Title: Four-Year Outcomes from the EVOLUT Low Risk Trial
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Dr Michael J Reardon

"So I'm Dr. Michael Reardon. I'm a cardiac surgeon from the Houston Methodist Hospital. I'm professor of Cardiothoracic Surgery and the Allison Family Distinguished Chair of Cardiovascular Research. And the subject today is the four-year results of the EVOLUT low-risk trial.

Unmet Needs of TAVR Patients

Well, I think there are a number of unmet needs of TAVR patients, one of which is defining the data for younger patients. If you look at the TVT registry, you'll see that last year in the US, we did 58,503 commercial transcatheter valve replacements. 2003, that's 2022. In 2023, we'll do over 100,000. Now, that has been driven by the data from randomised trials, like the randomised trial we're talking about today, that's led to EVOLUT being approved at all risk levels and that's even influenced our guidelines, which now no longer use risk as a standalone criteria for deciding between surgery and a TAVR. However, they do say, if you're under 65, we're going to live 20 years or more, you should still have surgery.

If we look at how people are following the guidelines, we can look at the Viziat national database in the US, a national database that covers about 95% of the academic medical centres, where they did a study between 2015 and 2021 of isolated aortic valve replacements. By 2021, 47.5 of these were now being done by TAVR in patients less than 65. So one of the things we want to know is, do we have data to support this? And one of the unmet needs is finding out, are the results we're going to see from these studies going to apply to younger studies? The mean age in the Low-Risk EVOLUT trial was 74 and only about 23% of people were less than 70. So we still need more data on younger patients. We need data on asymptomatic aortic stenosis, we need data on moderate aortic stenosis, we need more data on bicuspid valves, a randomised trial would be very helpful.

But for today, I think one of the unmet needs is, do we have data for what we're doing?

Medtronic TAVR System

So the Medtronic system is a nitinol base, which is a metal with a memory and has porcine pericardial leaflets. Now, most other valves have bovine pericardial leaflets, which are thicker. Porcine is thinner, it moves better. It has eight times the tensile strength you need. Allows us to then bring this down to a smaller size as we implant it. We do most of these with an inline approach, which then means it's a 14 French equivalent. Not just the sheath, but the actual device is. 14 French equivalent that goes in. It's a self-expanding suprannular valve and it's recapturable up to about three-quarters of deployment.

And one of the things we've noticed about this valve is it has superior hemodynamics to surgery in every randomised trial at every time point tested, which is somewhat unique to this valve in randomised trials. And it's been shown to have superior durability and superior performance. And the purpose of the four-year study is to see if this superior durability, superior hemodynamics, superior performance translate into better clinical outcomes.

Study Design and Patient Population

So this study was designed to study symptomatic severe aortic stenosis and those felt to be at a low risk for surgery mortality risk of 3% or less. They had to have anatomy that was suitable both for TAVR with an envelope core valve or surgery. They were all seen by a local heart team that had to make sure they had inclusion criteria, no exclusion and fit the anatomy. Then they went up to a national screening team. If they passed eligibility there they were randomised one to one between May of 2016 and May of 2019, between CorValve or EVOLUTE and surgery.

Now, we started actually with some original core valve 31 1st generation, about 3.1%. About three-quarters were the second generation EVOLUT R, and less than a quarter

were the third generation EVOLUT pro. So we were actually learning new valves as we went through this trial. They were randomised one-to-one. Our primary endpoint was all cause mortality or disabling stroke.

Key Findings

Well, the key findings were that at four years haver had significantly better all-cause mortality and disabling stroke than did surgery. And it represented a 26% relative reduction in the rate of death or stroke compared to surgery reached a p-value of 0.5. As close as you can get without being statistically superior.

I think the thing that's unique about this is we all know that TAVR has an early advantage over surgery as far as durability, stroke and recovery. The question has always been will that durability last or will surgery catch up and the lines collapse on each other and maybe even cross like they did in the PARTNER II A trial? Well, if you look at one year, the delta in favour of TAVR for evolution over surgery was 1.8%. At two years it was 2%, at three years it's 2.9%, at four years it's 3.4%. So not only has the durability, not only has its advantage persisted, it's actually widened. EVOLUTE is the only valve that's ever shown not just the persistence of its advantage over surgery, but a widening of that advantage. If we break it down into all cause mortality or disabling stroke, it's driven mainly by better all-cause mortality in TAVR. It's 9% for TAVR and it's twelve and a half percent for Surgery for P-Value of 0.7.

Look at strokes, the curves are flat. There's no increase in stroke in TAVR only because evidence has a very low rate of clinical and subclinical thrombosis. We look at an endpoint of all-cause mortality, disabling stroke or hospitalisation, we see that it's still statistically significant at to the zero four level in favour of TAVR. In fact, it's 3.7% delta at one year, 4.4% delta at four years. So again, not only is TAVR maintaining its superiority, it's widening over time. I think this is very impactful data.

Take-Home Messages

Well, I think there's a number of take home messages from this trial. I think that a trial like this has some significant clinical implications in low-risk patients. And it points to me that average should be with an EVOLUT valve, should be the first transcatheter valve used in a low-risk population like this that's likely to survive. That's evidenced by the fact that we've shown a 26% relative reduction of stroke, disabling stroke or mortality for EVOLUT versus surgery. Again a p-value of 0.5. We've shown a trending mortality in favour of TAVR to 0.7 level.

We've also seen that there's more better durability with TAVR. We have ten year data out of the notion trial, which also shows no mortality difference between a regional first-generation core valve and surgery. We've also shown that TAVR had better valve performance than surgery. And so when you look at the edit, has superior hemodynamics at every time points. When you look at the fact that EVOLUT is the only valve when randomised against surgery, has superior hemodynamics at every time point, has shown superior structural valve durability, has shown superior valve performance and now shows superior primary endpoint of all cause mortality, disabling, stroke or hospitalisation. It really should be the valve of first choice, particularly when used in younger active patients.

Further Study and Next Steps

I think the next step is that, as you saw early on, people are moving to lower-risk patients right now without a lot of data, and we'd like to make sure that we make this data available as often as possible. So instead of just reporting it one, two, five and ten years, we're going to report this data every year, because we think knowing the data and low risk is very important for the patients and the heart teams that help them make decisions. This trial will be followed out for ten years and we'll report the data every year for ten years. And as the further out we go, the more confident we can be that this valve is the valve of first choice.

No, I think that this is as a surgeon, I think this is really a fascinating trial. As a surgeon, I would not have predicted that TAVR would beat surgery at this level with this valve and it hasn't necessarily beat surgery with other valves. Next week at TCT, you'll see

the five year partner results. Dr Leon will present that we'll present these four year results and I think that's going to be a very interesting juxtaposition as we see how these two trials behave in these two fundamentally different valves and both these trials be followed for ten years. I think we are generating by far the best data that's been generated for structural valve disease ever."