ROUNDTABLE DISCUSSION

TAVR in Low-Risk Patients

Experts discuss the significance of recent data and the potential impact on their practice.

WITH KENTARO HAYASHIDA, MD, PHD, FESC, FACC, FJCS; ROBERT OSTFELD, MD, MSC, FACC; BERNARD PRENDERGAST, BMEDSCI, BM BS, MRCP, DM, FRCP, FESC; MICHAEL J. REARDON, MD; AND STEVEN J. YAKUBOV, MD, FACC, FSCAI

How do you think the recently announced low-risk transcatheter aortic valve replacement (TAVR) data will change your practice?

Dr. Reardon: I think it's going to change all of our practice. Right now, I would say this has to be the preferred therapy in the low-risk patient group that we tested who were 73 to 74 years of age. Moving forward, if a patient presents and is eligible for a bioprosthetic aortic valve, you need to talk with them about the potential of TAVR or you are not going to get truly fully informed consent.

Dr. Prendergast: TAVR is now clearly equivalent or superior to surgical aortic valve replacement (SAVR) in all patients, irrespective of surgical risk (and probably better in most). These trials will fundamentally change discussions within the heart team and when presenting treatment options to patients with aortic stenosis.

Dr. Hayashida: We are very pleased and honored to include six cases from our country (three from our hospital) in the PARTNER 3 trial. It will be easier for us to offer TAVR for patients with lower surgical risk. We have always discussed the patient's surgical risk in our heart team discussion, but these results make surgical risk scores less important.

Dr. Ostfeld: Given the data presented at the recently held American College of Cardiology (ACC) conference, with a few caveats, I will seriously consider TAVR for my low-surgical-risk patients with severe aortic stenosis. Frankly, if I personally had severe aortic stenosis, I would greatly prefer TAVR.

What are some caveats? First, it is important to highlight that the primary endpoint of the PARNTER 3 trial (stroke, death, or rehospitalization at 1 year) was driven, in part, by rehospitalizations, and rehospitalization is less medically dramatic in comparison to stroke or death. Second, the study duration was short and hopefully these low-surgical-risk patients will look forward to many decades of life. Hence, the long-term durability of the device will be important to monitor.

Furthermore, given that these low-surgical-risk patients will likely live many years, I wonder how TAVR may impact a patient's ability to undergo future percutaneous revascularization, if needed. Reinforcing the PARTNER 3 trial, the EVOLUT study of low-surgical-risk patients with severe aortic stenosis found that TAVR was noninferior to SAVR (based on statistical estimation, as full follow-up was not completed) with the less broad primary endpoint of mortality and stroke at 2 years. Given the statistical estimation of the primary endpoint, additional data will be important to obtain. Finally, these studies did not include patients with bicuspid aortic valves; however, nonrandomized "real-world" data presented at the ACC annual meeting supported TAVR use for severely stenotic bicuspid aortic valves.

Dr. Yakubov: It takes time for clinical trials to be implemented into guidelines, and we all try to adhere to practicing guideline-directed treatment strategies, but I believe that the patients, as well as referring

physicians and implanting physicians, all recognize the importance of these positive results regarding TAVR in low-risk patients. There will be more movement toward implementing TAVR in the appropriate low-risk patients relatively soon.

What would you tell any of your colleagues who are not yet referring patients for either TAVR or to a heart team for evaluation?

Dr. Ostfeld: I would tell these colleagues that across the spectrum of surgical risk (low, moderate, or high), we have robust data to support meaningful consideration of TAVR. Honestly, the potential to avoid undergoing sternotomy is highly compelling. Accordingly, when it comes to aortic stenosis, we may soon no longer say that "a chance to cut is a chance to cure."

Which patients would you now consider to be eligible for TAVR in your daily practice?

Dr. Yakubov: The findings from these low-risk clinical trials truly flip the question to who *shouldn't* get TAVR? The questions that I believe the trials haven't yet answered clearly are: (1) how young can the patient be and still have TAVR as the first option, and (2) is every valve anatomy appropriate for TAVR? There are still some patients with heavily calcified degenerated valves who might do better with surgery and the same might be true for some patients with dilated aortic roots. We still must carefully evaluate the anatomy in all cases to make sure we are treating the correct patients. Also, we do not yet have all of the answers for patients with bicuspid anatomy. We are getting there though, and there are bicuspid registries in place at the moment.

Dr. Prendergast: All patients who are 65 years or older should be considered eligible for TAVR.

Dr. Reardon: Any patient who is a candidate for a bioprosthetic valve is a reasonable candidate for TAVR. The question is: how low will we go with the age of the patient? Currently, bicuspid valves still have not been fully tested in the low-risk population. I'm a Study Chair of Medtronic's TAVR Low Risk Bicuspid study (NCT03635424), and I think that's going to help us understand how the bicuspids fit into this.

Dr. Hayashida: In Japan, patients in their early 80s without comorbidities are classified as low risk, as these patients can be good candidates for TAVR.

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The age cut-off point is 75 years in Europe, but we Japanese have a longer life expectancy, and therefore we imagine 80 years could be a good cut-off point for TAVR in Japan.

For your colleagues who are not part of a heart team, how do you believe they will react to the data?

Dr. Hayashida: These are randomized controlled trials with very high-quality results. I hope they will send lower-risk patients to TAVR. But, of course, it takes time to convince them that TAVR is as good as or better than SAVR.

Dr. Yakubov: At our institution, all of the surgeons, all of the interventional cardiologists, and many non-invasive cardiologists are part of the heart team. So, we must disseminate this information to all cardiologists and primary care physicians. I think they will find these data to be very strong for TAVR. There has been a significant movement of referring patients with aortic stenosis to the structural heart team rather than to a specific surgeon or interventional cardiologist. I believe that nonimplanting physicians like the idea that their patients are being evaluated by an entire heart team.

Dr. Prendergast: Surgeons will point out the excellent outcomes of SAVR in low-risk patients and the available data confirming the durability of surgical bioprostheses. General referring cardiologists will take 2 to 3 years to catch up with the emerging data and change their referral patterns.

Dr. Reardon: For my cardiology colleagues, I think they'll react with joy. For my cardiac surgeon colleagues who don't do TAVR, they are probably going to react with anger and disbelief. But for the cardiac surgeons who have gotten onboard and now offer TAVR, they'll be just as happy as a cardiologist because this is really good for patients. I've done a

Trial Name: EVOLUT Low-Risk Trial

Trial Sponsor: Medtronic
Trial Design: Multicenter, prospective, randomized 1:1, open-label
Sample Size: 1,468
Statistical Treatment: Noninferiority
Surgical Risk: Low

Primary Endpoints:	Study Arm	Control Arm	Posterior Probability
• All-cause mortality or disabling stroke at 2 y	5.3%	6.7%	> .999
Secondary Endpoints:	**Study Arm**	**Control Arm**	**Posterior Probability**
Noninferiority			
• Mean gradient at 1 y (mm Hg)	8.6 ± 3.7	11.2 ± 4.9	> .999
• Mean EOA at 1 y (0.1 cm^2)	2.3 ± 0.7	2.0 ± 0.6	> .999
• Mean change in NYHA class from baseline to 1 y	0.9 ± 0.7	1.0 ± 0.7	> .999
• Mean change in KCCQ score from baseline to 1 y	22.2 ± 20.3	20.9 ± 21.0	> .999
Superiority			
• Mean gradient at 1 y (mm Hg)	8.6 ± 3.7	11.2 ± 4.9	> .999
• Mean EOA at 1 y (cm^2)	2.3 ± 0.7	2.0 ± 0.6	> .999
• Mean change in KCCQ score from baseline to 30 d	20.0 ± 21.1	9.1 ± 22.3	> .999
Other	**Study Arm**	**Control Arm**	**95% Bayesian Credible Interval for Difference**
• 30-d safety composite of all-cause mortality, disabling stroke, life-threatening bleeding, major vascular complications, stage 2 or 3 acute kidney injury	5.3%	10.7%	(-8.3, -2.6)
• Heart failure hospitalizations at 1 y	3.2%	6.5%	(-5.9, -1.0)
• Atrial fibrillation at 30 d	7.7%	35.4%	(-31.8, -23.6)
• Permanent pacemaker implantation at 30 d	17.4%	6.1%	(8.0, 14.7)

Abbreviations: EOA, effective orifice area; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

little more than 2,000 TAVRs myself, and I've been doing heart surgery for more than 35 years—this is by far the biggest advance I've seen in my career.

What is the one piece of data that you believe is most important for patients to know regarding TAVR?

Dr. Hayashida: Death or stroke at 30 days was significantly lower in TAVR compared with SAVR. This short-term risk should be most important for patients to know.

Dr. Prendergast: Outcomes after TAVR are at least as good as surgery in all risk groups. TAVR is minimally invasive and offers swifter and safer recovery. The long-term durability of TAVR devices beyond 5 years remains relatively uncertain.

Dr. Yakubov: The most important data points of the clinical trials are the impact on death and on disabling stroke. The data are really clear that you have a lesser chance of dying or having a disabling stroke with TAVR compared to surgery.

Trial Name: PARTNER 3

Trial Sponsor: Edwards Lifesciences

Trial Design: Multicenter, prospective, randomized 1:1, open-label

Sample Size: 1,000

Statistical Treatment: Noninferiority; if noninferiority was met for the primary endpoint, testing for superiority of TAVR to surgery was planned; superiority to surgery was achieved

Surgical Risk: Low

Primary Endpoints:	Study Arm	Control Arm	*P* Value
• Composite of all-cause mortality, stroke, and rehospitalizations at 1 y	8.5%	15.1%	*P* = .001
Secondary Endpoints:	**Study Arm**	**Control Arm**	***P* Value**
• New onset atrial fibrillation at 30 d	5%	39.5%	*P* < .001
• Length of index hospitalization	3 d	7 d	*P* < .001
• All-cause death, all stroke, or rehospitalizations at 1 y	8.5%	15.1%	*P* = .001
• Death, KCCQ score < 45 or KCCQ score decrease from baseline ≥ 10 points at 30 d	3.9%	30.6%	*P* < .001
• Death or all stroke at 30 d	1.0%	3.3%	*P* = .01
• All stroke at 30 d	0.6%	2.4%	*P* = .02
Other:	**Study Arm**	**Control Arm**	***P* Value**
• New pacemaker implantation (%)	30 d: 6.5%	30 d: 4%	*P* = .21
	1 y: 7.3%	1 y: 5.4%	

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; TAVR, transcatheter aortic valve replacement.

Dr. Reardon: TAVR is incredibly safe and the durability shown in these data up to 6 and 7 years is every bit as good as surgery. In the EVOLUT Low-Risk trial, the hemodynamics are superior to surgery at every single time point. As you get into younger and more active patient groups, having an effective orifice area (EOA) > 2 cm^2 becomes increasingly important, because if your EOA is < 2 cm^2, it is hard to increase flow without increasing the gradient. Younger people are going to want to run half marathons, dance, and be active, and so this is going to be important in the low-risk population.

Dr. Ostfeld: I believe an important outcome for patients to know is that TAVR provides a less invasive option and that they should feel empowered to pursue informed, shared decision-making with their physicians.

How would you best communicate these new data to your referring cardiologists?

Dr. Reardon: I don't think we have to worry about it; patients will bring these data to them. Patients are very savvy now. Both of these studies were published in *The New England Journal of Medicine,* and they will both get wide press coverage. I have patients showing up to my valve clinic saying, "I want a TAVR." They've already read about it and they know about all of it.

Dr. Hayashida: We sometimes send a letter to our referral doctors to share up-to-date knowledge in this field. Social media (especially Facebook) is a powerful tool to share the idea in the community. Lectures at congresses are also important.

Dr. Yakubov: We are going to emphasize to our referring cardiologists that all patients are evaluated

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by the heart team. If the patient does have aortic stenosis, they should be considered to be seen by the heart team in every circumstance, and then the heart team can decide who really does need surgery. The overwhelming message is that we should consider TAVR as the first-line therapy for all risk patients with severe, symptomatic aortic stenosis.

It's going to take time for the information to be disseminated. There are still a lot of questions that need to be answered, but I think that the lessons that we learn from these clinical trials in the appropriately selected low-risk patients are lesser chance of death and of disabling stroke with TAVR compared to surgery.

Dr. Prendergast: Postgraduate education and referral network events are great for disseminating new data such as these.

Is there any additional evidence would you like to see in order to refer all of your severe symptomatic aortic stenosis patients to TAVR?

Dr. Ostfeld: To aid in the decision to potentially refer all severe symptomatic aortic stenosis patients to TAVR, I would like to see more data on long-term durability, the impact on future percutaneous revascularization if needed, and ongoing evaluation of the role for TAVR in subjects with bicuspid aortic valves. Nevertheless, I think PARTNER 3 and EVOLUT will meaningfully transform clinical practice.

When do you expect that the guidelines from the societies will begin to change?

Dr. Yakubov: I anticipate that the guidelines will change soon.

Dr. Reardon: It takes a while. I believe that for the next set of guidelines, TAVR is going to be class I across the board. I think risk has become an artificial separator; TAVR performs well across all risk groups. If you can show that your valve performs at high and intermediate risk, it's going to perform in low-risk patients as well.

Dr. Hayashida: We are in the process of renewing our guidelines in Japan, and it is anticipated that they will be published in 2020. I am still not sure if low risk will be included in the indication for TAVR, because in my country, we tend to be a bit conservative.

Dr. Prendergast: I believe the guidelines in Europe will change in the 2020/2021 time frame.

In light of these data, who should be excluded from TAVR and undergo SAVR?

Dr. Ostfeld: In the context of shared decision-making with the patient, I believe those who meet the above study's entry criteria should have the option to make an informed choice.

Dr. Prendergast: TAVR should be considered in all patients who are 65 years or older and have aortic stenosis. SAVR should be reserved for younger patients and those with complex anatomy precluding TAVR or accompanying cardiac disease requiring surgery (eg, dilated aortic root or complex coronary artery disease).

Dr. Reardon: The younger we get in patient age, the more I would advise against TAVR until we have more data, especially data on bicuspid valves and enlarging aortas. An aorta that is 4.5 cm alone doesn't meet the guidelines for operation, but the addition of having a bicuspid valve does meet the guidelines for replacement. Do you really want to only replace the aortic valve with a TAVR valve and leave the aorta for a later day? Right now, the better choice would seem to be a surgical valve and aortic replacement.

That being said, I'm working on a trial that's looking at replacing the aorta with a stent graft, and if we get that perfected, then maybe these patients will become candidates for TAVR and aortic replacement with a stent graft. I predict that will happen in the next 5 years.

Dr. Hayashida: Patients younger than 75 years or those who are not good candidates for transfemoral TAVR should be excluded from TAVR.

Dr. Yakubov: There are a couple of remaining questions with low-risk patients. For instance, we didn't study patients with bicuspid aortic valve, and TAVR is still not a solution for a dilated aortic root. Those patients need to be taken care of by surgery. There are going to be anatomic variations, such as bulky leaflets with low-lying coronary arteries, for which surgery should probably be the first-line therapy. So, the heart team is still essential. Careful evaluation of patients with CT scanning and proper decision-making is necessary.

An interesting question is, with the advent of these low-risk data and this patient population, will we see a decrease in the number of intermediate- and higher-risk patients down the road because we'll have identified these patients sooner and treated them in a low-risk indication?

I don't know for sure, but I can tell you that many of the patients that we considered to be intermediate risk in the past are now considered to be low risk by the Society of Thoracic Surgeons (STS) scoring changes, and those that we thought were high risk are actually intermediate risk. Surgery has improved over these past 8 years and STS risk scores have fallen proportionately. We are seeing fewer of the higher-risk and extreme-risk patients; they're still there, but there are fewer of them. ■

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