CoreValve: Assessing the Clinical Trials

A review of trial patient selection and results, as well as clinical implications.

BY STEVEN J. YAKUBOV, MD, FACC, AND KYLE FELDMANN, MD

The CoreValve clinical trials that have recently been published include the US Pivotal Extreme Risk study, the randomized US High Risk study, and the ADVANCE study.[1-3] In this article, we review the device, clinical trial patient selection and results, and clinical implications of these trials.

KEY FEATURES OF THE DEVICE

The CoreValve device (Medtronic, Inc.) consists of three unique components: a self-expanding support frame with a three-leaflet porcine pericardial tissue valve, an 18-F catheter delivery system, and a loading system (Figure 1). The lower portion of the nitinol frame exerts a high radial force for intra-annular valve anchoring and sealing; its constant outward force minimizes the possibility of recoil and also allows the frame to adjust to the native annulus size and shape over time, within its size design parameters. The middle part of the frame contains the valve leaflets. The supra-annular positioning of the prosthetic valve ensures proper valve function, even if the lower portion of the frame is noncircular. The frame's apposition to the sinus avoids the coronary arteries and allows both unimpeded coronary blood flow and coronary catheter access after implantation.

The superior portion of the valve frame (positioned into the ascending aorta) has the largest diameter and lowest radial force. Its primary function is to ensure optimal alignment of the prosthesis to blood flow.

The single-layer porcine pericardial tissue valve was specifically engineered to allow for a minimized profile while compressed in the delivery catheter without the risk of tissue damage. The valve is made of single-layer pericardial

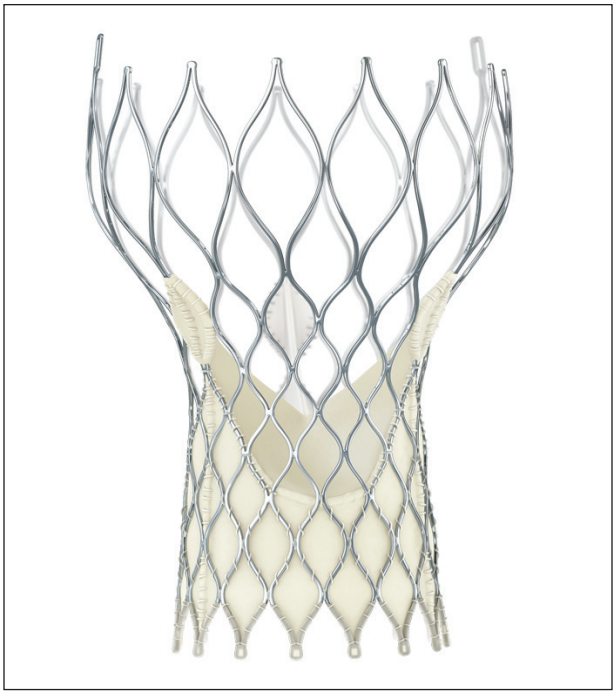


Figure 1. CoreValve image. ©2014 Medtronic, Inc. Printed with permission. CoreValve is a trademark of Medtronic, Inc.

elements sewn together and sewn to the frame. It is constructed of six individual pieces (three skirt elements and three leaflet elements) of porcine pericardium treated with standard tissue fixation and sterilization techniques.

Porcine pericardial tissue is approximately half the thickness of bovine tissue, leading to less occupied space in the folded configuration, while yielding identical or superior

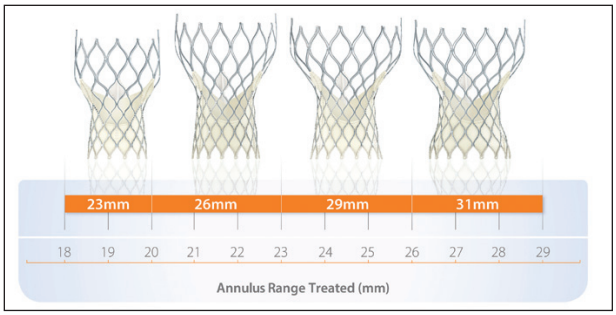


Figure 2. Annulus size versus CoreValve size. ©2014 Medtronic, Inc. Printed with permission. CoreValve is a trademark of Medtronic, Inc.

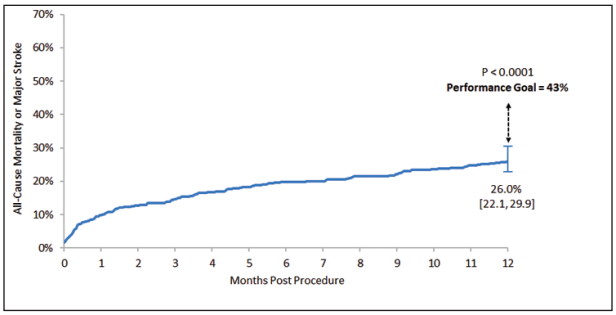


Figure 3. Primary endpoint of 12-month all-cause mortality or major stroke. Reprinted from the *Journal of the American College of Cardiology*, Vol 63, Popma JJ, et al, Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. Page 1977. Copyright (2014), with permission from Elsevier.[3]

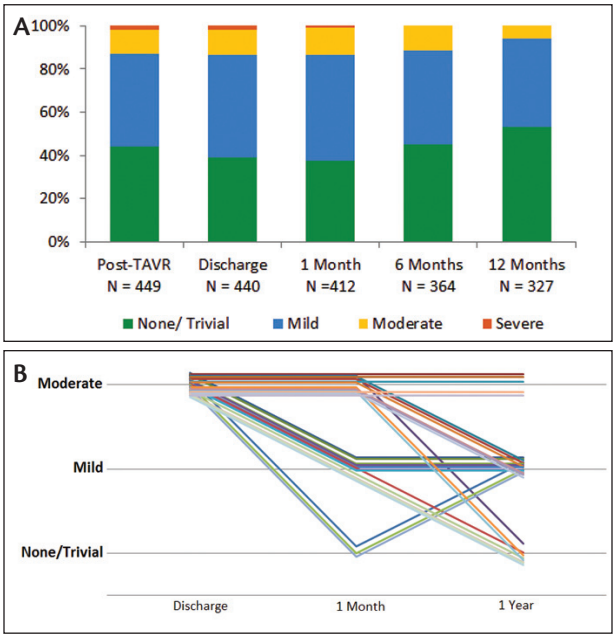


Figure 4. Amounts of (A) and changes in (B) paravalvular aortic regurgitation. Reprinted from the *Journal of the American College of Cardiology*, Vol 63, Popma JJ, et al, Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. Page 1979. Copyright (2014), with permission from Elsevier.[3]

elasticity, consistency, flexibility, and tissue strength characteristics.

The CoreValve is available in four sizes (23, 26, 29, and 31 mm) to serve a broad range of patient annulus sizes (from 18–29 mm) (Figure 2). All of the valve sizes fit into an 18-F catheter.

PATIENT SELECTION

The United States clinical trials for the CoreValve system have included patients with severe aortic stenosis (aortic valve area of 0.8 cm^2 or less and a mean gradient of 40 mm Hg or peak aortic valve velocity of > 4 m/s), who were either deemed to be inoperable or who were at high risk for surgery. The decision regarding inoperability or high risk was made by the independent evaluation of two clinical site cardiac surgeons and then confirmed by a trial screening committee. This clinical decision was assisted by the Society of Thoracic Surgeons Prediction of Mortality (STS PROM) score, but it also included several clinical variables factoring into surgical risk that were not adequately assessed by this score. The clinical trial results reflected the impact of these additional factors. The ADVANCE study enrolled 1,051 patients considered high risk for surgical aortic valve repair (SAVR) based on clinical evaluation and EuroSCORE evaluation.

CLINICAL RESULTS

US Pivotal Extreme Risk Trial

The CoreValve device was implanted in 489 patients who were deemed surgically inoperable. Valve sizes included 23-, 26-, 29-, and 31-mm valves. Most patients had predilation with balloon aortic valvuloplasty (BAV; 98.4%) and were under general anesthesia (94.4%). Device success was 84.6%, as defined by VARC-1.[4]

The primary endpoint of 12-month all-cause mortality or major stroke was 26% (Figure 3). This was significantly lower than a prespecified objective performance goal of 43% ($P < .0001$), meeting its primary endpoint. All-cause mortality rates at 30 days and 12 months were 8.4% and 24.3%, respectively, and the rates of major stroke at 30 days and 12 months were 2.3% and 4.3%, respectively. Permanent pacemaker implantation was required in 104 patients (21.6%) by 30 days and 123 patients (26.2%) at 1 year, most often due to atrioventricular block.

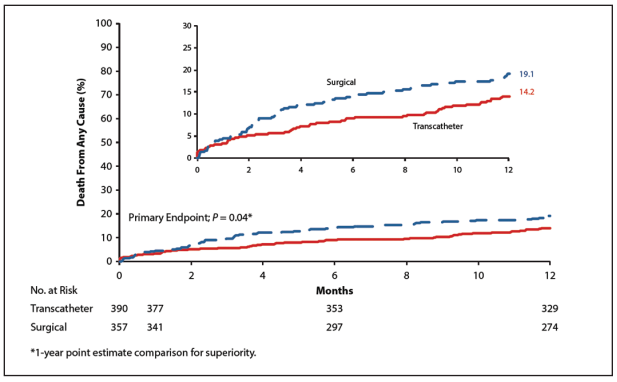


Figure 5. The rate of all-cause mortality at 1 year. From *The New England Journal of Medicine*, Adams DH, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis, Volume 370, Page 6. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.[1]

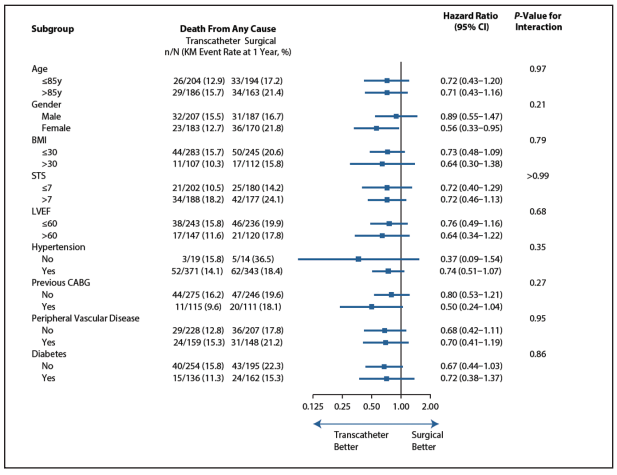


Figure 6. Subgroup analyses of death from any cause, TAVR versus SAVR. From *The New England Journal of Medicine*, Adams DH, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis, Volume 370, Page 7. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.[1]

Significant echocardiographic findings (Figure 4) included a reduction in mean aortic valve gradient, improved left ventricular ejection fraction, rare transvalvular aortic insufficiency, and improvement in moderate paravalvular aortic regurgitation (PVR) from discharge to 12-month follow-up (by paired analysis). There was rare worsening of aortic regurgitation. Late mortality was associated with severe aortic regurgitation.

US Pivotal High-Risk Trial

A total of 795 patients, who were deemed to be at high risk by clinical site evaluation and a central trial screening committee, were randomized to SAVR or transcatheter aortic valve replacement (TAVR). Iliofemoral access was used in 323 patients, 67 had an alternative access site, and 357 underwent SAVR. The average predicted mortality rate by STS PROM at 30 days was 7.4%. Procedural success was high, and the reduction in gradients and improvements in valve orifice areas significantly favored TAVR ($P < .001$). New York Heart Association class improvement and quality-of-life measurements were similar.

The key finding was that the rate of all-cause mortality at 1 year was significantly lower in the TAVR group than in the SAVR group (14.2% vs 19.1%; $P < .04$ for superiority) (Figure 5). The rates of any stroke were 4.9% in the TAVR group and 6.2% in the surgical group at 30 days ($P = .46$) and 8.8% and 12.6%, respectively, at 1 year ($P = .10$). All subgroup analyses favored TAVR over SAVR (Figure 6).

Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVR group than in the SAVR group. SAVR was associated with more bleeding, acute kidney injury, and new-onset or worsening atrial fibrillation. The rates of PVR were significantly higher in the TAVR group.

The primary endpoint, the rate of death from any cause at 1 year, was significantly lower in the TAVR group than in the SAVR group (14.2% vs 19.1%; $P = .04$). The results were similar in the intention-to-treat analysis (13.9% in the TAVR group, 18.7% in the SAVR group) as in the as-treated group.

ADVANCE Study

A total of 1,015 patients with a mean EuroSCORE of 19.4% ± 12.3% underwent CoreValve device implantation in the ADVANCE study. Significant improvements in hemodynamics, valve gradients, and effective valve area were observed. All-cause mortality was 4.5% (confidence interval, 3.2%–5.8%), cardiovascular mortality was 3.4% (2.3%–4.6%), and the stroke rate was 3% (2%–4.1%) at 30 days. The 12-month rates of major adverse cardiovascular and cerebrovascular events, all-cause mortality, cardiovascular mortality, and stroke were 21.2% (confidence interval, 18.4%–24.1%), 17.9% (15.2%–20.5%), 11.7% (9.4%–14.1%), and 4.5% (2.9%–6.1%), respectively. The 12-month rates of all-cause mortality were 11.1%, 16.5%, and 23.6% among patients with a logistic EuroSCORE ≤ 10%, EuroSCORE 10% to 20%, and EuroSCORE > 20%, respectively. Procedural success was high (97.5%), and predilation BAV was common (91%). The rate of new pacemaker implantation was 26.3%.

IMPACT ON CLINICAL PRACTICE

For patients with severe aortic stenosis and who are considered inoperable, there are three transcatheter

aortic valve devices approved by the US Food and Drug Administration—the Sapien and Sapien XT valves (Edwards Lifesciences) and the CoreValve system. These patients have a very high mortality rate with medical therapy alone, and the transcatheter valves have been a significant advancement in improving their quality of life. Additionally, those who are thought to be at high risk for SAVR (usually an STS PROM score of > 8) also have an option for TAVR because now both the CoreValve and Sapien valves are approved for use in these patients. Clinical trials with both devices are currently enrolling patients at lower risk for surgical intervention. The results of these studies will help to determine which lower-risk patients should be eligible for TAVR compared to SAVR.

An important finding in the CoreValve trials was the improvement in moderate PVR with time. This finding may be due to dynamic changes in the nitinol frame shaping to the annulus (remodeling of the frame to the annulus), less BAV, and use of preprocedural CT angiographic assessment of annular sizing to choose the proper valve.

The STS PROM score may not reflect all elements that are important to surgeons in evaluating risk, especially with regard to disability and frailty assessments that may hinder rehabilitation from surgical procedures. Frailty assessments, such as slow 6-meter walk times, poor nutritional status, and weak handgrip, can predict slow or poor recovery from a surgical procedure. These assessments have less predictive implications for TAVR recovery because surgery is avoided. Thus, TAVR appears to be a better choice for frail patients.

The CoreValve US Pivotal High-Risk trial resulted in enrolling patients with an average STS PROM of 7.4% ± 3.4%. Even at these somewhat lower STS PROM scores than were seen in the PARTNER trial, treatment with the CoreValve device demonstrated superiority to SAVR. Similar trends were also seen in the ADVANCE study. Therefore, it is reasonable to assess patients at lower surgical risk to demonstrate in whom TAVR or SAVR is most appropriate.

CHALLENGES, REIMBURSEMENT, AND FUTURE DIRECTIONS

The challenges for TAVR remain reducing postprocedure PVR and improving the profile of the valve delivery systems. CT angiographic (CTA) imaging has been greatly helpful in choosing the proper valve size. CTA guides appropriate valve oversizing. Newer devices by multiple manufacturers are focusing on incorporating technology to limit paravalvular aortic insufficiency by adding fabric, or a "skirt," to the lower part of the stent frame for better annular sealing. Other improvements are developing valve systems that can be precisely positioned and are fully recapturable or repositionable. The Medtronic Evolute R valve, currently under clinical evaluation, intends to address PVR and more precise positioning.

Other challenges include the ability to reduce the pacemaker implantation rate. This appears more commonly with self-expanding stent technology and was recently shown to be significantly reduced by implanting the valve at a higher level (≤ 6 mm implantation depth) within the aortic annulus. The same study showed no association between valve oversizing and the rate of new conduction disturbances or the rate of permanent pacemaker implantation.[5]

As is often the case with new technology, appropriate reimbursement has not kept pace with advances in device technology and does not yet accurately reflect hospital costs. Many hospitals experience negative margins for TAVR procedures. TAVR devices are far more expensive than surgical valves, yet they are currently reimbursed under the six MS-DRGs intended for surgical valve replacement. Much of the added expense of TAVR reflects the high cost of new device development and clinical trials. Medicare has proposed two new MS-DRGs specifically for TAVR, which will be based on TAVR cost inputs. Without these proposed improvements in the MS-DRG payment, access to this technology may be significantly limited.

In order for TAVR to consistently be a percutaneous procedure, smaller delivery systems are desirable to facilitate closure and decrease vascular complications. Until then, alternative access techniques, such as the direct aortic surgical approach, transapical surgical approach, or subclavian or carotid artery access, will be necessary. ■

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