SANJAY GANDHI: So my charge for the next 45 minutes is share with you a little bit, and hopefully you'll get a great sense of our passion for management of structural heart disease. I'm going to throw a lot of data at you. But the essence of this talk is really not so much the data. It's to backup, really, what we're doing. But more so, really, this is an exciting time for what we call the heart team approach to care of patients, really, with all types of different types of cardiac diseases, but specifically with this nitro patients, a really large group of patients, who've been tagged patients with structural heart disease.

So the objectives we have are, number one, to review the clinical challenges in treating high-risk patients with non-coronary cardiac disease. So when I first got into cardiology, and certainly for all of us, for most cardiologists, the bread and butter stuff that we do is really managing patients with atherosclerosic coronary artery disease, the patients with the MIs, unstable anginas, the ones that we either manage medically or refer for bypass surgery, take care of with coronary stents, and, really, all the diagnostic imaging, and interventional therapies that come along with those patients. But one thing that also we've come to greatly appreciate is really the potential that we have for managing these patients with non-coronary cardiac disease.

And I first became interested in this aspect of individual cardiology over 10 years ago. So it's really been really interesting to see how this has developed. Because it really is a merger and a marriage between a lot of different disciplines within medicine and surgery, within cardiology. And certainly we depend a lot on our colleagues outside of cardiology as well to provide, really, the best outcomes for these patients.

So, again, in talking about these patients, one of the exciting things really has been, in terms of the management of patients with aortic stenosis, we'll discuss the development of transcatheter aortic valve replacement, or TAVR as we call it in the United States-- you may also hear the term TAVI, which is the European term-- and really look at the uses, the indications for its use that have developed over the past couple of years, here in the United States. In addition, the bulk of the talk will be looking at the aortic valve patients. But we also talk a little bit about the mitral valve and, specifically, the mitral regurgitation patients. So looking at the indications for really evolving therapies, transcatheter therapies, for management of patients with mitral regurgitation, and then, real briefly, if we have time, talk about options for left ventricular device therapy.

So when we talk about structural heart disease, specifically within the context of this talk, really, what are we referring to? And, again, it's pretty simple. It's cardiac pathology exclusive of coronary artery disease. And really that means really a huge number of patients with a vast number of disease conditions, including, predominantly, valvular heart disease. And, again, really, the explosion for structural heart patients in the US, worldwide actually, has been treating patients with aortic valve disease, primarily aortic stenosis. But we also see, potentially, some therapies for targeting aortic regurgitation as well. In addition, mitral regurgitation,-- and these are a large subset of patients with valvular heart disease-- there's also some growing therapies and forces beyond the scope of this talk today, but excitedly extending and applying the technologies and the techniques that we have for aortic and mitral valve patients and looking at patients with isolated pulmonic or tricuspid valve disease.

And how I first got bridged into this, which was looking at patients with adult congenital heart disease and cephaly patients with atrial septal defects, PFOs, VSDs. In addition, that's the valvular patients. It's the congenital patients. In addition, we do have a large subset of patients with coronary disease. And their primary problem is not so much the coronary disease but it's the after effects of coronary disease, which is left ventricular dysfunction and stage heart failure. And those are patients who may need cardiac transplants but often, as bridge therapies to that destination, may need some other type of left ventricular assist therapy, whether it's surgical or percutaneous. And then even getting involved in the electrophysiology world, looking at patients with atrial fibrillation who may not be the ideal candidates for anticoagulation and, instead, targeting ways of occluding the left atrial appendage.

So, again, the commonality in all this is, again, outside, not coronary disease, and then, again, using techniques that we have in the cath lab, and also, most importantly, really, taking these patients with a heart team approach. And what does that mean? That means really, again, involving a lot of different specialties in taking care of these patients. So when we're taking care of these patients, we're really bringing together and utilizing the expertise of cardiothoracic surgery, interventional cardiology, cardiac anesthesia, cardiac imaging, pediatric cardiology, and electrophysiology.

I probably should say, since I see my vascular surgery colleague here in the room, most of the time we don't have to call these guys. It's really bad news if they do get a call from us. But we sometimes have to utilize their expertise as well. And then, most importantly, coordinating the care involved with these patients. And, again, it really is from start to finish, which is an outpatient evaluation, taking care of these patients in the hospital, really planning for their optimal outcome when they leave the hospital, and having really good, close, outpatient followup.

So let's talk, first of all, about aortic stenosis. Interestingly, in some ways, the disease process is really a sister disease to coronary atherosclerosis. Often when, with elderly, calcific aortic stenosis, the primary pathophysiology are calcium deposits that develop on the leaflets. The risk factors often are similar to patients with coronary disease. So, certainly, a higher risk factor in the elderly, patients with hypertension, patients with dislipidemia. Often there is concurrence of coronary disease and severe or progressive aortic stenosis in these patients. And, often, they really manifest in terms of the symptoms and outcomes in the 6th, 7th, 8th decades of life.

Interestingly, the patient's presentations and symptoms pretty much give us a clear idea of what their prognosis is going to be. And this is from some classic data from Carabello. But if you look at symptoms and the clinical triad for aortic stenosis patients, often these patients may present initially with syncope. That's pretty rare, but sometimes they will present with syncope. More often, they'll present with true anginal symptoms, even in the absence of significant epicardial coronary stenosis, and that's because it increased myocardial demand. As the heart valve narrows, the heart's got to work harder. You've got thickened myocardium. And that alone, potentially, could lead to chest pain or anginal symptoms. And, over time, there's going to be pressure overload on the ventricle, there's going to be left ventricular hypertrophy. Eventually the left ventricle is going to dilate, and these patients are going to come, present with symptoms of congestive heart failure.

When these patients start developing congestive heart failure as a result of the aortic stenosis, their prognosis, without any therapy, the mortality, the life expectancy, is two years. So that's how, most often, these patients will present. And at that point, they certainly need some type of intervention. It's a given that patients with symptomatic aortic stenosis need therapy. And actually the therapy that has been classically delivered for these patients, the impact, is one of the most striking in medicine. We know that aortic valve replacement in patients with severe aortic stenosis extends their life. And, again, this is classic data from Schwartz from several years ago where patients were randomized.

So patients with symptomatic severe aortic stenosis were randomized to medical therapy versus surgical aortic valve replacement. A marked difference. As you can see, the patients who had a new valve, their life expectancy, 90% of patients were living five years out, where the vast majority of those patients, unfortunately, with medical therapy, did not survive past two years. The surgeon, traditionally, has had multiple options as far as what type of valve.

These are some of the traditional tissue valves that are available, both what we call stented and non-stented tissue valves. In addition, again, depending on the patient's profile, whether anticoagulation is in the best interest of the patient, the option may be for a mechanical valve. And, again, historically, there have been several options for mechanical valves. The most common are bileaflet valves, which are the two at the bottom of the screen that you see. And, typically, what you often see would be the St. Jude bileaflet valve as well.

So here's the dilemma that we've had with patients with aortic stenosis for some time. We know that surgical placements have been associated, unfortunately, with higher surgical mobility and mortality in certain high-risk patients. So, typically, patients with aortic stenosis should get a new valve. But if they have a bunch of other medical morbidities, they may not be able to survive the surgery or the hospitalization or the days after they're discharged from the hospitalization to really benefit from the therapy that's being delivered. And who are those patients that are high-risk from the surgery in terms of the surgery itself? Patients who are elderly patients, 80s 90-year-old patient, patients with severely reduced left ventricular function, patients who have severe lung disease.

Typically, patients who don't have these disease processes, their surgical mortality may be, in general, 2% to 5% or 8%, again, depending on some of their subsets and the presentations. But in patients with these co-morbidities, their surgical mortality may exceed 20%. So, as a result of this, historically, and if you look at some of the European data, patients with a severe aortic stenosis who needed a new valve, historically, maybe up to one third of them never got a new valve because of concern about these co-morbidities and their potential for actually surviving either the surgery, their hospitalization, or the days thereafter. And this has been most classically shown with elderly patients. Remember, the older we get, the higher risk we are for developing aortic stenosis. And typically, even though we think that, again, 90% of comers with aortic valve replacement will be alive in five years, that number has traditionally been a lot lower for patients, elderly patients, with aortic stenosis who undergo surgical aortic valve replacement.

And, again, multiple studies have shown that, if you look at different patient populations here, either in the United States or in Europe, historically, tragically, many patients who needed aortic valve replacement never got the valve because, again, their risk for the surgery was considered to be prohibitive. And this is just one of the examples of one of the patients that we had in the CoreValve study that's here as an example of, really, the dilemma we often have with these patients. An 85-year-old lady who had multiple risk factors, including diabetes, hypertension, peripheral arterial disease, had severe lung disease, had already had open heart surgery once before and had already undergone bypass surgery, already had a prior sternotomy. Based on the calculation-- there's a couple of different calculations and risk models that we can take into play-- this patient's mortality, basically surgical mortality, was estimated to be over 20%. So a very high mortality risk associated with the surgery.

So, again, here's the dilemma that we've had over the past several years. We know that surgical valve replacement significantly improves long-term outcome and decreases mortality in symptomatic patients with severe aortic stenosis. But what are the options for patients who are, quote, too high for surgery and have been turned down for surgery? Prior to TAVR, really, the only other option we had aside from medical therapy was balloon valvuloplasty. And that's just a crude transcatheter procedure where we put a balloon inside a very calcified, rock hard aortic valve, blow it up, and try to stretch that aortic annulus as much as possible, open up the valve. Unfortunately, that's a pretty high-risk procedure.

Just the procedure itself was considered pretty high-risk, again, because of the patient's subset, the risk of developing acute aortic regurgitation, the risk of stroke and vascular complications. And if they actually survive the procedure, most of these patients had a recurrence or restenosis of the valve within six months to a year. So a very high-risk procedure with very limited benefit, and a very high likelihood, and really no curative therapy or potential at all. All of these patients would still have recurrence of the disease. So, interestingly, what were the options really for these, quote, inoperable patients with aortic stenosis? In the past, unfortunately, nothing at all. Medical therapy, and that's about it, and a one- to two-year prognosis.

So if you look at what our individual cardiologists look at, our mindset is opening blockages is good, putting stents in is even better. Why don't you take that same mindset and apply it to the aortic valve? Why not put a prosthetic valve inside a stent, deliver it with the catheter, and put it inside an aortic valve? And that's really, in a nutshell, transcatheter aortic valve replacement. So, in terms of proof of concept, Dr. Anderson first did the first successful animal study, or animal model delivery, of a transcatheter valve back in '89. So this was actually a porcine valve implanted on a stent, which was then implanted in a pig. So the first pig-in-pig transcatheter valve replacement successfully done by Doctor Anderson in 1989. For several years, cardiologists, cardiothoracic surgeons, really, I think, were very pessimistic of, really, the development of this technology and the application of this technology to successfully apply to human patients.

Alain Cribier really, I think, should be considered the father of transcatheter valve replacements. French interventional cardiologist, was very determined to see this technique and this technology through. And, as a result, really, of collaboration from, again, interventional cardiologists, cardiothoracic surgeons, and industry, developed what, at that time, was called the Cribier Edwards valve, which was initially a porcine valve also, again, crimped on a stent. And then that technology developed. And he performed the first successful in-man transcatheter valve replacement with the Cribier Edwards valve in 2002. And that's, of course, doctor Cribier with his first patient in France. Nice, smiling success. So it would be nice if all TAVRs turned out this way. Unfortunately, that's not the case because, often, it's done in a high-risk patients. But, certainly, I think we've seen a lot that's happened in the decade since Dr. Cribier's first successful patient back then.

So, in a nutshell, again, this is from the first initial paperwork. Cribier reported his first case series with patients in France. Again, basically the valve is delivered via a very large catheter, now, traditionally, through the femoral. In the past, the initials were actually done through the femoral vein, across the atrial septum, and then into the left ventricle. Now we do a retrograde approach. Basically, as you can see on that first picture on the left, that's the crimped valve inside, within the stent, and then a balloon within that. It's put across the aortic valve. The balloon's inflated and basically the stent's expanded up against the aortic valve.

One of the interesting and neat things about this technology is we can actually take advantage of all that calcium that's deposited along the aortic annulus. That calcium serves as the framework and mechanism of keeping that stent in place when it's expanded. And then basically the balloon's inflated, the stent's expanded within the annulus. The balloon's deflated and is removed, and the stent valve's in place. And basically you've crushed across the old aortic valve leaflets. They're crushed by the stent. The new leaflets take over, and basically you have a new, functioning aortic valve. And then, of course, you always want to make sure that you don't impede on the coronaries, which is those last two pictures there.

So from that, we've gotten now to where we are today. And the two valves that are now approved for use in the United States is basically the evolution of the Cribier Edwards valve, which is now the Edwards Sapien Valve, which you see there on the right. That is a balloon expandable stent valve. The original valve was porcine. But the current configuration of the Edward Sapien Valve is now a bovine valve, again, constructed within metallic stent. The CoreValve, which is on the right, is a little bit of a different technology. Instead of a balloon expandable valve, this is actually what we call a self-expanding valve.

The framework that you see there for the valve for the stent is made from Nitinol, which essentially is a compound that has a preserved memory. So if you fold it together and constrain it, once you release it, it will configure back to its original formation. So with Nitinol, the stent's configured in that formation. It's a porcine valve that's placed within it. And then basically you just fold it together inside the constrained area. And when it's in position, it's expanded. These valves have been compared both in vitro and in vivo and are comparable to the prosthetic valves, the tissue prosthetic valves, that are out there that have historically been used for surgical aortic valve replacement. So if you compare them in terms of dynamics, hemodynamics, et cetera, they perform quite excellently, similar to the traditional surgical valves.

Let me talk just a little bit about the two studies. Now we're a little bit behind the US in the sense of our availability. These two valves were approved for use in Europe in 2007. We've had studies here in the United States, but the valves had not been commercially approved until recently. The CoreValve earlier this year, the Edwards Sapien Valve at the end of 2011. But once this technique and this technology has been available here in the US, we've seen, really, an exciting expansion and, really, appropriate use of these techniques for, again, patients who in the past who may have not been offered this technique or would have suffered if they did undergo surgical valve replacement or were at high risk for significant morbidity and mortality.

So the partner study, which was looking at the Edwards Sapien Valve here in the United States, multi-center study here in the US, there were two arms to the partner study. First was an operable arm. So that's on the left side, or, excuse me, on the right side. Those were patients who were deemed not candidates for surgery. So they've been seen by surgery and turned down by two surgeons, just too high-risk. Those patients, again, the benefit of TAVR was really not as well established as we know now.

So, at that time, those patients in the inoperable arm were randomized to either TAVR versus medical therapy. Then the other arm was the high-risk arm. And those were patients who the surgeons evaluated and said, yeah, we'll operate. But we're very, very concerned of that you are going to have a high risk of either complication or even survival during your hospitalization. So those were the two patient arms that were randomized, a large subset of patients.

Looking, just simply, at the inoperable cohort and partners. And, again, that was for patients who were either randomized to TAVR with the Edwards Sapien Valve versus medical therapy alone. The main thing from this study was that there was a 50% reduction in mortality at 12 months in the TAVR patients. So that, I think, is the big takeaway on that patient population. Clearly, we knew that if we didn't do anything, these patients had a terrible prognosis. TAVR is a viable option for those patients. Although, still, there was a 50% reduction. But, at the same time, still some significant risks associated with TAVR as well. Looking at the high-risk patients, so looking at that other arm, patients who had been randomized to either transcatheter valve replacement versus surgical therapy, it showed that, certainly, TAVR provided equivalent therapy, was just as good as surgery at the time. So I think, based on that data, TAVR for the Edwards Sapien Valve was approved.

If we dig a little bit more into the patient subsets, what we did realize, even though TAVR certainly is, I think, for the inoperable patient, a very new and potentially hopeful therapy, these patients do have a lot of problems and are potentially at risk for complications. One of the things that was identified with partners is the increased stroke risk with TAVR patients for the inoperable arm versus surgery. In addition, also, vascular complications. Often, these patients have severe vascular disease to begin with.

Typically, delivering these valves, you have to go either through the femoral artery, and, often, these patients who have concurrent medical conditions have severe peripheral arterial disease, have very calcified aortas or very calcified iliac arteries, very calcified femoral arteries. Trying to navigate through all that-- and this is a very large catheter and sheath that we're putting through these patients who are at high risk for vascular complications. On the flip side, I think the bleeding risk as well as the risk of renal failure was much lower in the TAVR patients versus the operative arm. And, essentially, this data held out when we looked at these patients at two years out as well.

The other thing that we did see is in terms of, again, performance of the valves. So all these patients underwent echocardiograms at one month, one year, following TAVR In terms of the echocardiographic assessment of the valves, for the patients who made it to one year and we assessed their valve, the valve was functioning great. There was no gradient, which is one of the measurements that we used. LV function was good. So great valve and great option for patients who were at high risk for surgery.

We talked a little bit about the CoreValve. The CoreValve was a little bit different in the sense that, again, it's not a balloon expandable valve. It's a self-expanding valve. And, essentially, those three pictures from the cath lab at the bottom, to note how they work, the valve's placed, covered inside the delivery catheter across the valve, and then basically it's unsheathed. As you unsheath the valve, the stent expands, and the valve is in place.

All right. Real quickly, just talk about the CoreValve study, which was the pivotal study that led to approval of the CoreValve here in the United States. This past year, we were really honored and proud to be a participant at Wake Forest as part of the CoreValve study. The CoreValve patient population was very similar to the partners population. We had patients who either were high risk, so felt to be at high risk for problems but not turned down for surgery, or patients who were labeled extreme risk, the surgeons had turned them down and, again, multiple centers throughout the United States, including here in Winston-Salem at Wake

So looking at the extreme risk-- and, again, this is just a summary of the patients that were involved in CoreValve-- patients who had, by objective criteria, severe aortic stenosis, which means you are looking at the aortic valve area, less than eight centimeters squared, or potentially looking at their pressure differences across the valve. Those were really the most definitive criteria for this definition of aortic stenosis. The only patients that were excluded were either patients who were at very high risk for bleeding, since these patients would have to get anticoagulation during the procedure as well as beyond antiplatelet medications afterward, had severe renal dysfunction, had significant coronary disease that wasn't treated. So if they'd had bypass surgery that was effectively vascularized or they had a coronary stent to treat, they were still eligible, or if they had severely reduced left ventricular function with an EF of less than 20%.

So just real quickly about the extreme risk arm. The one difference between CoreValve and partners was, if you remember, four partners, they took patients who were inoperable and just randomized them to medical therapy versus TAVR. Since we had some initial data, again, showing that TAVR was beneficial, it was felt it wouldn't be ethical to turn down therapy for patients for the inoperable arms. So everyone who was considered extreme risk in the CoreValve underwent a TAVR. So there was no randomization for the inoperable patients. They all got TAVRs. Basically, historically, what they did then is looked at what would be the expected mortality for similar medical patients.

Really, the primary objective was to look at all-cause mortality and stroke rate in these patients, based on historical data. They had a cut-off of 42.7%. So that was going to be the expected combined mortality and stroke rate for these patients for medical therapy alone. So if that was the performance goal, basically saying that we need to do better than 43% of these patients, for these patients' CoreValve, it was reflected as, really, a true life-saving therapy. So if 43% of them was the benchmark, again, the combined at one year was 26%. Pretty remarkable for any therapy, really, in medicine. And, again, if you looked at all-cause mortality, all-cause mortality was 24% at one year in the extreme risk, and cardiovascular mortality 18%. Again, if you're expecting mortalities in the 40% to 50% range in those patients, a remarkable reduction in risk. So, again, similar to the partners' data, if these patients who are deemed inoperable, they certainly should be considered for the aortic valve replacement.

Now looking at the other arm of CoreValve, which were those patients who are high-risk. So not turned down, but felt to be at high risk for significant complications. Those patients were randomized to surgery versus TAVR. And, remember, in partners, it showed that either therapy was pretty much equivalent. Again, looking at the treatment arm. So when you looked at those patients, 394 patients were randomized to TAVR, 400 patients were randomized to traditional surgical aortic valve placement. So the surgical all-cause mortality at one year was 19%. For the CoreValve, not only was it actually not inferior, but it proved to be actually superior therapy for these patients.

All-cause cause mortality for TAVR with CoreValve versus surgical replacement was 14%. It really was the first time in looking at aortic stenosis that any therapy had been shown superior to surgical aortic valve replacement. So really a remarkable piece of data, looking at these patients. And, again, this benefit held out at one year and also held out at two years as well. The stroke rate, which is one of the things that we were concerned about, based on the partner's data, actually was pretty much similar in these patients, whether they underwent surgery versus CoreValve.

OK. There were some concern as far as outcomes. You have to be cognizant of hour in the TAVR patients with CoreValve. Again, one of them was the vascular complications. Again, large sheaths going in either to patients with significant peripheral disease or alternative accesses. The vascular complication rate was a little higher in the TAVR group. The way the CoreValve works, that stent initially starts below the aortic valve, and sometimes that can interfere with the conduction system. So, as a result, a higher number of these patients required permanent pacemakers versus the surgical valve. So, again, some very, very promising outcomes with the core values. But also things that are going to, I think, need closer followup. As expected, the bleeding complication rate was much lower with the TAVR group. The risk of aortic atrial fibrillation was lower in the TAVR group. And the risk of kidney injury was also lower.

One other thing I'll just talked about, which we know does put patients with TAVR at higher risk, is this phenomenon of what we call paravalvular regurgitation. So the idea is that you want that stent valve to basically seal up against the aortic annulus and start functioning well. But sometimes there can be regurgitation or leaking, not through the valve but around the valve. And that's a paravalvular regurgitation. And one thing that's been consistently shown, really, throughout the TAVR population is if there is what is deemed severe paravalvular regurgitation. Those patients do you have a poor prognosis. So that's one of the other challenges in really identifying patients who may be at risk for paravalvular regurgitation. And if they do have it, identifying and treating that early.

So that's all the data, most of the data. Next we'll just talk a little bit about the procedure and then talk about mitral valve stuff. So TAVR's definitely a very promising, potential therapy. So far it seems like it is a durable therapy. But, remember, the earliest patients from 10 years ago in the US experience is much, much shorter than that. These patients are, again, high-risk to begin with, which is why they're undergoing TAVR. So they are at higher risk of vascular complications, stroke risk, and, as we talked about, both pacemakers and the risk of aortic regurgitation.

We have a lot at Wake, just like a lot of centers in North Carolina and throughout the country, of interest in identifying and delivering the appropriate therapy for these patients. It's a complex evaluation process. But I think the key things for evaluating these patients, and certainly, is the severity of the aortic stenosis, determining what the valve size is and whether there's an appropriate TAVR valve that we can put there, and then figuring out what's the best access approach to these patients. Just a little bit about the two valves and the differences right now. At Wake, again, it's really patient-centered and patient-tailored as far as whether we do have the option of either putting in an Edwards Sapien Valve or a CoreValve.

The Edwards Sapient XT is the latest configuration of the Edwards Sapien valve. So these valves do have to be put in pretty large sheaths for the Edwards Sapien, depending on which valve size we're putting in. We can use either a 16-, 18-, or 20-French expandable sheath. The CoreValve, across the board, from all the different valves, is an 18-French sheath. The CoreValve is a porcine valve, Nitinol frame. The Edward Sapien is a bovine valve in a stainless steel frame. The shape of the Edwards Valve is circular. The CoreValve actually is more of an oval shape. The Edwards, again, as we talked about, is balloon expandable. The CoreValve is self-expanding.

This is more anatomic data. But the ideal location for putting the Sapien valve is actually right at the aortic annulus where leaflets are because of the physics of the self-explaining stent valve. The actual valve, where the valve is in relation to where the stent is, is actually above the annulus itself. Both of these technologies now are FDA approved. And if you can't get your valve there, through the femoral artery, there are alternative approaches that can be used, whether it's through the subclavian artery, whether it's working with the surgeons going directly into the aorta, or sometimes also the transapical approach. Again, the surgeon makes a small thoracotomy and we actually go backwards, actually go in through the left ventricular apex and then go through the valve in an antegrade fashion, not a retrograde fashion. So I actually put an incision in at the apex, put the large sheath into the apex, we cross the valve from that side, going from the left ventricle up into the aorta. So, traditionally, if you're not going to go into the femoral, either of these approaches is acceptable. You have femoral access approaches. If you can't go femoral, than alternative access, typically for the Sapien, would be either transapical or directly aortic, or, for the CoreValve, a subclavian approach or a direct aortic approach.

So this is an example here for a case in a patient with the Sapien balloon expandable valve. So you can see here. And this is a patient, you can see, there's sternotomy wires, there are markers of those rings up above, or markers for where there's a saphenous vein graft. So patient has already undergone bypass surgery, has already had one sternotomy. All these patients for the Sapien valve have to be paced at a very high rate because, again, you want to drop their blood pressure pretty low so that valve doesn't get, basically, ejected out of its position from a contraction of the left ventricle.

So what you see there is a temporary pacing wire that's going into the right ventricle. That's a pigtail catheter that's right above the aortic valve. And I don't think you can really appreciate it. Right below the pigtail, you can kind of see these markers of calcium. That's the aortic valve. We're just doing an aortogram right there to mark where the valve is. You can see where the coronaries are, filling above it.

So, often, before we deliver the valve, we will do a balloon aortic valvuloplasty, and that's just to stretch open the valve so that we have enough room to get the stent valve in. All right. So now you can see we have a wire across the aortic valve. We're pacing, you can see. And then that's the balloon that's just being expanded to open up the valve. So that's the balloon valvuloplasty right there.

All right. And then, after that, we then will basically put the catheter valve up. And you can see, coming down from below across the descending thoracic aorta, how big that catheter has to be, relative. So that's the pigtail catheter that you see with the little marks on it, on the right side. And then, to its left there, is the catheter that's encasing the valve system, so how much bigger it is. So that's going up, around the arch. And then we've got the wire. And you can see the undeployed stent that's across the aortic valve, right here.

So we'll pace real fast, drop the blood pressure, and then expand the balloon. And as we expand the balloon, that stent will expand and basically be anchored by the calcium in the aortic valve. Hopefully this will be it. Cross your fingers. All right. Here it is here. So pacing, balloon's being expanded, there is a stent valve being deployed. And then the balloon's deflated. And then the pressure usually is around 50 to 60. So everyone's holding their breath. Deflate the valve, cross your fingers, turn the pacer off, and hopefully the pressure comes back up. And, fortunately, it does. But it's a long five seconds there.

All right. And then this is the functioning valve afterwards, what it looks like. So you can't actually see the leaflets, but you can see the structure of the stent there. And the things that we're looking for, again, that's contrast. There's not much aortic regurgitation. The coronaries are filling. And you can actually see this big line coming down below, that's one of the bypass grafts as well. So that's typically the TAVR case. The last thing, which I'm not going to show is, after this, and still one of the most important parts of the procedure, is getting all that stuff that you've put in the femoral artery out again. So success here. And the next step then is getting everything out and having hemostasis at the femoral artery, and, hopefully, not having to call our friend, the vascular surgeon.

All right. So this is the CoreValve. Again, you can tell it's a little bit different in the way it's set up. So that's the CoreValve, that's basically encased inside the delivery sheath, right there. Again, there is the pigtail right there, the CoreValve, actually. So the bottom part of the stent you can see is just actually a little bit below the aortic annulus. There's a pacemaker wire that we have in place as well. This is also a patient who's had prior bypass surgery. You can see sternotomy and vein graft markers there.

All right. So this is a bit more of a controlled process. So with the Sapien valve, you've got to time it, get everything in position, drop the pressure, blow up the balloon, drop the balloon, cross your fingers, everything gets back. This is a little bit more of a controlled process here. So, again, we can slowly unsheath the valve. Remember, it's Nitinol. So once it's unsheathed it just configures as to what its original memory configuration is. This is in the early points right here. The patient still is vulnerable at this point, but basically because, essentially, you got a patient with sever aortic stenosis and you're already occluding it with this large, bulky device. So you still have to work pretty quickly and fast.

The valve is being, at this point, deployed. This is at two thirds deployment. And this is the most vulnerable phase right here because, at this point, the patient may be prone to wide open arotic regurgitation if the patient does not have a functioning valve. Let's see. Will this play? And, again, the valve itself, you can see the bottom portions of the stent. The valve's actually not there. It's a few millimeters above where the distal end of the stent is. So the stent actually does hang into the left ventricular alfuler track. The valve's actually above that position. This is actually pretty similar and in a good location for where we want the stent to be positioned in the end.

All right. And this is what it looks like at the end. Again, you can't see the valve itself, but we can see where the stent is. And it's in good position. You can see that the coronaries are filling properly. And then the bypass grafts were above it.

As I alluded to, we're always happy to get a good result with the valve. But the case isn't over at that point. Because one of the highest, as we talked about, morbidities associated with these patients are vascular complications. Take a preventive approach. If we're pretty confident that there's just not any way to get to this patient's heart from the femoral arteries, then the best choice is to go alternatively. But we have now, from the worldwide experience that we have from TAVR, we are learning, however, that if you can go through the femoral, that's the best option because there is a higher risk associated and a higher, really, acute immobility associated with non-formal approaches.

So we take a lot of time in evaluating these patients, assessing their peripheral anatomy. These are some of the unfortunate complications that have been reported from something as drastic as true evulsion of the external iliac artery. You can imagine that's a huge bleeding complication. Or, if we go through an alternative route, such as subclavian, the subclavian is a pretty irritable artery, we've learned, and they're often prone at risk for dissection as well. So if this occurs, fortunately, there are treatable options, including placing stents or covering stents, which often we can do at the time of the procedure. And, again, if you look at, as far as the options for the Sapien valve, for example, if you look at the bottom, there is an example of a transapical access on the lower right-- I guess it's actually on the-- excuse me, on the lower left there, where you've got the sheath going into the left ventricle, and basically the catheter is being delivered from the opposite direction.

So who should be considered, really, for transcatheter aortic valve placement? Really, anybody with severe aortic stenosis. Now many of these patients are going to do well with surgical aortic valve replacement. And certainly that should be, I think, one of the first-line therapies for these patients. But I think we worked very closely with the cardiothoracic surgeons. Our recommendation is, if you have a patient with severe aortic stenosis, send them to the heart team. And the heart team will make an evaluation and determine, based on, again, the patient subset, the anatomy, what their risk factors are, whether they are most appropriate for an open surgical valve replacement, or whether they should be evaluated for a transcatheter valve.

So I'm going to move on. Any questions about transcatheter aortic valve replacement? All right. OK. I'm going to, just for the next few minutes, talk a little bit about some of the other structural heart therapies. And mitral regurgitation is the other one that is really, in terms of valvular structural heart disease, we're getting more experienced with in the hybrid cath lab. As far as mitral regurgitation, what are the etiologies? Traditionally, these patients can often present with degenerative or myxomatosis mitral valve disease, so that patient with severe mitral valve prolapse. So that one, and then also really the ischemic functional patients are the one at the bottom there. Those are the most common subsets of patients that we see mitral regurgitation. And the ischemic patients are the ones that have severe left ventricular dysfunction, have dilatation of the annulus, or the mitral valve annulus, that leads to mitral regurgitation.

The other potential etiologies, which are not as common and really are not candidates for structural valve therapies, are rheumatic heart disease patients or patients with infectious etiologies, endocarditis. So, again, traditionally, patients with severe symptomatic mitral regurgitation were treated surgically. Ideally, these patients were treated with surgical repair. Those were the patients, really, that you had the best outcome for. If they were not really candidates for repairing the valve for anatomic reasons, then they would undergo a replacement of the mitral valve. And, again, this is just a summary of the anatomy that we're talking about.

Often, the most common repair or one of the more common repairs, at least at the surgeon's disposal, if you look at the mitral valve-- so you have the anterior leaflet and the posterior leaflet, which each have three pieces or scallops-- would be removal of the posterior scallop, bringing that in, and then putting an angioplasty ring around the annulus, which then brings everything together. So if you have a degenerative, floppy valve, really taking away part of that redundancy and closing that valve together. But this really is, in terms of a summary, the many different operative options that a surgeon would have for repairing the valve, again, in terms of angioplasty, resection of part of one of the scallops or replacement, and then also a ring placement.

The MitraClip, which is really the one percutaneous therapy that, right now, is taking hold here is based on something called the alfieri edge-to-edge repair. So the alfieri edge-to-edge repair, first described by Dr. Alfieri back in the late 90s, is actually a neat, straightforward concept. Essentially, again, looking at the mitral valve and the two leaflets, part of the problem is that they're not coapting correctly and you have a lot of regurgitation. Why not just put a stitch or a clip that basically attaches the anterior leaflet and the posterior leaflet and going from a single orifice to two smaller orifices across the mitral valve?

And this was actually shown to be effective in reducing mitral regurgitation. And this is from Dr. Alfieri's initial series, looking at 121 patients where they either had just an alfiere stitch alone or, in addition to an alfiere stitch, also an angioplasty ring. He took most all-comers, but mostly patients with degenerative or myxomatous mitral valve disease. These patients had five to six years, had excellent outcomes in terms of survival as well as their need for any additional operations.

So based on that comes the MitraClip. It's basically doing a percutaneous alfieri stitch on the mitral valve. And so, again, it's a big, bulky device. So if you look at the picture there on your left-- I'm always getting my-- because I'm looking at it from the other side from you guys. But actually, I guess, on the right side here-- on the right side, the clip consists of two arms that initially are open. And you can see those barbed, horizontal things above it. Those are called the grippers. Essentially, the goal is usually to use those arms basically capture each leaflet and bring it onto itself, and then leave that clip behind.

So this is a large, bulky device that basically, initially, we use femoral venous access. So we go initially from the femoral vein, up into the right atrium, and then do a transseptal puncture. So go from the right atrium, puncture the atrial septum, go into the left atrium, and that's basically what you see right there. Then position the undeployed clip right above the mitral valve. So you see the valve right there. So get it positioned above that, basically, then open up those arms.

OK. So right now, the catheter and the MitraClip itself is positioned above the mitral valve in the left atrium. Bring that down below, into the left ventricle, below the leaflets, and then basically manipulate the device so that you can capture both the anterior and posterior leaflet. Once that's in, you basically now have created a percutaneous version of that alfieri stitch. And you've got those two small orifices instead of the large orifice. And then, if everything's in place, essentially you'll leave the clip behind, take everything out.

So the MitraClip became approved in the US earlier this year. And we got our first experience with it from this spring as well. I won't really go through the data too much. The approval for the clip was based on the efforts to design, again, where patients were randomized. Patients with severe mitral regurgitation, either functional or degenerative mitral regurgitation were randomized, either to mitral valve repair or surgery versus the MitraClip. A pretty similar patient population, again, with either 3+ or 4+ mitral regurgitation.

So for all comers, in general, I think, actually was a greater benefit for the surgical arm. If you look at freedom, in terms of the primary outcome, which is freedom from death or for repeat surgery for mitral valve dysfunction or recurrent 3+/4+,-- again, because the surgeon has greater options and can, actually, visually look at the valve-- overall, there was, I think, benefit for the surgical arm versus the MitraClip. But there were some advantages distinctly noted for the MitraClip, specifically decrease bleeding complications. And a large number of these patients did have reduction in mitral regurgitation.

And, again, based on that has come, really, the approval of the MitraClip. And it's very similar to that high-risk or extreme risk patient population for TAVR, which are patients who are felt not to be candidates for surgical mitral valve repair or felt to be extreme risk. And there is a large number of those patients out there. Anecdotally, as well as the worldwide data on MitraClip, I think this is an effective therapy in reducing mitral regurgitation, and standardly, I mean, across the board, getting it from the 3+ to 4+ to 1+ to 2+ range. And it really has been remarkable on an anginal basis, what a difference this had made in terms of symptoms and functionality in patients who get this therapy. So what are the contraindications? Again, if they have rheumatic mitral valve disease or have evidence of an active infection.

All right. Last couple of things and we're at the end, after lunch. Talk just a little bit about left ventricular assist therapies and percutaneous options. The balloon pump, which is really the oldest available method that we have for percutaneous therapies for patients with left ventricular dysfunction. So these are patients with cardiogenic shock who present, are hypotensive, and have usually severely left ventricular dysfunction, [INAUDIBLE] of some type, and are refractory, just simply revascularization. They present with an acute MI or in cardiogenic shock, secondary to a large anterior MI. You open up the vessel, put a stent in the LAD, still markedly hypotensive or, again, have end-stage cardiomyopathy and are presenting in cardiogenic shock and are refractory to traditional therapies, including, again, revascularization, pressor therapy, etc.

In the past, those are patients that we may have initially would have put a balloon pump in, which has, again, over the years, been an effective therapy in the sense that we can put it in pretty quickly. It's pretty easy to manage. But on the flip side, the data to show how much it changed outcomes actually has been fairly minimal. So that has been pretty much the only thing that we had in our arsenal until the past decade. That's really the crudest, easiest thing.

And then, short of giving them a transplant, the most extreme option that we've had has been, really, the placement, surgical placement, of a left ventricle assist device, which is up on the top of the triangle there. the three options that we have, between and in addition to percutaneous therapies, in addition to the balloon pump or the impeller catheter or also the tandem heart or ECMO therapy as well. So those are pretty much development percutaneous options that we have to deliver better left ventricular support in these patients who either really, again, are not really benefiting from the balloon pump or we know, even just based on our clinical impression, that a balloon pump is not going to be enough for these patients.

The impeller's an interesting device. It's actually an impeller motor at the end of a catheter. And if you look at it here a little bit better, this is actually a fluoroscopic image of an appellate catheter in place. It's a pigtail catheter at the very distal tip. It has this impeller motor. It basically has a blood inlet area with an impeller motor that basically takes blood out of the left ventricle, and then there is an outlet area where, when it's positioned, that's in the ascending aorta above the aortic valve. So essentially, if you have a patient who's failing, suck blood out of the left ventricle and then just basically pump it back out into the aorta. And, again, simply placed. Usually it's placed from a femoral, so from the femoral artery, 14-French sheath, and then basically just up the thoracic aorta, up across the aortic valve.

In addition to the impeller catheter-- again, all of these, and I won't get into this, have their advantages and disadvantages-- is the tandem heart catheter. This is actually something that's probably more similar to a true left ventricular assist device. And essentially it's a device where we place a cannula that has both venous and arterial access points. So a cannula is placed into the femoral vein and is placed across, into the right atrium, across the atrial septum, and then basically a venous cannula that ends up distally into the left atrium. So that's one end of it. The other cannula is in the femoral artery.

And then basically the tandem heart's connected to both ends. And essentially what this does is it moves blood from the left atrium, pumps that through the tandem heart catheter, and then back into the femoral artery. So taking you out of a failing left heart, decompressing the left ventricle, and basically reducing left atrial pressures in patients with refractory heart failure, and then basically augmenting cardiac output through the femoral artery. So, again, some pretty exciting therapies, again, for patients who are incredibly sick and potentially dying.

So I'm going to stop there. Again, just to give you just at least a taste of what's involved in the structural heart world. And hopefully, in your next couple of years, we'll be able to talk a little bit more as far as the development further of left ventricular assist therapy, options for pulmonic and tricuspid valve disease, and then also treating patients with a-fib by just closing off the left atrial appendage.

So thanks for your attention. I hope you guys have a wonderful weekend.