What surprised you most about the recent findings from the CoreValve Extreme Risk study?

There were at least three clinical trial challenges in the US CoreValve Extreme Risk pivotal trial. First, with the presentation of the PARTNER B results at TCT 2010, there was no longer clinical equipoise with respect to the randomization of patients deemed unsuitable for surgery to transcatheter aortic valve replacement (TAVR) or medical therapy. We were faced with a challenge in clinical trial design, that is, the delineation of an objective performance goal (OPG) that would estimate the frequency of all-cause mortality or major stroke in patients treated with medical therapy and then use that OPG to evaluate the results of the Extreme Risk registry. We chose a very conservative OPG of 43% based on contemporary valvuloplasty studies, confirmed with the lower 95% confidence interval of the control group of PARTNER B.

Second, as we were simultaneously running a randomized trial of high-risk surgical patients along with an extreme-risk registry, we needed to make certain that there was no "risk creep" of high-risk patients into the Extreme Risk registry, just so that they would receive the CoreValve device (Medtronic, Inc., Minneapolis, MN) without randomization. Our National Screening Committee was chaired by Dr. Mike Reardon, a cardiac surgeon at Methodist-Debakey Heart and Vascular Institute in Houston, who was very meticulous and made certain that all patients accepted into the Extreme Risk study were truly unsuitable for surgery.

Our final challenge was to make certain that we could demonstrate that our Extreme Risk registry patients had indices of comorbidity, frailty, and disability that showed that the risk of surgery exceeded its benefits. One-quarter of our extreme-risk patients had severe lung disease, more than 60% had severe comorbidities based on the Charleston Comorbidity Score, 86% of our patients had a 5-meter gait speed > 6 seconds, and more than 25% of patients lived in an assisted living center.

We were pleased to find that nearly 75% of these Extreme Risk registry patients were alive and free of stroke at 1 year. Specifically, even though these patients had severe comorbidities, were frail, and were disabled, the frequency of all-cause mortality and major stroke was 25.5% at 1 year, a significant improvement of our OPG of 43%. We also found that the major stroke rate was much lower than we expected it to be: 2.4% at 30 days and 4.1% at 1 year. Our final finding was that the frequency of moderate or severe aortic regurgitation was low at 4.1% at 1 year, likely due to remodeling of the annulus over time by the self-expanding nitinol frame of the device. In fact, we found that in patients who had moderate paravalvular regurgitation at 1 month, 80% had a reduction in paravalvular regurgitation by 1 year.

So, we chose very ill patients in the US CoreValve Extreme Risk study and were able to perform the procedure safely, with three-quarters of patients surviving without a major stroke to 1 year, a major stroke rate of only 2.4% at 30 days and 4.1% at 1 year, and a very low rate of paravalvular regurgitation at 1 year. These findings were very encouraging to us.

To what do you attribute the reduction in paravalvular regurgitation after the 1-year threshold?

We are in the process of studying the echocardiographic findings further. However, we believe that the fact that we performed CT angiography in 100% of the patients helped us to select the appropriate valve size based on the three-dimensional geometry of the annulus. We tried to oversize the perimeter of the aortic annulus by 10% to 15% with the transcatheter heart valve and had 23-, 26-, 29-, and 31-mm CoreValve.
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devices available for the study. We also implanted the CoreValve device 4 to 6 mm or less below the noncoro-
nary sinus to maximize the frame diameter at the annu-
lus. Finally, after CoreValve deployment, we evaluated the result using echocardiography, hemodynamics, and aortography. Any significant paravalvular regurgitation was treated with valve repositioning, postprocedure balloon dilatation, or an additional valve. I believe that each of these factors contributed to the low rates of paravalvular regurgitation in our study.

As various alternative access routes are developed for TAVR, how do you decide the proper approach for each case?

We used CT angiography of the iliofemoral vessels to demonstrate whether the peripheral vascular anatomy would allow access for an 18-F sheath. We used a parameter of a mean iliofemoral diameter > 6 mm without calcification and > 7 mm with concentric calcification. If transfemoral access was not possible, we then used an alternative access (either a subclavian, axillary, or a direct aortic approach), which was performed either using a median sternotomy or a right thoraco-
tomy. As the trial evolved, the direct aortic approach was used more frequently. An alternative approach was required in approximately 20% of our patients.

Can you discuss the new generation of cerebral embolic protection devices that are in the pipeline for TAVR patients?

Embolism of atherosclerotic material to the brain has been a major concern after TAVR. Evidence from diffusion-weighted magnetic resonance imaging demonstrates that material is embolized to the brain in 70% to 80% of patients after TAVR. Fortunately, these embolic events less commonly manifest in a clinical stroke. The major stroke rate in our CoreValve Extreme Risk pivotal study was 2.4%, and in our Continued Access cohort, it was 1.8%. It may be higher in patients who have plaque in the ascending aorta or heavily calcified aortic valve leaflets. The majority of strokes manifest within the first 48 hours of the procedure.

I think that cerebral protection devices may lessen the occurrence of clinical manifestation and occult embolic stroke after TAVR. The two most frequently used devices are the Embrella device (Edwards Lifesciences, Irvine, CA), which is a flow deflector, and the Claret device (Claret Medical, Inc., Santa Rosa, CA), which has basket filters that are placed into the carotid and subclavian arteries. I would think that surrogate endpoints like diffusion-weighted magnetic resonance imaging would be the best method to show a reduction in embolic material. These devices may also be useful to prevent stroke during high-risk valve surgery as well. I do believe that this technology is going to be very important and may be a valuable adjunct tool to preserve neurocognitive function after TAVR.

As a coauthor of the Valve Academic Research Consortium (VARC) consensus document (which was written in 2011 and revised in 2012), can you tell us if these guidelines will be continually updated to reflect the data collected from ongoing clinical trials?

There is little question that our understanding of transcatheter valve therapy continues to evolve over time with more experience. The VARC-1 and VARC-2 consensus documents will also be refined as we learn more about the outcomes of patients treated with transcatheter valve therapy. In fact, there are already discussions about the creation of VARC-3. Much of the credit for the creation of VARC goes to Dr. Martin Leon, who coordinated the input from four academic clinical research organizations, as well as other expert clinicians who provided a practical perspective to these definitions. We now use the VARC definitions as standards in transcatheter clinical trial design and endpoint adjudication. Although it is difficult to make cross-trial comparisons among different transcatheter valves, the VARC definitions will be used to provide a more transparent and consistent understanding of the results of various valve therapies. The most important of these endpoints is the standardization of disability stroke (in VARC-2), formerly major stroke (in VARC-1), and the definitions for the presence and severity of paravalvular regurgitation. The mitral valve repair and replacement therapies will require their own lexicon for clinical trials.

What are some of the challenges of representing the needs of US interventional cardiologists when collaborating with government agencies on the device regulation process? Have you witnessed any significant breakthroughs?

Medical device innovation over the past 20 years has been critical for the improved outcomes that we have seen in patients with cardiovascular disease in the United States. There are many of us who spent the majority of our careers evaluating novel cardiovascular medical devices. Some of the new devices have been useful, and others have not. Our early days with excimer laser angioplasty, directional atherectomy, and transluminal extraction atherectomy taught us that plaque removal is not as important as providing a scaf-
fold for the coronary vessel with coronary stents—and now drug-eluting stents that prevent restenosis by inhibiting tissue growth. TAVR is another good example of a transformation therapy, as it has affected both the quantity and quality of patients’ lives.

There are substantial differences in the medical device approval process in the United States and Europe, and I think these differences are manifest by early availability of novel medical devices in Europe. Our US Food and Drug Administration (FDA) has a somewhat higher bar for regulatory approval and requires the demonstration of reasonable assurance of safety and efficacy in the intended population of patients rather than simply safety and performance as required for CE Mark approval. So our clinical trials in the United States are larger with sufficient numbers of patients to demonstrate safety and efficacy compared with standard therapy. This takes time and money. The clinical site infrastructure to perform these studies has also exploded in the United States—particularly with respect to compliance with FDA inspections. This has also led to an increased transparency of clinical trial design and support for the patients who participate in these studies.

Admittedly, this has resulted in time delays from the first meeting with the medical device sponsor at the FDA and clinical device approval. I think that these challenges have been recognized by both the FDA and clinical trial sponsors, and both agreed that refinements in the process are needed. There is a substantial effort by the FDA to bring early feasibility studies back into the United States and to study novel endpoints that may reduce the number of patients required to demonstrate clinical benefit. These have also been efforts to evaluate the total product life cycle, including both the premarket and postmarket, lessening the required evidence prior to approval but increasing the scrutiny of the outcomes after device approval. This will ensure that the results of the clinical studies in patients are maintained with commercial approval and will monitor for low-frequency events that may not have been identified in the clinical trial. A final effort to examine the value of large simple trials in established therapies has been another way to improve clinical trial efficiency. I am hopeful that these clinical trial refinements will improve the access of valuable medical devices to our patients in the United States. This will obviously require close communications between medical device manufacturers, the FDA, the Centers for Medicare & Medicaid Services, and the professional societies.

What do you enjoy most about your role as Chair of the C3 Summit for interventional cardiology fellows?

For the past 10 years, the C3 Summit has been a phenomenal opportunity for interventional fellows to present their own cases to each other and to a very select senior faculty. The criteria for the cases were simply based on cases that the interventional fellows participated in during the year in which they learned an important lesson to share with others. Sometimes, that important lesson is a complication, but sometimes it’s just a technique or being able to get out of trouble when it’s on the horizon. The interventional fellows have become very clever in their case presentations, and C3 Summit faculty is often intrigued by the “unknowns” of the cases. The discussion that develops between the faculty and the fellows about a case is a magical experience.

I must admit that I learn something from each case that is presented, and that is certainly a very humbling experience. All participants think collectively to problem solve, which is one of the most important aspects of the C3 Summit. When the interventional fellows have completed this 1-day summit, we hope that we have provided them the tools that they need to get out of trouble when trouble happens. We hope that we have helped them to sort out the etiology of complications that they may have, prioritize the treatment plan, and stabilize patients. The collective wisdom that is created is much better than that of any single individual.

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