[MUSIC PLAYING]

JOHN SCHINDLER: Thank you. I want to thank the organizers of the meeting, Dr. Hassan, Dr. Black, and Dr. Resnick. This is a great turnout. And hopefully, we'll get through all of the aortic valve questions that you might have that are pertinent to your geriatric population.

So I still work for my money, but I do have some disclosures that are pertinent to this talk. So, basically, TAVR has really been a true journey. This is the first publication in circulation in 2002. Alain Cribier, a Paris cardiologist, really came up with this whole concept and carried it through to fruition. And this is his first human case description. So it's really been almost a 20 year journey here, because he started really working on this in the late '90s with animal studies and forging forward.

And since then, you can see that these are just the randomized trials that have been carried out since his initial description in 2002. So this makes aortic stenosis one of the most rigorously evaluated cardiovascular conditions that we treat. So there are over 20,000 randomized patients involved in prior trials or ongoing trials. We're obviously not going to cover all of these trials individually, but basically, I do have some slides on what the guidelines say with where we stand in 2018. And so those are based, obviously, on these previously conducted trials.

And you'll notice that the first trial that was published-- a randomized trial comparing TAVR to just standard medical therapy for those patients who were deemed to be too sick to undergo an open aortic valve replacement was published in 2010. So, one obligatory slide on just prevalence of aortic valve disease.

We know that calcific aortic stenosis is thickening, and restriction of the trileaflet complex and high prevalence rates as patients age-- 2% to 3% in adults over the age of 70, and up to 5% to 10% of patients over the age of 80-- bicuspid aortic valve disease really has been excluded from all of these clinical trials because we know that presents at a much earlier onset. In most patients, in their fourth and fifth decades of life will present with symptomatic bicuspid disease. So the overall prevalence is 1% to 2% in the population.

But interestingly, that can be treated. And there are studies looking at using transcatheter heart valves. So originally, the mantra was that we could never treat bicuspid disease. But with advancements in technology, we are treating certain select patients with bicuspid disease. And there is a gender predilection in bicuspid disease. And what about aortic sclerosis? You'll get a lot of echocardiograms that say that your patient does have aortic sclerosis. It doesn't carry the same adverse prognosis as senile calcific stenosis. It's much more common. 25% of patients over the age of 65 will have it-- depending on how you image this-- and up to 50% of patients over the age of 80.

We do know that it has a very low predilection to transform into the calcific stenosis group. Less than 2% per year will progress and transition over. But it does carry adverse prognostic findings, in that it is associated with higher stroke rates, higher rates of myocardial infarction, higher cardiovascular death, and overall higher mortality.

So let's go into a case presentation. This is a woman that I just saw a few months ago, 96 years of age, living independently in her primary residence with hypotension. And she's had known aortic stenosis for about four to five years. She had had some intermittent echos over that time frame. She has been feeling well, and has been categorized as being asymptomatic. So this was just obviously in a surveillance state.

And when I met her, her nephew was with her. She did not have any of her own children. So her nephew and niece were with her. And the way he described her was that she was extremely healthy. She's only had two prior hospitalizations. One was in 2010. She had an endoscopic repair of an incarcerated paraesophageal hernia, where 80% of her stomach contents were in the thoracic cavity. And that was a successful surgery.

And then, 2017 in December, she presented with new onset atrial fibrillation. And I find that the combination of atrial fibrillation with severe aortic stenosis is just a very bad combination. Because when you lose that atrial kick, patients just go into congestive heart failure. And interestingly, this echo now shows that she has new LV dysfunction.

So her medications included a loop diuretic, NOAC, beta-blocker, and PPI. Interestingly, she did not have the genetics that you would think would carry her into her 90's. Her father died from occupational lung disease in his 50's, and her mother did have diabetes and died from a myocardial infarction in her early 70's.

On exam, she was a little hypertensive, in atrial fibrillation. And you can see, she's a very frail woman. She is 5'3", and only weighs 104 pounds, giving her a body mass index of 18 kilograms per meters squared. And she is in congestive heart failure on examination.

Her EKG shows atrial fib with a controlled ventricular response and a left bundle branch block pattern. Her chest X-ray-- clear, congestive heart failure with bilateral pleural effusions and increased interstitial markings. So no question that she is symptomatic now from the left-sided heart disease. And here is the final read on her echo. She has a normal RV function. As I said, the LV was slightly depressed, 40% to 45% ejection fraction. And by all parameters that we typically use with echocardiography, she's in the severe range. Her peak velocity across the valve is 4.7 meters per second. Mean aortic valve gradient is 48. And her valve area is 0.5.

This is just a review of the ACC/AHA guidelines, indicating whether someone has mild aortic valve disease, moderate, or severe, based on those three parameters of the jet velocity mean gradient and aortic valve area. The dimensionless index I report here is just a ratio of the velocity of the blood in the left ventricular outflow tract just below the aortic valve, as the numerator and the denominator is the velocity of the blood across the aortic valve leaflets. And when that number is less than 0.25, that is suggestive of severe aortic stenosis.

And I like to use that number in patients who have reduced left ventricular systolic function. Because sometimes, the gradients are not high, and you can be falsely misled that this is more moderate disease, when in fact, you're dealing with severe disease. And the other thing I point out is that sometimes, these echoes that you get from the echo lab can be very confusing. Because you might see that the aortic valve area is reported to be 0.6 centimeters squared. And yet, the mean gradient might be 22.

So if you go by the mean gradient, they have mild aortic stenosis. If you go by the aortic valve area, they have severe. So much like Jennifer was saying, with respect to diagnosing pulmonary hypertension, I have a lower threshold in patients when there's data that's a little discordant to take those patients to the cardiac catheterization lab to get direct pressure measurements. The echos are good, but they're not perfect. And in a lot of patients, like our patient here, the echo read, there's no question. The valve is restricted. It's calcified. And all of the parameters suggest that it's severely diseased.

I'm only suggesting that when there is some discordance in data, and when you're really trying to sort out, does this patient have a primary cardiomyopathy and they just have superimposed mild or moderate aortic stenosis? Versus, do they really have severe aortic stenosis that is driving afterload mismatch and reduction in their LV systolic function? So that's when the cardiac catheterization can be extremely useful.

So what are her risks? If we say, OK, you're 96 and pre-TAVR, we would say, would you want to undergo an aortic valve replacement with cardiopulmonary bypass circuit? So the cardiac surgeons have a great database. And they have used that data set to come up with these predictors of how patients will do with various operations.

So their specific database for aortic valve surgery is the STS-- Society of Thoracic Surgeons-- predict the risk of mortality for aortic valve disease. And we can put in all of those parameters that we just went over in her history and physical-- including her sex and her weight-- and that gives us a risk with open heart surgery. So her number came out at 8.2%. And that's mainly driven by the fact that she is a nonagenarian, that she has a low BMI, and that she has LV dysfunction. We know that all three of those adversely affect her outcome with open surgery.

And there is strong data suggesting that women do better with TAVR than with open surgery across the risk spectrum. There is a difference in how the genders respond to various procedures and operations that we expose them to. So, an STS PROM of 8% classifies her as being in a high risk category. So if your STS is less than 3%, we say you're at low risk. And that's basically saying that you have a 3% risk of dying from the operation within 30 days. So that's considered low risk. If you're 3% to 8%, that's considered intermediate risk. Above 8% is high risk.

But there are other factors that go into it in addition to these nice parameters and clinical features that we glean from a physical exam. There's frailty and disability. And I know I'm preaching to the choir, here. This is what you guys deal with every day. And I don't have to define it for you. But we do take this into consideration when we see these elderly patients in the aortic valve center, because we know that this affects their outcomes with surgery as well.

And the one parameter that we found to be particularly useful when we're trying to evaluate these patients who might be sitting there very nicely on the exam table, but we like to put them in a chair, have them get up, and then walk 5 meters. And if it takes them more than six seconds to do that, that tells us that they are slowing down, and that that is a marker of frailty.

And why is that so important? Because this is a data set out of the UK. They were really focusing on frailty. And they were looking at 300 TAVR patients over a one year period. And they basically put them through all different types of testing to try to define frailty. And the one that came out to be the most predictive was just what they classified as being poor mobility.

So this is the Kaplan-Meier survival curve. And if you look at, they had patients undergo a 6 meter walk test. And they drew a line in the sand-- six minute walk test. And if they did poorly on that walk test, you can see that their mortality rate at five years was 80%, compared to a mortality rate of 30% to 35% in patients who did fairly well with that assessment.

So we do know that frailty and disability is extremely important. So what is the current state of TAVR right now in 2018? The guidelines for aortic valve replacement/valvular heart disease were originally updated in 2014. And then there was a limited focused update in 2017. And that's what I'm referring to right here. So according to the 2017 focused update in patients who are considered to be prohibitive risk for open AVR, TAVR gets a class 1 recommendation level of evidence A because of those randomized trials that were done comparing TAVR to standard medical therapy. We know there's a 30% absolute risk reduction in mortality in patients who undergo TAVR, compared to just standard medical therapy.

So that's why the evidence is strong. And that's why the class recommendation is as high as it is. So our patient is in that category, because even though her STS was high risk by definition with the 5 meter walk test, she was considered to be frail. And we bumped up her risk into the extreme category. The cardiac surgeons walked into the room and said, I will not operate on this patient because I think I will make them worse than they are right now.

So, what about patients who are at high risk for surgical AVR, in that risk where the STS is greater than 8% but they might be a younger patient and not frail? Again, this is a class 1 recommendation level of evidence A. And then, for intermediate surgical risk patients, that STS score between 3% and 8%-- so typically, younger patients with less co-morbidities.

The recommendation is a 2A, which means that it's a reasonable alternative to surgical AVR for symptomatic patients. And the level of evidence was B. And unfortunately, when this focused update came out in early 2017, the second big intermediate risk trial comparing open heart surgery to TAVR was published. And that's called the SURTAVI trial. And that one strongly favored TAVR. When you combined mortality and stroke rate, there was a statistically significant benefit to TAVR over SAVR at the 24 month point.

So this came out just before that was published. So all of us in the field believe that on the next focused update, the intermediate surgical risk patient will be a class 1 recommendation what level of evidence A. But for board purposes, or just for what it says, it is now a 2A recommendation.

So what's the current state of TAVR in low surgical risk patients? That's the overwhelming majority of patients who undergo aortic valve replacement, and we're still weighting that clinical trial data. There are two major trials that have been completed by both major companies who make the two FDA approved transcatheter heart valves. And they will likely be presented at upcoming cardiology meetings, so stay tuned.

And the important thing to realize is that the low risk trials require that the patients were over the age of 65. And that's because, again, if you're below 65, the surgical guidelines suggest that you should receive a mechanical prosthesis in the aortic position. And transcatheter valves, we're not trying to compete with a mechanical aortic valve replacement because we know the durability of a mechanical aortic prosthesis can be a lifetime, as long as the patient continues to take warfarin.

So they excluded patients under the age of 65, and also required the patients had trileaflet valves. But I did mention that there are separate studies where bicuspid valves can be treated. So this is just a flow diagram summarizing those recommendations. So if you have someone with severe symptomatic aortic stenosis with stage D disease, the 2014 guidelines sort of did a little bit of a shift in how we classify and consider valvular heart disease. They went to A, B, C and D categorization, such that stage A patients or those such as they might be identified as having a bicuspid aortic valve. So they are at risk for future aortic stenosis or aortic valve problems, but they have no active signs or symptoms of valve pathology.

Stage B patients are those with mild aortic sclerosis, or even mild or moderate aortic stenosis. Stage C patients are those who have severe aortic valve disease, but are asymptomatic. And then the stage E the patients are those who are severely diseased with symptoms. And then, within stage D, it goes 1, 2, and 3, so that have D1 are those patients with a high transvalvular gradient, low aortic valve area, and normal left ventricular systolic function. Those are the easiest group to treat because there's no question that their symptoms are being driven by their aortic stenosis.

And then, the D2 patients are patients who have reduced LV systolic function. And they have a low transvalvular gradient and a low aortic valve area. So in those patients, the cardiomyopathy sometimes can be a little bit of a trick. And those the ones we have to discern. Are the symptoms really coming more from the valvular heart disease, or more from their cardiomyopathy?

And then, the stage D3 patients are the most challenging. Those are the patients-- typically, elderly females with hyperdynamic small left ventricles, a lot of LVH, and their aortic valve area will be reported to be low. And their mean gradient will be low as well. And so the question there is, are their symptoms really coming more from diastolic dysfunction? Or is it really coming from the valvular heart disease? And so there are other imaging modalities that need to be pursued in those types of patients.

So the important caveat to all of this, as Jennifer pointed out in the last talk about how there are pH centers, it is so important. And I have gained so much from participating in the multi-disciplinary heart valve clinic, because it truly is important for these patients to have physicians across disciplines talking about their condition. It's more important than even two physicians from the same specialty because we're typically all reading the same literature. But when you get physicians across disciplines, including geriatricians, noninvasive cardiologists, interventional cardiologists, cardiac surgeons, anesthesiologists, nephrologists, oncologists-- because so many of these patients have so many co-morbidities, that that's when the patient truly gets individualized care, and I think, has the most successful outcome.

So it is a class 1 recommendation that patients that are being considered for TAVR be discussed in a multi-disciplinary clinic. And it is still required by all of the insurance carriers, including CMS, that any patient that goes for TAVR has to have documentation in the chart from an interventional cardiologist and a cardiac surgeon that we are in agreement that TAVR is the best therapy for that patient.

So what about the complications? Unfortunately, there are things that do occur during these operations. So this is a nice summary slide of just the major things that I tell patients when they're in the clinic. The 30 day death rate-- I should step back. We don't have a risk predictor for TAVR yet that is being worked on, and probably, within the next two years, will be available-- just the way that STS database can be accessed and the parameters can be put in. And we figure out what the risk with surgery is, open surgery, and what the risk is with TAVR. But today, we don't have that.

But what we do have are the clinical trials that show us that in general, the 30 day death rates with undergoing TAVR with the current devices is on the order of about 2% to 2.5%. And that's pretty consistent, even if the patient has a much higher risk profile. Now, I will exclude-- and I have some more slides that will just expand upon that thought.

Pacemaker rates are between 12% and 15%, depending on the prosthesis that you put in. The Edwards SAPIEN valve has a slightly lower pacemaker rate than the Medtronic Evolut valve. And it's important to know that surgical pacemaker rates-- sometimes, people forget that there is a risk of needing a pacemaker when you undergo open AVR. And that rate is about 5% to 8%. So it looks like the transcatheter valves have about two times greater risk of needing a pacemaker than an open surgical operation.

And this is the one complication that has been improved upon dramatically since the beginning of TAVR-- the paravalvular regurgitation around the outside of the valve. So we learned that sometimes, putting a circular structure into an oval that is intensely calcified, that's not going to reshape that oval. So there is going to be blood that leaks back in every diastole into the left ventricle.

And initially, we didn't know how much of a problem that was going to be. But we have learned over the years that more than mild aortic regurgitation around the prosthesis carries an adverse prognosis at 12 months. So we strive to ensure that the patient has less than mild paravalvular regurgitation when we're in the operating room putting these valves in.

So, originally, with the original trials, we were using TEE-- transesophageal echocardiography-- to size the valves and decide what size prosthesis we were going to put in. And we've learned over the years that's woefully inadequate and inaccurate. And so now, all of our patients get a three dimensional CT scan, where we can actually assess the annulus and get very good measurements. And we work closely with our radiology colleagues. So with the current devices, the risk of paravalvular regurgitation of more than mild is on the order of about 3% to 5%, which-- as I said-- is a dramatic reduction from 20% that we were seeing with the first generation transcatheter heart valves.

And major disabling stroke-- this is the one that patients fear the most. Many of the patients who come to see me say, look, I'm fine if I die with the operation. But I don't want a stroke. And so you can see that it doesn't suggest that that's just the best stroke rate with that Edwards SAPIEN valve of 1%. It doesn't mean that the evolute has a 4% risk and the SAPIEN 3 has 1%. Actually, we know from the trials, the rates are about 2% to 3% for a disabling stroke. There's never been a head-to-head trial of the balloon expandable prosthesis versus the self-expanding prosthesis.

So, with all of that said, we need to get back to our patients, say, should we give this nonagenarian transcatheter heart valve? And so this was actually queried and questioned in the TVT registry. So every hospital that performs TAVRs has to participate in this registry. And at the time of this publication, there were about 320 hospitals participating. So they looked in the time frame from 2013 to 2015, and they just queried that data set, and looked at nonagenarians-- of which there were 3,700 or so-- and compared them to those less than 90 years of age, which were 20,000 patients over that time frame. And again, this is across the US.

And so, what you can see from the baseline characteristics, the nonagenarians did have a higher STS score, as expected. Because just by age alone, that will increase that risk score significantly. And every decade of life increases it exponentially. So their STS score was 9.2. The other patients were 6.3.

The other thing that's interesting is they sort of self-selected. So the nonagenarians were actually a little healthier. They had a little bit better LVEF. They had less incidence of vascular disease, so they did not have a prior history percentage-wise of CABG, compared to the other patient cohort. And then, the only thing they did have was more atrial fibrillation, which is to be expected-- because as we age, we know that that's a risk factor alone for AF. But they had less strokes, less TIAs, less peripheral arterial disease, less hypertension and diabetes.

And when we did that 5 meter walk test on these patients, you can see that they were slightly slower than the other patient cohort. So how did they do? Well, they did have higher rates of major bleeding complications-- 8% versus 6%. And in-hospital mortality was 6.5% for this group, compared to 4.5% for the other cohort.

Again, now, I said this was a little bit earlier. And that data I showed you of the risk of mortality of being 2% to 3%, that's using the current devices. Because all of the devices have undergone changes. The original-- we call it delivery systems-- that get the valve into the body were very large. And that's why the vascular complication rates were so high, because there were times where we were putting this device into an artery that was actually smaller than this delivery system, when we were just trying to snake it up there as best we could. So now, with the current delivery systems, it has dramatically reduced the incidence of stroke, vascular complications, and death.

So, looking at strokes specifically in this cohort, you can see that the nonagenarians did have a numerically higher rate of stroke, but again, within the procedure-related, around 3% versus 2% for the other cohort. Heart failure readmissions-- if the patient's got a good operation, they did well. And both patients stayed out of the hospital significantly, because we know that in patients who did not undergo TAVR, the readmission rates at 12 months in patients with severe aortic stenosis is over 60%.

And what about quality of life? So you can see at baseline, both the nonagenarians and the patients less than 90 had low. This is a Kansas City quality of life questionnaire. Its scores go from 0 to 100. So you can see that they perceive their health to be fairly poor baseline. At 30 days, went up significantly, and by one year, 72% and 81% of the patients had much higher Kansas City questionnaire scores.

So, back to our patient. As I said, we screen everybody with a CT. So we really look at this because if patients cannot be treated from a transfemoral approach, if their femoral artery or their iliac arteries are severely diseased and calcified, and we think that their risk of a vascular complication rate is high, we will look at the subclavian artery because that's our go-to alternative access site. This patient fortunately, has a very nice subclavian, as well as iliofemoral system. So we know that the studies show that if you go through the iliofemoral system, the patient gets the most favorable outcome.

So that's why we did this. We looked, we told her, OK, we can go through a transfemoral, which means it's no general anesthesia. It would just be conscious sedation. So we had a real informative discussion with the patient and her niece and nephew. And I quoted those numbers, where I said, you know, your risk of dying from the operation is somewhere between 2% and 6%, because the previous study had said six, current devices say two. But she is 96. So that's why I gave a little bit of wiggle room. And I quoted her risk of stroke of about 3%.

So I said, the chances are, 90% chance you're going to get through this fine. But there is a real 10% risk of something serious occurring. So she said she wanted to defer, talk to her niece and nephew. They went home, they talked about it all the way back to Altoona. And we got a call the next day that said that she wanted to schedule. So we brought her in. As I said, we do 96% of the patients with conscious sedation.

We put in a temporary pacemaker from the common femoral vein, which the pacemaker is coming up here on the bottom into the right ventricle. We have the wire across the aortic valve complex. This is a cobalt chromium frame that is being expanded by that balloon catheter in the center. And so you can see that the valve deployment itself, we paced the patient very rapidly, and the valve deployment just takes 30 seconds.

Now there's a fair amount that goes into it leading up to this. But the whole operation, because we are working together-- myself and a cardiac surgeon, or one of the other interventional cardiologists on the team and any of the cardiac surgeons, of which there are six total now with that within our team. But two of us are mandated to participate in the operation together. And so we can do these in just under an hour.

And as everybody knows with these patients who are very frail, and even when I do heart catheterizations on people in their late 80's, I just know that they're not able to lie on a table and be still and cooperate effectively for a long period. So the quicker you can get through this in a safe manner, the better for the patient.

So her post-operative course, her neurologic status was unchanged when I saw her the next morning. And through the day after the TAVR, she was electrically stable from a rhythm standpoint. So it didn't look like she was going to be in that category of requiring a pacemaker. We observed her overnight and she was released to inpatient rehab in Altoona on post-operative day number one. And then she only spent a few days there and was discharged to home within seven days.

And here she is at one month. And I asked if I could use her picture. And she said, oh, doctor. I can't come talk to all those people and tell them about the experience. And I said, that's OK. I'm not asking you to do that. I was just going to put your picture in the presentation. Her LV function normalized. Her echo-- we do an echo at post-operative day number one, and then at 30 days. Bioprosthetic valve was functioning very well. She had no leak around the outside of the valve. She was back in sinus rhythm now. The left bundle branch block was persistent.

So I'm just going to skip over this because of the time crunch. But I do want to go over this slide about some of the predictors of cerebrovascular events post-TAVR. This was published in *JACC.* And these are the four that appeared to be statistically associated with prediction of stroke rates. So being male actually protects you. So female sex has a higher rate of stroke, the presence of chronic kidney disease. Enrollment date-- so that's more of a procedural factor. So what that was is that if the physicians and hospitals were early on in the use of TAVR, you had a higher risk of stroke. So that really falls on the side of less experience for the operators, because there is a steep learning curve with this operation. So if you are being treated in an experienced center, the risk of stroke is significantly reduced. And then, finally, new onset atrial fibrillation-- which happens in about 10% to 20% of patients after the valve is put in-- that significantly increases your risk of a post-operative CVA, which is expected.

And what about age? So if you're over 90, you can see it looks like there's a trend towards, obviously, a higher stroke rate. Now, the confidence intervals are very wide here because there are very few patients compared to the tens of thousands of patients in the other categories. This is just data that was published by myself and Tom Gleason, looking at when patients do have strokes after TAVR, their mortality rates are through the roof-- 63% at one year and 75%. So we really have to get better. And these are some of the devices we're using now to catch some of the debris. These are filter devices that can be put in. And this is the basket of what we caught out of one of our patients.

You can see, just after we put this filter in the innominate artery in the carotid artery, we take these baskets out. And these are just the various things. You could see just this piece of tissue that comes from the valve itself, it's released into the bloodstream. So if you can capture that and prevent that from getting into the cerebrovascular circulation, obviously, intuitively, it makes sense. Here's a picture of the device in such a patient with this coming from the right radial artery. There's one filter in the innominate. And then, there's another filter in the left carotid.

So, in conclusion, the successful development of TAVR from concept to clinical reality has been a 20 year journey. With device modifications, improved patient selection, and operator experience, TAVR has been deemed to be equivalent to standard aortic valve replacement in extreme, high, and intermediate risk surgical patients. Continued procedure on device refinements strive to lower complication rates further, which will likely result in TAVR penetration into the low risk population-- those greater than 65 years of age. And the benefit of TAVR in the elderly population, including nonagenarians, has been well-established. However, appropriate patient selection remains critical. Thank you.