Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 17, Suppl S, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.707

Patient Selection for Transcatheter Aortic Valve Replacement

Michael J. Mack, MD, David R. Holmes, MD, John Webb, MD, Alain Cribier, MD, Susheel K. Kodali, MD, Mathew R. Williams, MD, Martin B. Leon, MD

Perspective: Cautious and Evidence-Based

Michael J. Mack, MD, David R. Holmes, MD†*

Transcatheter aortic valve replacement (TAVR) is transformative technology that offers a new and promising option for the management of patients with severe aortic stenosis who are either at high risk for traditional surgical aortic valve replacement (AVR) or inoperable. A significant clinical experience has been gained in these patients, with an estimated 60,000+ valves having been implanted since the initial experience was reported in 2002. This extensive experience is the result of two valves, the Sapien valve (Edwards Lifesciences, Irvine, California) and the Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) receiving CE Mark regulatory approval in 2007 in Europe and being available for commercial sale and use since that time, with an approximately equal proportion of each valve. Recently, 3 additional valves have received regulatory approval in Europe, the JenaValve (Jena Valve, Jena, Germany), Direct Flow (Direct Flow Medical, Inc., Santa Rosa, California), and the Acurate valve (Symetis, Inc., Lausanne, Switzerland). A significant amount of valuable clinical information regarding the introduction of transcatheter valves has come from the experience, not only in Europe, Canada, and Australia, but also from other parts of the world as well; the Sapien valve has now received regulatory approval in at least 43 countries worldwide. The lessons learned in this robust worldwide experience have helped to facilitate the excellent performance and outcomes of transcatheter valve therapy in the U.S. pivotal randomized clinical trial, the PARTNER (Placement of Aortic Transcatheter Valves) trial. Indeed, centers outside of the United States have been generously forthcoming in sharing the full breadth and depth of their experiences, both positive and negative during the adoption of this new technology in their countries, and have significantly aided the U.S. experience. Indeed, this global sharing of information, training, and experience, we believe, has shortened the learning curve and contributed to the success of the recent commercial launch of the first approved valve in the United States.

Device development and approval processes in the United States are somewhat different and generally more stringent than in the rest of the world. A fundamental component of the U.S. regulatory process is the performance of randomized clinical trials in addition to registries. The first randomized clinical trial of this technology, the PARTNER trial, has received great interest and attention, especially given the meticulous conduct of the trial as well as the results (1–4). Based upon the results of this single trial, which in actuality is 2 concomitant trials, and the worldwide registry experience, formal U.S. Food and Drug Administration (FDA) approval has now occurred (5). After this approval, there were important considerations relevant to the expansion of this technology beyond the sites that had participated in the pivotal trial. These considerations included clear definitions of proper patient selection, heart center experience, and operator selection criteria, as well as procedural performance. At this point, one needs to consider what lessons can be learned from the PARTNER trial as well as from the commercial experience outside of the United States that will help facilitate the safe, effective, and reasonable implementation of TAVR in this country.

Randomized clinical trials form the highest level of evidence available for evaluating new therapeutic strategies. Despite implantation in over 60,000 patients worldwide and an abundance of single-center and multicenter registry data, there is only 1 randomized trial, the PARTNER trial, comparing patients receiving TAVR to the existing standards of care, medical therapy for inoperable patients, and surgical AVR for high-risk, operable patients. This trial enrolled 1,057 patients in 2 arms, 1 of which included patients with severe, symptomatic aortic stenosis, who either were deemed inoperable (n = 358) or were judged to be at high risk for surgical AVR (n = 699). The inoperable arm (Cohort B) was randomized between transfemoral AVR and medical therapy, which included balloon aortic valvuloplasty in the majority of patients. The high-risk arm (Cohort A) randomized patients between transcatheter AVR (transfemoral or transapical approach) and surgical AVR. Both arms of the trial met the pre-defined primary endpoint. In the inoperable patients, TAVR was found to be superior to medical therapy for mortality at 1 year by an absolute difference of 20%. These results have recently been determined to be sustained and even more beneficial at 2 years (4).

JACC Vol. 62, No. 17, Suppl S, 2013
October 22, 2013:S1–S10

In the high-risk surgical patients, TAVR also met the primary endpoint of the trial by being noninferior to surgical AVR for mortality at 1 year. These results are likewise quite positive, and regulatory approval for commercial sale of the Sapien valve for use in inoperable patients was granted in November 2011. A second FDA Expert Panel recommended approval of the valve for use in high-risk, operable patients, and it was approved by the agency in late 2012.

However, the results of any randomized controlled trials need to be considered in the context in which they were obtained. Only when the parameters under which the study was performed are well understood, can the results of this or any randomized trial be reasonably expected to be "generalizable" when applied in the "real world." The results of the PARTNER trial were obtained in 25 centers: 22 in the United States; 2 in Canada; and 1 in Germany. All centers had significant previous experience in the surgical treatment of aortic stenosis and in the management of structural heart disease. The evidence of this expertise is the observed to expected ratio of 0.68 in the surgical arm of the PARTNER trial, indicating better than expected surgical results in these high-risk patients. As a condition of participation in the trial, all centers had a multidisciplinary heart team in place managing all aspects of patient care, including patient evaluation and selection, implantation of the transcatheter valve, and post-operative care.

The multidisciplinary heart team consists of interventional and general cardiologists, cardiac surgeons, imaging specialists, anesthesiologists, and allied health personnel. In addition, each patient selected by the multidisciplinary heart team as candidates for TAVR therapy at the clinical sites were presented to a national committee that included a minimum of 2 experienced surgeons and interventional cardiologists who approved the patient's candidacy. All trial results were monitored and adverse events adjudicated by a separate and independent clinical events committee. The question therefore is: Can the results of this trial, which were obtained in centers of excellence with a significant supporting infrastructure of both personnel and facilities in place, be generalizable to other populations and other centers after commercial regulatory approval? If so, can the conditions present at the trial sites, which in all likelihood contributed to the excellent results, be replicated in the real world?

The American College of Cardiology (ACC) and the Society of Thoracic Surgeons (STS) are working together and with the other professional societies in the field to help promote the "rational dispersion" of this promising new technology into the United States. The goal of these initiatives is to help facilitate the replication of the excellent results of the PARTNER trial as well as those results obtained in clinical registries in Europe in commercial use in this country. It is hoped that in this way, this transformational technology can fulfill its great potential and positively affect the care of these very high-risk patients. These initiatives are multifaceted and address all aspects of clinical introduction (Table 1).

Table 1 Joint Initiatives of the Professional Societies to Facilitate the Safe and Effective Introduction of TAVR

Professional society overview of TAVR
Operator and institutional requirements for transcatheter valve repair and replacement
Expert consensus document on TAVR
National coverage determination request
TVT (Transcatheter Valve Therapy) national registry

TAVR = transcatheter aortic valve replacement.

Professional society overview of TAVR. Simultaneously, the ACC and the STS recently published a perspective of the field in their respective society journals (6,7). This overview provided recommendations for a pathway to optimize the clinical introduction of this technology. This path includes performance of the procedures by a multidisciplinary heart team, in valve centers of excellence, which have suitable facilities including hybrid operating rooms or modified catheterization laboratories with state-of-the-art imaging capabilities. In addition, centers need to be staffed by sufficient supporting personnel to provide the robust level of care needed by these frequently ill and debilitated patients. In this joint document, it is also recommended that centers should have access to adequate numbers of patients with valvular heart disease in order to provide sufficient procedural volume and cadence to maintain proficiency. The emphasis in new centers should be on building programs, similar to transplant programs, and not just on performing procedures. Furthermore, the overview recommends mandatory participation in a newly constructed national transcatheter valve registry, which will be described in more detail here.

Operator and institutional requirements for transcatheter valve repair and replacement. This is a 4-society guideline document led by the Society of Catheterization and Angiographic Intervention and includes the American Association for Thoracic Surgery, the ACC, and the STS (8). This document outlines recommendations for structural cardiology and valve surgery operator and center requirements to be able to qualify for access to TAVR technology (Table 2). The goal of the guidelines is to provide criteria that maximize the opportunity to provide safe and effective dispersion of TAVR into new centers, yet not restrict access to care for patients in need of this therapy. It is estimated that approximately 400 of the 1,150 cardiac centers in the United States that are currently performing AVR would meet these initial criteria. To date, an estimated 260 centers are performing TAVR in the United States.

Expert consensus document on TAVR. The 4 aforementioned societies in collaboration with 8 other societies in specialty fields participating in TAVR and related aspects have written a consensus document assessing all aspects of TAVR-related patient care (9). This document helps to define the current state of TAVR practice and frame the questions that need to be addressed as more experience is gained with this procedure.

Table 2 Recommendations for Operator and Institutional Requirements for TAVR

Intervention
Program—1,000 catheterizations/400 PCI per year
Operators—100 structural procedures lifetime or 30 L-sided structural procedures per year (60% should be BAV)
Surgery
Program—50 total AVR per year, of which at least 10 are high risk (STS score ≥6%)
Operators—100 AVR career, of which at least 10 are high risk (STS ≥6%) or 25 AVR per year or 50 AVR in 2 years (at least 20 in the last year before initiating TAVR)
Outcomes for continued certification for both new and existing TAVR programs applies to "inoperable" (PARTNER Cohort B) TAVR patients
30-day all-cause mortality <15%
30-day all-cause neurological events, including transient ischemic attack, <15%
Major vascular complication <15%
>90% institutional follow-up
60% 1-year survival rate for nonoperable patients
All cases must be submitted to a single national database

AVR = aortic valve replacement; BAV = bicuspid aortic valve; L-sided = left-sided; PARTNER = Placement of Aortic Transcatheter Valves; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

Joint educational programs for cardiologists and surgeons regarding transcatheter valve therapy. ACC and STS have also joined forces in an initiative to educate cardiologists, surgeons, and all members of the multidisciplinary heart team in all aspects of TAVR. The first course occurred in December 2011, and courses continued through April 2013. Although it is the responsibility of device manufacturers to effectively train operators in the safe and effective use of their specific device, the professional societies will provide educational opportunities in the broader field of aortic stenosis disease management.

National coverage determination. The ACC and the STS have worked closely with the Centers for Medicare & Medicaid Services (CMS) to request national coverage so that Medicare beneficiaries can undergo TAVR procedures (10). A uniform national coverage policy ensures that all patients who meet the criteria as set forth by the FDA label of the device will have access to appropriate care. It will also allow for the ability to evaluate TAVR use in "off-label" patients by a "coverage with evidence development" approach that will examine outcomes in "orphan" populations. The national coverage determination document was published in May 2012, and it indicates that CMS will reimburse for FDA-approved indications. Currently, the FDA-approved indication is for the treatment of severe, symptomatic aortic stenosis of the native aortic valve in inoperable patients (Table 3). It is intended that off-label use will be reimbursed by coverage with evidence development studies nested within the TVT (Transcatheter Valve Therapy) registry. The first of these investigational device exemption studies to examine outcomes in inoperable patients undergoing alternative access other than transfemoral approach procedures has recently been submitted by the professional societies and received approval by the FDA although that has recently been placed on hold by the societies. Two more investigational device exemption studies in other alternative access patients and in patients who have degenerated surgical bioprostheses and need "valve-in-valve" TAVR are currently in the submission process.

The TVT national registry. The 2 professional societies currently maintain robust clinical databases that capture procedural outcomes in patients undergoing catheter-based interventions and cardiac surgery. The ACC's NCDR (National Cardiovascular Data Registry), which contains over 7 million patient records, captures and analyzes outcomes in approximately 80% of the cardiac catheterization laboratories in the United States. The STS's Adult Cardiac Surgery Database, containing over 4 million patient records, tracks and analyzes outcomes from over 95% of the 1,150 U.S. institutions performing cardiac surgery. The 2 professional society databases have partnered

Table 3 Highlights of the NCD for TAVR

TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to an FDA-approved indication and when all of the following conditions are met:
The procedure has received FDA pre-market approval for that system's FDA-approved indication
Two cardiac surgeons have evaluated the patient's suitability for open AVR surgery
The patient is under the care of a heart team: a cohesive, multidisciplinary team of medical professionals
TAVR must be furnished in a hospital with the appropriate infrastructure that includes:
On-site heart valve surgery program
Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system
Qualifications to begin a TAVR program for heart teams without TAVR experience: The heart team must include:
Intervention
Program—1,000 catheterizations/400 PCI per year
Operators—100 structural procedures lifetime or 30 L-sided structural procedures per year (60% should be BAV)
Surgery
Program—50 total AVR per year, of which at least 10 are high risk (STS ≥6%)
Operators—100 AVR career, of which at least 10 are high risk (STS ≥6%) or 25 AVR per year or 50 AVR in 2 years (at least 20 in the last year before initiating TAVR)
The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intraoperative technical aspects of TAVR.
The heart team and hospital are participating in a prospective, national, audited registry.
TAVR is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study.
TAVR is not covered for patients in whom existing comorbidities would preclude the expected benefit from correction of the aortic stenosis.

FDA = U.S. Food and Drug Administration; NCD = national coverage determination; other abbreviations as in Table 2.

JACC Vol. 62, No. 17, Suppl S, 2013
October 22, 2013:S1–S10

with the FDA and CMS to create a new TAVR database, the STS/ACC TVT registry, which will capture outcomes from all TAVR procedures performed in the United States (11,12). As well as reporting 30-day procedural outcomes, the new database module will be linked to the CMS administrative database to track long-term outcomes of patients undergoing the procedure. Furthermore, by linking with the existing clinical databases, comparative effectiveness and cost-effectiveness research will be able to be performed comparing TAVR with both surgical AVR and medical therapy. The ultimate goal of creating this database infrastructure is to have a platform for the clinical experiences with new medical devices to be able to be collated from the initial regulatory trial submission through post-market surveillance and through the total life cycle of the device. This would then have the capability of performing post-market device surveillance of subsequent device iterations as well as other new devices in the same field. Potentially, this model could then serve as the prototype for the introduction of medical devices into other subspecialties of medicine. Participation in a national database by centers performing TAVR is a requisite for Medicare reimbursement. The STS/ACC TVT registry meets the eligibility criteria for CMS reimbursement. As of August 2013, 245 centers in the Unites States are enrolling patients in the registry, with over 8,000 patient records captured to date.

Summary

The professional societies working closely together believe that this collaborative approach will set a new standard for the safe and rational dispersion of new technology and harken a new era in the field of cardiovascular disease management. The 2 specialty areas of cardiology and cardiac surgery have not always seen "eye-to-eye" over the years regarding issues of patient management. It is hoped that by expanding the multidisciplinary heart team approach, which has proven to be so successful in the introduction of TAVR in clinical trials in the United States and elsewhere in the world, to a more global approach, better patient-centric care and optimization of outcomes in an expanding number of patients will result.

Reprint requests and correspondence: Dr. Michael J. Mack, Heart Hospital Baylor Plano, 1100 Allied Drive, Plano, Texas 75075. E-mail: michael.mack@baylorhealth.edu.

From the *Department of Cardiovascular Surgery, Heart Hospital Baylor Plano, Baylor Health Care System, Plano, Texas; and the †Department of Cardiology, Mayo Clinic, Rochester, Minnesota. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
2. Smith CR, Leon MB, Mack MJ, et al., for the PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
3. Makkar RR, Fontana GP, Jilaihawi H, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.
4. Kodali SK, Williams MR, Smith CR, et al., for the PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.
5. U.S. Food and Drug Administration. 2011 Meeting Materials of the Circulatory System Devices Panel. 2011. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm280840.htm. Accessed August 28, 2013.
6. Holmes DR, Mack MJ, Writing Committee. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. Ann Thorac Surg 2011;92:380–9.
7. Holmes DR, Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:445–55.
8. Tommaso CL, Bolman RM 3rd, Feldman T, et al. Multisociety (AATS, ACCF, SCAI, and STS) expert consensus statement: operator and institutional requirements for transcatheter valve repair and replacement, part 1: transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:2028–42.
9. Holmes DR Jr., Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1200–54.
10. Centers for Medicare and Medicaid Services. Available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NcaName=Transcatheter%20Aortic%20Valve%20Replacement%20%28TAVR%29&bc=AiAAAAAAIAAA&NCAId=257&. Accessed August 29, 2013.
11. STS/ACC TVT Registry. Home page. Available at: www.tvtregistry.org. Accessed August 29, 2013.
12. Carroll JD, Edwards FH, Marinac-Dabic D, et al. The STS-ACC Transcatheter Valve Therapy National Registry: a new partnership and infrastructure for the introduction and surveillance of medical devices and therapies. J Am Coll Cardiol 2013;62:1026–34.

Perspective: Real-World Considerations

John Webb, MD, Alain Cribier, MD†*

Which patients should be considered candidates for transcatheter aortic valve replacement (AVR)? One possible answer is those patients for whom transcatheter AVR is better in terms of duration or quality of life than the alternatives.

Duration of Life

Medical management is a poor option for most symptomatic patients with severe aortic stenosis; for such patients who are refused surgery due to comorbidities, mortality may reach 50% by 1 year (1). In the randomized PARTNER (Placement of Aortic Transcatheter Heart Valves) Cohort B trial (Transfemoral TAVR vs. Medical Management) trial, there was an absolute 20% reduction in mortality at 1 year as compared with mortality for medical management (1). By 2 years, this survival advantage had increased to 25%. This represents a proven survival benefit more dramatic than surgery for left main disease, reperfusion therapy,

implantable defibrillators, or pretty much anything else cardiac medicine has to offer.

Transcatheter AVR is the *only* therapy shown in a randomized trial to reduce mortality in any group of patients with aortic stenosis (Fig. 1) (1,2). What about open heart surgery—the gold standard for management of aortic stenosis? There are no randomized trials comparing surgical AVR to medical management, although admittedly long experience provides a solid basis for recommending surgical AVR to patients with symptomatic aortic stenosis. But realistically, many patients refuse or are refused as candidates for open surgery, often for good reason.

What then of an operable patient with comorbidities, but in whom surgical risk is very high? From the PARTNER (Placement of Aortic Transcatheter Heart Valves) Cohort A trial (TAVR vs. Surgical AVR) trial, we now have a direct comparison of surgery to transcatheter AVR (3). Was this comparison representative of the best that transcatheter and surgical AVR can offer? The simple answer is no. Some of the best surgical programs were compared with transcatheter programs that were still learning how to perform a complex and immature transcatheter procedure with first-generation technology. Despite this, transcatheter AVR handily met the tests for "noninferiority" in terms of mortality (3.4% vs. 6.5% with surgery, $p = 0.07$), establishing it as a valid alternative to surgery in high-risk patients (Fig. 2).

Were the 2 therapies really "equivalent?" Examine the "as-treated" analysis that compared mortality 30 days after the procedure (as opposed to after randomization) with what is now generally agreed to be the preferred, less invasive transcatheter procedure: transarterial access via the femoral artery. It is hard not to notice that transarterial AVR mortality was less than one-half that of surgical AVR (3.7% vs 8.2%, $p = 0.046$) (1).

Transcatheter mortality and morbidity will likely continue to fall as the procedure and technology mature. By way of example, in the initial PARTNER 1B experience, major vascular complications—a major driver of mortality—occurred in 16.8% of patients. Subsequently in the larger European SOURCE XT (Sapien XT Aortic Bioprosthesis Multi-Region Outcome Registry), this rate fell to 6.7% with low-profile systems, improved screening, and experience. With even lower-profile valve delivery systems, many experienced centers are finding that major vascular complication rates are falling into the low single digits (4).

Quality of Life

Symptoms, functional status, and health-related quality of life can be dramatically improved with transcatheter AVR (1,3). As compared with surgery, a transcatheter procedure offers earlier functional improvement, less bleeding, less atrial fibrillation, less renal failure, earlier mobilization, a shorter intensive care and hospital stay, and reduced rehospitalization (3,5). For inoperable patients, transcatheter AVR has an incremental cost-effectiveness ratio comparable to other therapies generally considered acceptable economically. In high-risk operable patients, costs are comparable to surgery, although in intermediate- and low-risk operable patients, transcatheter AVR may be too costly (6–8). However, it is reasonable to expect that the costs of transcatheter AVR may parallel the ongoing procedural improvements, reductions in complications, hospital stay, and increased market competition.

The systolic performance of current transcatheter valves is comparable or superior to that of surgical valves (4). Paravalvular leaks are common, although most are mild and well tolerated. Admittedly, even milder leaks are associated with poorer late survival, although a cause and effect relationship is speculative (9). For the most part, post-procedural paravalvular regurgitation is less than pre-procedural valvular regurgitation (10). Ongoing improvements in prosthesis sizing, positioning, and design are likely to mitigate this concern (11).

Admittedly, long-term durability remains unproven. However, with a decade of clinical experience we can be confident that durability is adequate for the high-risk population currently being treated (12). Although we cannot yet know whether durability will match that of the best surgical valves, it is likely to be comparable to that of many widely used surgical valves. Importantly, favorable experience with valve-in-valve implants suggests that the procedure might be more easily repeated than surgery would be (13).

But what about stroke? Embolic stroke may occur with both transcatheter and surgical AVR. However, for inoperable patients, as in the PARTNER Cohort A trial, stroke risk was overwhelmed by survival benefit. The combined risk of death or persistent disability due to stroke was dramatically lower with transarterial AVR than with medical therapy (1). True, for operable patients, as in the PARTNER 1A trial, early strokes were more frequent after transcatheter as opposed to surgical AVR (14). However, over 1, 2, and 3 years, the combined risk of death and/or persistent neurological disability was actually lower with transarterial than with surgical AVR (1,3), and by 3 years, there were actually fewer strokes in the transcatheter AVR group (9). Subsequent experience in multiple registries suggest that stroke risk is falling with the development of improvements in patient selection and technique (5).

Adoption

Industry estimates indicate that adoption of transcatheter AVR has been rapid in Europe since it was first approved in 2007; implants increased 25% in 2011 alone. Germany, Austria, and Switzerland led with rates of 76 to 96 per million inhabitants followed by France, Italy, and the United Kingdom. Even so, a low penetration rate of 17.9% suggests that the procedure remains underutilized in high-risk surgical patients (15). Variable rates appeared to bear a relationship to healthcare spending per capita, transcatheter AVR–specific reimbursement systems, and national restrictions on the number of implanting centers (15).

JACC Vol. 62, No. 17, Suppl S, 2013
October 22, 2013:S1–S10

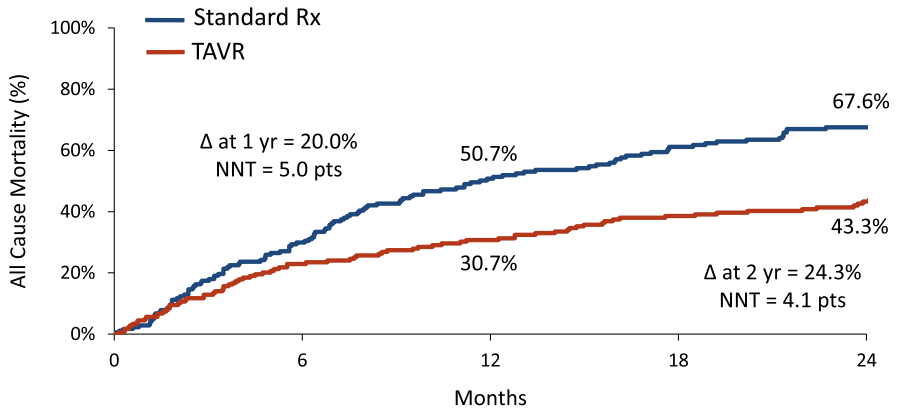

Figure 1 **Event Rates for Death or Stroke with Disability in PARTNER Cohort B**

The PARTNER Cohort B study compared transcatheter aortic valve replacement with conventional medical management in "inoperable" patients. Such a severely ill patient might reasonably ask: What were the chances of being alive in a year without any disability due to stroke in this very early experience? The answer was: about 49% with medical management, but about 67% with the transcatheter procedure (1). NNT = number needed to treat; Rx = treatment.

Adoption rates in the United States, after becoming the 43rd country to approve transcatheter AVR, have trailed Europe. This has largely been due to ongoing regulatory and, more recently, reimbursement concerns. According to industry estimates, approximately 60,000 patients undergo aortic valve surgery each year, and many more are not referred, not accepted, or decline surgery (16). These patients, along with the approximately 10% of surgical candidates that can be considered "very high-risk," represent a very large number of individuals for whom a potential for benefit is clear. The ongoing PARTNER II (Placement of Aortic Transcatheter Valves II) and SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) trials may extend this level of evidence to an additional 20% of patients at intermediate surgical risk. It is difficult to know when, if ever, we will see randomized evaluations in the great bulk (~75%) of patients who are at "low surgical risk." Nevertheless, a definite shift in practice is already evident as the focus shifts from mortality differences to what many physicians and patients believe is a clear potential to reduce morbidity with a less invasive procedure.

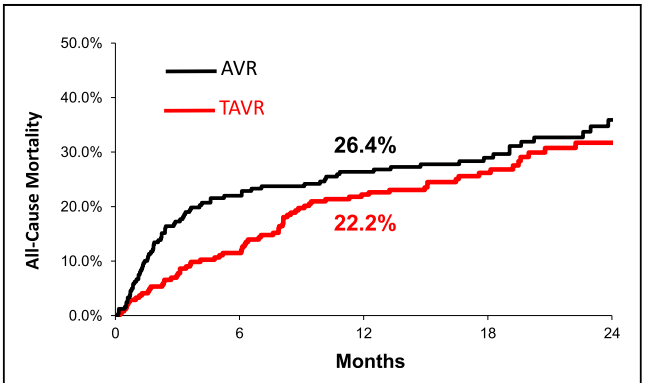

Figure 2 **Event Rates for Death in the PARTNER 1A Trial**

The PARTNER 1A trial compared transarterial transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (AVR) in high-risk operable patients (3). A patient might reasonably ask: "What were chances of being alive in a year?" The answer was: 73.6% with surgery and 77.8% with the transarterial procedure, but with less morbidity and an additional risk of about 1% of being left with disability due to stroke. It seems likely that a patient with fewer comorbidities and with access to newer TAVR devices and a more mature procedure might fare much better.

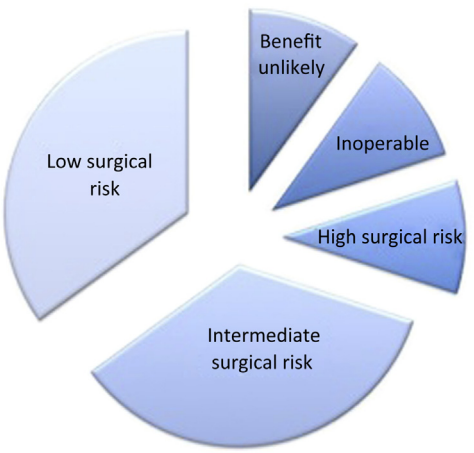

Figure 3 **Which Patients With Severe Symptomatic Aortic Stenosis Should Consider TAVR?**

Currently, patients at low surgical risk should undergo surgery. Intermediate-risk patients should also be offered surgery, although transcatheter aortic valve replacement (TAVR) can, in selected patients, be a reasonable alternative in centers with good outcomes. High-risk surgical patients should be evaluated case by case; many will do better with TAVR. Patients declined surgery should be offered TAVR unless excess comorbidities make benefit unlikely.

Perhaps more difficult and controversial than deciding who might benefit from transcatheter AVR is deciding who will not. It is increasingly apparent that costly and invasive therapies in patients with very severe comorbidities or extreme age sometimes offer little real chance of benefit. It appears that multidisciplinary oversight will be needed to ensure that poorly-selected patients with little chance of benefit are not exposed to futile interventions (Fig. 3).

So, how should transcatheter AVR be disseminated? In the United States, there are over 1,000 cardiac surgical centers, with an annual average of only 60 AVR per center and a concerning average of only 8 per surgeon (16). Neither transcatheter nor surgical AVR is ever truly a "low-risk" procedure. Regional centers with a high volume of cases and-multidisciplinary teams are more likely to achieve optimal outcomes (16). The implication is that there should be fewer full service cardiac programs, offering both surgical and transcatheter AVR in a more efficient and responsible manner.

Summary

The issues are complex, and the risks associated with transcatheter AVR are significant. Nevertheless, the evidence is mounting that transcatheter AVR will assume a mainstream, and possibly a dominant, role in the management of aortic stenosis.

Reprint requests and correspondence: Dr. John Webb, St. Paul's Hospital, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6, Canada. E-mail: John.webb@vch.ca.

From the *Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; and the †Service de cardiologie, Hopital Charles-Nicolle, Universite de Rouen, Rouen, France. Drs. Cribier and Webb have reported that they are consultants to Edwards Lifesciences Inc.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
2. Jilaihawi H, Chakravarty T, Weiss RE, Fontana GP, Forrester J, Makkar RR. Meta-analysis of complications in aortic valve replacement: comparison of Medtronic-CoreValve, Edwards-Sapien and surgical aortic valve replacement in 8,536 patients. Catheter Cardiovasc Interv 2012;80:128–38.
3. Smith CR, Leon MB, Mack MJ, et al., for the PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
4. Toggweiler S, Gurvitch R, Leipsic J, et al. Percutaneous aortic valve replacement: vascular outcomes with a fully percutaneous procedure. J Am Coll Cardiol 2012;59:113–8.
5. Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. J Am Coll Cardiol 2012;60:483–92.
6. Reynolds MR, Magnuson EA, Lei Y, et al., for the PARTNER Trial Investigators. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation 2011;124:1964–72.
7. Reynolds MR, Magnuson EA, Wang K, et al., for the PARTNER Trial Investigators. Cost effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the PARTNER trial (Cohort B). Circulation 2012;125:1102–9.
8. Cohen D, Reynolds M, Magnuson, et al., for the PARTNER Trial Investigators. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER trial (Cohort A). J Am Coll Cardiol 2012;60:548–58.
9. Kodali S, Williams M, Smith CR, et al., for the PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.
10. Makkar RR, Fontana GP, Jilaihawi H, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.
11. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol 2013:1125–36.
12. Toggweiler S, Humphries KH, Lee M, et al. 5-year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:413–9.
13. Webb JG, Dvir D. Transcatheter aortic valve replacement for bioprosthetic aortic valve failure: the valve-in-valve procedure. Circulation 2013;127:2542–50.
14. Miller DC, Blackstone EH, Mack MJ, et al., for the PARTNER Trial Investigators and Patients, PARTNER Stroke Substudy Writing Group and Executive Committee. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg 2012;143:832–843.e13.
15. Mylotte D, Osnabrugge RL, Windecker S, et al. Transcatheter aortic valve implantation in Europe: adoption trends and factors influencing device utilization. J Am Coll Cardiol 2013;62:210–9.
16. Holmes DR Jr., Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:445–55.

Commentary: An Evolutionary Decade

Susheel K. Kodali, MD,† Mathew R. Williams, MD,*† Martin B. Leon, MD*†*

Over 60,000 transcatheter aortic valve replacement (TAVR) procedures have been performed worldwide using either the balloon-expandable Edwards Sapien (Edwards Lifesciences, Irvine, California) or the self-expanding Medtronic CoreValve (Medtronic Corporation, Minneapolis, Minnesota) transcatheter heart valve systems. Most of the clinical data are in the form of prospective or retrospective case registries, which have been useful in providing "real-world" clinical outcome experiences, but they lack scientific rigor. Recent efforts by the Valve Academic Research Consortium have helped to standardize endpoint definitions that will facilitate ongoing efforts to accurately report and compare study findings (1,2).

The most robust evidence-based medicine TAVR data comes from the randomized PARTNER (Placement of Aortic Transcatheter Valves) trial, which compared standard-of-care therapies to TAVR using the Edwards Sapien valve in high-risk or inoperable patients with severe symptomatic aortic stenosis (AS) (3,4). The data clearly demonstrates improved survival with TAVR versus standard therapy for inoperable patients and equivalent survival

JACC Vol. 62, No. 17, Suppl S, 2013
October 22, 2013:S1–S10

with TAVR versus surgery in high-risk operable patients. Important concerns regarding periprocedural TAVR complications, including vascular and neurological events, were also raised in the PARTNER trial. After TAVR, compared with surgery, patients recovered more quickly with earlier improvement in symptoms and quality-of-life measures as well as reduced in-hospital length-of-stay and resource consumption (5,6). A PARTNER trial cost-effectiveness substudy demonstrated a cost of $50,000 per-life-year gained with TAVR, which is similar to many approved medical therapies (7) and was comparable to surgery.

The 2-year follow-up results were published last year for both arms of the PARTNER trial (8,9). In the inoperable patients, TAVR showed impressive incremental survival benefit between the first and second year after the index procedure. However, in patients with extreme comorbidities (Society of Thoracic Surgeons scores >15%), the mortality benefit of TAVR versus standard therapy was diminished, suggesting questionable value of performing TAVR in such patients. Compared with surgery in high-risk patients, TAVR had similar mortality at 2 years and similar prosthetic valve function without evidence of structural valve deterioration. There was no late hazard for increased neurological events with TAVR versus surgery after the initial periprocedural period. Importantly, echocardiography analyses revealed that even mild paravalvular aortic regurgitation following TAVR was associated with significantly higher 2-year mortality. This finding will require further analysis, but undoubtedly, efforts must be directed to reduce paravalvular aortic regurgitation after TAVR in the future.

There are several limitations of the PARTNER trial that should be acknowledged. First, PARTNER represented the initial experience with TAVR for the majority of investigator sites, using an early version of the device. Some of the outcomes may have been negatively affected by operator inexperience and/or suboptimal device performance. For instance, there were 30% higher vascular complications in transfemoral TAVR patients comparing the earlier inoperable cohort versus the later high-risk cohort. Second, the transapical TAVR arm was underpowered and could not be directly compared with surgery. Finally, valve durability assessments of this new transcatheter bioprosthesis will require extended follow-up beyond 2 years.

As operator experience increases and next-generation devices become available, outcomes following TAVR will continue to improve. Recently, data were presented from the PARTNER 2 trial comparing the Sapien XT to the Sapien transcatheter heart valve for inoperable patients (10). Mortalities were equivalent with the 2 devices, but vascular complications were significantly less with the Sapien XT device, which uses a smaller introducer sheath. Data from these and other randomized trials such as the recently completed CoreValve U.S. Pivotal Trial will add to the body of knowledge regarding outcomes after TAVR and help define the patient population that may benefit from this "transformative" therapy.

Patient Selection

Around the world, TAVR has been available for clinical use in severe AS patients who are either inoperable or at high risk for surgery. Clearly, operative risk assignment is a continuum, and discrete categories of risk severity are somewhat subjective. For instance, the so-called inoperable patient category in PARTNER was based upon a newly constructed definition representing the consensus of executive committee physicians: a >50% chance of death or irreversible morbidity after surgery. Our surgical colleagues were charged with the responsibility to declare that without the availability of TAVR, a given patient would not be a suitable candidate for surgery. Clearly, determination of risk is challenging and requires a multidisciplinary heart team, including clinical cardiologists, cardiac surgeons, imaging specialists, and interventional cardiologists. In particular, surgical input is critical to define operative risk categories. In the carefully regulated environment of the PARTNER trial, all patients were seen by 2 surgeons and then presented on a national web-based conference call with other surgeons and interventional cardiologists to adjudicate the risk assessment. Rigorous oversight is not feasible outside of a clinical trial environment. Although risk scores provide useful guidelines (e.g., Society of Thoracic Surgeons score), they do not capture many of the important variables affecting operative risk, including clinical conditions (e.g., frailty, severe chronic obstructive pulmonary disease, dementia, and hepatic disease) and anatomic factors (e.g., porcelain aorta, "hostile" chest, and vulnerable internal mammary implants). Therefore, risk categories ultimately must be assigned by an experienced multidisciplinary team familiar with the subtleties of patient screening. The development of a coordinated risk screening process is crucial in TAVR patient selection. Moreover, risk assessment cannot be standardized and will vary based upon the previous experiences and biases of a specific physician team at a particular clinical site.

Presently, TAVR should be considered the procedure of choice for high-risk patients with symptomatic AS who are not suitable candidates for surgery, have an expected survival of at least 1 year, and fulfill anatomic criteria for the available devices. In the high-risk operable category, TAVR is "noninferior" to surgery and should be considered an alternative to AVR in carefully selected patients. It is important to recognize that most of these high-risk patients are elderly (>80 years of age), and the benefits of TAVR must be viewed beyond crude mortality metrics and should extend to the value of earlier recovery and quality-of-life measures. In PARTNER, shortened intensive care unit and hospital stays and earlier recovery with reduced symptoms compared with those of conventional surgery were meaningful benefits, especially in elderly patients. In addition, concerns of long-term valve durability are less significant in elderly patients with more limited life expectancies. Discipline in the patient selection process also requires identifying the category of

futile patients, wherein despite a successful TAVR procedure, patients experience little improvement in symptoms or survival. Severe frailty, moderate or severe dementia, severe chronic obstructive pulmonary disease, and severe congestive heart failure unrelated to concomitant AS are examples of conditions that may shift patients from the inoperable to the futile categories. Such patients may be palliated with balloon aortic valvuloplasty to diminish symptoms, but definitive treatment with TAVR should be judiciously withheld.

Several caveats must be considered in this challenging patient selection process. Patient choice and referring physician preferences must be respected but discounted in importance during patient screening for TAVR. Significant downward "risk drift" should be actively discouraged, especially in the subgroup of AS patients who are at low or intermediate risk for surgery. Ongoing randomized clinical trials in intermediate-risk patients (PARTNER 2 and SURTAVI [Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement]) should provide evidence-based clarification for TAVR treatment possibilities in these patient subgroups. Some degree of "risk shift" over time is understandable and appropriate in high-risk patients, as we have gained worthwhile clinical judgment based upon earlier TAVR clinical research. For instance, the previous rigorous criteria for inoperable patients have been softened somewhat, considering the group knowledge acquired over the past 5 years. In clinical practice, many high-risk patients fall outside the parameters of a carefully regulated clinical trial. There are patient groups that would potentially benefit from TAVR, but are unlikely to be studied in a randomized trial, including the following: 1) patients with chronic kidney disease; 2) patients with a degenerated surgical bioprosthesis (so-called valve-in-valve TAVR); 3) patients with low-flow, low-gradient AS; and 4) patients with treatable malignancies or hepatic failure who require definitive AS therapy before concomitant conditions can be managed. TAVR should not be withheld in such patients, but the data should be captured in a universal TAVR treatment database.

Technology Dispersion

Perhaps an even greater challenge is how to incorporate this transformative technology into widespread clinical practice and maintain the excellent results seen to date. Clearly, TAVR requires a different advanced skill set that may not be possessed by many surgeons or interventional cardiologists. Current trainees may have had the opportunity to gain experience with TAVR in selected clinical trial centers, and there is an emergence of dedicated fellowships in structural heart disease. However, this is a nascent training process and such fellowships or tutorials are limited in number and lack uniformity. Moreover, busy clinical practitioners (surgeons and interventionalists) usually are without sufficient time and ready availability for an extended training experience. As such, intensive short-term training courses have been devised that incorporate the following components: 1) guidance in forming a heart valve team; 2) didactic lectures on technical, clinical, and procedural considerations; 3) simulation models with hands-on access to treatment devices; 4) imaging workshops including echocardiography and multislice computed tomography; 5) case presentations with direct feedback to refine the patient selection processes; 6) case proctoring by experienced operators for as long as is necessary before certifying a site as independent to perform TAVR procedures.

Considering the complexity of this training process, the inherent challenges of forming a cohesive heart valve team at each institution, and the case volume requirements to establish and maintain optimal proficiency with TAVR, it would be unacceptable to allow widespread dissemination of this technology to the majority of surgical and interventional programs in the United States. Last year, the Society for Cardiovascular Angiography and Interventions/American Association for Thoracic Surgery/American College of Cardiology Foundation/Society of Thoracic Surgeons published a consensus document listing guidelines for both physicians and facilities who desire to participate as TAVR centers (11). These guidelines are analogous to a credentialing process for operating physicians as well as institutions on a national scale, not dissimilar to certification of heart transplant or left ventricular assist device programs. This society-driven operator and site certification concept has advantages and disadvantages. From a positive standpoint, developing minimal performance criteria and uniform standards to help ensure patient safety and optimal TAVR efficacy is laudable and should be commended. Importantly, consensus criteria will help to impart a sense of "fairness" in the site selection process and will defuse potential biases associated with a sole sponsor-driven process. However, there are numerous unforeseen political and logistic ramifications of an overly rigid and/or conveniently simplistic schema developed by either societies or the Centers for Medicare and Medicaid Services. For instance, regional geographic availability to TAVR centers for patients must be a consideration that overrides to some degree absolute case volume requirements. Competition among centers in urban areas may be problematic, wherein a binary decision to allow or prohibit TAVR therapy at selected sites will undoubtedly disadvantage the future viability of many well-respected surgical or interventional programs. Case volume metrics may be a crude measure of quality and team skills, because we have observed that many high-volume centers lack the coordination and resolve to function as a cohesive heart valve team. Furthermore, younger physician operators (both interventionalists and surgeons) may be deficient in overall case volumes but are ideally suited to help lead a TAVR team based upon advanced imaging capabilities, recent TAVR training experiences, and a dedication to the heart team culture. Thus, a more flexible in-depth approach to operator and site selection is preferred, taking into account some of the aforementioned subtleties, such

JACC Vol. 62, No. 17, Suppl S, 2013
October 22, 2013:S1–S10

that worthwhile physician operators and institutions are not summarily excluded.

From our vantage point, having been involved in clinical TAVR procedures for almost 7 years, having performed over 800 TAVR implants, and having trained a significant number of the PARTNER and early commercial U.S. TAVR sites, we believe that 5 requirements are essential for TAVR site selection and successful activation. First and foremost, a multidisciplinary heart valve team must be established and functional before beginning TAVR procedures. The team members (including physician and nonphysician healthcare professionals) are charged with developing a treatment care strategy for each patient, which spans the range from case screening, decisions on the optimal treatment, procedural details, and to post-therapy management, including support services in and out of hospital. The establishment of an integrated heart valve team is the most difficult step in the TAVR process and a priori is the most difficult to assess during site evaluations. Second, a site must have the institutional infrastructure support to manage a TAVR program. Investment by hospital administration in the optimal procedure venue (often a hybrid operating room/catheterization lab in the United States), ancillary staff (including nurse coordinators), and intensive care unit facilities are an absolute necessity to manage elderly comorbid patients with severe AS. Third, the heart valve team members must have the necessary blend of experience and facility with novel technologies to manage the vagaries of learning a complex and changing device platform. This "necessary blend" incorporates the notion of sufficient case volume combined with advanced skills in high-risk patients from the surgical, interventional, and imaging representatives of the team. Fourth, all sites should enthusiastically embrace clinical data collection and participation in the national TVT (Transcatheter Valve Therapy) database. These data will be irreplaceable to benchmark performance standards, determine adherence to accepted case selection criteria, monitor and/or discover procedure- and device-related complications, and provide the substrate for reimbursement decisions now and in the future. Finally, there is an "X" factor that distinguishes the best performing TAVR sites. Optimal TAVR requires a level of individual and institutional dedication and commitment, unlike most other surgical or interventional procedures. Thus, a site culture must rapidly evolve that exudes the intensity and passion of having access to this new life-saving therapy.

Summary

In the past decade, TAVR has clearly changed the treatment algorithm for patients with AS. The careful and thoughtful expansion of TAVR in clinical practice will require evidence-based medicine validation in the form of clinical research. Ongoing trials with newer devices and in different patient populations will better define the role for TAVR over the next decade. Regulation of TAVR (use and abuse) on a national scale will affect, not only the role of TAVR, but also the landscape for surgical programs in the future.

Reprint requests and correspondence: Dr. Susheel K. Kodali, Columbia University Medical Center, New York–Presbyterian Hospital, 161 Fort Washington Avenue, 6th Floor, New York, New York 10032. E-mail: skodali@columbia.edu.

From the *Columbia University Medical Center/New York–Presbyterian Hospital, New York, New York; and the †Cardiovascular Research Foundation, New York, New York. Dr. Kodali has received honoraria for his service on the Steering Committees of Edwards Lifesciences and the Scientific Advisory Board of Thubrikar Aortic Valve, Inc. Dr. Williams has received consulting fees from Edwards Lifesciences and Medtronic. Dr. Leon has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.
2. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.
3. Leon MB, Smith CR, Mack M, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
4. Smith CR, Leon MB, Mack MJ, et al., for the PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
5. Reynolds MR, Magnuson EA, Lei Y, et al., for the PARTNER Trial Investigators. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol 2012;60:2683–92.
6. Reynolds MR, Magnuson EA, Wang K, et al., for the PARTNER Trial Investigators. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;60:548–58.
7. Reynolds MR, Magnuson EA, Wang K, et al., for the PARTNER Investigators. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (Cohort B). Circulation 2012;125:1102–9.
8. Kodali SK, Williams MR, Smith CR, et al., for the PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.
9. Makkar RR, Fontana GP, Jilaihawi H, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.
10. Leon MB. A randomized evaluation of the SAPIEN XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER 2, inoperable cohort. Paper presented at: American College of Cardiology Scientific Sessions (ACC) 2013, March 10, 2013, San Francisco, CA.
11. Tommaso CL, Bolman RM 3rd, Feldman T, et al. Multisociety (AATS, ACCF, SCAI, and STS) expert consensus statement: operator and institutional requirements for transcatheter valve repair and replacement, part 1: transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:2028–42.

Key Words: cardiac surgery ■ clopidogrel ■ CYP2C19 ■ genetics ■ interventional cardiology ■ platelet function ■ prasugrel ■ ticagrelor ■ transcatheter aortic valve replacement.