SANJAY GANDHI: As always, it's an honor to be at the partnership's conference. So thank you once-- for having me this year. Sounds like it's been a really productive morning. Hopefully you've had a good relaxing lunch, and we'll keep things going.

This is actually an area that certainly has been of particular interest to me, a lot of excitement. And it's really been an honor to be involved in the story that our medical center has played with advanced therapies for aortic stenosis. As many of you know, it's really something that has been a whirlwind in cardiology over the past couple of years. And it really-- I think for a lot of us we've been able to-- been able to see really the evolution this technology, and really the impact that it's had on our patients-- a game changer in cardiology. So we'll just as I said, real briefly, kind of go over this really interesting, fascinating story, and really kind of [INAUDIBLE] change we've seen. You're taking care of some of these very challenging patients.

So real quickly just the disclosures that pertain to this talk. I am an investigator for Medtronic, as part of our CoreValve study and also a consultant for Boston Scientific. Our goals for the next 45 minutes or so-- first of all is to review the clinical challenges in treating high risk patients with aortic stenosis, and then to discuss the development of transcatheter aortic valve replacement, and potential indications for its use. Let me also go ahead and get this out of the way. Sometimes it's confusion because the terminology is going back and forth. The latest terminology that we use is TAVR or transcatheter aortic valve replacement. As this technology was first being developed, it was initially referred to as transcatheter aortic valve implantation. So sometimes we use the terms TAVE and TAVR interchangeably. You may see that some in your hand out as well, but we're talking about the same procedure.

So just a real quick review regarding calcific aortic stenosis. Interestingly the mechanisms for aortic stenosis are very similar to atherosclerosis in general, and specifically what we see with coronary disease, with peripheral arterial disease, aortic stenosis develops as a development of calcium deposition within the valve collapse of the aortic valve. That's the majority of the aortic stenosis cases that we see. The risk factors interestingly are also the same risk factors that you have for coronary artery disease, and which is why often there is a large number of patients will present with a combination of both coronary artery disease and aortic stenosis. Aortic stenosis also is a disease of aging. We see it as we progress, and see more so in the sixth, seventh eighth decades of life and beyond, which is really where the relevance of TAVR has become so important over the past few years.

As far as prognosis of aortic stenosis, we know that when patients become symptomatic, that's a sign of a change in their prognosis. And specifically, as well all know, there are the classical symptomatic triad for aortic stenosis has been the development of syncope symptoms, angina symptoms and heart failure symptoms.

Most of these patients present with heart failure symptoms or kind of the equivalent of heart failure symptoms, shortness of breath, decrease in exercise, [INAUDIBLE] peripheral edema. Less cited heart failure.

Several studies have shown, when patients present specifically with these symptoms, but most importantly with heart failure symptoms, usually that indicates that their prognosis or their survival is two years at that point. So when these patients present with symptoms, we know that they need some type of intervention, otherwise their prognosis is poor.

One of the fascinating things with the AS story is as far as the therapies that were initially developed for treatment of aortic stenosis, one of the most remarkable in medicine, the mortality difference for people with symptomatic aortic stenosis treated with valve replacement. And in the past, traditionally these patients have been treated with surgical aortic valve replacement has really been quite remarkable.

This is from a classic study from Dr. Schwartz from two decades ago. They clearly show as far as with patients, of top patients who underwent surgical aortic valve replacement, you significantly impacted their survival. For patients who did not undergo aortic valve replacement had marked mortality within 1 to 2 years, so clearly one of the most really remarkable and dramatic therapies in modern medicine that does make a difference. As a result of this, surgical aortic valve replacement has been the standard of care for patients who present with symptomatic aortic stenosis.

And this is just, again, the surgeon has had really several options as far as what type of valves to implant. This is kind of again, we'll kind of review as far as the progression in terms of the valves that have been available. They've been bio-prosthetic valves, from tissues valves, bovines valves, pericardial valves. At that right, you can see some of the more typical stented tissue valves that are available.

We've also seen mechanical valves. Up at the top left, square A, that's the oldest version of the mechanical valve, the [INAUDIBLE] valve, now more commonly used are the two valves that you see in that lower row. Those are the dual-disk mechanical disk valves, such as the St. Jude's valve, which is most commonly used now.

So really as dramatic of therapy as surgical aortic valve replacement has been, it has however been associated with high surgical morbidity and mortality in certain high-risk subsets. And specifically these are the very ugly patients with co-morbidities, patients who already present with severely reduced with left-ventricular function, patients who have severe lung disease, and severe COPD.

In general, this is a safe surgical procedure. Surgical mortality in the general population presents is 2% to 8%, but has been shown to exceed more than 20% in certain high-risk populations.

And so part of the sobering part of the story is really the understanding that perhaps up to one third of patients with severe aortic stenosis who may benefit from aortic valve replacement traditionally in the past have been declined an operation because of the high mortality associated with the risks that they present with.

And as an example, this particular study shows that if you take these patients over 80 who undergo aortic valve replacement, those patients because of the several co-morbidities that they present with, often have a high surgical mortality short term, as well as decreased survival long term.

Several studies have shown that many patients who may benefit from surgical aortic valve replacement unfortunately do not receive this lifesaving therapy, because of the concerns that are associated with co-morbidities. And again, multiple studies have shown that perhaps as high as-- one study was even 60%, but probably more so realistically 30% of patients in the past who could benefit from surgical replacement, did not undergo surgery, again because of their high-risk profile.

And this is just an example of one of those types of patients that we have in the CoreValve study. An 85-year-old lady, who already had an extensive history of coronary artery disease, prior MI, had undergone prior bypass surgery, had reduced left ventricular function and ejection fraction was 35%, had presented already with advanced heart-failure symptoms, also had a history of prior atrial fibrillation and coronary disease, as you can see.

So there are two risk-scoring systems that can be applied to these patients. The one that's most commonly used here in the United States, the STS score, Society of Thoracic Surgery score, under their scoring system this patient would have a surgical mortality in excess of 20%, and a 50% risk of some significant morbidity or mortality post-operatively. So that's kind of the dilemma that many of these patients have had.

They have a poor prognosis. But unfortunately the therapy that's available to help them also carries a significant risk with it. So again, kind of summarizing, we know that surgical valve replacement significantly improves the long-term outcome, and decreases mortality in symptomatic patients with severe aortic stenosis. But unfortunately what options have been available so far for patients who are deemed too high-risk risk for surgery? And unfortunately the options have been very limited.

In the 1980s and early '90s, there was some interest in balloon aortic valvuloplasty, where you would take patients who were deemed to be inoperable and not candidates for surgery, and perhaps try to do some other type of temporizing measure essentially just crudely across the aortic valve, use a large balloon to open up and try to increase that overall valve orifice area.

Unfortunately, we learned that this is really an ineffective therapy. Most of these patients would have re-stenosis of the valve within one year. There was a high rate of mortality associated with the procedure itself. And there are also several potentially life-threatening and certainly life-disabling complications associated with this procedure, such as a high rate of stroke, vascular complications, and often these patients would develop severe aortic regurgitations. So you would take a patient who had severe aortic stenosis, and turn that person into patient with severe aortic regurgitation, and probably aortic stenosis in a few months as well.

So this was really a novel therapy. And the idea for this first really, again, was part of the interventional cardiology story from the late 1980s. Being interventional cardiologists, we like to think in general that opening blockages is good, putting stents in are even better. So if you can that with coronary arteries, if you can do that with other vessels, why not apply that to valve technology? Why not put a prosthetic valve inside a stent, and then deliver that with a catheter inside the old calcified aortic valve, put in a new valve that pretty much squashes out the old valve, and basically then acts as a new functional valve?

So this was a concept that initially seemed pretty, I think, challenging and difficult. But really through some very, very persistent dedicated pioneers, we now really are taking advantage of those initial ideas that they had. So the first stent valve that was actually put in, was put in by Dr. Rud Andersen, in Arizona 1989. It was actually a porcine valve, put on a stent, and it was put in a pig. So kind of you can call it the first in-pig successful procedure.

Carrying that through, the in-man main study was done by Dr. Alain Cribier in France. And Dr. Cribier rightfully really is recognized as the father of this technology and this procedure. It was really his vision, his dedication that led to development of the first in-man study of our time, which was called the Cribier-Edwards valve.

And the first successful implantation was done in April of 2002. You can see Dr. Cribier there standing with that first patient. His first series of patients was reported two years later. Again, I think, these were very, very high-risk patients, patients who were not candidates for surgery. So they had high risk associated with it. The valve was a really remarkable piece of technology, and really a remarkable technique.

Back then they used porcine pericardial tissue that was mounted on a stainless steel valve. It was a very, very large sheath that they had put in. So you can imagine trying put in a valve inside a tube, and getting that up to the heart. Because the catheters and sheaths that were initially required were so big, they actually had to do was called antegrade crossing of the valve.

So I won't get into all the details, but essentially what they had to do was actually through a variety of wires and maneuvers, go through the right atrium, through the left atrium, out the aortic valve, and then-- or right atrium, across the septum, into the left atrium, through the mitral valve, from the mitral valve into the left ventricle, and then take that device out across the aortic valve.

So a very, very cumbersome procedure, it carried a lot of risks, but with some remarkable successes. So that really was the first in-man transcatheter valve, successful transcatheter valve aortic replacement.

As you can imagine, again, these were risky patients. This was a new technology. A lot of potential risks associated, and we've certain learned. One of the concerns was how to properly place the valve. Do we anchor the valve? And there were reports initially of actually valve embolization, other things as well. And we'll get into that, but I think several potential complications, a very, very complex procedure.

Again, as in many things in medical science and certainly in interventional cardiology and cardiac surgery, a lot of dedicated people were involved in really refining both the science, refining the technology, and refining the technique. And as a result of that, we've seen really a new development, a new generation of therapies and valves.

Now these are all the potential valves that are out there, at least either in use or potentially in development. The two that you see up at the top, the Crimier-Edwards valve mentioned became-- evolved into the valve that's commercially available here in the United States now. That's the Edwards SAPIEN valve. Initially that valve was a porcine valve. It's now actually a bovine pericardial tissue valve placed on stainless steel stent.

That valve was actually deployed with an expansion of a balloon. So that valve was approved by the FDA here a little over a year ago. And we've seen-- the use of this technology has certainly grown over the past year.

The second valve that you see next to the Edwards is the other valve that's available in the United States as part of a clinical trial, which we are fortunately participating in at Wake Forest. That's the CoreValve. A little bit of a different design concept, it's made from nitinol, which is a metal compound with a strong memory. And also that valve was made from porcine tissue.

And the others are valves that are either at certain stages of development, of have been implanted first in-man outside of the United States, in Europe or elsewhere. Some of these are coming into development now, and probably will. For example, there's the SADRA valve that you see on the bottom left. That has evolved into what's called a LOTUS valve, and probably we will see clinical trials here in the United States next year looking at that particular valve as well. And I think what we've seen with all these technologies, is with each refinement they really are targeting some of the many challenges and complications that are inherent to this procedure.

We've been fortunate at Wake Forest. We are participating in the CoreValve study, and have access to the Edwards SAPIEN valve as well. We did our first implant in April of 2011, and did over 75 transcatheter valve replacements at Wake Forest. And I can tell you, you learn something with every one of them. Each patient has an interesting, unique story, interesting challenges. They are just some very, very sick patients. But it's quite rewarding when we see them come back really taking advantage of this life-changing therapy.

So some of the things that are important as far as these catheter valves, first of all, are they as good as the valves that are be implanted surgically? And so far, the data is very promising regarding that. So just looking at some of the bench testing, looking at the Edwards SAPIEN catheter valve, comparing it to one of the more common surgical valves that's used, the Carpentier-Edwards valve, a very, very favorable profile as far as how well is opens, its functionality compared to the Carpentier-Edwards valve.

And again, right now the two valves that are available are the Edwards valve there that you see on the left, which is commercially approved here in the United States for certain populations. We'll get into that. And then there's also the CoreValve, which is again, part of a study. The first arm of the CoreValve study has been done, as far as the randomized arm. There is a continued access, or actually, multiple continued access registries for certain patient subsets to obtain, as for implantation of the CoreValve.

So let's talk a little bit about the SAPIEN valve. That technology has an now evolved to what we can use, the retrograde technique. Remember, when Dr. Cribier was first doing the valves, he had to kind of use that very long convoluted route across the septum, across the mitral valve. With refinement of technology, then we can use a standard retrograde route, a much more direct route.

We're basically below the ascending aorta, across the aortic valve, and then we're able to actually just deploy the valve directly from the aorta, and to the left ventricle. Or when we're doing transapical cases, actually going the other way.

So the landmark study that led to approval of the Edwards valve for certain patients subsets was the PARTNER study here in the United States. And they looked at two specific patient populations. The first patient population, if you look at the one on the right, were patients who were deemed operable. So patients that had a very, very high risk of surgical mortality, greater than 50%, so patients who unfortunately were not considered to be viable candidates for surgical aortic valve replacement.

Those patients were enrolled in multiple studies here in the United States, randomized either to standard therapy which at that time would be no therapy, really, no surgery, no valve replacement, just what you would normally do in those circumstances; or randomized to replacement with a transcatheter Edwards valve. So that was the inoperable arm.

And then the other arm was looking at patients who were considered high risk. And these were a group of patients who were felt to have a surgical mortality based on the STS scoring system of at least 10%. So patients who the surgeons would operate on, but they were very, very concerned about having significant problems. And so those patients were randomized to either traditional therapy with surgically aortic valve placement, or to implantation of the Edward valve.

So let's look at the inoperable cohort first in the 1-year data. And I think the key thing that you can see, again looking at all cause mortality and cardiac death and other parameters, was that with the SAPIEN valve in the inoperable patients, there was a 50% reduction in mortality at 12 months. So again, very sick patients, but clearly a life-saving therapy for patients who were not going to have the opportunity to undergo surgical aortic valve replacement.

Now, and again, this kind of highlights the data we saw, at 30 days no significant difference, but a significant difference at one year. The overall mortality in the standard therapy group, almost 50% at one year versus 31% in the TAVR arm, the SAPIEN arm.

So let's look at the other subset. And that was a high-risk patient population. That was the patient population either who were felt to have a high risk, greater than 10% risk of surgical morbidity or surgical mortality, and again, undergoing surgery versus undergoing placement of the Edwards valve.

Essentially what the study showed was that patients basically in both groups had similar outcomes at 12 months. So if you put a SAPIEN valve in these patients, they did just as well as if the underwent surgical valve replacement. Now we can recognize that there were some important differences in outcomes between these two patients, two patient groups.

There was a higher risk of stroke in the TAVR arm, which we saw at 30 days, and again at one year. The stroke or TI rate at one year in the surgical group was 4%. It was 8% in the TAVR group.

Also because these patients also have significant, often peripheral arterial disease, because the big tubes and the sheaths that we're putting in, the incidents of vascular complications was also higher in the TAVR group versus the surgical group, again looking at that far right. Overall incidence of major provocations was 3% in the surgical route, versus 11% in the TAVR group. That was offset by a higher incidence of major bleeding complications in the surgical group. And that's at the bottom there.

So basically, overall in terms of there was [INAUDIBLE] in terms of overall outcomes, mortality in the TAVR group versus the surgical group, at the cost of a higher stroke rate and higher vascular complication rate in the TAVR group versus a higher bleeding rate. Which does also portend an increase in mortality in the surgical group.

Recently they published the 2-year data of PARTNER, and it pretty much was the same as the 1-year data. So the benefit in that high-risk group was-- or at least the similar benefit versus surgery in the high-risk group was sustained at 2 years for TAVR. Again, knowing that there was still that sustained difference in stroke when the two groups and vascular complications.

I'm going to actually-- and then if you go back and look at-- and they also looked as far as the durability of the valve. What they found is in terms of the valve based on echoes at 2 years, the valve was still a very good functional valve at 2 years in the patients who underwent TAVR. And that was assessed both in terms of the overall aortic valve area by echo, as well as the mean gradient by echo in the valve patients.

So I think we learned, at least those high-risk patients, at least at 2 years out, a sustained benefit or equivalence really between surgery and TAVR. From a statistical standpoint we say it was non-inferior with durability of the valve seen at 2 years as well.

And what about those patients that were inoperable? Again, the benefit for the inoperable patients was also seen at 2 years as well. So overall mortality at 2 years in the standard inoperable group was 68%, 70% at two years, versus 40%, 43% in the TAVR group. So I think the lesson from this, and based on this data, the FDA initially approved the Edwards-Sapien valve for inoperable patients. And then it broadened the indication as well for high-risk patients, as well.

So that's the Edwards SAPIEN valve, which is now available commercially. The second which is under investigation here in the United States, and we do have some experience with, is the CoreValve.

CoreValve is a little bit different in terms of both the design and technique. The Edwards valve again, is a bovine valve. It's what we call a balloon expandable valve. The CoreValve is a porcine valve, and it's what we call a self-expanding stent. So instead of actually opening it up with a stent, it's crimped inside a sheath. When you unsheath it, it automatically puts it in proper position. It will open on its own. And we'll look at some pictures on that.

Now the database on the CoreValve is from Europe. And this is based really on registry data. And what we've seen with the CoreValve is that there's a high rate of success based on registry data in Europe. But it's offset by a fairly high incidence of pacemaker placement, at least with the initial patients that underwent the CoreValve. If you look at the data at the bottom left there, about 10% or 9% of patients who underwent a CoreValve did require a permanent pacemaker because of heart block that was seen following the procedure.

So as we've mentioned, we're now participating in the CoreValve study, which has completed enrollment in the randomized portion of the study. There is still an ongoing registry. Just really quickly looking at the CoreValve, as far as the patient subset with the CoreValve, very similar to what was done with the PARTNER study. The terminology is a little bit different.

They randomized a group of patients who were considered to be extreme risk. And those were patients that were felt not to be operable candidates. Those patients, as long as they had good suitable anatomy, were all put in the CoreValve side.

So the one difference compared to PARTNER was if you were deemed inoperable, and it was felt that the peripheral anatomy was suitable for CoreValve, all those patients got a CoreValve. The other arm was the high-risk cohort, similar to PARTNER, basically patients who were felt to have a high risk a surgical mortality, but were felt not to be inoperable, they were randomized either to the CoreValve or surgical aortic valve replacement.

Criteria for the CoreValve, again a pretty sick patient population. First of all, they have to have severe aortic stenosis. And these are some of the parameters specifically looking for patients with severe aortic stenosis based on the aortic valve area, and also based on measurements of their gradients across the valve. Again, they are felt to be in a high-risk population.

The high-risk patients were felt to have a greater than 15% mortality risk. The extreme risk were again greater than 50%. But they did have to have at least an expected survival of one year, and they were felt to at least have anatomical suitable landmarks for a CoreValve.

Patients who were excluded were patients who had coronary disease that was not treated. So if they were treated with a stent, they'd be suitable at a later date. If they had severely reduced left ventricle functional, an ejection fraction less than 20%, significant chronic end stage kidney disease, or a history of a stroke within the past six months.

So that kind of summarizes really where we're at as far as the technologies available now, where we're going. Some the challenges that we've seen of transcatheter aortic valve replacement, again, the first question is, how long will these valves last.

So, so far, everything that we've on durability, both from bench testing as well as clinical follow-up, has been good. There are some specific issues that are involved as well. So durability is the first thing.

The second is, again, these patients are complex. They very often have associated peripheral arterial disease. These are big tubes, big sheaths that we either have to put in traditionally through the femoral ilia-thermal system or come up with some other creative alternative approaches. As a result of that, there is a higher incidence of vascular complications, as we saw with the PARTNER study. So that's something that we're still struggling with, and something that's going to be important to continue to work on to overcome.

As we've seen, there is a higher stroke risk with these patients. And again, the potential mechanisms for that are several really. First of all, these patients have severe atherosclerotic disease to begin with. So if we're putting a large catheter or tube up around an ascending aortic arch, they're certainly at risk for embolic events from that.

In addition this is a very calcified valve. So if we're basically crushing open that valve, either with a balloon procedure initially, and then implanting a stent on top of that, could there be some embolic phenomenon leading to stroke as well from the valve implantation itself. So a lot of interest in trying to recognize really the mechanisms for stroke in these patients, and really strategies to minimize the stroke risk for these patients.

In addition, again depending on which study you look at, a substantial subset of these patients do end up requiring a permanent pacemaker. We think potentially because of some disruption of the conduction system, and specifically [INAUDIBLE] system that could lead then to heart block, and the need for permanent pacing.

And really one of the greatest, most important hallmarks of prognosis regarding these patients is the development of aortic regurgitation. And regurgitation is often what we call paravalvular regurgitation. So we implant that valve, and sometimes there can be some regurgion flow between the valve, the new valve, and the old orifice of the aortic annulus. And clearly data has shown that the paravalvular regurgitation that you have that does impact long-term outcomes in terms of mortality.

So as far as durability, again so far everything is very, very promising. If you look at some of the initial patients from your Dr. Cribier, as well as some of the other centers in the world that have extensive experience including this one center in Vancouver, again, patients getting regular follow-up, looking at echos. In terms of really the echo parameters that you can look at to assess how good a valve is working, everything's been very promising.

Valve area has been open. And the gradients have been low.

So in terms of the other major complication, regarding vascular complications, the evaluation of these patients is very, very important. And so we really, I think, spend a lot of time and investigating to really number one, make sure that it's safe to do a TAVR in this patient. And number two, come up with really what's the most appropriate treatment strategy. And that involves choosing the right valve size, choosing the right approach, and the management strategy before and after for these patients.

So parts of the key valuation for this include really confirming the severity of the aortic stenosis, getting really a good assessment of the valve size. Because determining what the valve size does impacts which type of valve we'll put in. And then also really getting a good assessment of the peripheral vascular, because that impacts what type of access strategy that we use.

One of the things that has developed out of the whole TAVR story really is the development of the heart team. Because it really requires multiple areas of expertise to really deliver optimal care to these patients. So in terms of really developing this procedure, it's been a great collaborative effort between cardiac surgeons, interventional cardiologists, cardiac imaging specialists, cardiac anesthesiologists, and certainly the primary care physicians that are involved in managing these patients beforehand and afterward, and really the ancillary teams that are involved as well, both the teams from the cardiac surgery teams, as well as cardiac [INAUDIBLE] teams that collaborate together, to do this procedure.

So part of the assessment includes both a echocardiography as well as cardiac CT. And one of the things that's important, this is just a standard transthyretic echo. But you can see that where the mark is getting a measuring of where the aortic valve annulus is. And that's highlighted right there.

In addition, we try to get cardiac CTs in all of these patients. And reason there again, is getting an assessment of the aortic valve annulus, both in terms of diameter and area. And one thing that you can see there is often if you see that where the annulus is on the CT on the left there, the annulus is actually not a circular structure. It's more often an oval or a eliptoid structure. And so we're faced with the challenge of trying to put in a prosthetic valve which really is circular when fully expanded, to try to kind of fit in that space properly, and again make sure you get good valve function, to minimize the amount of regurgitation around that valve, paravalvular regurgitation.

So that's why it's really important in terms of getting optimal imaging, and then assessing this thing, and having good pre-procedural planning for these patients.

In addition to assessing the valve size, again, it's important to really determine what's the best access strategy. Traditionally that access strategy is going to be through ilia-thermal system. These patients all will get a CT angiogram of the pelvis. The things that we're worried about, first of all, are the size of the vessel. Again, at the common femoral level, going all the way up to the aorta. In order to put these valves in, they do require pretty large sheaths. And we'll look at that here momentarily. So that's the first thing. Is the vessel going to be large enough to accommodate the sheath that you need to put in to really access it up there.

Other things are how calcified and torturous is the vessel? If there's a lot of calcification or there's a lot of tortuosity, there's a higher risk of complications associated with the procedure. And that also potentially could serve as another obstacle in fact, of being able to place a sheath all the way from the femoral, up to the aorta in order to do the procedure. So that's an important part, is getting the proper measurements that you need.

Now there has been an evolution of the technology. This is an example, again, of the Edwards SAPIEN system. In the United States right now, for the commercially available product, there are two valve sizes available. There's the 23-millimeter valve, which requires a 22-French sheath size. So that's a large, very large sheath. And then there's the 26-millimeter valve that requires a 24-French sheath.

Their are again, newer generations of this system available in Europe now, and under investigation here in the United States, that are requiring smaller sheath sizes. And certainly the smaller sheath sizes you can use that kind of broadens the potential patients that would be eligible for a transfemoral approach.

Similarly, we've seen the same thing with the CoreValve as well. The first generation CoreValve required a 25-French system, so a huge system. Those first patients were actually done not only under general anesthesia, but were actually done under cardiac bypass.

The second generation CoreValve, they were able to reduce the sheath size down to a 21-French system. They used what we call a percutaneous left assist. And then the third generation, which is part of the CoreValve study, investigation here in the United States, that's down to an 18-French system.

So part of the promising part of the story is really kind of the continuing growth and evolution and refinement of the technology as well. You know, these patients are very ill. They have multiple co-morbidities. And certainly that does increase the risk of complications. And one of the most fearful ones are the ones related to vasculature.

There are, with these large sheaths, there is the risk not only of a section loss of flow, potentially the loss or link threatening flow, but even we see reports of avulsion or rupture of the artery. If you can't go through the femoral there are alternative routes. For example, with CoreValve potentially through the subclavian artery. But again that's also a very sensitive artery, and risk in dissection as well. As you can see, there's an example of a dissection in the subclavian you see the bottle right.

So as a result of that, we've come up with other strategies. If we can't get to the aortic valve from the femoral artery, are there other ways that we can get to the aortic valve, and implant a valve?

Potential options would include maybe just go above the femoral. If the femoral is too small, maybe working with our surgical colleagues we can do a cut-down higher up, and use a conduit that goes into the iliac artery, and then use that as a way to get up to the aorta, retrograde across the aortic valve. And that's a strategy that's suitable either for the SAPIEN valve or the CoreValve.

We've talked a little bit about, if you can't to through the femoral, maybe if there's a large enough subclavian artery, go through the subclavian artery. That's a strategy that's been utilized that we've used for the CoreValve.

And if you really can't use the vessels, is there another way to get to the heart? So what if we just go straight into the left ventricle? And that's the trans-apical approach. And that is a strategy that's available and that we've use with the SAPIEN valve. So traditionally again, we talked about the retrograde approach, going from the aorta, across the aortic valve into the left ventricle.

Another option, again, working with CT surgery do a small mini thoracogny over the left ventricle apex, actually make an incision into the left ventricle apex, put a sheath in the left ventricle apex, and then basically cross the aortic valve directly from the left ventricle, across the aortic valve. Use that, and then basically use your catheter going that way.

There is an example there you can see at the bottom left, basically of the trans-apical approach. You can see, kind of at the right part of that picture there, that's actually a sheath that's going into the left ventricle, right through the skin, through the incision and into left ventricle. And then basically the balloon will be expanded.

And then finally, there's also the potential direct aortic approach, or trans-aortic approach which has been utilized for the CoreValve. Instead of going through the femoral or the subclavian, and trying that way to get to the aorta. Maybe we can just go straight into the ascending aorta, and then just put the valve right there. Again working with the surgeons under direct visualization, making an incision and then basically putting a sheath right into the ascending aorta, and then crossing the valve, again retrograde and placing the CoreValve.

So as you can imagine, all these particular approaches have certain advantages. You kind take the risk of vascular complications in the ilia-femoral system out of the way. But there are also other potential risks and complications associated with an alternative route as well. But again, I think at least we do increase these options for patients who are really not candidates for the transfemoral approach.

So let me just finish by showing you a few cases here. Almost always before we place the valve, what we do is actually cross the valve, and then do a balloon aortic valvuloplasty. So here's an example here. You can see that there's a pigtail catheter right above the aortic valve. There's a wire crossed the aortic valve. And then there a balloon catheter that's placed, basically to kind of help open up that area so they can have enough room to maneuver and get the catheter in or the stent valve in.

So the first thing is, there is a balloon valvuloplasty. And again, we know for long term, balloon valvuloplasty is not a good option. But all we're doing here, is really just treating the valve, so we can get that big tube, and get the stent valve across.

So here's an example basically of deployment of an Edward SAPIEN valve. This is a balloon expandable valve. So this is a valve, the stent is crimped with the valve on a balloon. We do a balloon valvuloplasty, leave the wire in, take the valvuloplasty balloon out. And then we go up with the SAPIEN system where the stent is employed, or already on the catheter. Position our stent in the appropriate spot, using both radiographic and transesophageal echo landmarks.

Once we're all satisfied that we're in the proper position, and it's a one-shot shot deal. You've got to be sure that you're in the right spot. Because once you deploy it, it's deployed. So basically, again taking advantage of the calcification in the native valve, that kind of serves as an anchoring for the stent.

And then-- and this is typically what the valve would look like afterward. So you can't really see the leaflets, but you can see where the stent is. And there's a pigtail. We're just checking for aortic regurgitation. Fortunately, no regurgitation. As you can see, this was a sick patient, a pretty complicated patient that has external wires, previous bypass surgery. Those are the rings that you see there where the bypasses came off.

All these patients with the SAPIEN valve also basically we have to drop their pressure almost to nothing to make sure that the balloon and the valve doesn't move as we're deploying it. So all these patients have a temporary wire that's placed, a temporary pacing wire that's placed. You pace the heart at very high rates, 180 often. That then drops the blood pressure down.

That allows the undeployed valve to be stable, in stable position. We deploy the valve. And then so we pace, deploy the valve, deflate the balloon, and then stop pacing. And then everyone takes a big breath, and waits and waits to make sure the blood pressure comes back up. So that's probably the longest five seconds in interventional cardiology or cardiac surgery, at least for us these days. And fortunately his comes back. But it's a pretty dramatic change that you can see.

So the advantage with the CoreValve is it is a more controlled procedure. Remember I was talking about when you're deploying a SAPIEN valve, you've got that one shot to deploy it. Because when it's done, it's deployed.

The CoreValve, it's not a balloon expandable stent, or it's a self-expanding stent. So basically with nitinol, nitinol is a metal compound with real good positional memory. It's covered with a special sheath. So we position the CoreValve in the proper spot. And typically that should be about 8 millimeters actually below where we think the aortic valve leaflets are, or where the aortic annulus is.

Once everything is in good position, the valve is unsheathed, or the stent is unsheathed. Part of the challenges with this are there is a point where you don't have a functioning valve at all. You pretty much covered it up. And so that is a period where the patient is very, very vulnerable. So it's a more controlled procedure.

When you're deploying the valve, if there is a sense that it's too ventricular or too aortic, there is an opportunity to change the position of the valve as you're deploying. But that's also the time when the patient is particularly very vulnerable to hemodynamic compromise. So that's the first part right here. The valve is not functioning.

At this point, you can see that if you look at the bottom part, that stent is kind of hanging out a little bit more. This is what we call the second position. If we're satisfied with that, then we'll unsheath it more. Here the valve is two thirds deployed. The stent and the valve itself is working. And again, we're looking for basically positioning here.

And then this is what the CoreValve looks like at the end of the procedure. So again, you don't see the leaflets. But you can see basically where the positioning of the valve is. You want the valve itself to be again a certain amount actually in the left ventricular outflow track. Because the proper performance in this procedure does require actually placing the stent itself in the left ventricular outflow track. We think that may be the mechanism for why some of these patients become pacemaker dependant, maybe tickling the conduction system at that point.

So the other interesting thing you can see, and this is a real hemodynamic data, is before the procedure if you look at the wave form, you're measuring basically the difference in the systolic pressures and the pressures between the left ventricle and the ascending aorta. So you can see there's a difference between, for example, the peak pressures. There's a large difference between top pressure, which is the left ventricular pressure, and the aortic before the valve implantation.

After the valve implantation, we measure the pressures again. Those top numbers or those peaks are pretty much super imposed. So that gradient has completely gone away. And that's immediately post procedure.

So that's kind of where we're at now. And right now, this is a procedure that really is reserved for either patients who are not candidates for surgical aortic valve replacement, or for patients who may or are at risk for significant complications or mortality related to surgical aortic valve replacement. But that brings to question, is this something that all patients with symptomatic aortic stenosis should undergo?

And your that's a question that, I think, has brought about a lot of debate. We still don't know the answer to that. Right now certainly, surgical valve replacement is the standard of care for patients who are felt not to be high risk. But there is a study that's undergoing right now, and we're fortunate to be participating, SURTAVI, which is looking specifically at that patient population, patients who are felt to be what they call intermediate risks.

So symptomatic aortic stenosis, not high risk. And they're actually being enrolled and randomized either to traditional surgical valve replacement or implantation of a CoreValve. And that story is still unfolding. Hopefully we'll have some data to share with you in a couple years regarding that.

So in summary, as far as regarding transcatheter valve replacement, it's clearly a breakthrough technology and treatment. The downsizing of delivery systems under development should reduce complications. Durability so far is yet to be determined. There's a lot of interest in it. One of the other things is really making sure that there is standardized training, uniform training, for this procedure. Right now fortunately we've seen the development of the heart team approach, where the surgeons, cardiologists, all work together.

And right now the ultimate role in treatment of which patients with severe aortic stenosis has yet be determined. So, appreciate your attention. Thanks.