blood pressure management after an aortic valve replacement. If we have something that we know is driving up the blood pressure, we need to think about that before we move forward with

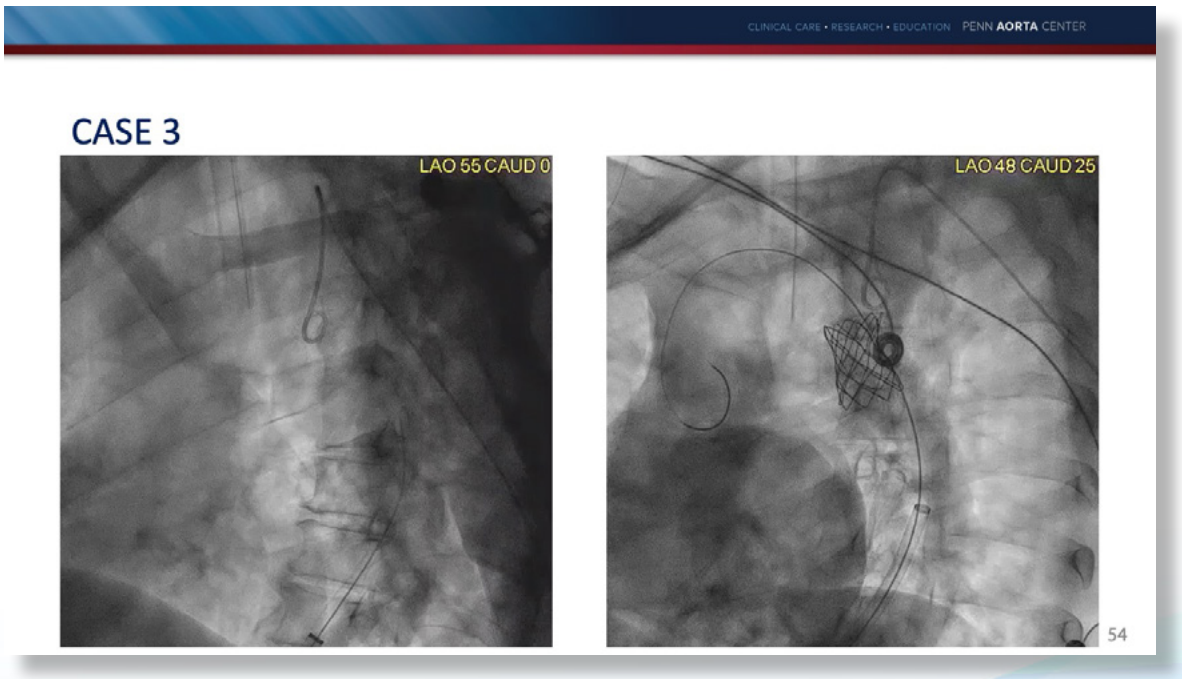
an intervention. Dr. Desai, we're thinking this man – he's 66. We're talking about a surgical aortic valve. I think we'll agree on that, but how do you approach a patient like this in thinking about order of operations or procedures for when we're going to intervene on a coarctation and when we're going to do surgery?



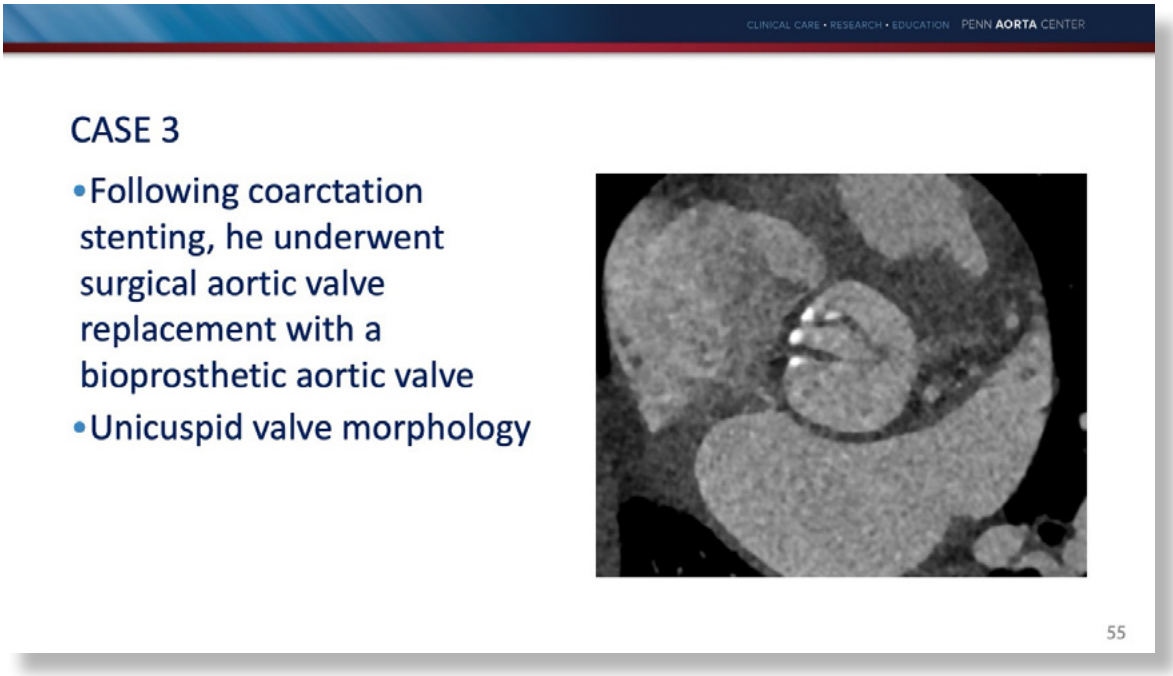
Dr. Nimesh Desai: Yeah, that's a great question. So this case brings up a very practical problem as a heart surgeon that when we go on the heart-lung machine, the blood pressure isn't pulsatile anymore. That is you don't have a pulse anymore, that it's flat. Your blood pressure is at one pressure, usually about 65, 70, somewhere in there. You don't have that big spike of blood pressure. Let's say normal blood pressure is 120/80. When you don't hit that

120, you're not getting a lot of flow through that coarctation. So, from a practical perspective, we actually have to fix the coarctation before we go onto the heart-lung machine. From a long-term perspective, as you said, we really want to get that pressure – it's basically like a vice on the aorta. There you can see how narrow it gets. We want to depressurize the aorta as much as possible because that will take the stress off of our valve and take the stress off of the heart and allow maximum recovery of that heart that's been struggling from the aortic stenosis as well.

In this situation, there's two areas of obstruction or blockage and we actually have to deal with both of them. They can both be dealt with surgically, but that's two very big surgeries done with two very different incisions. To manage it, we came up with a hybrid solution.

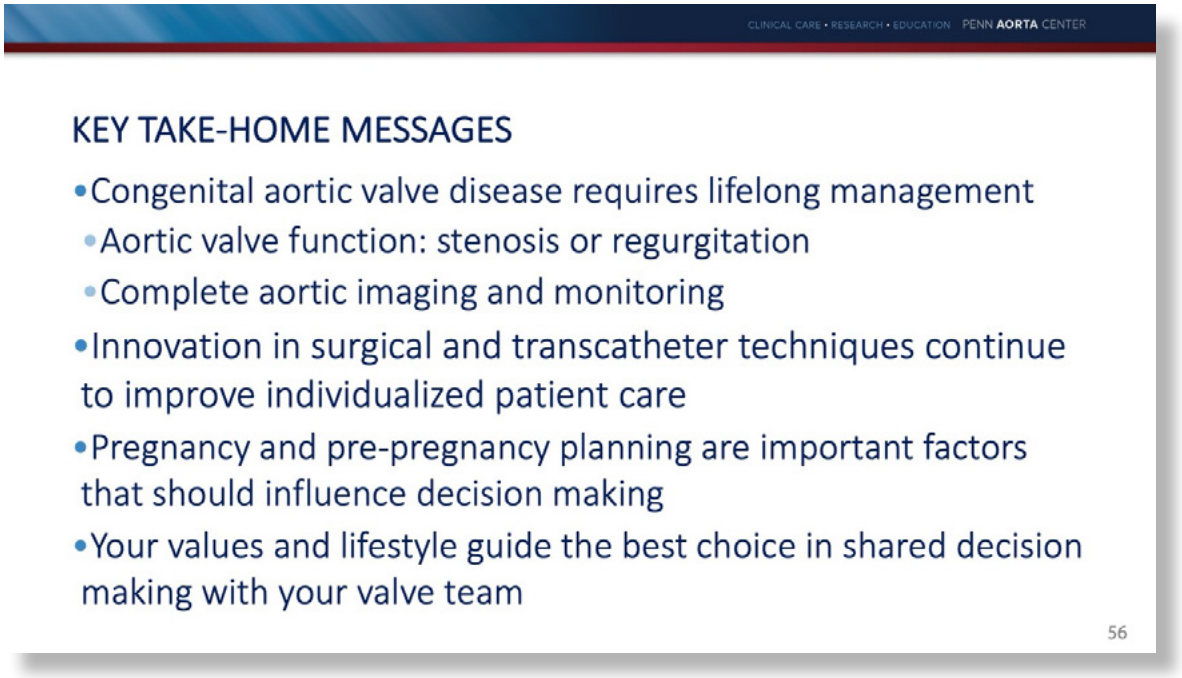


Dr. Allison Tsao: So this is – we're in the cath lab and we did this as a hybrid procedure. There's a picture on the right of that same CT image. This is now invasive imaging. We placed a covered stent. We blew it up with a balloon very similar to the TAVR that you saw with a balloon and a stent that goes up. That stent is now opening up that blockage to relieve that coarctation. We actually equalize the pressure. There was no pressure difference across there again. Sorry if those aren't playing. There we go; that repeat image. We have a nice open area. Blood pressure was much better controlled.



Then after that coarc intervention, he recovered for a few days and then he underwent a surgical aortic valve replacement. Interestingly, this is a picture of that unicuspid valve I showed at the beginning. Again, these calcified valves can be hard to know the exact anatomy. Then Dr. Desai is able to get that surgical follow-up.

Key Take Home Messages



Dr. Allison Tsao: So just some take-home messages. I hope we're relayed to you that congenital aortic valve disease really requires lifelong management for various valve dysfunctions. It can change over the course of a lifetime. I think that second case really highlighted the different aspects that come together with that. There's a lot of innovative surgical and transcatheter therapies that are just improving individualized care for patients. Your life events should be a part of this conversation. We really value the collaboration we have in our valve center and being able to work with interventional cardiologists, cardiac surgeons together in one room to come up with the best answer for you.

Adam Pick:I want to extend a huge thank you to you, Dr. Desai and you, Dr. Tsao, for these incredible prepared remarks and all of the work that you're doing on behalf of patients with valvular disease, more specifically congenital aortic heart valve disease. So that being said, I want to thank you for being here today.

Patient Resources

Since 2006, HeartValveSurgery.com 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.

- Adam's Free Patient eBooks - Download 10+ free eBooks about heart valve disease and treatment options for aortic, mitral, pulmonary and tricuspid valves.
- Heart Valve Learning Center - Visit the Heart Valve Learning Center to access over 1,000 pages of educational information about valvular disorders.
- Patient Community - 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.
- Surgeon Finder - Find and research patient-recommended heart surgeons that specialize in heart valve repair and heart valve replacement procedures.
- Heart Hospitals - Learn about medical centers that have dedicated teams and resources that specialize in heart valve therapy.
- Adam's Heart Valve Blog - Get the latest medical news and patient updates from our award-winning blog.
- Educational Videos - Watch over 100 educational videos filmed by the Heart-ValveSurgery.com film crew about heart valve surgery.