

New TAVR Devices: European Experience and Status of US Trials

An overview of the design features and data related to three next-generation valve systems.

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The last decade has witnessed an incredible transformation in transcatheter therapies for valvular heart disease, from early clinical trials to widespread clinical application. Transcatheter aortic valve replacement (TAVR) has become the standard of care for appropriately selected inoperable patients with severe aortic stenosis, has shown equal or superior results as compared with surgical aortic valve replacement for high-risk patients, and has shown promising early results in intermediate-risk populations.¹⁻⁵ The US Food and Drug Administration (FDA) has approved the Edwards Sapien, Sapien XT, and now the third-generation Sapien 3 valve (all Edwards Lifesciences Corporation), as well as the Medtronic CoreValve and second-generation Medtronic CoreValve Evolut R systems (Medtronic, Inc.).

Given the early success of these valve systems, along with the large incidence of calcific aortic stenosis among an aging population, it is no surprise that many other device companies are engaged in developing safer and more effective alternatives to the existing technologies. Using the lessons learned from the large randomized PARTNER and Medtronic CoreValve trials in the United States, newer valves are designed to improve upon the most frequent complications of the early TAVR experience, including vascular complications from large femoral delivery sheaths, conduction system disease from compression of the left ventricular outflow tract (LVOT), and most importantly, paravalvular leak (PVL), which is a modifiable predictor of long-term survival in early trials. Finally, there was great desire to develop a device that was repositionable and retrievable, something absent from early balloon- and self-expandable devices. Although many devices have initiated first-in-human trials, three devices have recently achieved CE Mark approval and have entered into pivotal randomized trials in the United States. These devices will most likely be alternatives to the valves currently available in the United States market in the

foreseeable future. In this review, we will discuss each of these valves, along with their unique design features, data from early European experience that set the stage for CE Mark approval, and the current status of ongoing pivotal trials in the United States.

THE DIRECT FLOW MEDICAL TRANSCATHETER AORTIC VALVE

The Direct Flow Medical Transcatheter Aortic Valve System (Direct Flow Medical, Inc.) is unique in that it is specifically designed to focus on reducing the incidence and severity of paravalvular aortic regurgitation, a problem that has been associated with significantly worse outcomes in patients undergoing TAVR with both balloon- and self-expandable devices.^{6,7} After balloon aortic valvuloplasty (preferably performed with aggressive sizing and dilation, because the valve itself does not have a rigid frame), the Direct Flow Medical prosthesis is delivered through an 18-F sheath (Figure 1). The bovine pericardial tissue valve does not have traditional metal scaffolding; rather, its structure is created from the inflation of a system of rings (one on the ventricular side and one on the aortic side of the valve). These rings are first filled with a saline/contrast solution via hollow positioning wires after the collapsed valve is advanced into the left ventricle. With the superior ring briefly deflated, the valve is withdrawn via the positioning wires to place the ventricular ring at the aortic annulus. Both rings are fully inflated, and a complete hemodynamic evaluation is performed. If elevated prosthetic valve gradients or PVL are demonstrated due to improper positioning or sizing, the valve can be repositioned or fully retrieved, respectively. Once the valve is positioned optimally, the saline/contrast solution in the device is exchanged for an epoxy-based polymer that rapidly solidifies, and the valve attains its permanent structure.

The most robust data supporting the use of the Direct Flow Medical valve are from the prospective, nonrandomized

DISCOVER CE Mark trial, which enrolled 100 patients at high surgical risk in Europe and demonstrated a remarkable 99% freedom from all-cause mortality at 30 days.⁸ The investigators reported a 93% device success among the 75 patients studied after an initial 25 patient roll-in period. There were three major strokes, two patients with life-threatening bleeding due to femoral access site complications, one periprocedural myocardial infarction, and one acute surgical conversion to aortic valve replacement. The rate of permanent pacemaker implantation after device placement was 17%. Paravalvular aortic regurgitation was judged as none in 70.3% of patients, mild regurgitation was present in 28.4%, and one patient had moderate regurgitation. As a result, the device received CE Mark approval in January 2013.

Recently, additional data from the original 100 patient cohort were published, and demonstrate excellent durability of the valve with 79% of patients having none to trace paravalvular regurgitation at 1 year.⁹ Furthermore, results of 200 consecutive patients enrolled at 1 year in the DISCOVER postmarket study were presented at the Transcatheter Cardiovascular Therapeutics meeting in October 2015. Freedom from all-cause mortality was 82%, and freedom from cardiovascular mortality was 90% at 1 year. Additionally, 95% of patients were reported to have mild or less paravalvular regurgitation, with 85% having trivial or no regurgitation. Similarly, 2-year follow-up on the original 100-patient cohort in the DISCOVER premarket study was reported at EuroPCR in

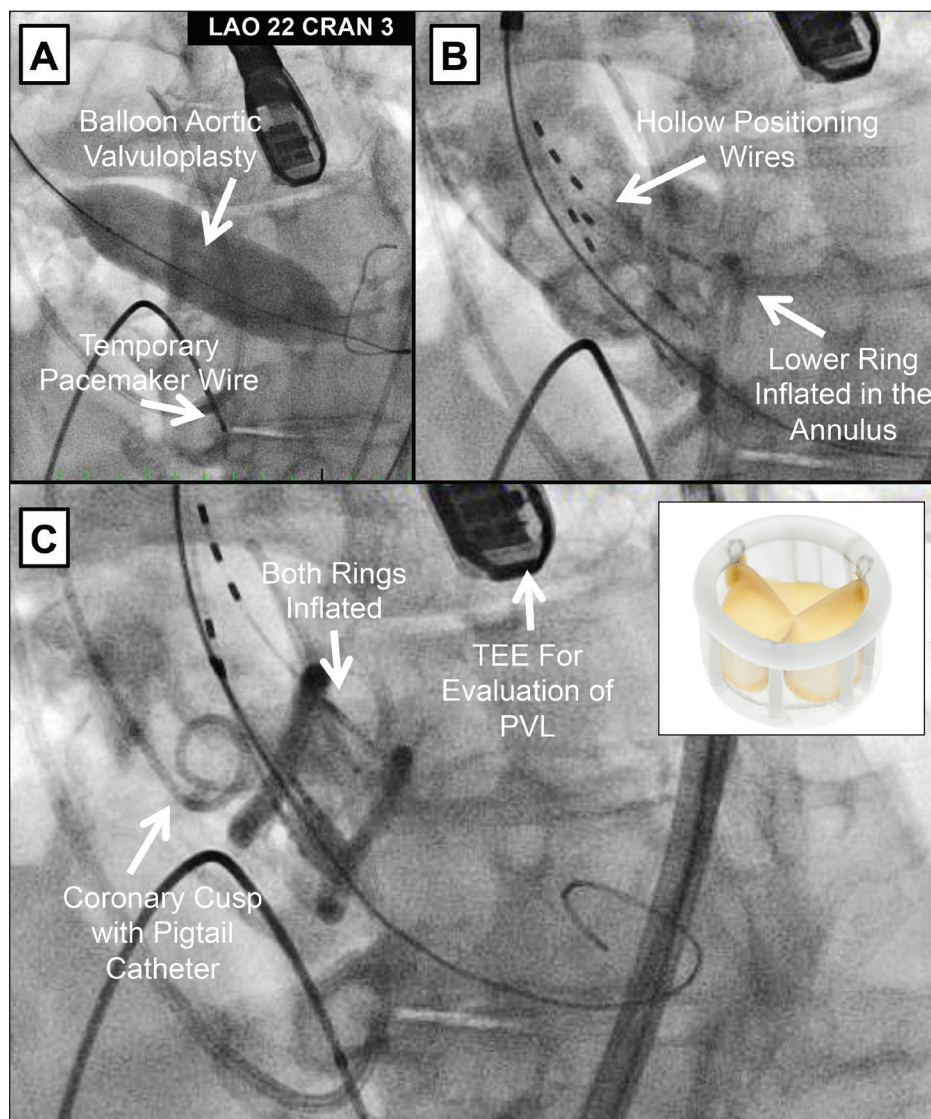


Figure 1. Placement of the Direct Flow Medical valve (inset image). First, traditional balloon aortic valvuloplasty is performed as a required step (A). The valve is advanced into the left ventricle, and the ventricular ring is inflated with a saline/contrast solution, then the valve is withdrawn to the level of the aortic annulus by the hollow positioning wires (B). Once in the correct position, the aortic ring is also inflated, and the valve can be evaluated by transesophageal echocardiography or root angiography for the presence of PVL (C). Finally, when the position is confirmed, the polymer is injected into the rings, and the positioning wires are removed.

May 2015 and demonstrated 90% survival at 1 year and 80% survival at 2 years. The rate of permanent pacemaker implantation in that cohort was 17% at 30 days and 21% at 1 year. The Direct Flow Medical valve has been implanted in more than 2,500 patients in Europe to date and is commercially available in four sizes (23 mm, 25 mm, 27 mm, and 29 mm).

In the United States, the Direct Flow Medical valve remains investigational as part of the SALUS trial. An initial

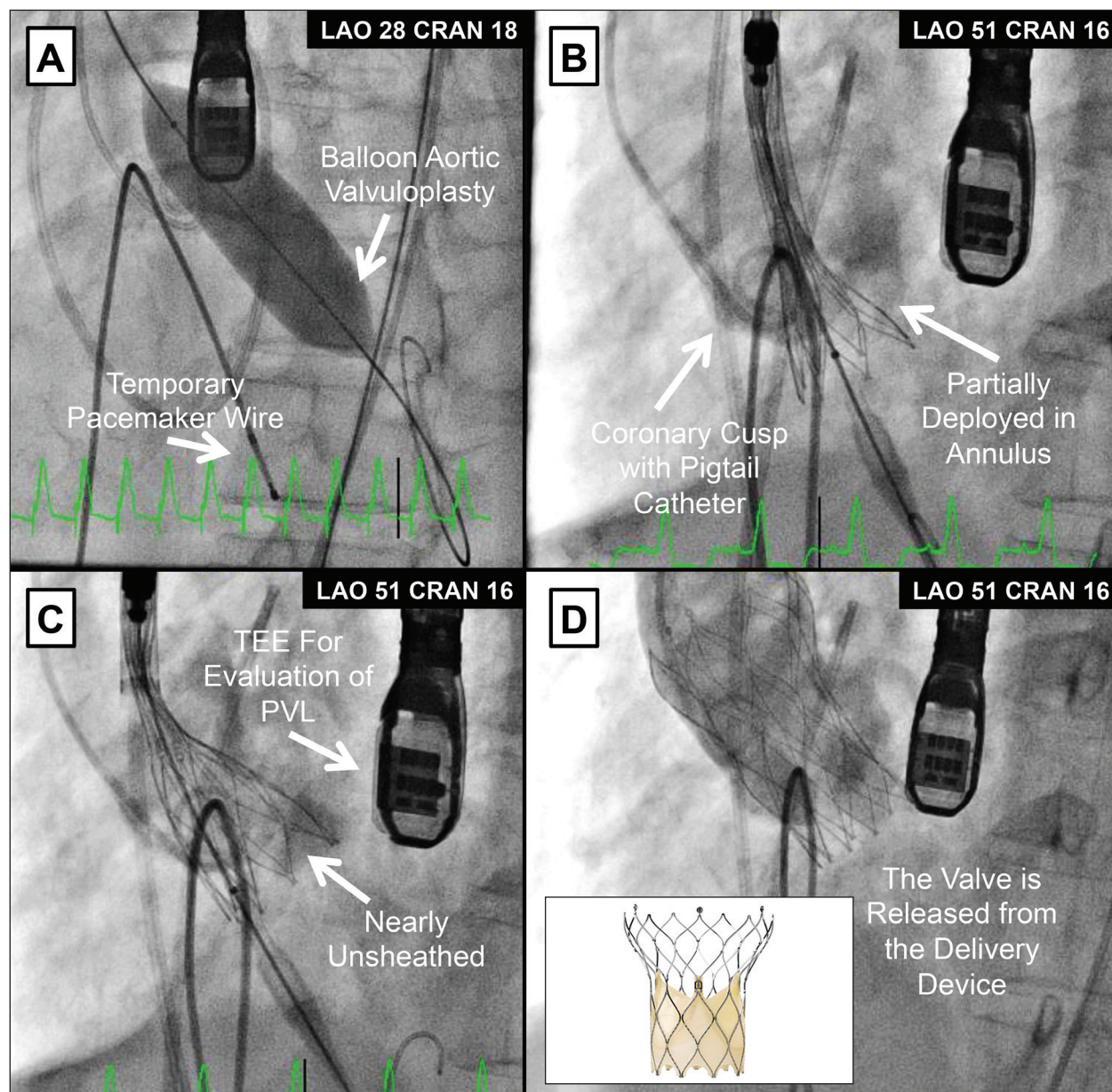


Figure 2. Placement of the Portico transcatheter aortic valve (Portico TAVI System) (inset image). First, traditional balloon aortic valvuloplasty is performed as an optional step (A). The Portico valve is advanced across the native aortic valve, and the lower portion of the prosthesis begins to self-expand as the position is confirmed by root angiography (B). With the valve nearly unsheathed, transesophageal echocardiography or root angiography can be used to assess for PVL (C). Finally, the valve is released from the delivery catheter and assumes its expanded position (D). Portico and St. Jude Medical are trademarks of St. Jude Medical, Inc. or its related companies. Inset image reproduced with permission of St. Jude Medical, ©2016. All rights reserved.

feasibility phase of the United States trial was conducted in 30 extreme-risk patients in 2013 and demonstrated 97% survival at 30 days, with mild or less aortic regurgitation in all patients, no strokes, and only one patient requiring permanent pacemaker implantation. Subsequently, the FDA approved an expansion of the trial to include 648 inoper-

able and high-surgical-risk patients at up to 45 United States sites in a 2:1 randomized phase, which compares the Direct Flow Medical device to the commercially available Medtronic CoreValve Evolut R and Edwards Sapien 3 valves. Enrollment in this pivotal trial began in June 2015 and is ongoing.

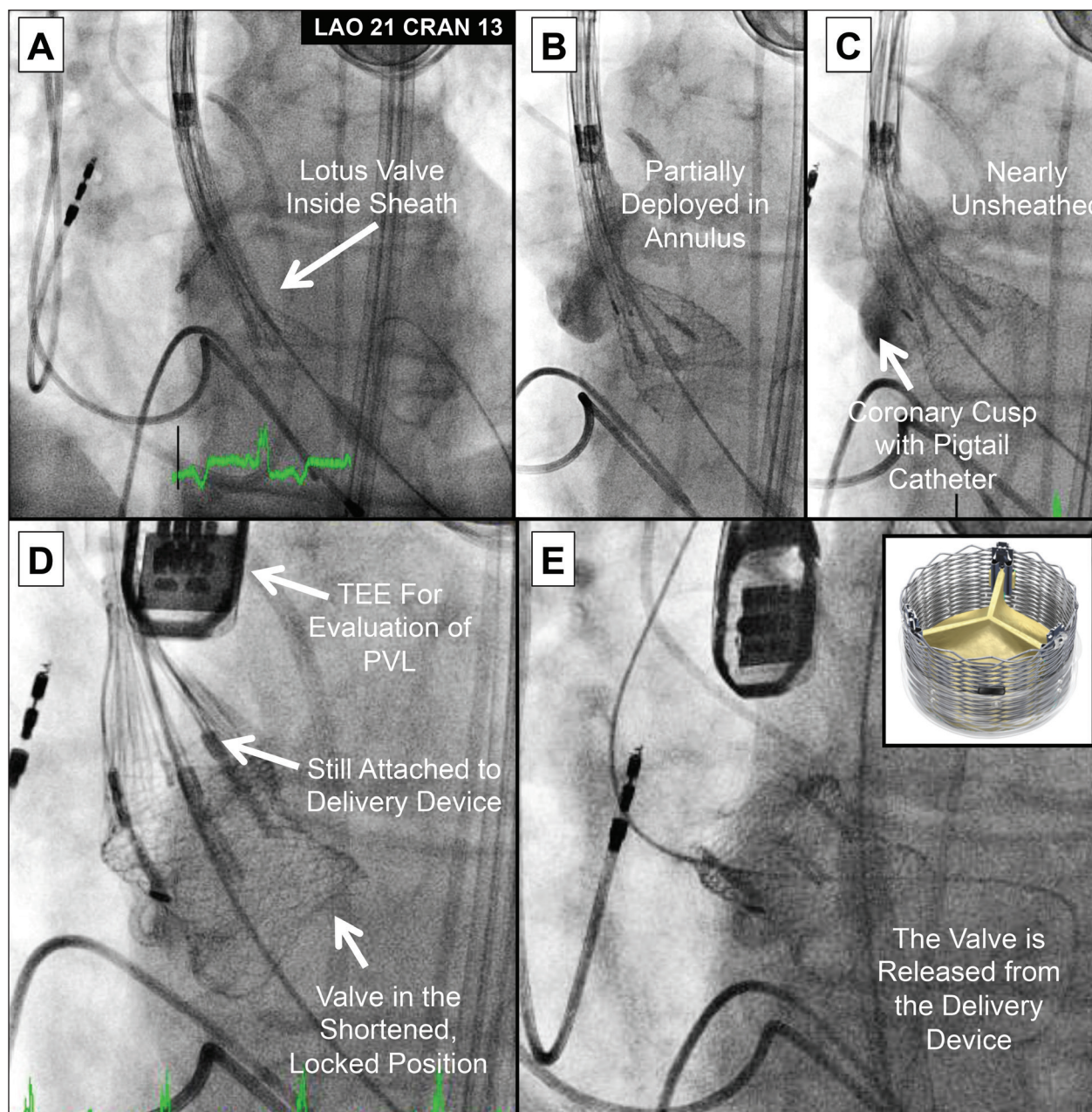


Figure 3. Placement of the Lotus valve (inset image). The valve is advanced across the native aortic valve inside the delivery catheter in a collapsed, elongated form (A). The distal portion of the prosthesis is then gradually self-expanded in the annulus (B, C). Once unsheathed, the valve is brought into a shortened, expanded position, and transesophageal echocardiography or root angiography is used to evaluate for PVL (D). Finally, when the position is confirmed, the valve is permanently locked into position, and the delivery device is released (E).

THE PORTICO TRANSCATHETER AORTIC VALVE

The Portico Transcatheter Aortic Valve Implantation System (St. Jude Medical, Inc.) is a bovine pericardial valve mounted on a self-expandable nitinol stent. Despite having a similar appearance to the Medtronic CoreValve, the

Portico valve differs on a few key design features. First, the valve tissue is located closer to the inferior margin of the stent frame to allow for device deployment at a higher level in the LVOT, with the aim of reducing the incidence of conduction abnormalities. Additionally, the stent cells are much wider than those of the Medtronic CoreValve, which

is intended to allow for better sealing of the tissue against the calcific annulus and presumably reduce the incidence of PVL. Finally, the valve is designed to be fully retrievable and repositionable up to the point of full deployment (Figure 2).

The initial first-in-human experience with the Portico valve was completed in 2011 in Canada involving 10 high-risk patients, with no deaths, myocardial infarctions, major bleeding, or major vascular complications at 30 days and only one minor stroke.¹⁰ No patients required permanent pacemaker placement, and two developed new left bundle branch block after valve implantation. Paravalvular aortic regurgitation was judged as trivial or less in four patients, mild in five, and moderate in one patient. One patient had intermittent failure of a single leaflet, which led to valvular regurgitation and required a second Portico valve 7 days later, resulting in resolution of the valvular regurgitation with only trivial PVL. A first-in-human study was also conducted in 10 patients in Europe with good results, which led to CE Mark approval in November 2012. The subsequent Portico CE Trial enrolled 83 patients and found an all-cause mortality rate of 3.6% and 8.4% at 30 days and 1 year, respectively, and a 10.8% incidence of new pacemaker implantation.¹¹ Moderate PVL was found in 5% and 3% of patients at 30 days and 1 year, respectively.

Given the initial promising results in Canada and Europe, the FDA granted approval for the Portico United States investigational device exemption (IDE) study, which began enrolling patients in May 2014. The US study protocol contained a prespecified subgroup of patients who were analyzed with four-dimensional CT to evaluate the stent frame of the valve. Surprisingly, the four-dimensional CT identified reduced leaflet motion in one patient who had a stroke after TAVR, and additional core laboratory reviews showed that this finding was present in other asymptomatic patients as well. As a result, St. Jude suspended worldwide implantation of the Portico valve in September 2014 to conduct additional investigations and temporarily lost its CE Mark. Subsequently, two physician-initiated registries were formed to evaluate bioprosthetic leaflet function, and the results of these registries, along with the initial results of the Portico IDE study, were recently published.¹² The authors found that reduced bioprosthetic leaflet motion was found in 22 of 55 patients (40%) in the Portico IDE study and in 17 of 132 patients (13%) in the pooled registries after both TAVR and surgical aortic valve replacement, was similarly present among multiple prosthesis types (Portico, Edwards Sapien, and Medtronic CoreValve), and had a significantly lower prevalence in patients who were therapeutically anticoagulated, possibly indicating subclinical thrombosis as a causative mechanism.

Because prophylactic therapeutic anticoagulation in the TAVR patient group is not without its own risk, the over-

whelming recommendation has been to avoid routine anticoagulation except in specific clinical situations where it is otherwise indicated such as patients with atrial fibrillation or venous thrombosis. Furthermore, causality between leaflet thrombosis and cerebrovascular events could not be established, as the clinical event did not always correlate with the time of CT scan acquisition, and several patients in the small group with leaflet thrombosis and neurologic events also had atrial fibrillation. It was determined that the finding of leaflet thrombosis was not unique to the Portico valve, and CE Mark approval for the Portico valve was regained as of March 2015 based on these results and those of internal safety reviews by St. Jude Medical. The Portico United States IDE trial was allowed to resume shortly thereafter, with initial results expected in 2019. The CT substudy of this trial will hopefully provide greater insight into the issue of valve thrombosis, its clinical consequences, and possibly therapeutic measures.

THE LOTUS VALVE

The Lotus Valve System (Boston Scientific Corporation) consists of a nitinol frame that houses a bovine pericardial valve and has a number of unique features. The valve comes preloaded to the 18-F Lotus delivery catheter system, and the lower (ventricular) margin of the nitinol frame has a polyurethane sealing membrane that is designed to reduce paravalvular regurgitation. The most unique feature is the method of valve delivery, which involves positioning the valve across the annulus and then, as the overall height of the stent frame is shortened, the valve rapidly expands to fill the aortic annulus and assume its final position. At this point, the valve is fully functional but remains connected to the delivery catheter and can be hemodynamically interrogated (Figure 3). If the positioning is suboptimal or if PVL occurs, the device can be fully repositioned and redeployed or even retrieved completely. Once the valve is in the optimal position, the stent frame is locked in its shortened and expanded state, and the catheter is detached.

Initial feasibility studies were conducted in 11 high-risk patients in Australia (the REPRISE I study) and demonstrated successful placement of the valve in all patients, four of whom underwent successful repositioning prior to final deployment.¹³ Overall, nine of the 11 patients were free of major adverse cardiovascular or cerebrovascular events at 30 days, one patient suffered a major stroke at day 2, and one patient was discharged with a mean aortic gradient of 22 mm Hg. No paravalvular regurgitation was present in eight patients, and trivial or mild regurgitation was present in the remaining three patients. New permanent pacemaker implantation was required in four patients. Subsequently, the REPRISE II study enrolled 120 high-surgical-risk patients in Europe with severe aortic stenosis, all of

whom had successful valve implantation, 26 of whom had successful repositioning, and six of whom had a successful retrieval followed by implantation.¹⁴ At 30 days, the mortality rate was 4.2%, the rate of disabling stroke was 1.7%, and the incidence of permanent pacemaker placement was 28.6%. Moderate paravalvular aortic regurgitation was present in 1% of patients at 30 days, 20.8% had mild or trivial aortic regurgitation, and 78.1% of patients had no PVL.

Most recently, the pivotal REPRIZE III trial was launched in September 2014 and completed the target enrollment of more than 1,000 patients in the United States and internationally in December 2015. Patients were randomized in a 2:1 fashion to the Lotus valve versus Medtronic CoreValve, and results are eagerly anticipated.

CONCLUSION

Each previously discussed TAVR device system has shown very promising results in initial clinical trials, and the results from ongoing randomized trials are enthusiastically anticipated. Each device has its unique strengths, but common to all of these next-generation designs is the opportunity for repositioning the valve if initial deployment yields either suboptimal anatomic placement and/or hemodynamic results. Patients with severe aortic stenosis who previously had no options for surgical aortic valve replacement may soon benefit from a variety of device systems, and heart teams will have more options to tailor individual strategies based on patient risk factors, annulus size, vascular access options, and other anatomical considerations. ■

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