Implications of Contemporary Clinical Trials

Transcatheter Aortic Valve Implantation
The Interventionist Vision

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Percutaneous catheter-based interventions are an emerging area in the treatment of valvular heart disease. Percutaneous aortic balloon valvuloplasty was initially introduced by Cribier et al in 1985 for patients with severe calcific aortic stenosis. This technique results in moderate hemodynamic improvement and significant clinical improvement, but it is associated with significant periprocedural morbidity and mortality and with a very high hemodynamic and clinical restenosis within 6 to 12 months after the procedure. Today, this technique is used mainly as a bridging technique to surgical aortic valve replacement (AVR) or to transcatheter aortic valve implantation (TAVI).2–4

The early results of percutaneous catheter-based valve replacement are promising. The first percutaneous heart valve replacement was performed by Bonhoeffer in 2002 in the pulmonary position5,6 and by Cribier in 2002 in the aortic position.7,8 Nowadays, TAVI has evolved to become a valid therapeutic option for patients with severe aortic stenosis who are inoperable or are at very high risk for surgical AVR.7–10

Recently, TAVI has been offered to select patients with good results. In Europe, TAVI is now an established, evidence-based alternative to open AVR in patients with aortic stenosis who are unsuitable for conventional cardiac surgery. Recent reported studies from the United States have demonstrated that for patients with severe aortic stenosis who are not candidates for surgery, TAVI with the Edwards SAPIEN valve significantly reduced mortality compared with standard treatment (Placement of Aortic Transcatheter Valves [PARTNER] trial, cohort B).9,10

Currently, there are 2 first-generation percutaneous valves in clinical application, a balloon-expandable Edwards SAPIEN and a self-expandable valve (CoreValve), with several other second-generation new players achieving first-in-human application. Since 2002 when the first TAVI in a human was reported by Cribier et al,7 percutaneous heart valves have already undergone several modifications from the first-generation devices. Nonetheless, it is inevitable that as technology develops to overcome the present limitations and to result in safer and more effective techniques, percutaneous heart valve replacement will undoubtedly increase in frequency. Other meticulously designed clinical trials must be performed to definitively determine the short- and long-term results of TAVI compared with the gold standard of open surgical replacement and to define the appropriate patient population who will benefit the most.

The pivotal PARTNER trial is the first randomized (1:1), controlled, multicenter study assessing the effectiveness and safety of TAVI in patients with severe, symptomatic aortic stenosis who are at high risk for conventional surgery. The study device (Edwards SAPIEN) is available in 23- and 26-mm valve sizes and is delivered via a 22F or 24F sheath for the transfemoral approach or a 26F sheath for the transapical route. The balloon-expandable bioprosthesis is composed of a stainless steel frame inside of which a trileaflet bovine pericardial valve is mounted. In the PARTNER trial, the criteria used to define severe degenerative aortic valve stenosis were an aortic valve area of <0.8 cm² (or aortic valve area index <0.5 cm²/m²), a mean aortic gradient of >40 mm Hg, or a peak aortic jet velocity of >4 m/s. All patients had a New York Heart Association functional class ≥2. Some of the exclusion criteria included recent acute myocardial infarction (≤1 month), recent stroke or transient ischemic attack (within 6 months), congenital unicuspid or bicuspid aortic valves, a preexisting prosthetic heart valve in any position, severe ventricular dysfunction (left ventricular ejection fraction <20%), renal insufficiency (creatinine >3 mg/dL), and a life expectancy <12 months.

Subjects enrolled in the PARTNERS I trial were separated into 2 groups, and each cohort was separately powered and analyzed. In the first group, called cohort B, which was composed of patients who were deemed to be unsuitable candidates for surgery, TAVI was compared with standard medical therapy. Inoperability was judged by a cardiac interventionist and 2 separate surgical investigators and was based on a 30-day probability of death or serious, irreversible condition >50% after surgical valve replacement. In cohort A, TAVI was compared with surgical AVR in high-risk surgical candidates who were characterized by a Society of Thoracic Surgeons risk score >10% and the presence of comorbidities resulting in a ≥15% predicted 30-day mortality as assessed by a cardiac surgeon. Depending on their eligibility for transfemoral access, cohort A patients were further assigned to either the transfemoral or transapical arm of the trial. Within each arm, patients were randomized between TAVI and surgical AVR. The primary end point was all-

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cause mortality at 1 year, but patients will be followed up for at least 5 years.

The PARTNER cohort B was composed of 358 patients with severe, symptomatic aortic stenosis deemed inoperable for traditional open heart surgery. Patients were evenly randomized to receive either the Edwards SAPIEN valve or standard therapy. Although the 30-day rates of stroke (3.8% versus 2.1%; \( P=0.20 \)) and vascular complications (11% versus 3.0%; \( P<0.001 \)) were higher in the TAVI group, survival at 1 year was dramatically higher in patients receiving the valve compared with those who received best medical therapy (69.3% versus 49.3%; \( P<0.001 \)). Furthermore, patients who received the valve had fewer hospitalizations and better symptom relief than those receiving standard medical care. Two-year outcomes in the PARTNER B trial showed that survival curves are continuing to separate and the number needed to treat to save 1 life dropped from 5 at 1 year to 4 at 1 years. The Food and Drug Administration approved the SAPIEN valve for the US market on the basis of the PARTNER B results. Two-year follow-up data continue to support the role of TAVI as the standard of care for symptomatic patients with aortic stenosis who are not surgical candidates.

The PARTNERS Trial Cohort A was composed of 699 patients with severe, symptomatic aortic stenosis deemed at high risk for traditional open heart surgery. Patients were evenly randomized to receive either the Edwards SAPIEN valve with transfemoral or transapical delivery or traditional open heart surgery. The study achieved its primary end point at 1 year, concluding that survival of patients treated with the Edwards SAPIEN transcatheter aortic valve was equivalent to the survival of those treated with surgical AVR. In this cohort, the study found that TAVI was noninferior to surgical AVR for all-cause mortality at 1 year, 24.2% versus 26.8%, respectively. At 1 year, the rate of death resulting from any cause was 30% with TAVI versus 50.7% with standard treatment. However, TAVI patients had a higher incidence of strokes and major vascular complications compared with standard treatment. The rate of major strokes was 3.8% in the TAVI arm versus 2.1% in the surgery arm at 30 days and 5.1% versus 2.4% at 1 year, a difference that was not statistically significant \( (P=0.20 \) at 30 days and \( P=0.07 \) at 1 year). However, when strokes and transient ischemic attacks were considered together, there was a statistically significant benefit favoring surgery at both 30 days and 1 year \( (P=0.04) \). Quality-of-life data analysis showed that high-risk, surgery-eligible patients treated via a transfemoral route in PARTNER A cohort had substantial quality-of-life benefits compared with surgery in the early weeks after the procedure. This was not the case for patients treated via a transapical route. In this latter group of patients, there was no benefit of transcatheter AVR over surgical AVR at any time point; in fact, quality of life tended to be better with surgical replacement at both 1 and 6 months. Two-year follow-up data from the PARTNERS I trial were recently reported by Kodali et al. They reported that outcomes between TAVI and surgery were comparable at 2 years of follow-up. Nevertheless, further follow-up of this data is required because the main unanswered question concerns the duration or longevity of the percutaneous valve.

The more important news to address duration or longevity of TAVI will probably come from 4- or 5-year follow-up studies. The point that there is more aortic insufficiency with TAVI is valid. The fact that risk for stroke was not significantly different at 2 years is still not completely reassuring because it looks like more strokes occurred with TAVI than with surgical AVR (8 versus 12 strokes).

A second prospective, randomized, multicenter trial, the PARTNER II trial, is currently ongoing and was designed to investigate the procedural clinical performance and outcomes after TAVI with the next-generation Edwards SAPIEN XT THV and the new 18F NovaFlex system (Edwards Lifesciences). The newer SAPIEN XT valve has several key differences from the previous-generation device, including a cobalt chromium frame and modified leaflet design that may improve durability. The PARTNER II cohort B includes patients with severe aortic stenosis deemed to be inoperable. In this trial cohort, the old device versus new device noninferiority trial was designed. The primary end point is a composite of death, stroke, and repeat hospitalization at 1 year. In addition, cohort A of the PARTNER II trial will randomize patients between TAVI with the SAPIEN XT valve and surgical AVR in moderate- to high-risk patients. This trial will enroll patients with a lower surgical risk score than the patients in the PARTNER I trial had.

In December 2010, Medtronic began its pivotal US trial designed to evaluate the safety and efficacy of the CoreValve system. The study will seek to enroll >1300 patients at 40 clinical sites. The trial includes 2 studies in different patient populations: 1 study of patients diagnosed as high risk for aortic valve surgery and a second study of patients diagnosed as extreme risk. Patients deemed at extreme risk will not be randomized to optimal medical management; rather, they will be evaluated against a performance goal derived from contemporary studies. Patients in the high-risk group will be randomized 1:1 to either TAVI with CoreValve or surgical AVR. The primary end point will be all-cause death or major stroke within 12 months.

The immediate and intermediate long-term outcomes of TAVI have provided happiness and enthusiasm to interventional cardiologists who felt that they have conquered the percutaneous treatment of calcific aortic stenosis. However, this is vastly a multidisciplinary team approach, and a collaborative exercise for the heart valve team is necessary for successful program outcomes. Optimal patient selection is critical to a successful TAVI procedure. This multidisciplinary team is essential during the screening, during the procedure, after the procedure, and during the follow-up of these patients, and it plays a big role given the multiple areas of expertise. Patients should be screened into a TAVI program by a member of the multidisciplinary team, not by an individual specialist. Selection of candidates for TAVI should involve multidisciplinary consultation between interventional cardiologists, surgeons, echocardiographers, other imaging specialists, anesthesiologists, pulmonologist, and other specialists if necessary. The use of a team approach has been shown to improve outcomes in these types of complex procedures.
Transcatheter AVR is performed with either local or spinal anesthesia, with sedation or with general anesthesia in a cardiac catheterization laboratory, or in an operating room equipped with fluoroscopy and transesophageal echocardiography. TAVI is performed through either the transfemoral or transapical approach. The concept of a hybrid room was developed for this technique and requires a large room equipped with high-resolution fluoroscopy and cineangiography with Dyna CT (Siemens USA, Washington, DC) and transesophageal echocardiography capability. It requires double-ventilation circulation and a readily available heart-lung machine, intra-aortic balloon pump, and pacemaker. The screening tests usually necessary in the evaluation of these patients include clinical evaluation; ECG; transthoracic echocardiography; chest, abdominal, and pelvic computed tomography angiography; cardiac catheterization with coronary arteriography; pulmonary function tests; and noninvasive carotid studies. Surgical risk of the patients is assessed by the use of special scoring methods for risk stratification. They include the EuroSCORE, the Society of Thoracic Surgeons score, and the Frailty Score. When tests are completed, the results of the evaluation are discussed openly with the multidisciplinary group to determine the best way forward for each individual patient.

Assessment of the anatomy of the aortic annulus is an important component of case selection. Both manufacturers currently have only 2 sizes of bioprostheses in widespread use to treat a wide range of annuli. They have thresholds for sizing of their prostheses for the annular dimensions of a particular patient dictated by estimated need for oversizing. It is clear that measured dimensions by various imaging modalities used for this purpose vary significantly. Although transesophageal echocardiography acts as an useful screening tool in this regard, transesophageal echocardiography, sometimes as an immediate pre-TAVI confirmatory evaluation, is regarded as the current standard of care. Computerized tomography provides additional information on the noncircular nature of the aortic annulus, which is poorly appreciated by echocardiographic modalities. Each manufacturer has set clear boundaries for each bioprosthesis size. The Edwards SAPIEN device requires an annulus of 18 to 21 mm for its smaller 23-mm bioprosthesis and 22 to 25 mm for its larger 26-mm bioprosthesis, with 21 to 22 mm remaining a gray zone, at the operator’s discretion. A larger 29-mm Edwards SAPIEN device now has CE mark (manufacturer’s visual identifier that the product meets the requirements of relevant European’s Directives; mandatory for a wide range of products sold within or exported to the European market) for the transapical route. The Medtronic CoreValve device requires an annulus of 20 to 23 mm for its smaller 26-mm bioprosthesis and 24 to 27 mm for its larger 29-mm bioprosthesis. Although 23 to 24 mm is an unspecified gray zone, the larger bioprosthesis is generally prescribed for these dimensions.

The implantation procedure involves accessing a femoral artery, performing balloon valvuloplasty, and then advancing the device across the native valve. During rapid right ventricular pacing, a balloon is inflated to deploy the valve and the stent frame. Transfemoral TAVI represents the most commonly used access approach overall. However, the safety of this approach depends heavily on careful iliofemoral assessment by computed tomography angiography. Important aspects of relevance are vessel sizing, assessment of tortuosity, and calcification. Recently, there has been a new version of the Edwards Sapient device, the XT, with a corresponding reduction in profile 18F (minimum femoral dimension, 6 mm) and 19F (minimum femoral dimension 6.5 mm), respectively. However, these sheath sizes are based on internal dimensions of the access sheaths, which have larger external dimensions. Indeed, the femoral access risk ratio, defined as sheath size divided by minimal femoral access diameter, with a threshold of 2.6, has been identified as an independent predictor of major vascular complications. This study suggests that to avoid major vascular complication, minimal femoral dimensions of 7.0 mm for 18F, 7.3 mm for 19F, 8.5 mm for 22F, and 9.2 mm for 24F should be used. The same study has also shown that excessive calcification at the site of femoral access is an independent risk factor for major vascular complication.

The future of percutaneous AVR depends on the development of smaller-diameter collapsible, repositionable, and compressible valve prostheses; anticalcification treatment; and adjunctive techniques to decrease the incidence of cerebrovascular embolic events. TAVI is definitely a breakthrough technique that has revolutionized the treatment of aortic stenosis at the start of this century. Although today these techniques are targeted to patients at high risk for AVR, they may be extended to the lower-risk groups in the future, if the initial promise holds true after careful evaluation. The road is long and demanding, but the interventionist dream for percutaneous AVR has become a reality. Further development and improvement of current available TAVI devices are expected to increase success, to decrease complications, and to broaden TAVI indication to larger number of patients. The next generation of devices may help to reduce the frequency of procedure-related complications. In older patients with vascular disease, it is difficult to insert the larger device used in the PARTNER trial. The next-generation devices such as the SAPIEN XT (Edwards) that is 40% smaller and more durable or the European Union–approved CoreValve (Medtronic) will obviate the vascular complications and reduce the bleeding complications. The SAPIEN valve system initially used has evolved, and current platforms, now fourth generation, have a much smaller diameter (18F) and thus should decrease vascular complication and stroke rates. These complications will be further reduced as operator experience increases and potentially with the routine use of embolic protection devices. If stroke rates are reduced, then certainly TAVI will march even further forward and may well be tested in lower-risk populations with aortic stenosis in whom surgery is indicated. Such optimism should be welcomed by both patients and interventionists alike, but only after the efficacy and longer-term durability of TAVI have been rigorous evaluated.

Disclosures
Dr. Palacios serves on the following scientific advisory boards: Siemens, Medtronic, St. Jude, and Ample Medical. Dr. Palacios serves as a proctor for Edwards Life Sciences. He does not receive compensation for any of these positions.
References


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