CHET RIHAL: Hi, I'm Dr. Chet Rihal, Professor and Chair of the Division of Cardiovascular Diseases at Mayo Clinic in Rochester, Minnesota. It's my pleasure to speak to you today about an exciting revolution in medicine-- transcatheter aortic valve replacement. Here are my disclosures. I do research in this area. We do not take any personal consulting fees from any of the device companies in this area.

Our learning objectives for this brief presentation include the following. Number one, to be able to identify candidates for transcutaneous valve placement. Two, to understand novel alternatives for the management of aortic stenosis. And three, to review the latest randomized clinical data, which inform our clinical practice and our conversations with patients.

I will start off with a case. This is a 75 year-old man who presented with symptoms of severe exertional dyspnea, as well as angina. He had had multiple co-morbidities recorded, including prior bypass surgery, complicated by sternal dihiscence, requiring sternal rewiring. There was a previous history of cerebral vascular disease with TIAs, strokes, carotid endarterectomy, hypertension, hyperlipidemia, sleep apnea, and a prior bleeding duodenal ulcer. Basically, a typical TAVR candidate.

The echocardiogram demonstrated good ventricular function, severe aortic stenosis, with a mean gradient of 68 millimeters of mercury, and the coronary angiogram showed that his bypassed grafts were patent. The next step of his evaluation, we performed a quantitative assessment of his surgical risk, using the online Society of Thoracic Surgeons tool, the sts.org site. We determined that the risk of mortality was over 12%, so this is extremely high. I'll remind you that the mortality for first time aortic valve replacement in good surgical candidates is normally less than 1%. So an anticipated mortality risk of over 12% is high risk, no matter how we look at it.

So what are the options? Well, for this particular gentleman, he was enrolled in the partner trial, and this is the prosthesis that was being used back then-- the original SAPIEN prosthesis. The beautiful thing about this is that it's a hand-sewn valve into a steel cage that can then be crimped onto a balloon, which is then mounted onto a catheter, and then it can be inflated into the aortic valve. So this is how the delivery system works. It allows us to go up and around the aortic arch, down into the aortic valve, and then to deploy the valve by hand.

We took this gentleman to the catheterization laboratory, and one can see that between the left ventricle and the ascending aorta, there was a significant gradient-- 180 to 125 or so. We initially performed a balloon valvuloplasty. One can easily see the dark nodules of calcification. One can also appreciate how easily the balloon manages to push the nodular calcification apart, but immediately, we appreciate there's recoil. This is why balloon valvuloplasty as a standalone procedure is generally not a good therapeutic option for our patients.

Following preparation of the valve, then the prosthetic valve is crossed into the native valve, and then deployed by hand. And this was the deployment, as you can see, leaving the valve perfectly in position and anchored by the calcified annulus. Immediately post-procedure on the table, we saw a complete reduction and disappearance of the gradient. Well actually, it's down to less than 10 millimeters of mercury. This really represents a revolution in the treatment of patients with aortic valve disease. No sternotomy, and immediate benefit.

Now this is not a new concept. This is Dr. Henning Andersen, who first conceived of this idea in 1988 and was the holder of the original United States patents, and I'll draw your attention to the fact that he first did the animal work in 1989. So it's sobering to think it took 20 years, almost, for this technology to make it into human trials. And this is a famous photograph of Dr. Alain Cribier, one of the pioneers of this procedure, and the very first human patient on whom the procedure was performed back in the year 2002.

Now we would think that most patients with severe aortic stenosis are undergoing surgical treatment or some sort of treatment, but in fact, 30% to 40% of all patients with severe symptomatic aortic stenosis essentially go untreated. The reasons, of course, are clear. Many of these patients are extremely high risk, and either turn down surgery or are never offered surgery in the first place. I've already mentioned why balloon valvuloplasty does not work. Even though the balloon can push aside these nodules of calcification, they immediately will recoil.

In the remainder of the talk, let's ask ourselves the following questions. One, what is the role of TAVR for inoperable patients? Two, how does TAVR compare with aortic valve replacement? for high risk aortic stenosis? Three, what is the risk of stroke? Four, does paravalvular leak matter? And five, can we even afford this?

The PARTNER trial was the first randomized trial that was published in this area-- had two arms. The first arm that we will talk about are the patients with inoperable disease. And here, they were compared to standard treatment, which is basically just medical therapy. I would draw your attention to a number of important facts. The mean age of patients enrolled in the PARTNER trial was 83. The SDS score was, by design, extremely high.

These were extreme risk patients. Almost all were a New York Heart Association class three or four. Many had prior bypass, prior MI, prior PCI, and cerebral vascular disease. Many had COPD, and in fact, 20%-- over 20% had oxygen dependent COPD. So by any standard, these were an extremely sick cohort of patients. In fact, the sickest patients ever enrolled in a randomized trial in cardiology, other than perhaps for patients in the LVAD studies.

At one year, it was clear that patients treated with TAVR, shown here in the blue, did much better than those treated with standard medical therapy, shown here in the yellow. In fact, of the patients treated medically, just over half of them had died at one year, whereas 30% of those treated with TAVR had died. Still high, but much, much better than plain, medical therapy.

In fact, this 20 absolute percentage point difference is, again, the highest difference in a treatment study ever seen in cardiology. In fact, we would say the number needed to treat is only five, and there are essentially 200 lives that are saved per 1,000 patients treated. In comparison, we can see how low the number of lives saved per 1,000 patients treated is for many other standard treatments that we use in cardiology, such as beta blockers post MI, aspirin, reperfusion therapy, ACE inhibitors.

We generally talk in the single digits or 10 or 20 lives saved per 1,000 patients treated. With TAVR, we are talking about 200 lives per 1,000 patients treated. Fortunately, it appeared that out to three years, the valves were holding their own with mean gradients remaining a low 10 millimeters of mercury or less, and the effective orifice areas remaining at about 1.5 to 1.7, which is very good and certainly livable.

Second question. How does TAVR compare with aortic valve replacement-- open aortic valve replacement-- for high risk patients with aortic stenosis? This was the cohort A in the PARTNER trial, and we can see at one year, there was essentially no difference in all-cause mortality between patients treated with TAVR, here in the blue, and those treated with open aortic valve replacement, here in the yellow. Roughly 24% or 25% of patients in each group had died at one year, and at two years and three years, the results were essentially equivalent. In both arms-- both the open aortic valve replacement arm and the TAVR arm-- patients were symptomatically improved, and from an effort tolerance standpoint, they were they were able to increase their six minute walking distance by over 100 meters. So that's over the length of a football field. So for patients whose median age is in the 80s with extremely high risk characteristics, this is a substantial functional improvement.

Now what about the risk of stroke? This has been one of the more controversial areas in the entire field of TAVR. Well it's true, there is a risk of stroke with TAVR, and in the original inoperable cohort, one can see that at 12 months, 11% had had a stroke. But I would draw your attention to the fact that 5.5% of patients treated medically had also had a stroke. In other words, these are extremely high risk patients. They have widespread atherosclerosis. They have underlying cerebral vascular disease. They have diabetes, hypertension, atrial fibrillation, and a large number of predisposing factors for stroke.

Now when we compare open aortic valve replacement to TAVR, we see that initially, in the first 30 days, there was a higher risk of stroke-- about twice as high in patients undergoing TAVR, but by 18 months in two years, there actually really was no difference, and by three years, it actually flipped. So perhaps the best way to look at this is not so much in terms of individual endpoints, but to ask ourselves a question. What is the likelihood of your patient being alive, free of stroke, and with an improved quality of life at one year?

This is the question that really is important from the patient's standpoint, and when we look at the data for all-cause mortality or any stroke, we'll see that they're almost superimposable. All-cause mortality and stroke occurred in 27% of patients treated with TAVR and in 28% of patients treated with open aortic valve replacement, and the curves are basically superimposable. So in other words, the important functional outcomes of being alive, free of stroke, and improved symptomatically are essentially identical between the two procedures. Importantly, the results of TAVR have continued to improve since the early days of the PARTNER trial. This slide demonstrates that as with passing time eras, the overall mortality dropped at one year and the risk of stroke dropped from 10.8% percent to 7.0%, and finally to 3.7%.

So there has been a significant improvement in outcomes with procedural and operator experience. In the future, we will soon have protection devices that can be placed through the radial artery or through the femoral artery to protect the great vessels from particulate emboli, such as the Claret Tandem Device that's placed into both carotid arteries or the Embrella device that can be placed from the radial artery, and will deflect particulate embolic matter from the heart. I would caution, however, that these devices themselves may have a certain risk with them, so they do have to be tested in a rigorous fashion.

Next, what about paravalvular leak? Is this really the Achilles heel of TAVR? Well the reason paravalvular leak occurs is that the native valve leaflets remain inside you. They're not excised, and nodular calcific particles can interfere with proper apposition of the stent of the new valve against the aortic annulus. So this is a typical example with the SAPIEN valve in place in the aortic valve, and one can see that there is retrograde regurgitation into the left ventrical right beside the valve, where this dense, nodular calcification occurs.

What we have learned from the PARTNER trial is that any paravalvular regurgitation, whether it's mild, moderate, or severe, is associated with worse outcomes. So in other words, the mortality rate was about twice as high at 12 months in the presence of paravalvular regurgitation. So what do we do about this? By the way, here is the total aortic regurgitation and mortality. When we take into account mild regurgitation through the valve itself, it clearly shows a stepwise, prognostic importance of aortic regurgitation. With no regurgitation, mortality at one year is only 12%. With mild, it's 26%, but with moderate or severe, it goes up to 35%. It triples with moderate or severe aortic regurgitation.

Again, this is the reason-- the red here represents large, nodular calcification on the native valve leaflets, and particularly in the aortal mitral curtain, when it occurs, can be associated with severe paravalvular regurgitation. So to treat this, a number of strategies have been employed. Rehabilitation of the valve is performed in about 5% of patients. A second valve can be placed at the time of the initial valve implantation, and that's also required in 4% or 5% of patients. Rarely, we will take some patients back to the catheterization lab and put in plugs into the paravalvular space to control the regurgitation.

Now, is TAVR cost effective? This is an expensive procedure, just as open aortic valve replacement is. And in fact, when one looks at the overall cost of transfemoral TAVR and the aortic valve replacement, they're not that different. The TAVR is perhaps $2,000 to $3,000 less expensive than open aortic valve replacement, and I would point out that a large proportion of this is due to the acquisition cost of the valves themselves, and hopefully with time, these costs will come down.

Now so far, I've talked largely about the PARTNER series of trials and the SAPIEN valve, but there are other valves now being tested and commercially available. This is the Medtronic CoreValve. This is a self-expanding prosthesis that's placed up from the leg into the diseased aortic valve and gently released, so that it expands-- the Nitinol cage will expand and adhere to the annulus and the aorta, holding the valve in place. Well in the CoreValve trial, the findings were extremely interesting. In high risk patients, TAVR performed with a CoreValve was actually superior to open aortic valve replacement with surgery at one year, in terms of all-cause mortality. Only 14% of patients who received TAVR had died at one year, in comparison to 19.1% of patients who had open aortic valve replacement, suggesting that this technology, rather than being an alternative, may soon become the preferred method for treating aortic stenosis amongst elderly, high risk patients.

There has been one direct head to head comparison between a balloon expandable prosthesis and the self-expanding prosthesis that I just spoke about, called the Choice Randomized Clinical Trial. Somewhat of a small study, but nonetheless, demonstrated that both valves performed quite well, but that there may be some important differences, including the fact that patients with the self-expanding prostheses had a higher rate of requiring a new permanent pacemaker.

Now TAVR is a revolutionary technology, and it continues to evolve, continues to iterate, continues to improve. We currently are using the third generation of the SAPIEN device, and the next generation-- the so-called SAPIEN 3 device-- will have a skirt around its base that will unfurl after placement, thereby preventing paravalvular regurgitation, which would really essentially eliminate that problem. The CoreValve self-expanding design continues to improve, as well, with greater ease of deliverability, safety, and efficacy.

Other new entrants in the market include the St. Jude Medical PORTICO device, which also is a self-expanding prosthesis and is currently in clinical trials, and the Boston Scientific Lotus Valve, which also features an adaptive skirt around its base to prevent paravalvular regurgitation, as well as being fully recapturable and repositionable. Direct Flow makes a very interesting valve that's actually inflated with a polymer that hardens within the patient's body, allowing complete sealing and placement of the valve. And in the future, we may be able to treat not only aortic stenosis, but aortic insufficiency, as well.

So what can we conclude from this presentation? Number one, I think we would all agree that TAVR is vastly superior to medical therapy for inoperable patients with severe symptomatic aortic stenosis. Number two, TAVR compares favorably with open aortic valve replacement for high risk patients with aortic stenosis. I would caution that we cannot draw this conclusion yet for low risk or intermediate risk. Those studies are being done.

Conclusion number three, there is a risk of stroke with both TAVR and surgical aortic valve replacement in these high risk patients. Four, paravalvular leak is important. It's due to the calcification and it is predictive of outcomes. Five, transfemoral TAVR is cost effective. So I'd like to thank you for your attention and hope this has been useful to you in your clinical practice.