Stephen Brecker

CoreValve® Evolut R™: insights from the latest clinical evidence

Transcatheter aortic valve replacement (TAVI) is an established treatment for aortic stenosis in patients unsuitable for surgery or at high risk from surgery. Medtronic's latest device, the Evolut R™, was designed for transcatheter valve implantation for use in patients with extreme or high risk who have severe aortic stenosis. *Confluence* spoke to Dr Stephen Brecker from St George's Hospital in London to discuss the design features of the valve that contribute to its performance, and the latest clinical data from the Evolut R™ CE trial. Long-term data for the CoreValve® and the implications of this for future TAVI use were also discussed.

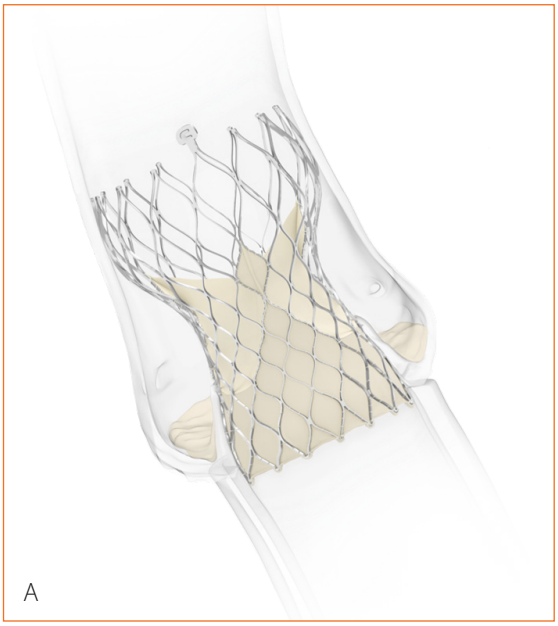

fig. 1

CoreValve Evolut R™ transcatheter aortic valve (A) and CoreValve Evolut R™ system, including CoreValve Evolut R™ transcatheter aortic valve, EnVeo™ R delivery system and EnVeo™ R loading system (B).

Could you describe the structural and functional differences between the Evolut R™ and the CoreValve®?

Dr Stephen Brecker (SB): There are a number of differences between these two types of valve that have led to better outcomes with Evolut R™ (figure 1); these relate to the design of the frame and the design of the skirt of the valve itself. Firstly, there have been some changes in the geometry of the cell design and the structure of the frame. These differences mean that at a target implant depth, the actual frame of the Evolut R™ is a little larger for any given valve size than CoreValve®. Secondly, the shape of the frame is less tapered with Evolut R™, which provides better anchoring with less paravalvular leak (PVL). Thirdly, the overall frame height of Evolut R™ is reduced. And finally, the radial force characteristics of the frame are

improved, with more consistent radial force across the range of annular sizes for which a given valve size is designed. Those are the changes in the frame.

With respect to the skirt, in Evolut R™ this extends downwards, filling at least half of the bottom half-cell of the frame, whereas in CoreValve®, the whole of the bottom half-cell is unfilled. The end result of all of these changes is a better fit with better sealing and less PVL.

Finally, unlike the CoreValve®, Evolut R™ is fully recapturable and repositionable in case the correct position is not achieved on first attempt.

Can you tell us about the Evolut R™ CE trial, in terms of the trial design, types of patients involved, and the trial objectives and endpoints?

SB: This was a multi-centre, prospective, non-randomised study that included 60 patients.[1] It was a CE mark trial, carried out in centres already experienced with CoreValve® implantation. The trial enrolled high-risk patients undergoing TAVI, so really they were all-comers undergoing TAVI. The study was designed to test safety and efficacy of the Evolut R™ valve, with the aim of achieving a CE mark. All of the conventional endpoints used in any valve study were assessed, so 30-day and 1-year survival rate, 30-day stroke rate, the rate of any complications and then haemodynamic performance. Also assessed were valve areas, PVL rate and then finally new pacemaker implant rate. Really it was a very standard valve study.

What were the key findings from the trial?

SB: When interpreting the results, I should point out that one has to bear in mind the fact that it was a relatively small study, predominantly used to test safety and efficacy. The primary endpoints of clinical performance were that there were no procedural deaths and in 98% of cases (59/60 patients) there was correct positioning of one valve in the proper location. There were only four cases (just over 6.7%) of more than mild aortic regurgitation present; all cases were moderate. At 30 days that had reduced to 3.4%. In other words, there was some evidence that those who had a moderate leak at implantation got better. At 1 year, the rate of moderate PVL was 4.3%. There were no cases of severe PVL at implantation or at 1 year. It is important to comment that this lack of PVL was an independently adjudicated assessment from a core lab.

Looking at safety endpoints, when one goes out to 1 year, all-cause mortality rate was extremely low at 6.7%. Indeed, this is the lowest mortality reported in any TAVI trial. When we look at stroke rates, these were also very low; zero at 30 days and 3.4% at 1 year, which is very low. At 1 year, these are the lowest rates of stroke and mortality that have been reported compared with other studies.

There were no cases of coronary obstruction and no cases of annular rupture. Pacemaker implantation rates were 11.7% at 30 days and 15.2% at 1 year – again this is very low. I do think there can be further reductions in these rates, but when you compare these rates with rates of pacing with other second-generation valves, like Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) and Lotus™ (Boston Scientific, Natick, MA, USA), they are very favourable.

When we look at valve performance, there are some of the highest effective orifice areas recorded in any TAVI study with effective orifice areas of 1.9 cm^2, which was consistent over the period from implant to 1 year. Mean gradients were between 7.5 and 9.2% from implant to 1 year.

What do you think it is about the Evolut R™ that makes patients less susceptible to requiring pacemaker implant?

SB: There are two things: first of all, the position of the implant. One of the issues that we recognised in previous studies was that low implants were associated with higher pacing rates, so the deeper into the ventricle you implant the valve, the higher the rate of pacing. Previously, if you implanted the CoreValve® too deeply, there wasn't a lot you could do. Now if you implant the Evolut R™ too deeply, you can recapture it, retrieve it and redeploy it higher up. That is the first thing.

The second thing is that there is a more optimal radial force exerted, particularly when the valve is being implanted into the smallest size annulus for that valve size. With CoreValve®, there would have been relatively more radial force; with Evolut R™ there is a more consistent degree of radial force, such that excessive radial force is not exerted, so that is the second reason why pacing rates may be lower.

How does your clinical experience of using the Evolut R™ valve compare with the results from the trial?

SB: Our clinical experience in high- and intermediate-risk patients, just based on the clinical use of the valve since it has had the CE mark, very much mirrors the trial experience. We are seeing very low rates of anything more than mild PVL. We are seeing very good haemodynamic results and low rates of pacing as well.

Although we do not yet have long-term data for Evolut R™, we have not seen any issues with CoreValve® in terms of durability and I would be very surprised if we did with Evolut R™. Thinking about the future, I fully expect Evolut R™ to be widely used in clinical practice.

What impact do you think physician experience has on outcomes? Is the Evolut R™ an easy system to use?

SB: I can give you my experience of teaching the procedure to completely inexperienced operators, operators who have not done TAVI ever before, and I can tell you that it is a very easy system to teach.

Have you done any valve-in-valve procedures with the Evolut R™?

SB: Yes, plenty. It is really ideal for valve-in-valve, where it is really important to get the valve correctly positioned, because it is a recapturable system so you can reposition it. You need to implant it such that the Evolut R™ has supra-annular function, because then you get better haemodynamics. You need to implant it relatively high, but if you don't like the position, or if there is a concern about coronary flow, you can recapture it.

Moving on to think about CoreValve®, there are a few studies that have published longer-term data (ADVANCE trial has 3-year outcomes,[2] 4-year outcomes from the CoreValve® CE pivotal study,[3] and 5-year outcomes from an Italian registry[4]). Based on these, what do you think we have learned about the longer term use of CoreValve®?

SB: TAVI has only really been done for 7 to 8 years in most countries, so many of these studies started early in the TAVI experience. Where one is getting the 4/5/6-year data, these are patients that were implanted very early on in the experience with TAVI. What we have learned, is how to select patients now. In the past, the late mortalities were dominated by the fact that these were very elderly patients with a lot of comorbid pathologies, so we have certainly learned how to select patients better. I think we have learned how to implant patients better, so I think we know a lot more than we did when these trials started. We also know how to manage complications better. Those trials have taught us that long-term outcomes are robust and reliable, and the other key thing is that there are no fatal flaws with the technology. Sometimes with new technologies you start to see problems after 3, 4, 5 years, and we have certainly seen this with various forms of other technologies. We have not seen that really with CoreValve®; patients are not presenting with valve thrombosis, valve failure or valve stenosis.

Do you think these encouraging long-term data will mean TAVI is used in a greater proportion of patients in the future?

SB: My suspicion is there will be a gradual increase in the percentage of patients requiring aortic valve replacement who are treated with TAVI and a gradual reduction in surgery. There will always be some patients who need to have surgery, particularly if they need other valves operated on or coronary artery bypass surgery or other issues, but I think there is going to be a gradual increase in the percentage of patients that are treated with TAVI compared to surgery.

What data do we need, to see TAVI becoming an option in intermediate- or low-risk patients?

SB: There are two trials in progress at the moment, SURTAVI[5] and UK TAVI,[6] that are looking at intermediate-risk patients. There are already some data from the US pivotal trial of the intermediate subgroup, and they did better with TAVI than surgery.

Leaflet thickening data from Dr Raj Makkar's have been published,[7] and were presented at the 2015 Transcatheter Cardiovascular Therapeutics conference. What do you think the data tell us about this complication of aortic valve replacement?

SB: This is an interesting study.[7] There has been a further study subsequent to Dr Raj Makkar's paper, from the Mayo Clinic, showing that a significant proportion of patients with failed

aortic bioprostheses have leaflet thrombosis.[8] There probably is a genuine syndrome of leaflet thrombosis, but it is far too early for us to know. There is more that we don't know about this than we do know at present, and it is an interesting observation. It is seemingly more common with certain types of valve, and this includes surgical valves. There are a number of points that this raises, and they are these: first, some patients who present with what is thought to be surgical bioprosthetic valve stenosis may have leaflet thrombosis and may respond to a period of anticoagulation. Second, the syndrome has also been seen with TAVI valves, but is not commonly recognised with CoreValve® or Evolut R™; that is not to say it couldn't happen, and the number of patients in which it has been seen is small. Theoretically, having a supra-annular valve like CoreValve® or Evolut R™ may make patients less prone to this problem. Third, we have no real idea how best to treat these patients following TAVI insertion – whether it should be single antiplatelet therapy, dual antiplatelet therapy, warfarin, a novel anticoagulant, or some combination thereof. We don't know what the best regime is.

Those are my observations on it. It does seem to be a real phenomenon, because it occurs with both TAVI valves and surgical valves, but we have got a lot to learn about the significance and management of it.

Is there any suggestion as to why it occurs with some valves and not others?

SB: There are not enough data at this point to be clear on that. In Makkar's paper,[7] there were only four patients with CoreValve® studied, and they did not have any reduced leaflet mobility, but this is a really small number of patients so you can't come to a conclusion on just four patients. I think we just simply do not have enough data at this point, but as we get more data it will become clearer.

Are there any questions you think we still need to answer regarding TAVI devices?

SB: There are lots and lots of questions we still have to answer. There are some big questions about whether patients should have coronary revascularisation before TAVI, whether patients having TAVI should have cerebral protection with devices. We have ongoing questions on patient selection, subsets of patients who may or may not benefit, patients with low gradient aortic stenosis – there are still more data required. Yes, there are lots of unanswered questions at this point, but there are studies ongoing in all of these issues.

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DISCLOSURES: SB has acted as a consultant for Medtronic and Boston Scientific.