

Current Status and Expectations for Low-Risk TAVI Trials

An expert opinion on how current clinical trials will impact the future of TAVI procedures in low-risk patients.

WITH MARC DWECK, MD, PhD

What are the low-risk transcatheter aortic valve implantation (TAVI) trials that physicians should be aware of?

You can split low-risk TAVI trials into two groups: (1) trials assessing patients with severe aortic stenosis (AS) with low surgical risk who are symptomatic and (2) trials evaluating patients with severe AS who are asymptomatic.

If we start with the symptomatic low-risk patients, the two major trials are PARTNER 3 (NCT02675114) and the Medtronic TAVR in Low-Risk Patients trial (NCT02701283). These trials are large, ongoing, open-label randomized control trials. The PARTNER 3 trial is aiming to recruit 1,328 patients with follow-up at 1 year and a primary composite endpoint of death, stroke, and rehospitalization. The Medtronic TAVR in Low-Risk Patients trial is estimated to recruit 1,200 patients with a primary endpoint of all-cause mortality or stroke at 2 years. We already have some results from the much smaller NOTION trial, which included 280 patients, of whom 81% were low risk.¹ The takeaway from NOTION was that short-term outcomes were equivalent between TAVI and surgical valve procedures after 1 year.

Overall, what are the challenges that need to be addressed in the low-risk population?

Low-risk patients are typically younger, more fit individuals. These are people who might outlive their valve or certainly live with their valve for a longer period of time than has previously been studied; in that context, there are specific concerns to consider.

These patients generally undergo surgery at very low risk, so it's mandatory that the TAVI procedure is performed at a similarly low complication rate. All the data from the current TAVI trials suggest that is eminently achievable.

We also have to think about valve durability. This is not much of an issue in the higher-risk patients currently treated with TAVI but becomes important as we consider fitter patients. For example, if we're going to perform TAVI in a relatively fit 70-year-old who we think is going to live for 10 or even 20 years, then we would like some reassurance that TAVI valves are going to last for a similar duration to the equivalent surgical valves. This is where some uncertainty still exists for TAVI, as we lack long-term outcome data. Early data looking at 5-year outcomes appear favorable, but we really need to know about the 10- to 15-year durability before we can be confident in using it widely in this new population of younger, fitter patients. Hopefully, registry data and novel imaging studies will be able to address these concerns in the near future. I also hope that the randomized controlled trials will be able to provide data on longer-term follow-up.

Finally, we need to think about the increased rates of aortic regurgitation and permanent pacemaker implantation associated with TAVI. Ideally, novel techniques should aim to limit these complications as both are not ideal in the long term for patients with stiff hypertrophic left ventricles.

With regard to this younger and fitter low-risk patient population, how will valve-in-valve (ViV) procedures play a role in the treatment plan?

TAVI opens up several different intriguing strategies. Even if TAVI valves turn out not to last as long as surgical valves, although I suspect they will, then ViV TAVI presents an attractive work-around for that problem. Let us say that all patients can have a single shot at open heart

surgery. You can then imagine an approach that might work, even for very young patients, where you insert a TAVI valve then perform ViV if TAVI fails. When this second valve degenerates, the patient can have a surgical procedure with the back-up option for an additional ViV TAVI down the line. Clearly, this kind of strategy requires validation and would be quite expensive, but it indicates that patients could potentially be managed for a prolonged period of time with these valves.

Based on these challenges, what do you anticipate will be the potential pitfalls for TAVI in low-risk patients?

The potential pitfalls are achieving a very low periprocedural TAVI complication rate, valve durability, and the long-term effects of the increased rates of aortic regurgitation and pacemaker implantation. However, TAVI holds several important advantages including its minimally invasive approach, short hospital stays, and the large opening areas achieved. Although we can discuss these pros and cons at length, randomized clinical trials are the best way to evaluate novel treatments in different populations, and I am excited to see the results of the ongoing low-risk and early TAVI trials.

Based on Dr. Danny Dvir's presentation at the 2016 European Society of Cardiology conference on the initial durability and valve failure outcomes, were you surprised by the data? Were the data a surprise to the field?

You can argue it both ways. TAVI valves have larger opening areas associated with lower mechanical stress, which would suggest that the valve might last longer. On the flip side, there is more aortic regurgitation, and TAVI valves are less well opposed to the aortic wall than surgical prostheses. Also, there is the issue of crimping that might damage the epithelial surface of the valves and promote degeneration. It is therefore a matter of considerable debate as to whether TAVI should last as long as surgical valves. The truth is we don't know and need to wait for long-term durability data from valves implanted in humans. These may involve novel imaging techniques that can show early signs of degeneration in these valves, such as the recent data suggesting that CT can detect areas of valve thrombosis and degeneration.² This is an important area where we're going to see a lot of research over the next couple of years, trying to focus in on how long these valves are going to last.

As a clinician, this is critical. If you are caring for fit, relatively young patients, they want to know how long their valve is going to last. The fact that TAVI durability remains somewhat uncertain at present is an important

gap in our knowledge and one that we really need to work hard to narrow down.

How might technology need to be adjusted or developed to specifically address this low-risk population?

As you're moving to low-risk patients, you're generally moving into younger patient categories. The proportion of patients with bicuspid valves will therefore be higher. Bicuspid valve disease has generally been an exclusion criterion for many of the larger TAVI studies, and although recent observational data suggest that TAVI is a reasonable technique in this subpopulation, we still need more data for confirmation.

Another aspect is the use of pacemakers. As you go into lower-risk populations, with younger patients, you want pacemaker rates to decrease because long-term pacing is not good for ventricular function. Similarly, we want lower aortic regurgitation rates because that's also believed to be detrimental to cardiac function in the long-term, especially in patients with stiff hypertrophic ventricles. The major valve vendors are looking at designs to address these important issues, which will be of particular importance to the low-risk populations that will live longer with their valves.

Outside of the bicuspid patient population, do you think that the TAVI technology as it currently stands is appropriate for the rest of the low-risk population?

I believe the technology as it stands is ready to be tested in the low-risk patient population. Of course, there are improvements that can be made, and if further developments yield reductions in pacemaker and regurgitation rates, then these would definitely be welcomed.

What is the rationale for moving away from only treating symptomatic patients, and what trials are underway?

Traditionally in cardiology, you only operate on patients with AS when they have symptoms. But the data actually supporting this approach is rather weak; it's certainly not based on randomized controlled trial data. Moreover, assessing symptomatic status in the elderly patients we see in current practice is quite challenging. We're often seeing people with multiple comorbid conditions, and trying to work out whether their symptoms are due to valve disease or these other conditions is difficult. Therefore, there is interest in moving away from a symptom-based approach toward other strategies that are perhaps a bit more objective in deciding whether people should undergo surgery or TAVI.

The EARLY TAVR trial (NCT03042104) is investigating a strategy of performing TAVI in patients who have severe AS but are asymptomatic and assessing whether that is an effective strategy in terms of patient outcomes.

The EVOLVED trial (NCT03094143) is slightly different. It is again looking at patients with asymptomatic severe AS but not all-comers. Instead, early aortic valve replacement or TAVI will be targeted only to patients with evidence of myocardial scarring as a sign that the heart is starting to decompensate.

The idea of early intervention in AS has been discussed for many years, but we're finally seeing a couple randomized controlled trials dedicated to testing whether it might be effective.

Do you have any other final thoughts that you would like to share?

Overall, TAVI is an extremely exciting technology and technique. The question now is, should we be using it even more widely than is current practice? I believe the technology is good enough that we should be running trials even in low-risk patients and trying to answer that question. However, these trials are not a slam dunk

where we can be confident of the outcome, because we have to think about issues such as durability, bicuspid valve disease, aortic regurgitation, and pacemaker rates where surgery performs extremely well. We therefore need to acknowledge that low-risk patients are a slightly different patient population than we have looked at previously and we should be excited to learn from the clinical trials currently underway. ■

1. Thyregod GH, Steinbruchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis. *J Am Coll Cardiol*. 2015;65:2184-2194.

2. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015-2024.

Marc Dweck, MD, PhD

Consultant Cardiologist
University of Edinburgh
Edinburgh, Scotland, United Kingdom
marc.dweck@ed.ac.uk

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