Coronal oblique CT views of aortic root (left) and three-dimensional volume-rendered image (right) of the ascending aorta in an male patient 2 weeks after transcatheter aortic valve replacement (TAVR) with a Medtronic CoreValve®. The CT was performed due to the suggestion of suspected paravalvular aortic regurgitation seen on a surveillance echo.

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The Methodist DeBakey Cardiovascular Journal editors wish to thank Neal Kleiman, M.D., and Michael J. Reardon, M.D., for serving as guest editors of this special issue on transcatheter aortic valve implantation. Both physicians have a long-tenured relationship with The Methodist Hospital and have played key roles in the leadership of the Methodist DeBakey Heart & Vascular Center (MDHVC). Kleiman and Reardon are principal investigators for Medtronic CoreValve® US Pivotal Trial at Methodist.

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INTRODUCTION TO TRANSCATHETER AORTIC VALVE IMPLANTATION

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Medical scientists and cardiologists in particular have always been excited about breakthrough technologies that offer new modalities for treating common diseases. In cardiac surgery, the advent of the heart-lung machine led to groundbreaking procedures such as valve repair and replacement, coronary artery bypass, and heart transplantation. Interventional cardiology as a field began in 1977 when Andreas Gruntzig first began the practice of balloon coronary angioplasty. Coronary stent placement in the 1990s and drug-eluting stent implantation in the 2000s took center stage in this field — and in cardiology in general. As complication rates declined precipitously and the indications for stent placement narrowed somewhat, interventional cardiologists searched elsewhere for new frontiers. The refinement of new imaging modalities such as echocardiography and magnetic resonance imaging focused attention on structural abnormalities of the heart. At the same time, an aging population made degenerative aortic stenosis a prime target for further therapeutic advances.

In an often-cited statement in his 1931 textbook of cardiology, Paul Dudley White wrote: “There is no treatment for aortic stenosis.” In an autopsy study of narrowed aortic valves, McGinn and White noted that the average duration between the onset of symptoms and death was approximately 1 year. However, surgical replacement of aortic valves in the 1960s altered the paradigm for management of this disease and led to nearly normal survival for postoperative patients after aortic valve replacement. By far, the most common etiology of aortic stenosis in patients older than 75 years is degenerative calcification of the valve. However, the major caveat of an open surgical approach is that to benefit from surgical aortic valve replacement, the patient must first survive the surgery. The issue of perioperative mortality and morbidity is particularly important in patients with degenerative aortic stenosis, as the frequency of the disease is age-dependent, ranging from about 2.4%, in patients between the ages of 75 and 84, to 7%, in men aged 85 or older. Obviously, the risk associated with open-heart surgery is higher in these patients than in those who are younger. Consequently, a substantial proportion of elderly patients with degenerative aortic stenosis do not undergo surgical valve replacement.

The advent of balloon aortic valvuloplasty in the 1980s led to novel thinking about catheter-based management of aortic valve disease. Originally derived from balloon dilation of the pulmonic valve in pediatric patients, this technique initially offered moderate symptom relief in patients who were not candidates for surgery. However, the results proved to be short lived, subsequent survival was dismal (< 25% at three years), and enthusiasm for the procedure waned. The advent of percutaneous valve replacement by Cribier — inspired by pulmonic valve implantations in late survivors of Tetralogy of Fallot corrections and first performed in a 57-year-old patient with a congenitally bicuspid aortic valve — led to the gradual development of more user-friendly valves and broader application of their use.

In 2010, the PARTNER cohort B study treated 358 otherwise inoperable patients suffering from critical aortic stenosis with transcatheter valve replacement (TAVR). Compared with medical therapy, TAVR saved one life at the end of a year for every five patients treated. By the end of the second year, the number needed to treat had fallen to four. These findings ignited enthusiasm for this procedure and assured it of a place in the mainstream of modern cardiac interventions. One valve is currently approved in the United States for use in this population (Edwards SAPIEN), another valve is undergoing clinical trials (Medtronic CoreValve®), and two more are about to enter clinical trials. In Europe, three different valves are approved for clinical use. Investigators and regulatory authorities are currently evaluating expansion of the TAVR population to include patients in lower-risk categories who might otherwise undergo surgical aortic valve replacement albeit at higher-than-average risk.

This issue of the Methodist DeBakey Cardiovascular Journal includes contributions from a variety of internationally renowned experts who collectively have considerable experience in the historical development of TAVR and its evaluation and practice. Although the field has developed very rapidly and the use of TAVR has become accepted in extremely high-risk patients, there are hurdles that have yet to be surmounted before its use becomes more widespread. The learning curve for valve implantation is very steep. A recent report indicates that technical indicators of procedural success start to show improvement after about 30 procedures have been completed. Even among experienced practitioners, multiple sources indicate that residual aortic insufficiency occurs in a substantial proportion of patients and is associated with a high mortality. In addition, the single randomized trial comparing TAVR with surgical aortic valve replacement indicates a risk of stroke that is slightly higher in patients undergoing TAVR. Thus, the technique remains considerably more complicated than intracoronary stent placement and, although performed percutaneously, should still be regarded as a form of cardiac surgery.

In this issue of the Methodist DeBakey Cardiovascular Journal, we highlight the background, benefits, and economics of the TAVR/TAVI procedure and use both terms interchangeably depending on the author’s preference. The articles herein offer an overview for practitioners who are beginning or considering whether to begin a TAVR program.
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Keywords: transcatheter aortic valve implantation, TAVI, TAVR, aortic stenosis, aortic valve replacement, surgical valve repair, surgical aortic valve replacement, PARTNER trial

References


Abstract
Conventional aortic valve replacement (AVR) surgery has been in clinical use since 1960. Results, particularly in high-risk populations such as the very elderly and frail, continue to improve in response to the challenges posed by this growing segment of the patient population. Transcatheter aortic valve implantation (TAVI) is a fairly recent development, performed for the first time in 2002. The last decade has seen an exponential growth in the application of this technology in higher-risk populations. Results of recent randomized prospective trials demonstrate both the future promise and current problems of the TAVI approach. Many patients deemed inoperable for AVR have been treated successfully by TAVI. However, elevated procedural and late mortality rates, excessive early and late stroke, and a significant incidence of periprosthetic aortic valve insufficiency and patient-prosthesis mismatch all suggest caution in extending this technology to patients able to undergo conventional AVR with a low risk of early or late complications.

Introduction
The first successful surgical implantation of an aortic valve prosthesis was reported by Harken et al. in 1960. Many patients who had been terminally ill from aortic valve stenosis or insufficiency and unresponsive to medical therapy could now be restored to good health. Over the ensuing 50 years, numerous innovations and refinements of these early techniques and prostheses have been developed.

In 2002, Cribier reported the first transcatheter aortic valve implant (TAVI) in a human subject for treatment of calcific aortic stenosis. Since then, another era has opened for patients with critical calcific aortic stenosis (AS) who had been considered too ill for conventional surgical AVR. Now, a decade later, there is good evidence that TAVI represents a true treatment advance for AS patients who are considered too ill to undergo AVR. In these carefully selected patients, TAVI has produced a markedly improved survival and relief of symptoms. In the United States, TAVI using the Edwards SAPIEN device is now approved by the FDA for use in patients considered too sick for conventional AVR and who have a calcified aortic annulus.

Throughout its history, however, TAVI has been associated with the risk of five persistent major complications: high perioperative and late mortality, elevated early and late stroke rates; major vascular complications; patient prosthesis mismatch; and the occurrence of significant and progressive post-implant periprosthetic insufficiency. Additionally, the long-term natural history after TAVI of the progressive proliferative disease that causes calcific AS is unknown.

Results of the PARTNER Trial
The PARTNER trial represents the most definitive data available to compare TAVI with other therapies. The PARTNER Cohort B randomized prospective trial compared the results of TAVI in 179 patients considered to be surgically inoperable for AVR with standard medical therapy (including balloon aortic valvuloplasty if needed) in 179 similarly ill control patients. In the TAVI group, 30-day mortality was 6.4%. At 1 year the overall mortality for TAVI was 30.7% vs. 50.7% for standard therapy (P<0.0001). The overall stroke rate at 1 year was 10.6% vs. 4.5% for standard therapy.

• Bicuspid or noncalcified aortic valve
• Aortic annulus diameter (echo measurement) <18 mm or >25 mm
• Aortic dissection or iliac-femoral dimensions or disease precluding safe sheath insertion (especially calcification)
• Severe LV dysfunction (LVEF <20%)
• Untreated CAD requiring revascularization
• Severe AR or MR (>3+) or prosthetic valve (any location)
• Serum creatinine >3.0 mg/dL or dialysis dependent
• Acute MI within 1 month
• Upper GI bleed within 3 months
• CVA or TIA within 6 months
• Any cardiac procedure, other than BAV, within 1 month or within 6 months for DES
• Hemodynamic instability (e.g., requiring inotropic support)

Table 1. Key exclusion criteria for PARTNER trial. LV: left ventricular; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; AR: aortic regurgitation; MR: mitral regurgitation; MI: myocardial infarction; GI: gastrointestinal; CVA: cerebrovascular accident; TIA: transient ischemic attack; BAV: Balloon aortic valvotomy; DES: drug-eluting stent.
At 1 year the incidence of significant paravalvular leak was unchanged at 12.2% and the rate of relief of aortic stenosis in the TAVI group was stable. At 2 years of follow-up, the overall mortality was 43.3% for the TAVI patients and 67.6% for those receiving standard care. The stroke rate at 2 years had risen to 13.8% in the TAVI group and 5.5% in the standard group (P = 0.009). Of the 61 patients alive with echo data at 30 days and 2 years, the paravalvular AI with TAVI was improved in 42.6%, unchanged in 41%, and worse in 16.49%. Relief of severity of aortic stenosis was well maintained in the TAVI group at 2 years, with a mean gradient of 10.6 mm and aortic valve effective area of 1.68 cm². Thus the 2-year data from the Partner Cohort B study continues to confirm the view that TAVI should be seriously considered for patients who are not deemed operable with AVR and who fit the selection criteria of the PARTNER Cohort B trial, including the many exclusion criteria shown in Table 1. The very high early and late mortality and morbidity in some of the most severely ill of these already critically ill patients suggest that some patients may be too ill to even tolerate TAVI.

Cohort A of the PARTNER trial reported the role of TAVI as a replacement for conventional AVR in patients thought to be operable but who have a higher predicted risk for surgery. In addition to the exclusion criteria shown in Table 1, these patients were expected to have a score of at least 10% on the Society of Thoracic Surgeons risk model. The predicted surgical mortality for the patients enrolled was 11.8%. The results of this study documented an “as treated” 30-day mortality of 5.2% for TAVI and 8.0% for AVR, a nonsignificant difference (P = 0.15). Survival at 1 year was also similar: TAVI 24.2%, AVR 26.8% (P = 0.44). The stroke rate at 30 days was 5.5% for TAVI and 2.4% for AVR, a significant difference (P = 0.04), and at 1 year it was 8.3% vs. 4.3% (P = 0.04). At 30 days post-operatively, gradient reduction was similar, and significant periprosthetic leaks were present in 12.2% of TAVI patients vs. 0.9% for AVR.

The seriousness of the occurrence of moderate or severe regurgitation after TAVI was recently reported by Sinning et al. in 108 consecutive patients. At 2 years of follow-up, overall mortality was 31.4%. Patients with no residual aortic paravalvular regurgitation had a mortality of 18%; it was 31% with grade 1 and 67% with grade ≥2 aortic regurgitation. They concluded that moderate to severe periprosthetic aortic regurgitation is a strong predictor of adverse short and midterm outcome after TAVI. In the U.K. TAVI Registry report, moderate to severe aortic insufficiency was reported to be an important univariate and multivariate predictor of mortality at 1 year. Thus significant periprosthetic aortic insufficiency is established as a serious complication and occurs in a significant proportion of patients undergoing TAVI.

A little-noted but important problem in the design of the high-risk portion of the Cohort A PARTNER study was the inclusion of patients who had undergone previous coronary artery bypass surgery (CAB). Therapy by catheter does not involve a redo chest surgical procedure. The death rate at 1 year in the patients undergoing redo chest AVR after CAB was 19.1% (29 of 152), and the death rate in patients older than 85 years was 26.1%. These figures are high for surgical patients and disproportionately affected the overall surgical mortality. Stortecky et al. compared TAVI vs. AVR in patients with aortic stenosis and a previous CAB, and they reported a perioperative mortality for AVR after CAB of 2.5%. Thus, in terms of an unbiased comparison of TAVI and isolated aortic valve replacement for aortic stenosis, the CAB patients would have been better omitted.

### Results of Conventional AVR in Patients Similar to the PARTNER Trial Cohort A (High-Risk Group)

At the American Heart Association 2008 annual meeting, I reported on the risk of AVR in 1,223 of my patients, of whom 203 were older than 80 years of age. This data was updated in 2011 to include 1,514 patients operated on in our surgical service. Of these, 256 were over 80 years of age, and 92 of these patients underwent isolated AVR. These patients were similar to the PARTNER high-risk group in age, sex, pre-op ejection fraction, and severity of aortic stenosis. The perioperative mortality was 2.7% (3 of 92), and the perioperative stroke rate was 4.3% (4 of 92). The 1-year survival rate was 85% (Kaplan-Meier). There were no periprosthetic leaks. These outcomes indicate that in selected elderly patients treated in an experienced center, surgical results superior to those receiving AVR in the PARTNER trial high-risk cohort can be achieved with fewer late complications such as ongoing strokes and progressive aortic insufficiency.

### Current Intrinsic Limitations of TAVI

A comparison of the capabilities of TAVI vs. AVR is shown in Table 2. In our unselected total series of 1,514 AVR patients, only 44% had undergone an isolated AVR. The remainder have received concurrent CAB, ascending aortic aneurysm repair, or mitral or tricuspid valve surgery. While most patients had pure aortic stenosis, about one-third had some degree of aortic insufficiency, which is a contraindication to TAVI. AVR allows treatment of any size of aortic “annulus” because prosthetic valves are available up to a diameter of 33 mm.

Ascending aortic aneurysm surgery may be required in conjunction with AVR most commonly because of atherosclerotic degeneration, Marfan's syndrome, or aneurysmal disease from bicuspid aortic valve disease. The latter may be present in a significant proportion of these patients. Bicuspid aortic valve disease is currently considered to be a contraindication for TAVI because the single-slit opening may not conform to the circular shape of the deployed prosthesis. The aortic root and ascending aorta also tend to be larger in these patients.

### Comparison of Current Indications for TAVI vs. AVR

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Table 2. Differences in indications for TAVI vs. AVR. AS: aortic stenosis; AI: aortic insufficiency; MR: mitral regurgitation; CAB: coronary artery bypass; LV: left ventricular.
Patient-Prosthesis Mismatch (PPM)

The TAVI prostheses are designed to have maximal geometrical orifice area. This is achieved through direct attachment of the tissue leaflets to the stent and the absence of an external sewing ring. The Medtronic CoreValve has the leaflets attached above the “annular” fixation zone to further enhance the post-implantation effective orifice area (EOA). Despite these technical advantages, the EOA achieved by TAVI is intrinsically limited by the presence of the retained calcified aortic leaflets (which are not removed) and by the extent to which the calcified ascending aortic root and annulus can be safely dilated. In addition, the range of sizes currently available is limited.

Ewe et al. reported on data from a multicenter study in which 165 patients were evaluated for PPM. Studies were performed at baseline, before hospital discharge, and 6 months after TAVI. They found that 30 patients (18.2%) had an indexed EOA of <0.85 cm²/m². A substantially higher proportion of these patients with PPM did not show clinical improvement compared with those without PPM (36.7% vs. 1.5%, P <0.001). The major adverse cardiovascular- and valve-related events did not differ. In the PARTNER trial of TAVI vs. AVR for high-risk patients, data for PPM was not reported. However, postoperative aortic valve areas and gradients were slightly better for TAVI than AVR: 1.59 ± 0.48 vs. 1.44 ± 0.4 cm² (P = 0.002); 10.2 mm & 11.5 mm (P = 0.008). At 1 year, relief of symptoms was similar in both groups. The reported valve areas suggest that smaller prostheses were implanted in both groups. In addition to having no capability for aortic leaflet resection, TAVI has no capability for aortic root enlargement. Dacron patch graft angioplasty is commonly employed during AVR to enlarge small aortic roots at least one size to allow implantation of a larger conventional prosthesis.

At present, only biological prosthetic valves are available for TAVI. Mechanical valves are still considered the optimal choice in younger patients. While some patients who have experienced biological valve failure may have undergone “resleeving” procedures during a second TAVI procedure, it is currently not established as a standard therapy. Concurrent CAB was performed in 27% to 34% of our patients. Although angioplasty would be an option in some cases, many had diffusely calcified multivessel disease.

Finally, TAVI requires adequate peripheral arterial access. Peripheral vascular disease was noted to be present in 43% of the PARTNER trial patients.

Future Evolution of TAVI

Studies using new prostheses are attempting to overcome issues with vascular access by reducing the size of the unit that has to be introduced into the femoral artery. Thinner, steerable catheters designed to minimize contact with the aortic wall are also in development. TAVI systems that are easier to align and deploy, and can be redeployed if needed, will soon be available.

However, the current family of TAVI devices is still based on the concept of fixing the prosthesis in position by forceful dilatation and compression of the stentotic calcified aortic valve leaflet tissue. The material that must be present for this to be achieved is only available in the presence of calcific degeneration of the aortic valve, as seen in aortic stenosis; this is because the aortic valve has no annulus. AVR by surgical implantation involves resecting the diseased aortic leaflets, leaving a narrow rim at the base of the leaflet that consists of the junction of the leaflet with the aortic wall, aorto-mitral continuity, membranous septum, and the shoulder of the left ventricular myocardium. The left ventricular outflow tract begins at the lower margin of the anterior mitral leaflet and extends to where the aortic leaflets attach to the aortic wall and left ventricle; the posterior one-third to one-half consists of the aorto-mitral continuity and the anterior mitral leaflet. Thus, in the absence of the ring of calcified tissue seen with calcific aortic stenosis in the elderly, some other approach for prosthetic fixation will need to be developed.

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**Figure 1.** Aortic valve pathology. (A) Normal tricuspid valve. (B) Moderately severe calcific aortic stenosis. (C) Calcific stenosis of congenital bicuspid aortic valve. (D) Severe calcific aortic stenosis with left main coronary impingement (arrows). (E) Severe calcific aortic stenosis. (F) Rheumatic aortic stenosis with commissural fusion but no calcification of annulus or leaflets.

**Figure 2.** Severe calcific aortic stenosis (left) with radiographic study (right) showing the severe extent of calcium accumulation in the leaflets. (Modified from Edwards JE, An Atlas of Acquired Diseases of the Heart and Great Vessels, Vol. 1. Philadelphia: WB Saunders; 1961. Used with permission.)

**Figure 3.** Intraoperative appearance of severely insufficient TAVI showing the areas of nonopposition of the prosthesis with the aortic commissure due to severe calcification. Used with permission.
In the natural history of untreated calcific aortic stenosis, the size of the obstructing calcific masses progressively increases. The extent of these changes is shown in Figures 1 and 2. The disease is characterized by the formation of large exophytic masses. This material is unstable, and it is relatively easy to break off small pieces. Since the untreated disease induces death as the stenosis becomes critical, the ultimate natural history of the compressed and displaced leaflets is unknown. Data from the PARTNER trial at 2 years shows stable aortic gradients and areas; for the critically ill patients approved for treatment by the FDA, this may not be an issue at this time. However, if use of TAVI is expanded to younger patients with the expectation of a long survival, close observation will be required for monitoring of restenosis, stroke, and more periprosthetic leaks due to the unstable nature of this calcified material.

The serious problem of moderate to severe periprosthetic leakage after TAVI has been mentioned above. This occurs in some cases mainly because the implantation process is unable to turn the diseased orifice, which is trefoil or triangular in shape, into a circle to match the deployed prosthesis (Figure 3). The backwashing of blood across the calcified tissue has led to erosion of residual calcium and enlargement of periprosthetic leaks after conventional aortic valve replacement.

Undoubtedly, this problem will eventually be solved with a prosthesis or prosthetic annulus that is more conforming. It is now well recognized that some patients are unsuitable for TAVI because of the pathoanatomy of their calcified aortic roots and leaflets (Figure 1). Detailed preoperative CT studies of the aortic root are considered essential to avoid displacement into the coronary ostia of calcified masses (Figure 1 D).

**Clinical Perspective**

While TAVI has proven to be a valuable addition to the care of patients with “inoperable” aortic stenosis, it is important to note that the risk of conventional AVR surgery in these patients is declining due to a variety of factors. During preoperative patient selection and evaluation, there is a significant focus on assessing the patient’s frailty, neurocognitive reserve, and recent history of activity and independent living. The important concept of identifying patients “dying with” rather than “dying of” aortic stenosis has been proposed. It seems that in the future, TAVI will not be offered to some of the most severely ill patients who have had very short survival times despite successful TAVI. Screening is routinely performed for carotid and coronary atherosclerosis. Renal function is evaluated and optimized if possible, and pulmonary function is critically assessed. Intraoperative management has progressed considerably with regard to stroke avoidance and pulmonary complications. Myocardial protection and management of the significant diastolic dysfunction routinely seen in these patients is better understood.

Postoperative care has undergone a complete revolution in the last 10 years. Our patients receive care 24 hours a day by our in-house, full-time CV surgical intensivist team. This has led to superior management of the postoperative period. Programmatic goals to avoid ventilator-dependent pneumonia, ICU-acquired infections, sepsis, and excessive blood usage have all had incremental benefit. Aggressive and early management of hemodynamic instability with prompt availability of echocardiography has assisted these patients. Early mobilization, nutritional support, and a formal perioperative physical therapy program have aided recovery. Thus, significant improvements in care have lowered the historical morbidity and mortality of these elderly patients. The commitment to a collaborative team-based approach is essential for the care of these critically ill patients.

**Expansion of Indications for TAVI**

Expanding the role of TAVI from treatment of inoperable patients with aortic stenosis to other less-sick populations has been studied in two randomized prospective trials. In the PARTNER Cohort A trial for high-risk patients, described in detail above, the conventional AVR results were competitive with TAVI at 1 year in terms of mortality. However, excess stroke and paravalvular leaks remain a problem in TAVI patients. The ultimate magnitude of these problems and the risk of progressive aortic insufficiency will be answered by ongoing follow-up for the Cohort A, such as the 2-year data mentioned above for the Cohort B patients.

In a study of stroke after TAVI in 253 patients, Tay et al. showed that while the incidence of stroke was highest in the first 24 hours, it remained high for 2 months post-procedure. Proposed mechanisms for perioperative strokes included embolization of atheromatous or calcific debris and periprocedural hypotension. Later strokes were attributed to thrombus formation on the prosthesis or in periprosthetic spaces.

The STACCATO trial compared transapical TAVI with surgical AVR in elderly patients (mean age: TAVI 80 ± 3.6 and AVR 82 ± 4.4 years), all of whom had severe aortic stenosis but who were otherwise not at an elevated risk for surgical AVR. The mean STS score was 3.3. Of the original 200 patients planned to be enrolled, 70 patients were treated and then the trial was terminated by the Data Safety and Monitoring Board. Of the 70 patients, 34 underwent transapical TAVI and 36 underwent surgical AVR. The primary endpoint of all-cause mortality, stroke, and renal failure requiring dialysis was elevated in TAVI vs. AVR: 14.7% vs. 2.8%, P = 0.07. Death rate for TAVI was higher (8.8% vs. 0%) as was stroke (5.9% vs. 2.8%). The incidence of moderate/severe aortic insufficiency was 13% vs. 0%. The authors of this small trial concluded that in these lower-risk elderly patients, transapical TAVI may be inferior to surgical AVR. These surgical results resemble those obtained in our own series of elderly (>80 years) surgical AVR patients.

**Conclusion**

While TAVI seems like a low-risk and simple catheter-based therapy compared with surgical AVR, it is still in its developmental phase and should be considered a major intervention with the risks of serious early and late complications. It is of proven value in the care of patients considered to be inoperable because of extensive irreversible comorbidities or frailty. We feel that in experienced centers, conventional surgery is feasible in most patients despite advanced age. In our own data, age alone has not been a predictor of mortality, but rather mortality is associated with easily identifiable extensive comorbidities and frailty. It is generally agreed that patients should be seen for a surgical evaluation before a final decision is made to employ TAVI.

This recommendation is in agreement with that of the FDA, which has approved TAVI only for treatment of inoperable patients. Both conventional AVR and TAVI will continue to improve. Results of ongoing and future studies will influence patient selection for each of these valuable therapies.
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Keywords: transcatheter aortic valve implantation, TAVI, surgical aortic valve replacement, AVR, aortic valve stenosis, Edwards Sapiens device, PARTNER trial, ascending aortic aneurysm surgery, STACCATO trial, Medtronic CoreValve

References
**NEXT-GENERATION TRANSCATHETER HEART VALVES: CURRENT TRIALS IN EUROPE AND THE USA**

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**Abstract**

Transcatheter aortic valve implantation (TAVI) has proven to be a viable alternative for patients with symptomatic severe aortic stenosis who are at high risk for surgical aortic valve replacement. At the same time, there is increasing evidence that moderate-to-severe periprosthetic aortic regurgitation after TAVI is associated with dramatically increased mortality and morbidity. The issue of proper positioning of the valve, including the ability to reposition and recapture the device, must be dealt with before the use of TAVI can be extended to younger, healthier patients. The next generation of transcatheter heart valves will most likely address repositionability to facilitate accurate placement with additional features that minimize paravalvular leakage. Upcoming devices promise to improve outcomes and usability of current TAVI systems.

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**Introduction**

With more than 60,000 implanted transcatheter heart valves in patients around the world, TAVI has been shown to be a viable treatment for patients with symptomatic severe aortic stenosis who are at high risk for traditional surgical aortic valve replacement (SAVR). The PARTNER trial was the first randomized controlled trial to demonstrate that TAVI is not inferior to SAVR in high-risk patients, since both procedures had similar rates of survival at 1 year. According to the German TAVI registry, approximately one-third of all implanted aortic valve prostheses in 2011 were anticipated to be transcatheter heart valves.

Although the PARTNER trial recently underscored the value of TAVI for high-risk patients, distinct TAVI-related drawbacks have been identified, including important differences in periprocedural risks, periprosthetic aortic regurgitation (AR), and the occurrence of significant conduction disturbances. Concerns remain around the higher, mostly procedure-related incidence of paravalvular leakage compared to SAVR. Since transcatheter heart valves are implanted without sutures, using oversizing to expand a stent at the level of the aortic annulus, several etiologies can be invoked to explain periprosthetic AR after TAVI, such as heavily calcified cusps, misplacement of the prosthesis, and/or annulus-prosthesis-size mismatch. Recently published studies report an incidence of periprosthetic AR in more than 70% of all TAVI patients that is graded as moderate or severe in approximately 10% to 20% of them. Since there is growing evidence that more-than-mild periprosthetic AR after TAVI is associated with dramatically increased mortality and morbidity, this issue must be addressed before TAVI can be extended to younger and healthier patients.

This next generation of transcatheter heart valves addresses the issue of repositionability to facilitate accurate placement and include additional features to minimize paravalvular leakage, which should further improve TAVI outcomes.

**Sadra Medical Lotus™ Aortic Valve**

The Sadra Medical Lotus valve (Boston Scientific, Natick, Massachusetts) consists of a tri-leaflet bovine pericardial tissue valve mounted on a braided nitinol stent structure that expands in the native annulus as it shortens (the “Chinese finger trap” principle). This deployment procedure enables a more flexible delivery system, provides radial strength, and makes repositioning or recapturing of the device possible at any time prior to release. The accurate placement of the valve is facilitated by a radiopaque center marker that allows alignment with the native valve. The preloaded prosthesis is positioned over a three-armed, self-centering system (Figure 1). An additional so-called “adaptive seal” at the lower part of the prosthesis skirt helps to conform to irregular surfaces of the native anatomy and to further reduce periprosthetic AR. The Sadra Lotus system is delivered percutaneously over an 18-Fr introducer sheath. In 2011, the REPRISE CE Mark trial with two valve sizes, 23 mm and 27 mm, was initiated in Germany, France, the United Kingdom, and Australia.

**Direct Flow Medical Aortic Valve**

The Direct Flow Medical Aortic Valve (Direct Flow Medical, Santa Rosa, California) consists of a bovine pericardial tissue valve that is mounted between two inflatable polyester rings...
(Figure 2). These two rings are able to adapt to the native aortic annulus and the left-ventricular outflow tract to prevent periprosthetic AR. The device is delivered over an 18-Fr catheter-based, four-armed system after balloon valvuloplasty (BAV) of the native aortic valve. To better visualize the prosthesis under fluoroscopy for optimal positioning, the polyester rings of the prosthesis are filled with a mix of saline and contrast dye. Before final deployment of the valve, this fluid is exchanged against a hardening medium to firmly anchor the prosthesis in the native annulus. If necessary, the rings can be fully deflated and the valve prosthesis can be retrieved with a net basket. The profile size has been reduced from 22 Fr to 18 Fr with the second-generation transcatheter heart valve. CE Mark approval is anticipated at the end of 2012.

**Symetis Acurate TA™ Aortic Bioprosthesis**

The Symetis Acurate valve (Symetis, Lausanne, Switzerland) consists of an aortic stentless porcine valve that is mounted and sutured in a self-expanding nitinol alloy stent (Figure 3) with a Dacron interface at the lower part of the stent frame. This transcatheter heart valve comes in three sizes and can accommodate native annulus sizes of 21-27 mm. After BAV, device deployment begins with the release of the stabilization arches and the upper crown of the valve in the ascending aorta. Two radiopaque markers help deploy the valve in a proper axial position. After the upper crown has engaged the cusps of the native leaflets, the lower crown is fully expanded and anchors the new valve in the native annulus. During release, the stabilization arches self-position the device with axial alignment. The Dacron skirt at the lower valve crown provides a seal at the level of the native aortic annulus, reducing paravalvular leakage to a minimum.

Symetis received CE Mark approval for the Acurate transapical TAVI system at the end of September 2011. The prosthesis has shown promising results with a 30-day survival rate of 92% in the first 90 patients. The commercial launch of the transcatheter Acurate valve took place during the European Association for Cardio-Thoracic Surgery meeting in Lisbon/Portugal in October 2011, with an initial focus on Europe. In parallel, a 150-patient, 15-center pivotal trial will be conducted in the United States. The CE Mark trial for the transfemoral version of the Symetis Acurate will be finished until August 2012.

**St. Jude Medical Portico™ Aortic Valve**

The Portico valve (St. Jude Medical, St. Paul, Minnesota) is comprised of leaflets made of bovine pericardial tissue that have been treated with anti-calcification technology and sutured in a nitinol self-expanding stent. This valve is designed for transfemoral (18-Fr delivery system via transfemoral sheath) and transapical use (24-Fr delivery system with integrated sheath) (Figure 4). The open cell design of the stent frame allows access to the coronaries and a low crimp profile. A tissue cuff at the lower part of the valve frame has been designed to minimize periprosthetic AR. After deployment of the valve, the prosthesis frame only minimally protrudes into the left-ventricular outflow tract, which is made possible by the low placement of the leaflets within the stent frame. This might help to reduce significant conduction system interference and the need for pacemaker implantation. The Portico valve can be completely resheathed, allowing it to be repositioned at the implant site or retrieved before it is released from the delivery system. A first-in-man study with 10 patients evaluated the technical feasibility, safety, and device deployment characteristics of the 23-mm Portico valve transfemoral delivery system. The study showed promising results at 30 days, with no device- or procedure-related adverse events or death and only trivial or no paravalvular leak. Both a European and US trial are planned for 2012.

**Edwards SAPIEN® 3 and Edwards CENTERA Aortic Valve**

Edwards (Edwards Lifesciences, Irvine, California) will unveil two next-generation transcatheter heart valve platforms in 2012. The Edwards SAPIEN 3 is a lower profile, balloon-expandable valve that is designed to further reduce paravalvular leak. For percutaneous use, this valve has treated bovine pericardial tissue leaflets and is delivered through a 14-Fr sheath that might help to further reduce vascular complications. The profile for the transapical approach will also be reduced considerably. The new Edwards CENTERA valve is an ultra-low profile, self-expanding transcatheter heart valve that is repositionable and delivered with a...
motorized system for single operator use. First-in-man results with this device were very promising. European clinical trials for both of these new products will start in 2012.

The PARTNER II Trial, which is studying the Edwards SAPIEN XT valve in an expanded patient population, is currently underway in the United States. Enrollment in Cohort B of this trial was completed in January 2012. Enrollment also began in PARTNER II Cohort A, which is studying patients with a lower risk profile than those who were enrolled in The PARTNER Trial.

**Medtronic Engager™ Aortic Valve**

The Medtronic Engager aortic valve prosthesis has shown promising first results in a registered trial and will be launched soon.13 Designed for transapical use, this valve has a trileaflet bovine pericardial tissue design mounted on a self-expanding nitinol stent frame that is covered with a polyester skirt to prevent periprosthetic AR (Figure 5). In addition, this prosthesis has a low device implant height to ensure clearance from coronary ostia and positioning arms that are anchored over the native leaflets to enable optimal alignment of the valve in the native annulus and to prevent periprosthetic AR.

**JenaValve™ Aortic Valve**

The JenaValve (JenaValve, Munich, Germany) consists of a porcine root valve sewn onto a Nitinol self-expanding stent (Figure 6). The JenaValve is available in three sizes (23 mm, 25 mm, and 27 mm) and covers aortic valve annuli from 21 mm to 27 mm. The Nitinol stent has three self-expanding feelers that allow the prosthesis to be accurately positioned in the aorta. Furthermore, before being sewn onto the stent, the lower part of the valve is fitted with an outer porcine pericardial skirt to minimize paravalvular leakage. The JenaValve system is fully repositionable and retrievable and is delivered transapically via a 32-Fr introducer sheath. After the feelers have been placed in the correct position in the sinuses of the native valve, the lower part of the prosthesis is released. The Nitinol stent self-expands to anchor in the native annulus, and the new valve immediately starts to function. During release, the native valve leaflets are clipped between the feelers and the base of the prosthesis. This JenaClip mechanism firmly anchors the JenaValve in the correct anatomical position and provides active fixation and resistance to migration. The delivery system can then be safely retracted. Results in 67 patients have been very promising, with a 30-day survival rate of 92%.14 JenaValve Technology received CE Mark approval for their device at the end of September 2011.

**Conclusion**

In conclusion, TAVI has been established as an alternative to surgical aortic valve replacement in inoperable and high-risk patients with severe, symptomatic aortic stenosis. Next-generation transcatheter aortic valve devices promise to improve outcomes and usability of recent TAVI systems. Thus, younger and healthier individuals might benefit from TAVI in the near future.

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**Funding/Support:** The authors have no funding disclosures.

**Keywords:** Aortic stenosis; transcatheter aortic valve implantation; peri-prosthetic aortic regurgitation; paravalvular leakage; TAVI

**References**


Introduction

Degenerative aortic stenosis is the most common acquired valvular heart disease in the developed countries, affecting more than 300,000 people in the United States alone. Symptoms of aortic stenosis are latent until there is critical narrowing of the aortic valve that results in left ventricular hypertrophy, increased left ventricular diastolic pressure and left ventricle mass, and increased myocardial oxygen demand causing subendocardial ischemia. Once symptoms develop, the prognosis changes dramatically unless the aortic stenosis is corrected.

Surgical aortic valve replacement (sAVR) is the recommended therapy for patients with symptomatic aortic stenosis. The most recent American College of Cardiology and American Heart Association (ACC/AHA) guidelines for sAVR are found in Table 1. It is important to note that none of these recommendations are based on evidence from large-scale, randomized clinical trials but instead rely on the expert opinion of experienced clinicians. The Society for Thoracic Surgery Predicted Risk of Mortality (STS-PROM) has been used to estimate 30-day mortality operative risk. Other surgical risk scores, such as the logistic EuroSCORE, while correlated with overall prediction of risk, are poorly calibrated to estimate precise sAVR mortality rates.

Many patients cannot undergo sAVR due to excessive surgical risk, including porcelain aorta, hostile mediastinum, severe lung or liver disease, frailty, renal failure, advanced age, and prior CABG, among other factors, many of which are not included in current surgical risk assessment algorithms. In patients who are deemed unsuitable for sAVR due to comorbidities, transcatheter aortic valve replacement (TAVR) has been used as an alternative to relieve symptoms and extend life. Almost 50,000 patients have been treated worldwide with one of the two commercially approved TAVR devices, including the balloon-expandable Edwards SAPIEN Transcatheter Heart Valve (Edwards LifeSciences, Irvine, California) and the self-expanding CoreValve Revalving System (Medtronic, Minneapolis, Minnesota). A number of additional transfemoral and transapical devices are under evaluation.

The purpose of this report is to review the clinical trials used to evaluate TAVR in patients who are at higher risk for sAVR. The clinical evidence base includes both prospective registries and randomized clinical trials. Future trial designs evaluating TAVR in intermediate populations will also be discussed.

<table>
<thead>
<tr>
<th>Class</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>AVR is indicated for symptomatic patients with severe AS.</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>AVR is indicated for patients with severe AS undergoing coronary artery bypass graft surgery (CABG).</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>AVR is indicated for patients with severe AS undergoing surgery on the aorta or other heart valves.</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>AVR is recommended for patients with severe AS and LV systolic dysfunction (ejection fraction less than 0.50).</td>
</tr>
<tr>
<td>IIA</td>
<td>B</td>
<td>AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves.</td>
</tr>
<tr>
<td>IIB</td>
<td>C</td>
<td>AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension).</td>
</tr>
<tr>
<td>IIB</td>
<td>C</td>
<td>AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset.</td>
</tr>
<tr>
<td>IIB</td>
<td>C</td>
<td>AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate to severe valve calcification, that progression may be rapid.</td>
</tr>
<tr>
<td>IIB</td>
<td>C</td>
<td>AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area less than 0.6 cm², mean gradient greater than 60 mmHg, and jet velocity greater than 5.0 m per second) when the patient’s expected operative mortality is 1.0% or less.</td>
</tr>
<tr>
<td>III</td>
<td>B</td>
<td>AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIA/IIB recommendations.</td>
</tr>
</tbody>
</table>

Extreme-Risk or Inoperable Patients for sAVR

Early clinical evaluation of TAVR included patients deemed unsuitable for sAVR. The logistic Euroscore was the primary risk algorithm used for reporting these series, but a number of specific clinical factors, including advanced age, prior CABG, cirrhosis, pulmonary disease and pulmonary artery hypertension, right ventricular failure, or mediastinal radiation were used for inclusion of patients in TAVR studies.

Balloon-Expandable TAVR Registries and Randomized Clinical Trials

The Edwards SAPIEN Transcatheter Heart Valve consists of a trileaflet bovine pericardial valve and a balloon-expandable, stainless-steel support frame. The SAPIEN valve has undergone clinical study in the United States in 23-mm and 26-mm sizes. It is placed by means of a 22-French (Fr) or 24-Fr sheath from the femoral artery or via the transapical approach using a modified frame and larger delivery sheath. A second-generation 18-Fr RetroFlex II delivery system and a 29-mm SAPIEN XT valve are both available outside the United States and are currently undergoing US-based clinical trials through the PARTNER II study.

A number of single-center series have evaluated the outcomes of TAVR using the Edwards SAPIEN system.13 The largest of these is the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry, which assessed the initial clinical results of TAVR in consecutive patients in Europe using the SAPIEN valve after commercialization; patients undergoing the transapical approach had a higher logistic EuroSCORE that those undergoing the transfemoral approach (29.1% versus 25.7%, respectively).14 Short-term procedural success was observed in 93.8% of patients, with reported complications including stroke (2.5%), valve embolization (0.3%), and coronary obstruction (0.6%). Thirty-day mortality was 6.3% in transfemoral patients and 10.3% in transapical patients.14 The SOURCE registry reported a total Kaplan Meier 1-year survival of 76.1% overall, with 72.1% for transapical patients and 81.1% for transfemoral patients.14 At 1 year, 73.5% of surviving patients were in New York Heart Association (NYHA) class I or II.15 The cause of late mortality was cardiac in 25.1%, noncardiac in 49.2%, and unknown in 25.7%.14 The most frequent noncardiac causes of death were due to pulmonary complications (23.9%), renal failure (12.5%), cancer (11.4%), and stroke (10.2%).14 Multivariable analysis identified logistic EuroSCORE, renal disease, liver disease, and smoking as variables with the highest hazard ratios for 1-year mortality.14

Two randomized clinical trials demonstrated the value of balloon-expandable TAVR in patients poorly suited for sAVR (Table 2). The PARTNER I-B study included 358 patients who were deemed inoperable and randomly assigned to standard therapy (including balloon aortic valvuloplasty) or transfemoral TAVR.15 The primary endpoint, 1-year all-cause mortality (Kaplan-Meier analysis), was 30.7% with TAVR and 50.7% with standard therapy (hazard ratio with TAVI: 0.55; P < 0.001).15 The frequency of severe cardiac symptoms (New York Heart Association class III or IV) in 1-year survivors was lower in patients who had undergone TAVR than in those who had received standard therapy (25.2% versus 58.0%, P < 0.001).15 Major strokes were higher at 30 days in patients treated with TAVR (5.0% versus 1.1% in medically-treated patients, P = 0.06), and major vascular complications were also higher in patients undergoing TAVR (16.2% versus 1.1% in medically-treated patients).

Table 2. Trial design for ongoing and completed studies for TAVR.

<table>
<thead>
<tr>
<th>Extreme-Risk or “Inoperable” Patients</th>
<th>Definition</th>
<th>Trial Design</th>
<th>Control</th>
<th>Number Pts</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER I-B</td>
<td>&gt;50% risk of death or irreversible morbidity at 30 days</td>
<td>Prospective, randomized 1:1</td>
<td>Medical Therapy including BAV</td>
<td>358</td>
<td>Rate of death from any cause over the duration of the trial</td>
</tr>
<tr>
<td>PARTNER II-B</td>
<td>&gt;50% risk of death or irreversible morbidity at 30 days</td>
<td>Prospective, randomized 1:1</td>
<td>Medical Therapy including BAV</td>
<td>NR</td>
<td>1-year time to death, major stroke, and repeat hospitalization</td>
</tr>
<tr>
<td>US CoreValve</td>
<td>&gt;50% risk of death or irreversible morbidity at 30 days</td>
<td>Prospective Registry</td>
<td>Performance Goal</td>
<td>487</td>
<td>1-year all-cause mortality and major stroke (versus performance goal)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Risk Surgical Patients</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER I A</td>
<td>&gt;15% risk of 30-day death (with STS &gt;8)</td>
<td>Prospective, randomized 1:1</td>
<td>SAVR</td>
<td>699</td>
<td>1-year all-cause mortality</td>
</tr>
<tr>
<td>US CoreValve</td>
<td>&gt;15% risk of 30-day death</td>
<td>Prospective, randomized 1:1</td>
<td>SAVR</td>
<td>790</td>
<td>1-year all-cause mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate-Risk Patients</th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER II A</td>
<td>STS PROM 4-8</td>
<td>Prospective, randomized 1:1</td>
<td>SAVR or SAVR-CABG</td>
<td>2000</td>
<td>2-year all-cause mortality and major stroke</td>
</tr>
<tr>
<td>SURTAVI</td>
<td>STS PROM &gt;3 for OUS and &gt;4 for US patients</td>
<td>Prospective, randomized 1:1</td>
<td>SAVR or SAVR-CABG</td>
<td>1200</td>
<td>2-year all-cause mortality and major stroke</td>
</tr>
</tbody>
</table>
patients, \( P < 0.001 \).\(^{15}\) There was no deterioration in bioprosthetic valve functioning at 1 year, as assessed by evidence of stenosis or regurgitation on an echocardiogram.\(^{15}\)

Cohort A of the PARTNER Trial randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either transcatheter aortic valve replacement with a balloon-expandable bovine pericardial valve (using a transfemoral or transapical approach) or surgical replacement (Table 2).\(^{16}\) The rates of death from any cause were 3.4% in the TAVR group and 6.5% in the sAVR group at 30 days (\( P = 0.07 \)) and 24.2% and 26.8%, respectively, at 1 year (\( P = 0.44 \)), a reduction of 2.6 percentage points in the TAVR group (\( P = 0.001 \) for noninferiority).\(^{16}\) The rates of major stroke were 3.8% in the TAVR group and 2.1% in the sAVR group at 30 days (\( P = 0.20 \)) and 5.1% and 2.4%, respectively, at 1 year (\( P = 0.07 \)). At 30 days, major vascular complications were significantly more frequent with TAVR (11.0% versus 3.2%, \( P < 0.001 \)); adverse events that were more frequent after sAVR included major bleeding (9.3% versus 19.5%, \( P < 0.001 \)) and new-onset atrial fibrillation (8.6% versus 16.0%, \( P = 0.006 \)). More patients undergoing TAVR had an improvement in symptoms at 30 days, but by 1 year there was not a significant difference between groups.\(^{16}\)

The PARTNER II (Cohort B) Trial is designed to determine the safety and effectiveness of the Edwards 18-Fr SAPIEN XT™ device and NovaFlex delivery system in inoperable patients with symptomatic critical aortic stenosis.\(^{17}\) Patients will be randomized in a 2:1 fashion to the SAPIEN XT device or the SAPIEN RetroFlex III device.\(^{17}\) The primary noninferiority endpoints are all-cause mortality, major stroke, and repeat hospitalization at 1 year.\(^{17}\)

### Self-Expanding TAVR Registries and Randomized Clinical Trials

The Medtronic CoreValve ReValving System (Medtronic, Inc., Minneapolis, MN) consists of a trileaflet porcine pericardial valve and a self-expanding nitinol support frame. The CoreValve is available for clinical study in the United States in 23-mm, 26-mm, 29-mm, and 31-mm sizes. It is placed by means of an 18-Fr sheath from the femoral artery or subclavian (axillary) arteries or via direct aortic access.

The 18-Fr Safety and Efficacy Study included 126 patients (logistic EuroSCORE = 23.4%) with severe aortic valve stenosis.\(^{18}\) The overall technical success rate was 83.1%, and the 30-day all-cause mortality was 15.2%.\(^{18}\) All-cause mortality was 38.1% at 2 years. There was a significant difference in 2-year mortality between moderate-risk and high-risk groups (27.8% versus 45.8%, respectively; \( P = 0.04 \)), mainly attributable to an increased risk of noncardiac mortality among patients in the high-risk groups.\(^{18}\)

Table 3. National registries with self-expanding CoreValve TAVR.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Age</th>
<th>Males, %</th>
<th>Logistic EuroSCORE</th>
<th>NYHA Class III-IV, %</th>
<th>Mean Gradient, mmHg</th>
<th>Vascular Complic, %</th>
<th>Stroke, %</th>
<th>PPM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian(^{19})</td>
<td>81±7.3</td>
<td>44</td>
<td>23±13.7</td>
<td>71.5</td>
<td>51.8±17</td>
<td>2.0</td>
<td>1.2</td>
<td>16.6</td>
</tr>
<tr>
<td>Belgian(^{20})</td>
<td>82±6</td>
<td>44</td>
<td>25±15</td>
<td>78</td>
<td>49±16</td>
<td>—</td>
<td>4</td>
<td>22.0</td>
</tr>
<tr>
<td>French(^{21})</td>
<td>82.5±5.9</td>
<td>48.5</td>
<td>24.7±11.2</td>
<td>74.6</td>
<td>46±15</td>
<td>7.5</td>
<td>4.5</td>
<td>25.7</td>
</tr>
<tr>
<td>Spanish(^{22})</td>
<td>78.6±6.7</td>
<td>45.4</td>
<td>16±13.9</td>
<td>58.4</td>
<td>55±14.3</td>
<td>5.6</td>
<td>0</td>
<td>35.2</td>
</tr>
<tr>
<td>UK(^{22})</td>
<td>83</td>
<td>52</td>
<td>20.3</td>
<td>74</td>
<td>—</td>
<td>4.0</td>
<td>4.3</td>
<td>26.0</td>
</tr>
<tr>
<td>German(^{24})</td>
<td>81.4±6.3</td>
<td>44.2</td>
<td>20.5±13.2</td>
<td>88.2</td>
<td>48.7±17</td>
<td>4.0</td>
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<tr>
<td>Australia-NZ(^{25})</td>
<td>82.7±7.7</td>
<td>59.3</td>
<td>18±12</td>
<td>84</td>
<td>51±16</td>
<td>6.5</td>
<td>1.9</td>
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Complic: complications; NYHA: New York Heart Association; PPM: permanent pacemaker placement; TAVR: transcatheter aortic valve replacement

Although there were no consistent definitions, procedure success rates ranged from 92.6 to 98%, and 30-day mortality rates ranged from 84.9 to 92.1%.\(^{19-25}\)

The United States CoreValve Extreme Risk Pivotal Registry has completed enrollment of 487 patients deemed to have a predicted 30-day surgical mortality risk or irreversible serious morbidity risk that exceeds 50%. The primary endpoint, the combination of 1-year all-cause mortality or major stroke, will be compared with a performance goal determined from the PARTNER B study and contemporary balloon valvuloplasty registries. In addition, up to 200 patients diagnosed as extreme risk but whose iliofemoral anatomy precludes placement of an 18-Fr sheath will undergo either an axillary or direct aortic approach described below.

The CoreValve US Pivotal Trial includes 790 high-risk patients deemed to have an estimated 30-day mortality risk of between 10% and 15% due to the presence of comorbidities. Patients are assigned in 1:1 fashion to either TAVR or to sAVR. The primary endpoint, 1-year all-cause mortality, will assess the noninferiority of TAVR with sAVR. Up to 20% of patients can be treated using a noniliofemoral approach. Patients with significant residual coronary artery disease are excluded as coronary artery bypass surgery is allowed at the time of sAVR.

An important aspect of these studies is the inclusion of patients who are treated with an alternative noniliofemoral access route. In patients with a minimal lumen iliofemoral diameter of <6.0 mm in a noncalcified vessel and <7.0 mm in a calcified vessel, those with aneurysmal dilatation of the abdominal aorta or with prior surgical or percutaneous aneurysm repair will be treated using either the subclavian (axillary) or direct aortic approaches.\(^{26-30}\)
Clinical Condition

- Aortic valve is a congenital unicuspid or bicuspid valve; or is non-calcified.
- Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency.
- Severe ventricular dysfunction with LVEF <20.
- Renal insufficiency (Creatinine >3.0) and/or end-stage renal disease requiring chronic dialysis.
- Low-gradient low-output aortic stenosis.
- Patients who have significant associated valvular lesions that cannot be treated surgically.

Recommended Endpoints

- Mortality
- Functional improvement per NYHA functional class
- Stroke
- Other major adverse cardiovascular events
- Length of hospital stay

Table 4. STS-ACC recommendations for continued evidence development.31 STS: Society of Thoracic Surgeons; ACC: American College of Cardiology; LVEF: left ventricular ejection fraction

>3, and patients enrolled in the United States will have an STS-PROM >4. Clinical centers with previous experience in TAVR will be eligible to participate in the study. SURTAVI will use a heart team approach that includes an interventional cardiologist and cardiac surgeon. The study’s primary endpoint is 2-year all-cause mortality and major stroke. Secondary endpoints include valve failure, endocarditis, and regression of the left ventricle and need for PPMI.
Continuing Evidence Development

The STS and American College of Cardiology have recommended that additional clinical study be performed to determine the value of TAVR in patients who are not included in the randomized trials and registries (Table 4).32 For the majority of patients who are poor candidates for sAVR, there is little question of the profound clinical benefit from undergoing TAVR. Implementation of a multidisciplinary team is essential for appropriate patient selection. Several complications with TAVR require careful procedural attention during the peri-procedural period, including stroke,33 vascular complications, perivalvular regurgitation,34, 35 and the need for permanent pacemaker placement.36 New TAVR designs will be available to potentially lower these complication rates (Table 4). In addition, multidetector CT imaging has been very valuable in predicting the appropriate valve size and guiding vascular access.

Based on growing evidence, TAVR is now recognized as superior to medical therapy in patients who are not suitable candidates for sAVR and equivalent for 1-year mortality in patients who are deemed high-risk for sAVR, albeit with an improved quality of life within the first 6 months. Randomized clinical trials are assessing the value of TAVR in intermediate-risk patients. Registry studies will provide increasing insight into patients with bioprosthetic valve failure (valve-in-valve), bicuspid disease, low-gradient/low-output aortic stenosis, and in other clinical subsets not currently included in randomized clinical trials.

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Keywords: transcatheter aortic valve replacement, surgical aortic valve replacement, TAVR, TAVI, aortic stenosis, Edwards SAPIEN Transcatheter Heart Valve, EuroSCORE, SOURCE registry, PARTNER trial, Medtronic CoreValve, SURTAVI trial

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ROOM CONSIDERATIONS WITH TAVR

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Abstract

While transcatheter aortic valve replacement is considered a viable alternative to traditional surgery for patients with critical aortic stenosis, it is still a cardiac surgical procedure with a steep learning curve. Space consideration is a key aspect of the procedure’s success. A TAVR program requires the commitment from and investment of institutional resources, the outfitting of an appropriate procedure room, and meticulous training of a multidisciplinary TAVR team. Careful integration of the various imaging modalities, medical specialties, and equipment is necessary to ensure the safety and efficacy of the procedure and to treat complications that may arise.

Introduction

Transcatheter aortic valve replacement (TAVR) has gained traction as a successful therapeutic option in patients with critical aortic stenosis who cannot have surgery and is much less invasive than open surgical aortic valve replacement. Even so, the procedure remains considerably more complex than other percutaneous cardiac procedures and should still be viewed as a form of cardiac surgery. This concept should become more apparent as physicians grow more comfortable with the direct aortic approach, which requires either a mini sternotomy or a small thoracotomy incision. It is also important to recognize that the learning curve for performing TAVR is steep, particularly given the nature and comorbidities of the patients who are currently candidates for the procedure.

As TAVR evolves and the devices become smaller and easier to use, it is very likely that access site difficulties will diminish. For the near future, however, consideration should be given to determining which of the available rooms to use for the procedure or deciding how best to design a suite for this purpose. This idea should be driven by the fact that while TAVR is less invasive than surgical AVR, it is nonetheless a cardiac surgical procedure and, more akin to aneurysm repair or valve replacement than to coronary stent implantation. Accordingly, beginning a TAVR program requires the investment of considerable institutional resources, the outfitting of an appropriate procedure room, and meticulous training of a TAVR team. The approach that has been generally encouraged has been to form a multidisciplinary team that includes members from the cardiac catheterization laboratory, cardiovascular operating room, cardiovascular imaging, and cardiovascular anesthesia. Commitment of the parent institution to support such a program and to recognize that considerable resources are required is invariably needed to allow the procedure to be performed safely.

Although most attention has been directed at equipment to be placed in the suite, an extremely important early consideration is the suite’s physical location and outfitting. The primary aim in selecting or designing such a suite should be to allow valve team members to work together efficiently without interfering with one another and without compromising the safety of the procedure. Thus, the major challenge in preparing a suite for TAVR involves integrating the various imaging modalities, the medical specialties, and the equipment—all of which are required to perform the procedure safely and effectively and to treat complications that are likely to occur. As TAVR teams become more experienced, and as valve prostheses evolve, some of these modalities may no longer be used routinely. However, there is currently enough case-to-case variability inherent in the procedure that they will be useful on many if not most occasions.

TAVR Space Requirements

TAVR procedures can be performed in specially outfitted cardiac catheterization laboratories. The general recommendation is for space exceeding 800 square feet. In many parts of the world, TAVR procedures are performed in such catheterization laboratories; in the United States, “hybrid” operating rooms are frequently used. Joint recommendations from the cardiac and surgical societies are to be published in the near future. However, it is important to recognize that outfitting catheterization laboratories so that surgical procedures can be performed there, and outfitting operating rooms so that high-quality angiography and hemodynamic measurement can also be accommodated, is often a daunting task. Surgical removal of the prostheses is exceptionally difficult, and since the infections of percutaneous valvular prostheses are likely to be lethal, appropriate aseptic conditions are mandatory. These include appropriate ventilation and laminar air flow, appropriate venting for anesthetic gases, and restricted access to nonessential personnel who may not be familiar with the more rigorous standards required in operating rooms as opposed to catheterization suites. Other considerations include adequate overhead lighting with adjustable lamps for open surgical procedures, and adequate electrical supply and booms for running anesthesia and other equipment—including cardiopulmonary bypass or other forms of ventricular support, transesophageal echocardiography, and possibly transcranial Doppler.)
While easy accessibility for the interventional cardiologist and cardiac surgeon is important, accessibility for the anesthesiology department is probably more critical; although some procedures are now performed with moderate sedation, many are still performed with general anesthesia. In both cases, the presence of an anesthesiologist is needed. Accessibility to the blood bank and to laboratory facilities for blood gas, hematology, and electrolyte results should be considered when selecting the location. The other aspect of location concerns the availability of equipment, including the instruments needed to perform open-chest procedures, adequate suction, red cell rapid autotransfusion, and percutaneous rescue procedures. Maintaining a full stock of angioplasty equipment to manage coronary arterial complications and a full stock of various covered stents and peripheral vascular balloons is not likely to be possible. However, the suite must have enough room available to store the basic array of guiding catheters, guide wires, stents, and equipment needed to treat vascular access and coronary complications. In addition, the room needs to be situated in a location that allows rapid transport of unusual equipment that may occasionally be needed to manage a complex and unstable clinical scenario.

Planning should also include provisions for adequate imaging chains and hemodynamic recording systems. Although the procedure can often be performed with standard coronary angiographic equipment, the features of the patient population who receive TAVR mandate that advanced imaging capabilities be present. First, because of the age of this patient population and the frequency of accompanying atherosclerotic disease, severe peripheral vascular disease is common. Consequently, advancing large catheters (18-24 Fr) through tortuous and calcified iliofemoral or subclavian vessels frequently requires modifications of the original treatment strategy. It also mandates large-format image intensifiers or flat-panel detectors to guide catheter placement and rapid diagnosis and treatment of vascular access-site complications, particularly dissection, perforation or rupture of the aorta, iliac vessels, or subclavian arteries. Additionally, the X-ray gantries need to be selected so these issues can be addressed. Consensus statements from the American College of Cardiology, Society for Thoracic Surgery, and Society for Cardiac Angiography and Interventions clearly indicate that freestanding portable C-arms are not acceptable for use in TAVR.\(^5,6\) Selection of high-quality radiographic equipment that can sweep from the upper thorax to the femoral artery without having to interrupt the procedure to rotate the C-arm is preferable. Second, renal compromise is also common in this patient population, so management of femoral access issues is made safer by digital subtraction angiography to reduce the amount of contrast that is required. Finally, compromise of coronary circulation by compression of calcified valve leaflets against the coronary ostia is a rare (<1%) but rapidly lethal complication of TAVR.\(^7\) Even in the absence of ostial occlusion, transient decreases in cardiac output are fairly common, and in the absence of an obvious explanation, the implanting operator may feel compelled to perform emergency coronary angiography. Therefore, it is important to have imaging capabilities including the ability to perform cranial and caudal angulation necessary for emergency coronary angiography and stenting.

Another important imaging consideration is the use of transesophageal echocardiography. Although this modality is not used universally, in many cases it is useful for assessing paravalvular leaks and left ventricular contractility after rapid pacing runs, to check for pericardial effusions during periods of hypotension, and to ensure that the anterior leaflet of the mitral valve is not compromised in the case of low implants of self-expanding valve prostheses. Considerable space is required for placement of the echocardiographic equipment, and it is important that placement of the recording console not interfere with anesthesia. In our practice, the transesophageal probe is extended over the patient’s left shoulder and directed slightly caudally.

A final consideration in selecting angiographic equipment involves integrating other imaging modalities into the angiographic viewing monitors. The ability to use one monitor as a “slave” to the transesophageal echocardiogram facilitates the operator’s ability to select implantation depth of the valve and to evaluate postprocedure echocardiographic findings. To facilitate valve implantation, it is helpful to have available X-ray systems that can integrate software currently being developed. A variety of additional features designed to integrate other images, such as CT angiography, and to co-register them with fluoroscopic images are becoming available. These programs are particularly useful and may obviate the need for repeated contrast injections when selecting the optimal angle for valve implantation and when negotiating tortuous iliac vessels. Finally, because valve implantation must be performed with a good deal of precision, software is now available to help operators calculate optimal implanting views and overlay masks corresponding to the available valves over the fluoroscopic image of the aortic root to indicate the optimal placement depth within the aortic annulus.

**Conclusion**

It is likely that the specifications for procedural suites will continue to evolve as the valve technology undergoes further development. As the procedure becomes easier to perform, as the catheter size required for valve implantation decreases, and as valve seating within the aortic orifice becomes easier, the number of support services that are needed will decrease and suite selection may become easier. On the other hand, extension of TAVR to low-risk populations, which is planned in at least two current clinical trials, will result in greater expectations concerning procedural results and lower tolerance of complications. Additionally, trials incorporating percutaneous coronary interventions performed at the same sitting as TAVR will require high-quality angiographic equipment and will require that both procedures be performed in a streamlined fashion. As such, it is unlikely that the basic requirements outlined above will become less rigorous. Therefore, one should anticipate that outfitting suites for the procedure will be more rather than less encompassing.

**Conflict of Interest Disclosures:** All authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and the following was reported: Dr. Kleiman is a principal investigator for the CoreValve® US Pivotal Trial.

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**Keywords:** transcatheter aortic valve replacement, TAVR, TAVI, aortic stenosis, catheterization laboratories, hybrid operating rooms, percutaneous valvular prostheses, transesophageal echocardiography
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TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR): ACCESS PLANNING AND STRATEGIES

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Abstract
Transcatheter aortic valve replacement (TAVR) has proven to be a viable tool for the high-surgical-risk population with severe aortic valve stenosis. Vascular access complications are not uncommon with TAVR and may increase early and late mortality. Avoiding these serious complications is the goal. With experience and careful screening, we are now able to risk-stratify patients who may be at increased risk of vascular complications. While the traditional iliofemoral access remains the most common for TAVR, alternate access sites that have proven to be viable and safe alternatives include the transapical, direct-aortic, and subclavian techniques. TAVR teams should be familiar and comfortable with these approaches as each of them has its own advantages and weaknesses. The best option is usually one in which the procedure is tailored to the patient. The present review examines our current access planning and strategies for TAVR.

Introduction
Aortic valve replacement is a class I indication for patients with severe aortic stenosis and symptoms in the ACC/AHA guidelines for the treatment of cardiac valvular disease. Since some patients can be judged too high a risk to undergo surgery, they may be denied aortic valve replacement. Transcatheter aortic valve replacement (TAVR) has been developed as a potential option for this patient group. To date, there are two studies that have evaluated two valve devices: The PARTNER Trial using the Edwards SAPIEN valve, which was approved for use in nonsurgical candidates by the FDA in December 2011, and the CoreValve US Pivotal Trial (using the Medtronic CoreValve) that is currently active and accruing patients. Both of these devices require large bore access for placement. The Edwards SAPIEN valve used in the PARTNER Trial can be inserted using an iliofemoral access or a transapical cardiac access. For the valves used in the PARTNER Trial, the small valve (23 mm) required a 22-Fr sheath and the large valve (26 mm) required a 24-Fr sheath for iliofemoral access. Both valves used a 26-Fr sheath when direct transapical cardiac insertion was used in patients who were not candidates for iliofemoral access. A newer version, the SAPIEN XT, can be inserted using an 18-Fr sheath via the iliofemoral route. The Medtronic CoreValve currently comes in 23 mm, 26 mm, 29 mm, and 31 mm sizes and all are inserted through an 18-Fr sheath. For both valves, the femoral route is the preferred method of insertion whenever possible. When iliofemoral access is not possible with the CoreValve, both subclavian artery and direct aortic approaches have been used.

Planning access for TAVR requires knowledge of the luminal size as well as the degree of vessel calcification and tortuosity. We consider a high-quality thin-slice CT scan with contrast that extends from the femoral artery to the subclavian artery the cornerstone of evaluation. Arteriography and intravascular ultrasound (IVUS) can add additional data but are not considered acceptable as standalone imaging modalities. For the non-interventionist, it is important to remember that the size of the catheters to be used is listed as the outer diameter (OD), while the size of the sheaths to be used is listed as the inner diameter (ID). In the French sizing system, 3 Fr equals 1 mm — therefore, the ID of the 18-Fr, 22-Fr, and 24-Fr sheaths are 6 mm, 7 mm, and 8 mm respectively. In general, the outer diameter is about 1 mm larger, which is important in planning access. In noncalcified arteries, we can generally insert a sheath through an artery that is about 0.75% of the sheath’s outer diameter; in a heavily or circumferentially calcified artery, we need an artery that is 1.25% of the sheath’s outer diameter. This translates into minimal vessel diameters of 6 mm, 7 mm, and 8 mm in noncalcified arteries and 7 mm, 8 mm, and 9 mm for heavily calcified arteries using the 18-Fr, 22-Fr, and 24-Fr sheaths, respectively. Most tortuosity will straighten adequately for sheath insertion once a stiff wire is placed, but extreme tortuosity should be avoided as it may lead to sheath kinking and an inability to deliver the device. Two special circumstances deserve mention. The first is previously placed Dacron grafts in the aortoiliac position. These may prove problematic to cross with large sheaths as they can accordion and bind the sheaths. While they may be used, the size, path, and any redundancy of the graft should be considered. Second, abdominal aortic aneurysm (AAA) can pose a hazard in crossing and device insertion if the sheath ends within the aneurysm itself. If the iliofemoral route is to be used with an AAA, it is important to choose a sheath with enough length to extend above the AAA so that all device changes occur outside of and not within the AAA. At the Methodist DeBakey Heart & Vascular Center (MDHVC), our approach is to always use the iliofemoral route when possible. Vascular complications are common with TAVR and can increase early and late mortality, and they are best avoided by careful screening and choosing a non-iliofemoral approach in questionable cases. This manuscript discusses our approach to TAVR access, closure, and complications that can occur.
Femoral Access

Femoral access is the preferred placement methodology when possible, and we have discussed our requirements in considering this approach above. We generally access both femoral arteries for femoral access TAVR — one femoral artery is for placement of the 18-Fr sheath, and the other is for placement of a 5-Fr graduated pigtail catheter through a 6-Fr sheath into the noncoronary sinus as a marker for valve placement and to allow arteriography during placement for positioning. We occasionally use access from the arm for this. The nondevice sheath femoral artery is punctured first using a micro puncture needle, and a 6-Fr sheath is placed after fluoroscopic confirmation of appropriate wire position from the micro puncture needle. A contra or a lima catheter and a 0.035-mm glide wire are used to access the opposite iliofemoral system and then place a 0.018-mm safety wire. The safety wire allows access contralateral to the iliofemoral system on the sheath side if injury is noted during sheath insertion or removal. The sheath side may be accessed by direct surgical cut down or percutaneously, which is our preferred approach when appropriate. For the percutaneous approach we use fluoroscopy and the safety wire to guide puncture of the common femoral artery and placement of a 6-Fr sheath. A soft, J-tipped 0.035-mm wire is placed into the descending thoracic aorta (DTA), and two ProGlide closure devices are used to “pre-close” the puncture site. The soft J-tipped wire and an exchange catheter are inserted into the DTA. The soft wire is exchanged for a super-stiff Amplatz wire, and the catheter and 6-Fr sheath are removed. Progressive dilators of 10 Fr, 12 Fr, 14 Fr, and 18 Fr are used to dilate the access vessels, and the 18-Fr sheath is then inserted into the proximal abdominal aorta. Balloon aortic valvuloplasty and subsequent device placement are then done through the 18-Fr sheath.

Noniliofemoral Access

Femoral access is our preferred insertion route. When this is not possible or safe, we use a noniliofemoral approach. Since the MDHVC is a CoreValve Trial site, we use the subclavian artery as our next option and, after that, a direct aortic option if subclavian artery insertion is not possible or safe. We have recently begun implantation of the Edwards SAPIEN Valve, which may be inserted directly through the left ventricular apex via a small left thoracotomy or by the direct aortic approach.

Subclavian Access

The subclavian artery has recently become a site of access for TAVR.4 5 The subclavian artery can be easily exposed in the deltopectoral groove of the anterior chest wall (Figure 1). We make a 3-cm incision in the deltopectoral groove that is carried down to the fibers of the pectoralis major, which are split along the lines of their fibers and retracted. The pectoralis minor can then be retracted or divided to expose the subclavian artery. It is important to remember that the brachial plexus is just superior to the subclavian artery, and care should be taken in this dissection. The artery is surrounded with a vessel loop and a purse-string suture of 5-0 polypropylene placed in the anterior artery wall. The center of this purse string is punctured with a standard needle, and a soft, J-tip 0.035 wire is placed with a 6-Fr sheath placed over this. A catheter is placed over the wire into the ascending aorta, and then the soft wire is exchanged for a super stiff Amplatz wire. Dilators of 10 Fr, 12 Fr, 14 Fr, and 18 Fr are then passed over the stiff wire. This allows the 18-Fr sheath to then be passed through the subclavian artery into the proximal ascending aorta. From this point the device insertion follows a standard procedure. In general,
we have found it easier to insert and control the position of the device due to the proximity of the insertion site to the annulus. After the sheath is withdrawn at the end of the procedure, the purse-string suture is tied and additional sutures placed under direct vision as needed.

Two points should be noted when using the subclavian artery. Use of the right subclavian artery is possible but becomes technically difficult for device positioning if the aortic valve annulus is much more than 30 degrees off the horizontal plane. Additionally, if a patent internal mammary artery (IMA) graft is present, ischemia must be carefully watched for since sheath obstruction or artery injury can limit flow during or after device placement. To access a video of the subclavian access approach, visit www.debakeyheartcenter.com/journal/video

Direct Aortic Access

When iliofemoral or subclavian access is not possible, a direct aortic approach can be carried out via a small right upper “J” hemisternotomy (Figure 2) or a small right anterior thoracotomy (Figure 3).6,7 Both approaches allow exposure of the proximal ascending thoracic aorta. The pericardiun is opened and sutured to the skin edges to create a cradle in which to work and serve as retractors to keep lung and mediastinal tissues out of the working field. Two concentric pledged purse-string sutures of 3-0 polypropylene are placed at the intended insertion site. The center of these sutures is punctured with a standard needle; similar to subclavian access, a soft J-tip 0.035 wire is placed and a 6-Fr sheath placed over that. We then use an AL1 catheter and a soft straight-tip 0.035 wire to cross the aortic valve. The AL1 catheter is advanced into the left ventricle (LV) and a soft 0.035 J wire is placed. An angled 6-Fr pigtail catheter is then placed over this wire into the LV. A super-stiff Amplatz wire is then advanced over the pigtail catheter into the LV for support. The pigtail catheter is removed with the 6-Fr sheath, and the 18-Fr sheath is inserted. All currently available sheaths are intended for peripheral insertion and therefore have a long dilator segment and no “bumper” on the catheter to seat against the aortic wall, as have most aortic cannulae for cardiopulmonary bypass (CPB).

To insert a Medtronic CoreValve, we need 55 mm for the length of the valve itself and a planned 10 mm for the sheath in the aorta as the depth of sheath insertion into the aorta. Prior to sheath placement we obtain an arteriogram with a graduated pigtail catheter in the non coronary cusp of the aortic valve and a marker at the site of planned sheath insertion to assure that at least 65 mm of space exist from the planned depth of valve insertion to the sheath itself to allow for valve release. We currently modify a standard 18-Fr sheath by placing a silicone ring from an aortic cannula to mark the 1-cm mark, which controls insertion depth. Once inserted, one of the purse-string sutures is tightened with a tourniquet and tied to the cannula. The other is tightened with a tourniquet but not tied to the cannula to allow rapid tightening if the cannula is to dislodge in any way. With little cannula inside the aorta, we suture the cannula to the skin with a second suture for added security. Valve insertion tends to be relatively easy with this approach as the operator is close to the insertion site and has not had to come around the arch, so that much less tension builds within the catheter system. When finished, the purse strings are tied under direct vision similar to decannulation after CPB. Chest wall closure is in standard surgical fashion. The hemisternotomy approach has the advantage of not transgressing the pleura and usually gives a broader field of aorta to choose from for insertion. The thoracotomy approach has the advantage of avoiding patent coronary bypass grafts which are usually on the left side of the aorta, and in that future refinement could lead to a port-access approach. To access videos of a direct aortic access mini sternotomy and right anterior mini thoracotomy, visit www.debakeyheartcenter.com/journal/video

Transapical

The Edwards SAPIEN valve has been inserted using a direct transapical approach in patients without suitable iliofemoral vessels. A small left anterior thoracotomy is made to expose the apex of the LV after opening the pericardiun (Figures 4A, 4B). The pericardium can be sutured to the skin edges to expose and stabilize the heart. Two concentric purse-string polypropylene sutures are placed with generous bites of the ventricular wall. The 26-Fr transapical sheath can be inserted directly into the LV apex inside of these purse-string sutures. After valve deployment, rapid ventricular pacing is used during sheath removal and suture tying to reduce pressure until the repair is complete.
Transapical vs. Direct Aortic

Transapical and direct aortic have the disadvantage of both being “surgical” procedures that violate a body cavity. Neither destabilizes the chest wall as the thoracic cage is left intact. Both avoid crossing the aortic arch with the device during delivery and this has theoretical advantages in stroke prevention. Both allow delivery of the valve from an area much closer and without the tension inherent in a curved system such as the delivery system going around the aortic arch. Operators have generally found implantation to be easier and more accurate with these approaches. One significant difference is that the direct aortic approach can be used with both the CoreValve and the SAPIEN valve while the transapical can be used with the SAPIEN alone. Most cardiac surgeons have cannulated the ascending aorta hundreds to thousands of times in their careers for standard cardiac surgery and are very comfortable with this technique, whereas few have substantial experience with the cardiac apex.

Closure

All non-iliofemoral and open-access femoral approaches are closed under direct vision using standard surgical techniques. We use two ProGlide devices to close our percutaneous iliofemoral access cases. Technical aspects of closure and results have been previously reported and are not the subject of this manuscript. An arteriogram is obtained after femoral or subclavian closure to insure vessel patency without flow-limiting lesions prior to leaving the hybrid room.

Complications

TAVR is a complex procedure in high-risk patients, and a large number of complications are possible. The most common complications are vascular and related to access. Early papers on TAVR complications can be difficult to interpret due to a lack of uniform definitions for the complications. Recently, the Valve Academic Research Consortium (VARC) issued a consensus report suggesting definitions for vascular complications to allow standardization and comparison between studies. Major bleeding complications occurred in 16.2% of TAVR patients in the PARTNER B trial and 11.0% of TAVR patients in the PARTNER A trial. Bleeding complications tend to occur more frequently and be more severe in transapical cases. Follow-up of patients who experience and survive a major bleeding event shows that it has an adverse effect on midterm survival.

Conflict of Interest Disclosure: All authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and the following was reported: Dr. Reardon is a consultant for Medtronic and is a principal investigator for the CoreValve® US Pivotal Trial.

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Keywords: transcatheter aortic valve replacement, TAVI, TAVI access, iliofemoral access, femoral access, aortic stenosis, PARTNER trial, Edwards SAPIEN valve, Medtronic CoreValve, ProGlide device

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COST-EFFECTIVENESS ANALYSIS OF TAVR
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Abstract
Transcatheter aortic valve replacement (TAVR) has rapidly gained worldwide acceptance for treating very high-risk patients with symptomatic severe aortic stenosis. Two valve systems are currently in common use worldwide and under trial in the United States. The Edwards SAPIEN valve has completed its PARTNER trial and has been approved for use in nonoperative patients. The Medtronic CoreValve is currently completing its US pivotal trial. Both plan studies of intermediate-risk patients. The use of TAVR in Europe has grown rapidly and is now about 23% of the total aortic valve replacements done in which a tissue valve is chosen (generally patients over 60 to 65 years of age). This technology is used in a patient population that was either not receiving any surgical therapy due to extreme risk or was considered very high risk for conventional surgery. The procedure requires a highly trained TAVR team, advanced imaging, and the devices themselves, which are expensive. Medical device trials are generally designed to establish if the device works as planned. For TAVR in today’s world of rising health care costs, the additional question of cost effectiveness is important to address. Fortunately, the PARTNER trial addressed this and the CoreValve trial has built this into the trial design as well. This article examines what is currently known about the cost-effectiveness of TAVR.

Introduction
Cardiac valve disease is the basis for about a third of cardiac surgical procedures and is associated with substantial mortality and morbidity. As our population ages, it can be expected that cardiac valve disease will increase in parallel. More and more, clinicians are seeing patients with symptomatic severe aortic stenosis who are very advanced in age and have severe comorbidities or significant frailty, making operative intervention either impossible or very high risk in the eyes of the referring physician and/or cardiac surgeon. Transcatheter aortic valve replacement (TAVR) has recently emerged as a possible solution for this patient population. The rising cost of health care has stimulated increased interest in the cost-effectiveness of new treatments such as TAVR. Most published studies on TAVR to date have focused on feasibility and effectiveness without much attention focused on cost. Only one randomized clinical trial (RCT) has been completed and published thus far, and that is the PARTNER trial. A second RCT, the CoreValve US Pivotal Trial, is enrolling. Both of these trials captured economic and quality of life data that will make cost-effectiveness analysis of TAVR possible. The ideal time to evaluate the cost-effectiveness of a new therapy is during the initial RCTs used to evaluate effectiveness. Although this is rarely done, with TAVR, the PARTNER Trial and CoreValve US Pivotal trial are designed to allow this. The purpose of this manuscript is to discuss the cost-effectiveness of TAVR based on information gleaned from these trials to date.

Analyzing Cost Through Quality Adjusted Life Years
Most clinicians are used to looking at a new therapy and asking if it will make their patient live longer and/or live better. Cost-effectiveness analysis adds cost to this decision. The most commonly used metric is “quality-adjusted life years” (QALY), a composite of the extra years of life gained with a treatment and the quality of that life as measured by a utility. The utility is on a scale of 0 to 1, where 0 is no different than death and 1 is perfect health. This utility number is then multiplied by the additional survival to obtain QALY. The utility score is generally an empiric measurement extracted from patient interviews or quality of life questions. Although QALY is the most commonly used metric to compare cost-effectiveness, clinicians recognize that utility scores are subjective and may not always match the wishes of individual patients. Noting these limitations, we will use QALY as our yardstick to ask if TAVR is reasonable from a cost-effectiveness standpoint.

A number of effectiveness studies and registries exist in Europe and Canada, where TAVR is already in commercial use. These are all observational studies with no RCT. Cost data are not consistently available and common definitions for complications are not often used in early studies, making inter-study comparisons difficult. These studies have generally been interpreted to show efficacy of the therapy but cannot address cost effectiveness. The Health Technology Inquiry Service of the Canadian Agency for Drugs and Technologies in Health published a study called Percutaneous Heart Valves for Valvular Heart Disease: An Updated Review of the Clinical and Cost-Effectiveness and Guidelines on April 30, 2010. This study examined the English and French literature on TAVR and asked three research questions:
Table 1. A comparison of QALY costs for TAVR to other generally accepted procedures.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>QALY</th>
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<tbody>
<tr>
<td>TAVR (PARTNER Cohort B)</td>
<td>$61,889</td>
</tr>
<tr>
<td>AVR (octogenerians)</td>
<td>$27,182</td>
</tr>
<tr>
<td>CAB (BARI data)</td>
<td>$14,294</td>
</tr>
<tr>
<td>Stenting (BARI data)</td>
<td>$15,179</td>
</tr>
<tr>
<td>Heart Transplantation</td>
<td>$38,000</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>$77,000</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>$26,000</td>
</tr>
<tr>
<td>LVAD</td>
<td>$78,000</td>
</tr>
<tr>
<td>Driver side air bag</td>
<td>$24,000</td>
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</table>

Grades for Adoption

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Compelling evidence for adoption and appropriate utilization. The new technology is as effective as or more effective than the existing one and is less costly</td>
</tr>
<tr>
<td>B</td>
<td>Strong evidence for adoption and appropriate utilization</td>
</tr>
<tr>
<td></td>
<td>a) The new technology is more effective than the existing one and costs less than $20,000 per QALY gained</td>
</tr>
<tr>
<td></td>
<td>b) The new technology is less effective than the existing one, but its introduction would save more than $100,000 gained</td>
</tr>
<tr>
<td>C</td>
<td>Moderate evidence for adoption and appropriate utilization</td>
</tr>
<tr>
<td></td>
<td>a) The new technology is more effective than the existing one and costs $20,000 to $100,000 per QALY gained</td>
</tr>
<tr>
<td></td>
<td>b) The new technology is less effective than the existing one but its introduction would save $20,000 to $100,000 per QALY gained</td>
</tr>
<tr>
<td>D</td>
<td>Weak evidence for adoption and appropriate utilization</td>
</tr>
<tr>
<td></td>
<td>a) The new technology is more effective than the existing one but costs more than $100,000 per QALY gained</td>
</tr>
<tr>
<td></td>
<td>b) The new technology is less effective than the existing one but its introduction would save less than $20,000 per QALY gained</td>
</tr>
<tr>
<td>E</td>
<td>Compelling evidence for rejection. The new technology is less effective than or as effective and as the existing one and is more costly</td>
</tr>
</tbody>
</table>

1. What is the clinical effectiveness of percutaneous heart valves for the treatment of patients with valvular heart disease?
2. What is the cost-effectiveness of percutaneous heart valves for treatment of patients with valvular heart disease?
3. What are the guidelines for the use of percutaneous heart valves for patients with valvular heart disease?

At the time of this publication, the PARTNER Trial had not been published and the authors noted that the lack of RCT and baseline differences made interpretation difficult. They summarized that “no conclusion about the cost-effectiveness and guidelines for percutaneous heart valves could be made from the identified literature.” This is in contrast to studies showing the cost-effectiveness of surgical aortic valve replacement (AVR) in the elderly population. Long-term survival and quality of life following cardiac surgery in the elderly has been shown to be good.4 Surgical AVR in the elderly has also been examined and found to yield a cost of $13,528 per QALY gained.5

Fortunately in the only RCTs — the recently published PARTNER Trial and the currently enrolling CoreValve US Pivotal trial — both collected extensive cost and quality of life data. Adding economic data to these already complex clinical trials is costly. The funds for these research trials, like funds for health care in general, are limited and the sponsors are to be applauded for their inclusion. This is especially true since the aim of the sponsor is generally to get their device approved; economic data does not aid this approval and could conceivably produce data that is harmful to device acceptance. Both trials have similar designs, with each having two arms: an extreme-risk or non-operative arm, and a high-risk arm in which patients could undergo open AVR but at high risk. The cost-effectiveness data for the nonoperative arm of the PARTNER Trial, known as Cohort B, was presented at the American College of Cardiology meeting in New Orleans in 2011 by Matthew Reynolds on behalf of the PARTNER investigators.6 The PARTNER Cohort B compared TAVR to best medical therapy and had a 20% absolute survival difference in favor of TAVR at 1 year. Reynolds established a primary endpoint of incremental cost-effectiveness based on survival, quality of life, medical resources used, and billing data. His secondary endpoint was QALY based on survival, quality adjusted survival, and costs beyond 1 year. He used $30,000 as an estimate for the cost of the valve itself and an initial TAVR procedure cost of $78,563. Data was available for the first year of the trial, and EQ-5D7 utilities (a standardized measure of health status) were measured at baseline, 1, 6, and 12 months. This was combined with a parametric survival model fitted to trial data to extrapolate patient survival beyond the current follow-up period to determine QALY. Costs during the last 6 months in [6]% was applied to all future costs, life years, and QALY, which is consistent with guidelines. TAVR in 175 patients was available for analysis. Of those patients, 164 (93.7%) received one device, 10 (5.7%) received two devices, and 1 (0.6%) received three devices. This resulted in a procedure cost of $42,806 +/- $15,206. There was $30,756 for nonprocedural costs and $4,978 for physician fees to account for the total cost of $78,563. Increased post-procedure hospitalizations led to a first-year cost of $52,724 in the control group compared to a first-year post-procedure cost of $29,352 in the TAVR group. The final assessment finds the cost of QALY for TAVR in the PARTNER trial Cohort B nonsurgical arm to be $61,889. This cost-effectiveness analysis cannot be extended beyond the nonsurgical Cohort B arm of the trial. The 1-year survival in the high-risk surgical arm (Cohort A) was not significantly different between patients receiving TAVR and those receiving standard open AVR. Hopefully an economic analysis of Cohort A will be published in the near future.
Comparative Cost of TAVR vs. Standard Procedures

Is a cost of $61,889 for QALY for TAVR reasonable? This is a complex question, and the answer may differ according to the point of view of the questioner. Clinicians care for one patient at a time, and everything that occurs to that individual patient is a 100% occurrence. The goal of the physician is to aid that individual in achieving better survival and better health. Untreated symptomatic severe aortic stenosis is associated with a mortality of about 2% per month in this patient cohort and continued decreased quality of life during survival due to continued symptoms that are often severe and limiting. Almost any cost would appear worthwhile if treatment was successful at reasonable risk. For health care planners, this question is generally aimed at population health versus individual health. It can be helpful to compare QALY costs for TAVR to other generally accepted procedures. Standard AVR in octogenarians who are already candidates for open surgery has a QALY cost of $27,182. Coronary artery bypass from the BARI study has a QALY cost of $14,292 and stenting a QALY cost of $15,179. Heart transplantation yields a QALY cost of $38,000, lung transplantation a QALY cost of $77,000, and liver transplantation a QALY cost of $26,000. Left ventricular assist devices have a QALY cost of $78,000. Even driver-side air bags in cars have a QALY cost of $24,000 and extend to over $66,000 if a passenger-side airbag is included. This would appear to place TAVR well within the financial cost structure that society already accepts (Table 1).

The actual acceptance of TAVR or any other new technology is a complex combination of therapy effectiveness, economics, politics, and ethics. Planners within the Canadian system have attempted to quantify the economics of acceptance of new technology. They graded new technology into five grades based on cost and effectiveness. Grade A technology is as or more effective than older technology and costs less — a compelling reason to accept this technology. Grade E technology is less effective than old technology and costs as much or more — clearly reason to reject the new technology. Grades B, C, and D are broadly defined by increased cost of the new technology being less than $20,000 in grade B, $20,000 to $100,000 in grade C, and more than $100,000 in grade D (Table 2). Grade B technologies are routinely accepted by society as a good use of healthcare resources; coronary artery bypass is a good example of a grade B technology. Grade C technologies are also generally accepted by society as reasonable, with a good example being hemodialysis for renal failure. Grade D technologies can be more difficult to assess and in countries such as Great Britain can exceed what is considered reasonable, which is generally £30,000 ($47,452 US). This is further complicated by the fact that new procedures in surgery and interventional cardiology are often adopted based on their ease of use rather than efficacy, and TAVR is a complex procedure with a substantial learning curve.

Further data on the cost-effectiveness of TAVR should be forthcoming after analysis of the PARTNER Cohort A study and the CoreValve US Pivotal Trial. Given the high level of acceptance in Europe, where the TAVR valves are already commercially available, there is a high likelihood of acceptance in the United States if efficacy data from the two US randomized controlled trials is positive.

Conflict of Interest Disclosure: All authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and the following was reported: Dr. Reardon is a consultant for Medtronic and is a principal investigator for the CoreValve® US Pivotal Trial.

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Keywords: transcather aortic valve replacement, TAVR, PARTNER trial, Medtronic CoreValve, CoreValve US Pivotal Trial, quality-adjusted life years, QALY, percutaneous heart valves

References

MULTIMODALITY NONINVASIVE IMAGING FOR TRANSCATHETER AORTIC VALVE IMPLANTATION: A PRIMER

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Abstract
Transcatheter aortic valve implantation (TAVI) has recently emerged as a treatment option for patients with severe aortic valve stenosis (AS). For patients who are deemed inoperable for surgical aortic valve replacement (SAVR), TAVI has a significant mortality benefit compared to medical therapy. This review discusses established and emerging roles for multimodality imaging and focuses on the application of these technologies for patient selection, intraprocedural guidance, and the detection and quantification of acute and chronic complications of this novel procedure.

Background
Currently there are two different valve systems that have been approved for TAVI (Table 1). The Edwards SAPIEN Transcatheter Heart Valve System was approved in Europe in 2007, and its use has been reported widely in multiple registries including the Source registry. It was also studied in two recent landmark randomized controlled trials. Both trials reported a significant mortality benefit in patients with extreme risk for SAVR and noninferiority to SAVR in patients who had a high preoperative risk assessment. The Edwards SAPIEN valve is a balloon-expandable valve that is cylindrical in shape and is constructed from leaflets made of bovine pericardium sewn within a stainless steel stent. The valve was designed to be implanted with the prosthesis positioned 2 to 4 mm below the annulus in the left ventricular outflow tract (LVOT). The current version comes in two sizes: the 23-mm valve, which is designed for patients with an aortic annulus of 18 to 21 mm in diameter, and a 26-mm valve designed for patients with an annulus from 22 to 25 mm diameter. The Edwards SAPIEN valve was recently approved by the US Food and Drug Administration for use within the United States.

The other major percutaneous aortic valve system is the Medtronic CoreValve ReValving System®. This system has also been in clinical use in Europe and Canada for several years, but its current use within the United States is limited to an ongoing clinical trial. This valve is an hourglass-shaped device that is considerably longer than the Edwards SAPIEN counterpart. The Medtronic CoreValve is designed of porcine pericardial tissue mounted within an asymmetric self-expanding nitinol stent frame (Figure 1). The lower edge of the device is designed to be implanted proximal to the aortic annulus, within the LVOT. The leaflet coaptation is considerably supra-annular, which is evident on the post-implant echocardiogram (Figure 2). The current commercially available CoreValve also comes in two sizes: a 26-mm valve designed for patients with an aortic annulus of 20 to 23 mm diameter, and the larger 29-mm valve designed for patients with annular diameters of 24 to 27 mm. A larger valve (31 mm) is under evaluation in a US registry and is approved for clinical use in Europe.

<table>
<thead>
<tr>
<th>Table</th>
<th>Aortic Annulus Diameter</th>
<th>Appropriate Valve Size *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards SAPIEN Valve</td>
<td>18-21 mm</td>
<td>23 mm</td>
</tr>
<tr>
<td></td>
<td>22-25 mm</td>
<td>26 mm</td>
</tr>
<tr>
<td>Medtronic CoreValve</td>
<td>20-23 mm</td>
<td>26 mm</td>
</tr>
<tr>
<td></td>
<td>24-27 mm</td>
<td>29 mm</td>
</tr>
<tr>
<td></td>
<td>26-29 mm</td>
<td>31 mm</td>
</tr>
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</table>

Table 1. Comparison of commercially available transcatheter heart valves. *Valve sizing is determined by the diameter of the most proximal portion of the valve stent. The larger CoreValve sizing reflects the more flared design of the proximal portion of the valve.

Figure 1. The two most commonly implanted transcatheter valves are the Edward SAPIEN valve and the CoreValve.

Figure 2. TEE depicting a deployed CoreValve. Note that the prosthetic leaflet coaptation point (blue arrow) is considerably distal to the aortic annulus (red line).
Selection of candidates for TAVI is complex and involves a multidisciplinary team approach; the process often employs a multimodality imaging strategy to fully delineate the complex anatomy of the aortic valve, aortic root, the entire thoracic aorta, and the peripheral arterial vasculature. In general, the severity of AS has been defined using echocardiography (echo) criteria. Most studies to date have defined severe AS as a mean transaortic valve gradient of at least 40 mmHg or a peak velocity of at least 4 m/second and a calculated valve area of less than or equal to 0.8 cm² (less than or equal to 0.5 cm²/m²). As such, a transthoracic echo with Doppler evaluation is the primary screening method to identify patients with severe AS. Echo is also used to assess aortic annulus size and to screen for the common anatomic or physiologic exclusions for TAVI.

Patient Selection

The appropriate patient for a TAVI procedure has senile degenerative AS of a trileaflet valve. Currently, TAVI is not indicated to treat aortic regurgitation or bicuspid valve stenosis. Although current AHA and ACC Guidelines define severe aortic stenosis as a valve area of less than 1.0 cm², the inclusion criterion for both the recent Edwards SAPIEN valve as well as the ongoing Medtronic CoreValve US Pivotal Trial both require a valve area of 0.8 cm² or less.

Echocardiography

In addition to establishing the severity of AS, a screening transthoracic echocardiogram is important to exclude common contraindications to TAVI, which include severe aortic regurgitation, severe mitral valve regurgitation, and significant hypertrophy of the proximal septum. Significant septal hypertrophy is a concern with the Edwards SAPIEN valve in particular as it has been associated with post-implant device migration. Another important role for the initial transthoracic echocardiogram is to determine the diameter of the aortic annulus to facilitate appropriate prosthetic valve sizing.

In general, the annulus is measured at the point of leaflet insertion into the LVOT tissue. It is widely acknowledged that this is not a true annulus, like the mitral valve annulus, but rather a reasonable anatomic reference. The method of measurement is made using a parasternal long-axis zoomed view of the LVOT (Figure 3). While the LVOT diameter can be used for determining LVOT stroke volume (via application of a continuity equation to determine aortic valve area), the annular diameter must also be reported to facilitate appropriate device sizing. In a patient with mild to moderate calcification, this measure is fairly reproducible and should be taken from the point of aortic cusp implantation into the tissues contiguous with the LVOT. On two-dimensional (2D) echocardiogram, the standard is to follow trailing edge to leading edge, meaning that the measurement starts at the anterior tissue-blood interface and continues down to the posterior blood-tissue interface. However, when there is severe valve calcification with ballooning artifact, one approach is to start at the anterior and posterior measurements adjusted roughly 1 mm into the calcification. This measurement methodology can be difficult when there is significant calcification and likely leads to some of the variability in measurements between transthoracic echo and CT or MRI discussed below. The other significant discrepancy between these multimodality measures is the fact that 2D echocardiogram is measured on a single plane that may not bisect the aortic annulus at its largest point, particularly if the aortic annulus is elliptical (Figure 4). For this reason, CT angiography is often a preferred method to more fully define the long-axis and short-axis diameter (and circumferential area) of the aortic annulus.

CT Angiography

Contrast computed tomography (CT) is a noninvasive technique that allows an accurate three-dimensional (3D) assessment of cardiac and vascular structures (Figure 5). In this regard it is well suited for evaluating potential candidates for TAVI, where adequate vascular access (Figure 6) and proper sizing of the valve prosthesis to the aortic annulus are critical issues.

Due to the relatively large diameter of the delivery sheaths (>18-20 French, 6-7 mm), the vascular diameters of the femoral and iliac arteries must be measured to determine whether the sheath and catheters can be safely advanced to the aortic root (Figure 7). CT allows assessment of not only the lumen diameter but also the arterial wall with regard to plaque composition and severity of calcification. Small luminal diameter and/or stenosis in addition to extensive and circumferential calcification increase the risk of complications such as arterial dissection or perforation. The 3D-rendered images display vessel tortuosity, information that assists the operator in safely advancing the device. In patients with either extensive lower-extremity peripheral vascular or aortic atherosclerotic disease (Figure 8), CT can measure the diameter of both subclavian arteries to determine whether they are suitable for deploying the device.

Figure 3. Transthoracic echo is used to assess AS severity and aortic annular diameter. (A) LVOT diameter (blue line) is usually used to derive LV stroke volume whereas aortic annular diameter (red line) is used for to determine appropriate prosthetic valve size. (B) Continuous wave Doppler recording is used to measure peak velocity and mean transvalvular gradient across the aortic valve.

**Figure 4.** Aortic annulus measurement by CTA. The annulus is defined at the transverse plane immediately below the lowest insertion point of the aortic leaflets as assessed by double oblique transverse images of the aortic root at the level of the basal ring. Measurements are taken from the systolic phase of the cardiac cycle when the valve is maximally opened. The perimeter of the basal annulus is traced manually. The measurements are performed in two planes because the annulus is usually elliptical in shape. First the major diameter through the center of the annulus is measured. The minor diameter is measured by tracing perpendicularly to the major diameter and through the center of the annulus. Note in this case, that the basal ring is fairly circular.
Figure 5. Three-dimensional (3D) volume-rendered image of aortic-iliofemoral vasculature by adjusting the CT attenuation threshold of the entire dataset (left to right) and using the bone-removal tool. The far right is a 3D volume-rendered image of the aortic-iliofemoral vasculature with bone removed. These images display the presence of significant arterial stenosis, areas of minimal luminal diameter, the presence and extent of arterial calcification and degree of vessel tortuosity. Presence of extensive calcified plaque, small arterial size, and significant tortuosity represent contraindication for transfemoral approach for TAVR.

Figure 6. Three-dimensional (3D) volume-rendered CTA image (left) and curved multiplanar reformation/reconstruction (right) displaying the right iliofemoral arteries of an 88-year-old female patient transferred from an outside institution for TAVR after an invasive coronary angiogram. This figure shows an example of an large pseudoaneurysm (*) of the right femoral artery. The patient underwent an ultrasound-guided direct thrombin injection into the pseudoaneurysm with a good result and she subsequently had a successful TAVI through the left femoral artery.

Figure 7. Curved multiplanar CT reformation and reconstruction using a centerline approach of the peripheral iliofemoral arteries and the entire aorta. Centerline image processing of the distal aorta and iliofemoral arteries allows measurement of the maximum and minimum arterial diameters at various levels as well as assessment of vascular dimensions, arterial calcification, and tortuosity of the vessels from the site of femoral puncture up to the aortic annulus. This figure shows an example of a 93-year-old male patient who was accepted for a transfemoral TAVI approach since he had adequate arterial sizes, paucity of calcification, and minimal vessel tortuosity.

Figure 8. Coronal oblique CT projection of distal aortic arch and aneurysmal descending thoracic aorta in an 86-year-old female. The presence of extensive and severe atherothrombotic plaque burden along the aorta (*) is a contraindication for the transfemoral approach.

Figure 9. Aortic valve area (AVA) by CTA. Computed tomography angiographic double-oblique transverse images of the aortic valve at the level of the cusp tips during systole when the valve is maximally opened (typically 30%-40% of RR-interval). The smallest aortic valve area is identified by scrolling up and down through the dataset. The AVA is then measured by planimetry. In this patient, planimetry reveals critical aortic stenosis with only a slit-like opening. The extent of leaflet calcification can also be quantified on either the contrast (above) or non-contrast CT study.

Figure 10. CTA of left ventricular outflow track (LVOT) aortic root angulation (ARA). Measurement of LVOT-ARA is performed using a coronal oblique projection and is defined as the angle between the axis of the first portion of the ascending aorta1 corresponding to the upper part of the bioprosthesis, and the LVOT axis2 corresponding the distal portion or landing zone of the prosthesis. This measurement is critical for determining whether the prosthesis will properly sit within the aorta. Patients with an LVOT-ARA >90 degrees are not candidates for TAVI.
Figure 11. Coronal oblique views of aortic root and thoracic aorta show a severely calcified aortic valve. Standard diameter measurements in the aortic root are made in systole at the level of the annulus, sinus of Valsalva, and sinotubular junction (STJ). Additional aortic root measurements include the maximum ascending thoracic aortic diameter and the sinus Valsalva height defined as the distance between the annulus plane and the STJ.

Figure 12. Assessment of the aortic arch and great vessels by CTA. (A) Assessment of ascending thoracic aorta, proximal aortic arch, and great vessel origins using a coronal oblique projection. Note the marked thickening and calcification of the aortic valves and relative absence of significant aortic atherosclerotic plaque. The distance between the aortic annulus and the left main coronary artery (arrow) can be accurately measured by CT so as to ensure that the prosthesis does not impede coronary blood flow once inserted. The great vessels arise normally off the aortic arch. (B) Transverse images of the aorta at the level of the ascending and descending thoracic aorta with measurement of their respective major and minor diameters. Note the absence of significant aortic atherosclerotic plaque.

Figure 13. CMR for the identification of aortic valve morphology and valve area.

CT provides a detailed evaluation of the aortic valve, the annulus, and its relationship to the coronary arteries. In this regard, AS severity can be evaluated by planimetry of the aortic valve orifice during systole (Figure 9). Previous studies have shown a good correlation between anatomic assessments of AS by CT as compared to functional assessments by echocardiography. The extent and severity of aortic valve leaflet calcification can be quantified from both contrast and noncontrast images. This is important since recent studies suggest a higher rate of post-procedure balloon dilation is required in patients with heavily calcified valves. Since the aortic annulus is generally oval in shape rather than circular, CT can also provide accurate measurement of the major and minor axes of the annulus, and its perimeter can be measured by planimetry (Figure 4). These measurements are critical for choosing the proper size prosthesis. An oversized prosthesis can result in damage to the annulus with subsequent heart block or potential coronary artery occlusion. An undersized prosthesis can lead to significant aortic insufficiency as well as device migration.

The ascending thoracic aorta and its relation to the LVOT (i.e., root angulation) can be assessed by contrast CT (Figure 10).

Root orientation is critical for precise positioning of the device along the centerline of the aorta and perpendicular to the valve plane. In addition, measurement of the aortic root, sinotubular junction, and sinus of Valsalva height are critical for proper positioning of the device and ensuring there is no infringement on the coronary ostia (Figure 11). As is routine for CT, the thoracic aorta can be assessed for aneurysmal dilatation, and the aortic arch and the great vessels can be visualized (Figure 12). In this regard, CT is a critical imaging tool when choosing the proper patient for a TAVI procedure, selecting the safest device delivery route, and properly sizing the device to the individual patient.

Cardiac Magnetic Resonance

While the full potential of cardiac magnetic resonance (CMR) in the preoperative and postoperative evaluation of TAVI is still being realized, there are a number of areas where it is showing great promise and in some cases is considered a mandatory imaging modality necessary for a structural heart program. In preoperative patient selection, CMR may be especially useful in quantifying the severity of AS if there is a discrepancy between clinical and echocardiographic examinations. Specifically, in individuals with technically limited echocardiographic images, CMR offers the ability to obtain an independent measure of peak aortic valve velocity using a phase contrast technique. High-resolution cine CMR imaging can provide a detailed anatomic assessment of the aortic valve that can be used to (1) identify the presence of congenital valvular abnormalities that may preclude TAVI (i.e., bicuspid aortic valve), and (2) obtain a directly planimetered aortic valve area (Figure 13). This has been shown to correlate well with transesophageal echocardiography (TEE) but does not require a semi-invasive procedure.

In those with AS and associated aortic valvular regurgitation, CMR is unique in that it is used to directly quantify valvular regurgitation in ml/minute rather than provide an estimate using another surrogate measure. It is also important to exclude the presence of significant associated mitral insufficiency as this can pose a relative contraindication for TAVI. CMR is a superb
associated coronary artery disease, helped to identify the occasional patients in whom determining optimal time for intervention but also for identifying using delayed-enhancement CM for significant concomitant valve dysfunction (M and aortic annular and annular root anatomy, and it can evaluate role.

Cine angiography remains the primary imaging modality to identify how the valve lesion(s) affects CM or coexisting lung disease. In addition to identifying the severity of valvular disease, CMR is the optimal modality to identify how the valve lesion(s) affects LV performance. Cine CMR techniques can be used to obtained highly reliable measures of LV regional function, dimensions, volumes, mass, and ejection fraction (Figure 14). Accurate assessment of these parameters is important not only in determining optimal time for intervention but also for identifying patients in whom TAVI is contraindicated (i.e., left ventricular ejection fraction <20%).

In patients with reduced LV systolic function, CMR can provide information about myocardial viability and scarring using delayed-enhancement CMR (DE-CMR). In patients with associated coronary artery disease, DE-CMR can help identify the extent of myocardial infarction, and in our experience it has helped to identify the occasional LV systolic dysfunction due to an associated infiltrative cardiomyopathy such as cardiac amyloidosis.

Procedural Guidance

Echocardiography

Cine angiography remains the primary imaging modality during a TAVI procedure. However, TEE plays a very important role. It can provide the baseline evaluation of aortic valve function and aortic annular and annular root anatomy, and it can evaluate for significant concomitant valve dysfunction (MR or AR). TEE also provides a baseline assessment of LV segmental wall motion and pericardial fluid collections that may be important should complications arise. The standard intra-procedural TEE typically includes a complete baseline study of all chambers and valves followed by a more detailed analysis of the LVOT and aortic root geometry. Deep transgastric views are often employed to optimize the Doppler assessment of LVOT stroke volume and aortic valve gradient. A midesophageal probe position, typically at 110 to 130 multi-plane degrees, permits a long-axis view of the left ventricle, left atrium, and LVOT (i.e., the “three-chamber view”) (Figure 15). At this view, the aortic annulus can be accurately measured as described above for transthoracic imaging. In addition, the proximal ascending aorta can usually be well delineated and the coronary sinuses easily identified. Often, a TEE within the operating room or hybrid OR-cath lab can be used to provide the required measurements of sinotubular junction diameter, sinotubular height from aortic annulus, and sinus of Valsalva diameter. The distance from the aortic annulus to the sinotubular junction is an important measure, particularly with the Edwards SAPIEN valve, to ensure that the length of the longest aortic cusp is less than the distance from the aortic annulus to the sinotubular junction of the ascending aorta. Failure to assess this may result in coronary ostial occlusion after device deployment. This initial view is also very helpful to assess the degree of aortic cusp and annular calcification as well as to delineate whether the calcification is symmetrically distributed throughout the valve circumference. Following this study of baseline morphology and function, the emphasis then turns to an evaluation of catheter and device positioning. As the interventional team places a pig-tail catheter into the noncoronary cusp (anatomically, the lowest cusp), they may ask the echocardiographer to confirm this catheter positioning. This can be accomplished by a 2D multi-planer assessment of the aortic valve in short-axis and long-axis, but it can be more quickly assessed using the x-plane (bi-plane) imaging feature now available when using a Matrix 3D TEE probe. When the aortic valve cusps and at least a portion of the fluid-filled catheter can be identified in simultaneous short- and long-axis views, then catheter position can be determined with confidence (Figure 16).

Currently, all patients undergo balloon dilatation of the native aortic valve immediately prior to TAVI. This critical step is not dependent on TEE guidance; however, an assessment of aortic valve regurgitation severity is often required immediately following balloon dilatation (Figure 17). The critical step of
deploying the stent-valve is often performed without real-time TEE imaging. In fact, in a minority of cases the TEE probe must be partially withdrawn because it may obstruct the cine angiographic views of the aortic valve. This imaging “conflict” is largely secondary to the chosen implant angle but may also be affected by other patient-specific features including the anatomic relation of the esophagus to the aortic valve.

Detection of Early or Late Complications

Echocardiography

The potential complications that can be encountered during a TAVI procedure have been well described. In general, they fall into three categories:

1. Disruption or perforation leading to acute hemopericardium and tamponade. This can occur with catheter perforation of the LV, pacemaker perforation of the RV, or balloon disruption of the aortic root (Figure 18). Intraprocedural tamponade requires emergent recognition by the echocardiographer and urgent action by the interventionalist-surgical team. It is important to evaluate for any pericardial effusion at baseline so that even a small change in pericardial fluid volume during the procedure will be quickly recognized.

2. New LV segmental wall motion abnormalities. An obvious concern after TAVI deployment is that of complete or partial occlusion of the left or right coronary ostia. While this is a rare complication, it must be recognized quickly to allow appropriate intervention. However, other events may cause transient changes in regional LV systolic function. Activation of the temporary pacemaker within the right ventricle may alter LV apical contraction. Likewise, a new left bundle branch block may occur immediately following TAVI (especially with the CoreValve) and must be considered when new wall motion abnormalities are encountered. In addition, global LV function may be adversely affected (often transiently) following rapid pacing and balloon aortic valvuloplasty.

3. Residual paravalvular aortic regurgitation (PVAR). Although trace or mild paravalvular AR is common, moderate or greater PVAR may have important acute and chronic hemodynamic consequences and must be further evaluated. Assessment of both the mechanism and quantification of PVAR often requires focused efforts immediately following the stent-valve deployment. The mechanism is often attributed to less than ideal device location either too low or too high relative to the aortic annulus. It is also recognized that other risk factors for significant PVAR include large annulus size and asymmetric annular and leaflet calcification.

The color Doppler jet of a paravalvular leak is often best appreciated from the deep transgastric TEE view (Figure 19). This view usually permits the best axial alignment for the quantitative Doppler measure of regurgitant pressure half-time. The midesophageal views provide the cross-sectional and long-axis views to facilitate identification of the site and extent of paravalvular leak. The vena contracta diameter and area can be assessed using 2D and 3D color Doppler application, respectively (Figure 20).

CT Angiography

Although rarely required, CT can be used to gauge the correct anatomic position of a catheter-deployed valve. Because of its excellent special resolution, CT can accurately indicate the depth of implant within the LVOT and can be used to assess stent shape. The latter may be particularly useful when there is concern about complete or partial stent deployment (Figure 21).
Figure 19. Doppler echocardiography is used to quantify paravalvular regurgitation severity. A deep transgastric TEE view with color Doppler is used to identify the site of regurgitation relative to the prosthetic aortic leaflets (identified in red). Spectral Doppler exam permits quantitative and qualitative assessment of the regurgitant jet (shown with perimeter traced for pressure half-time determination).

Cardiac Magnetic Resonance

CMR is also showing promise in evaluating postprocedural complications after TAVI. Care must be taken to utilize optimized imaging sequences to minimize metallic artifact from the implanted Core valve. In general, standard steady-state free precession (SSFP) cine sequences will yield greater artifact, but use of gradient recalled echo (GRE) based sequences with short echo times can help to reduce image artifact (Figure 22). Additionally, GRE-based phase contrast CMR techniques allow quantification of postprocedural aortic insufficiency volume by measuring aortic forward and reverse flow in the aortic root. While this requires further study, CMR may become the optimal method for assessing postprocedural aortic insufficiency as it is independent of jet morphology, unlike most echocardiographic techniques.

An important consideration is the performance of CMR in patients with implanted cardiac devices. Since a significant proportion of patients post-TAVI will require permanent pacemaker placement, the use of CMR would seem to be limited in this population. However, several recent studies have demonstrated that MRI may be safely performed in patients with implanted cardiac devices but requires device reprogramming and careful monitoring. While the worldwide experience with CMR in patients with devices is limited, the procedure is no longer considered an absolute contraindication at some centers with selected expertise. However, it is important to note that patients with recent devices (<6 weeks) cannot undergo MRI scanning, therefore the role of CMR in the immediate postoperative period may be limited. Nonetheless, for the more than 70% of TAVI patients who do not require permanent pacemaker placement, CMR may be a viable option if performed at centers with expertise.

Summary

As TAVI technology continues to evolve, so do the imaging modalities that support its use. Today the use of echocardiography (TTE and TEE) is firmly established for both patient selection and live intraprocedural imaging guidance (Figure 23). CT has also become a critical imaging component for patient selection. Not only is CT required to assess the peripheral arterial vasculature for catheter access and navigation, but CT has become increasingly important to assess the aortic root geometry and orientation to the LVOT — relationships that often cannot be assessed by echocardiography. Although CMR has a more limited role today,
it has already been shown to accurately assess AS severity, aortic root geometry, and peripheral vascular anatomy and function. It is likely that CMR will emerge as an increasingly important modality for the functional assessment of catheter-deployed valves over the next few years.

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References


Figure 22. Cardiac magnetic resonance uses phase contrast techniques to derive regurgitant flow by comparing total forward flow and reverse flow within the ascending aorta.

Figure 23. Three-dimensional TEE depicts comparative views of the aortic valve before and after TAVI. In this case, the lower portions of an appropriately deployed CoreValve are clearly visible within the LV outflow tract. The base of the anterior mitral valve (MV) is identified to orient the reader to this enface view of the aortic valve from the perspective of the LVOT.


COMPLICATIONS AT THE TIME OF TRANSCATHETER AORTIC VALVE IMPLANTATION

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Abstract

Transcatheter aortic valve implantation (TAVI) improves the prognosis of patients with severe aortic stenosis who are deemed too high risk for surgical valve replacement. However, this evolving technology is associated with a wide range of potential complications — some specific to TAVI, some often fatal. Prevention, early recognition, and effective treatment of these complications will significantly improve the outcome of this procedure and are essential prerequisites before the therapy is extended to lower-risk patient subsets.

Introduction

Complications at the time of transcatheter aortic valve implantation (TAVI) can be classified as cardiac vs. non-cardiac. Furthermore, some of these complications may be specific to TAVI as for example, valve malposition, paravalvular aortic regurgitation, and coronary obstruction or not specific to TAVI as vascular access complications and cardiac perforation/tamponade seen with also others endovascular interventions. Proper patient selection is essential to maintain a heightened awareness for possible complications that may occur during particular steps of the procedure. Operators must have an in-depth knowledge of the implantation technique and be familiar with techniques and materials required for bail-out procedures. In addition, each hospital should identify a heart team (specifically, an interventional cardiologist and cardiac surgeon); this is crucial for a successful outcome and for managing potential complications that may arise during implantation of the CoreValve ReValving System (Medtronic, Inc.). Among the possible cardiac complications of aortic stenosis repair, this manuscript will describe only those more specific to TAVI and will not discuss the less-specific vascular access complications.

Valve Malposition

Deployment of the Medtronic CoreValve prosthesis is performed in a controlled and step-wise manner. Even so, valve positioning remains one of the most challenging steps of the procedure, since valve malposition may still occur even after all necessary precautions have been taken. Normally, the CoreValve prosthesis should be positioned approximately 4-6 mm below the “aortic valve annulus.” A “too-low” implantation is defined as the distal edge of the valve frame (commonly referred to as the “inflow” aspect) positioned more than 12 mm below the annulus, into the left ventricular outflow tract (LVOT). A “too-high” implantation is defined as the inflow aspect positioned above the annulus level.

Low Implantation

Except in cases of severe left ventricular hypertrophy, a low implantation is generally associated with moderate (Grade II) to severe (Grade III-IV) degrees of aortic regurgitation (AR) on contrast aortography. Transesophageal echocardiography (TEE) can confirm the nature of the regurgitation (i.e., paravalvular vs. central).

In the case of “too-low” positioning associated with significant AR and hemodynamic instability, the first objective would be to manually reposition the valve using a “goose-neck” catheter (i.e., the “Lasso” technique). If unsuccessful, the second option would be to implant a second valve inside the first one (i.e., valve-in-valve technique) but positioned slightly higher.

Primary option: The “Lasso” Technique

The choice of projection on fluoroscopy is crucial and is dictated by the valve frame, which should be aligned as perfectly as possible. This will provide a reliable reference line when repositioning the valve. With this option, the operator advances a regular 20-35 mm “goose-neck” catheter alone or through a 7-Fr guiding catheter to engage one of the “loops” of the implanted valve. At this stage it is critical to understand that the success of this maneuver depends on applying torsion to the frame ("unscrewing the valve") rather than applying direct axial force, which frequently results in ejection of the valve into the ascending aorta. It is for this reason that the simultaneous use of two “goose-neck” catheters is strongly discouraged. Upon “loop” engagement, the operator applies gentle and slowly increasing torsion/traction to the “goose-neck” catheter under constant fluoroscopic guidance. After confirming mobilization of the valve with hemodynamic analysis, angiogram, and TEE, the “goose-neck” catheter is carefully detached and retrieved.

Alternative option: The Valve-in-Valve Technique

If the previously described technique of repositioning the valve is unsuccessful or is deemed too dangerous, correction of the severe AR can still be obtained using a second CoreValve implanted inside the first one in a slightly higher position. As with the previous technique, the correct projection is crucial and is dictated by the frame of the valve, which should be aligned as perfectly as possible. The operator advances the second valve into the previously implanted valve and calculates the position for
implantation with regard to the patient’s anatomy. In the case of complex anatomy (as per vertical aortic root), the operator secures the previously implanted valve using a “goose-neck” catheter, as previously described, to avoid dislodging the first valve into the left ventricular cavity when advancing the second valve. The operator then measures the overlap distance of the two valves to better understand the position of the second valve that will be implanted.

Certain steps can be taken to improve the accuracy of implantation. While focusing on the distal (inflow) aspect, the operator can release the second valve until it is one-third deployed, then focus on the proximal (outflow) aspect of the second valve and determine the optimal distance between the frame loops of the first and second valves. For this part it is important not to focus on the distal aspect (inflow) of the valves, because the “criss-cross” appearance of the struts will make it difficult to differentiate the individual valve frames. Once optimal distance between the outflow tips is determined, the operator can deploy the remainder of the valve while strictly maintaining the prescribed distance between the two frames.

After complete release of the second valve, it is likely that there will be no significant AR observed and, as a result, no need for balloon aortic valvuloplasty (BAV) post-implantation. When AR (grade ≥2) is observed, or when tortuous anatomies challenge the implantation of the second valve, the operator should assess for incomplete expansion and axialization of the second valve’s frame using control TEE or rotational fluoroscopy. If this is confirmed, BAV post-implantation should be considered.

**High Implantation**

With the possibility of full valve retrieval up to four-fifths of the way through the deployment process, such a situation should rarely occur except in cases of technical mistakes during the last steps of the procedure. Examples include (A) failure to notice incomplete disengagement of both frame loops from the delivery catheter before withdrawing the catheter; (B) failure to manage the distal tip of the delivery catheter (i.e., nose cone) through the prosthesis after successful valve deployment, resulting in tip displacement of the valve frame; (C) post-implant dilatation without the use of rapid pacing, or rapid pacing terminated too early relative to balloon inflation, resulting in ejection of the balloon-valve unit into the ascending aorta.

Unfortunately, a high implantation does not offer the same attractive options for correction as a low implantation. However, it is important to first clearly define the criteria for acceptable parameters despite a “too-high” implantation. To a certain extent, the sealing effect of the native calcified aortic valve around the frame (similar to a chimney above the annulus) can make a “too-high” implantation perfectly compatible with a good result, with no to mild or moderate AR. The control angiogram and the hemodynamic analysis provide the criteria for an acceptable result: (1) AR grade ≤2; (2) no ventricular-aortic gradient; and (3) no coronary occlusion. The last criteria, being the most important to analyze, may require additional aortograms in different projections and/or eventually selective catheterization of the coronary ostia to ensure coronary flow.

In cases where valve implantation is definitively “too high” and incompatible with an acceptable result, the valve can be repositioned into the ascending aorta. The primary goal is to ensure a safe area for the implantation of a second valve. As a result, the operator must reposition the first implanted valve high in the ascending aorta to avoid jeopardizing the functioning of the second valve by (1) severely restricting second-valve expansion, and (2) potentially compromising coronary arterial flow by creating a long skirt — a potential consequence of two valves placed in continuation.

Because the CoreValve prosthesis measures approximately 50-53 mm in height depending on valve size, a safe distance of >50 mm above the annulus level is optimal. Note that the “Lasso” technique for frame loop engagement to achieve higher repositioning of the valve has been previously described. In small anatomies, this technique may not be feasible due to lack of space in the ascending aorta that can nullify any axial force exerted through the frame loop. In such a case, the “goose-neck” catheter can be advanced through the struts of the frame towards the inflow aspect and “hooking” at that point. This allows for effective retrieval of the valve when pulling on the “goose-neck” catheter. Finally, and again for additional safety, the first valve should be secured in the correct position high in the ascending aorta with the use of the “goose-neck” catheter when a second valve is advanced through the first valve.

**Paravalvular Regurgitation**

Albeit not a true complication, AR grade ≥2 on a control angiogram or TEE is not rare (>20% of overall cases). This can occur for the following reasons: (1) Low implantation of the valve; (2) under-expansion of the frame in a severely calcified aortic valve; or (3) under-evaluation of annulus measurement. Severity of the AR should be evaluated carefully, but specific guidelines on how to quantify and classify the severity of paravalvular regurgitation in the context of TAVI are lacking.

Minimum basic rules should be followed. Transesophageal echocardiography requires longer duration of the regurgitant signal, eccentricity of the jet, and extension of the jet signal deep into the left ventricular cavity. Aortography requires a minimum of 20 ml of contrast media injection, right anterior oblique projection, and position of the pigtail catheter slightly above the functioning portion of the implanted valve for the angiogram to reflect an accurate AR evaluation. Despite adherence to these rules, different parameters can influence the degree of AR, such as blood pressure, heart rate, and LV dysfunction. Therefore, there is still the risk of underestimating the severity of the regurgitation at the time of implantation and having to face — during follow-up and under different hemodynamic conditions — a more severe AR. Also, the experience with TAVI does not differ from BAV in aortic valve disease, where grade III AR could be well-tolerated in the presence of left ventricular hypertrophy or previous AR and grade II AR not tolerated in the presence of poor left ventricular function.

Therefore, in addition to TEE and aortogram to evaluate the severity of AR, it is recommended that a hemodynamic analysis be added to assess the tolerance of AR.

As a result, one should always measure LV and aortic pressures before and after valve implantation to better define the strategy when facing AR grade ≥2 after CoreValve implantation. Simple criteria can be proposed to establish the potentially bad hemodynamic tolerance of AR grade ≥2 after valve implantation that could lead to a discussion of BAV. Examples of such criteria include: (1) ≤10 mmHg elevation of the LV end-diastolic pressure above the value prior to the implantation, or an absolute value above 25 mmHg; (2) ≥10 mmHg decrease of the diastolic pressure below the value prior to the implantation for a similar systolic pressure, or an absolute diastolic pressure value below 50 mmHg; (3) no “dicrotic notch” on the aortic pressure tracing; and (4) tachycardia.
The decision to perform BAV after CoreValve implantation should always be evaluated carefully with regard to the potential consequences of BAV, such as dislodgement of the valve and structural damage to the valve tissue, which may not become evident before mid- or even long-term follow-up. Although to date nothing is known about the effect of BAV on long-term durability of the valve, a conservative approach is mandatory.

**Pericardial Effusion/Pericardial Tamponade**

The causes of pericardial effusion are multifactorial. It is important to note that an effusion can occur promptly during valve implantation or it can be delayed. The source of bleeding can be the right or left ventricle, the aortic root, or the ascending aorta. Injury of the right ventricle may result from perforation of the transient pacemaker wire. Injury of the left ventricle may result from perforation of the stiff guide wire or of the catheters after valve passage. Aortic root rupture may occur after balloon valvuloplasty or after valve implantation, especially in elderly women with fragile tissue where bulky calcifications can perforate the aortic root. Some preventive strategies can help to avoid those injuries; for example, to prevent aortic root rupture, meticulous annulus measurements should be performed by computed tomography, TEE, and transthoracic echocardiography to avoid oversizing of the balloon or prosthesis.

The following describes an algorithm for managing pericardial effusion. As a standard of care, all patients should undergo echocardiography to identify possible pericardial effusion at the end of the implantation procedure. Small effusions <10 mm without hemodynamic impairment should be monitored echocardiographically at close intervals. Patients with rapidly increasing effusions and effusions with hemodynamic impairment (central venous pressure increase, blood pressure decrease, tachycardia) should undergo pericardial puncture. If improvement of symptoms is not achieved, an emergent surgical sternotomy should be performed.

**Low Cardiac Output/Cardiogenic Shock**

Intraprocedural circulatory depression may occur in up to 20% of patients during implantation. Cardiac depression with low cardiac output may follow long periods of rapid pacing or may be the consequence of inadequate coronary perfusion due to low intra-aortic pressure. Coronary perfusion may also be impaired when the remaining aortic valve orifice is partially or completely occluded during the placement of the catheter-mounted valve. Another reason for cardiac depression may be the sudden onset of severe bradycardia or third-degree AV block following balloon dilatation of the aortic valve or deployment of the valve prostheses. Furthermore, obstruction of coronary ostia or severe AR after balloon dilatation or after deployment of the valve prosthesis may also cause severe cardiac depression.

To prevent or react adequately to this complication, it is mandatory that anesthesiologists keep in close communication with the implant team. In cases of bradycardia or sudden onset of third-degree AV block, ventricular pacing may quickly improve the circulatory condition. In other cases, if mild hypotension does not resolve spontaneously, it may easily be treated with bolus injections of catecholamines or a continuous infusion of low-dose dopamine or dobutamine. In cases of a more severe blood pressure drop, the management of norepinephrine, milrinone and/or levosimendan should be determined by the anesthesiologist.

Intraprocedural ventricular fibrillation is treated by electrical conversion followed by cardiopulmonary resuscitation. If those measures do not help to restore circulation, emergency institution of extracorporeal circulation is the only safe rescue therapy. In those cases, implantation of the valve should be continued during extracorporeal circulation so that the patient is weaned with the valve prostheses already in place.

**Coronary Obstruction**

Coronary obstruction during implantation is a rare entity, occurring in less than 1% of patients. The reasons for this potentially catastrophic event include (1) displacement of calcium deposits or large native aortic valve leaflets in front of the coronary ostia during valve deployment; (2) embolization of calcium debris into one of the coronary arteries; (3) aortic dissection with continuity of the rupture into the intima of one of the coronary ostia with resultant obstruction; and (4) a valve prosthesis that is implanted too high. In addition, coronary air embolism can lead to myocardial ischemia. The first reason described may be more frequent in the setting of a low-lying coronary artery and small coronary sinus diameters and may lead to subacute coronary occlusion. Except in cases of subacute obstruction, the first clinical sign of coronary obstruction is usually ST-segment elevation in the EKG recording or rhythm disturbances such as sudden third-degree AV block or ventricular fibrillation. In those cases, severe cardiac depression usually ensues, and the patient may go into cardiogenic shock. In cases of suspected coronary obstruction, a bolus angiogram of the aortic root may reveal which coronary vessel is involved. After that, selective intubation of the vessel ensues, followed by balloon dilatation or stenting of the coronary ostium. If the valve is implanted too high and coronary flow is impaired by the valve skirt, the prostheses must be immediately retracted into the ascending aorta to relieve the obstruction. The majority of coronary obstruction cases result in emergency cardiopulmonary bypass. If interventional measures fail to reconstitute coronary flow, emergent coronary artery bypass grafting or open removal of a malpositioned valve prosthesis is required.

**Conduction Abnormalities**

Considering the anatomic proximity of the conduction system to the aortic valve, it is not surprising that conduction abnormalities such as AV or bundle-branch block are known complications of TAVI even in the absence of surgical excision of valve or annulus tissue. The requirement for permanent pacing has been described as necessary in up to 20% of patients. The occurrence of new-onset left bundle-branch block (LLBB) during the procedure may occur in up to 40% of patients. Possible explanations include transient periprocedural inflammation, edema, and mechanical stress due to balloon or stent trauma or myocardial necrosis in the basal interventricular septum due to ischemia. In addition, this population of elderly patients, all with underlying organic heart disease, frequently exhibit pre-existing conduction abnormalities that are known to be associated with aortic stenosis.

There are no definitely known risk factors for peri- and postprocedural complete heart block; however, the occurrence of intraprocedural complete heart block, even when it is transient, and the presence of right bundle-branch block seem to be predisposing factors. In addition, relatively low positioning of the
valve within the left ventricular outflow tract and efforts to oversize the implanted prosthesis to securely fix it within the aortic annulus and thus minimize paravalvular regurgitation might play a role.

Prior to the implantation procedure, conduction abnormalities should be thoroughly documented by a 12-lead ECG to diagnose pre-existing AV block or left and right bundle-branch block. Intra- and postprocedural monitoring with a 3-lead rhythm strip has to be done continuously up to 5 days after the procedure since there have been case reports describing the late occurrence of complete heart block after TAVI. Other pre-existing episodes of bradycardia such as sinus node disease or symptomatic bradycardia may have been undetected in some patients before the procedure and are unrelated to TAVI. If there is an indication for a pacemaker implantation postoperatively, it is important to distinguish between a new-onset high-grade AV block, which may be related to TAVI, and other pre-existing bradycardias unrelated to TAVI.

A new-onset LBBB is not an indication for the implantation of a permanent pacemaker; the clinical implications of new-onset LBBB are currently unknown, but its occurrence after surgical aortic valve replacement is associated with 1-year mortality. Taking care not to implant the prosthesis too deeply may help to prevent the occurrence of high-grade AV block. Adequate sizing of the balloon and valve are mandatory to avoid serious complications such as valve migration or severe paravalvular leak. As with the use of relatively larger valve sizes, the risk of damage to the conduction system due to balloon and frame trauma might be higher; therefore, the balance between the anticipated complications must be considered carefully. Whether or not immediate pacemaker implantation is indicated even in cases of intermittent AV block is the subject of ongoing debate. In our opinion, with this population of elderly patients, all with underlying organic heart disease, we opt for patient safety.

Rhythm Disturbances

Patients scheduled for TAVI are considered to be a high-risk population with multiple comorbidities. One-half of these patients have coronary artery disease, one-third have atrial fibrillation, and up to one-fifth have left ventricular dysfunction and concomitant valve disease.

Atrial Fibrillation

Atrial fibrillation (AF) is known to increase the risk of stroke, which makes it difficult to distinguish between TAVI-related cerebrovascular accident (CVA) and AF-induced thromboembolic stroke. Keeping the higher stroke risk in mind, specific attention should be paid to anticoagulation management with Coumadin and recommended antiplatelet therapy. So far, there are no data concerning the optimal combination or duration of antiplatelet therapy and anticoagulation after the implantation of a catheter-based aortic bioprosthesis, especially in a population with a high risk of major bleeding events. When there is an indication for Coumadin intervention after TAVI, we first ensure that no bleeding complications have occurred (i.e., pericardial tamponade, bleeding at the vascular access site) and that the antiplatelet loading dose has been administered before initiating Coumadin. Patients who warrant anticoagulation therapy only receive aspirin in combination with Coumadin because we consider the risk of Coumadin therapy combined with a dual antiplatelet therapy to be too high.

Ventricular Tachycardia (VT), Ventricular Fibrillation (VF)

Considering the incidence of left ventricular dysfunction and significant coronary artery disease in these patients, spontaneous and sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) occur rather seldom during TAVI procedures (1-2%). Short self-limited VT is common, especially when manipulating the guide wire loop within the left ventricle. Sustained VT or even VF can follow the iatrogenic VT induced by rapid ventricular pacing, particularly in patients with preoperatively compromised left ventricular function. Of course, VT or VF can always be indicative of severe coronary ischemia during the intervention. Patients who have received an implantable cardioverter defibrillator prior to TAVI should have the antitachycardia algorithms turned off during the intervention so as not to interfere with the episodes of rapid ventricular pacing.

Conclusion

While TAVI is a promising therapy for high-risk patients who are not candidates for traditional open surgery, the procedure has inherent challenges that must be overcome before it can be considered a truly safe alternative. It is the responsibility of the heart team to collectively work towards decreasing the complication rate of TAVI and ensuring a safe and effective alternative therapy for patients.

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Keywords: transcatheter aortic valve implantation, TAVI, TAVR, aortic stenosis, Medtronic CoreValve, Lasso technique, paravalvular regurgitation

References

CYTOMEGALOVIRUS LOCALIZATION IN ATEROSCLEROTIC PLAQUES IS ASSOCIATED WITH ACUTE CORONARY SYNDROMES: REPORT OF 105 PATIENTS


Abstract

It has been shown that cytomegalovirus (CMV) is present in coronary atherosclerotic plaques, but the clinical relevance of this presence remains to be elucidated. In this study we sought to examine CMV infection in atherosclerosis patients defined by different methods and to identify the clinical significance of CMV replication in the atherosclerotic plaques. The study included 105 consecutive patients who were admitted to our department and underwent coronary artery bypass grafting (CABG) surgical interventions. Coronary atherosclerotic specimens as well as 53 specimens from the mamillary artery of these same patients were analyzed. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) methods were used for evaluations. The CMV PCR test result was positive for 28 (26.7%) of patients with coronary artery atherosclerosis. After adjusting for other risk factors, coronary artery disease patients with a history of acute coronary syndrome were more likely to be positive for CMV PCR test (P = 0.027; odds ratio: 4.2; 95% CI: 1.18-15.0). They were also more likely to have a positive family history for cardiovascular diseases (CVD). This study confirms previous evidence about the replication of CMV virus in the atherosclerotic plaques of coronary arteries and brings clinical significance to this observation by showing a higher prevalence of acute coronary syndromes in those patients with CMV-infected plaques. Our study also suggests a familial vulnerability to CMV replication in the coronary artery walls.

Introduction

The first evidence of a potential link between infective agents and atherosclerosis was found in bacterial infections and dates back to 1891, when Huchard suggested an association between childhood infections and the development of atherosclerosis in his article “Infectious diseases of childhood as potential cause of inflammation.” Shortly after, Weisel (1906), Klotz (1906), and Osler (1908) reported relationships between atherosclerosis and infective agents including streptococci, typhoid, scarlet fever, measles, and acute infections.1

After measles, Marek’s disease virus (MDV), a herpes-type DNA virus that is a well-demonstrated cause of T-cell type lymphomas, was the first viral agent to be associated with the development of atherosclerosis in the 1940s.2 Fabricant et al.3 also indicated that atherosclerosis appears only in MDV-infected chickens, which were fed with regular diets, but not in non-infected chickens that were fed with cholesterol-rich diets. Moreover, infected animals were much more likely to have visible atherosclerotic lesions compared to uninfected animals.4

Cytomegalovirus is one of the viruses accused of inducing endothelial injury, which has one of the highest prevalence rates in human populations. This virus causes a wide spectrum of disorders in human beings, ranging from a slightly symptomatic mononucleosis-like syndrome to life-threatening disseminated disease that occurs mostly in immunodeficient patients. CMV infection is also associated with severe birth defects when it occurs in pregnant mothers. Although it has been shown that CMV infection is associated with atherosclerosis, the exact pathogenesis of CMV-induced atherogenesis has not been well defined. Several studies have investigated the potential latency and replication sites of CMV to determine whether and how CMV infection can lead to atherosclerosis. Moreover, there is no mention as to whether or not CMV replication in the arterial walls can result in inauspicious outcomes.

In the current study, we sought to examine the prevalence of CMV antibody positivity rate in patients with atherosclerotic lesions. We also sought to use PCR methods to define the existence of CMV virus in these lesions. Finally, we wanted to determine whether CMV infection as a whole (antibody positivity alone)
is associated with atherosclerosis or if existence of the CMV virus detected by PCR methods is an independent predictor for atherosclerosis. Moreover, we tried to identify the clinical significance of CMV replication in the atherosclerotic plaques.

**Methods and Material**

Our study included 105 consecutive patients who were admitted to Baqiyatallah University of Medical Sciences hospitals between 2008 and 2010 with various manifestations of ischemic vascular disease and who underwent CAGB surgery. In addition, 53 specimens from biopsies of macroscopically healthy regions of the left internal mamillary artery were collected from these patients at the National Forensic Medicine Department. Data on demographics, smoking habits, lipid profiles, and medical histories were recorded for all subjects. Acute coronary syndrome was defined as myocardial infarction and/or unstable angina. A positive family history was defined when a positive history was reported on the first and second family members including parents, siblings, offspring, grandparents, uncles, and aunts. This study was approved by the University Research Review Board (URRB) and the Ethics Committee of Baqiyatallah University of Medical Sciences. All subjects provided written informed consent to participate in the study and were assured that their personal information will remain anonymous and confidential. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Tissue samples were dissected in the operating room and stored under sterile conditions. Artery segments were placed in microcentrifuge tubes without using binding buffer. Transport vials were sealed in the operating room and opened only in the laminar airflow safety cabinet at the microbiology laboratory. All of the specimens were kept at -20 degrees until processing. For preparation of genomic DNA and PCR, DNA was extracted from endarterectomy specimens by using the QIAamp DNA Mini-Kit (Qiagen, Inc., Valencia, CA, USA). The DNA absorbed in the QIAamp spin column was eluted with 55 µL of Tris-EDTA solution and then subjected to the PCR.

PCR was carried out for CMV using primers selected from the gB region of the CMV genome. The forward and reverse primers were 5'-CGG TGG AGA TAC TGC TGA GGT C-3' and 5'-CAA GGT GCT GCG TGA TAT GAA G-3' respectively. The reaction mixture of the PCR contained a total volume of 50 µL, including 75 mM Tris-HCl (pH 9), 1.5 mM MgCl2, 50 mM KCl, 20 µM of (NH4)2SO4, 50 µM of each one of the deoxyribonucleotide triphosphates, 20 µM of primers gBIand gB2, and 1 µg of DNA obtained from tissue. The reaction mixture was first incubated at 94°C for 3 mixtures, followed by 40 cycles at 94°C for 30 seconds, 55°C for 30 seconds, 72°C for 30 seconds, and finally for 3 minutes at 72°C. The PCR products were subjected to electrophoresis on a 2% agarose gel, and 257-bp amplicons were visualized by ultraviolet light after ethidium bromide staining. Each PCR assay included a positive control with HCMV AD169 DNA and a negative control containing no template (only distilled water). Serological evaluation of CMV IgG and IgM was performed using ELISA.

**Statistical analysis**

Data was analyzed using SPSS software version 17.0 (SPSS Corp., Chicago, IL, USA). Chi-square test, Fisher's exact test, and Kruskal-Wallis test were used where appropriate. Logistic regression models were used to evaluate independent associations of various factors with acute coronary syndromes. All statistical analyses were performed at the 0.05 significance level.

**Results**

Characteristics of the study participants are summarized in Table 1. Data of all 105 patients and their biopsy specimen were entered into analysis. CMV PCR test results were positive for 28 (26.7%) patients with coronary artery atherosclerosis, serologic test results showed only 4 (3.8%) positive cases for CMV IgM but 90 (85.7%) for CMV IgG tests, and 28 (26.7%) patients had a history of unstable angina or myocardial infarction. Coronary artery disease patients with a history of acute coronary syndrome were more likely to be positive for CMV PCR test (P = 0.05; Table 2). In order to evaluate a potential independent impact of CMV replication in the coronary artery wall on the incidence of unstable angina and/or myocardial infarction, we entered our data into a multivariable logistic regression model enrolling all factors that may affect these events, including age, gender, BMI, history of diabetes mellitus, triglyceride level, LDL level, and fasting blood glucose level. This model demonstrated that PCR-positive test for CMV is the only factor that independently increases the rate of unstable angina and myocardial infarction (Table 3).

We also reanalyzed data to find out whether CMV replication in the atherosclerotic plaques has any predictors. For this purpose, we correlated demographic and medical history of the patients (age, gender, weight, BMI, biochemical examinations, history of hypertension, smoking, and diabetes mellitus) with their CMV PCR test results. We found no difference between the two patient groups regarding any of the parameters.

### Table 1. Characteristics of the study participants.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (yr)</td>
<td>58.2 ± 10.6</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>73 (69.5)</td>
</tr>
<tr>
<td>Mean weight ± SD (kg)</td>
<td>76.7 ± 10.6</td>
</tr>
<tr>
<td>Mean BMI ± SD (kg/m2)</td>
<td>28.1 ± 4.0</td>
</tr>
<tr>
<td>IgG CMV (%)</td>
<td>90 (85.7)</td>
</tr>
<tr>
<td>IgM CMV (%)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>PCR CMV (%)</td>
<td>28 (26.7)</td>
</tr>
</tbody>
</table>

**Biochemical examinations**

| Triglyceride (mean ± SD)    | 195.3 ± 110.4   |
| Fasting blood glucose (mean ± SD) | 150.9 ± 67.2 |
| Cholesterol (mean ± SD)     | 203.8 ± 54.8    |
| LDL cholesterol (mean ± SD) | 97.1 ± 38.5     |
| HDL cholesterol (mean ± SD) | 42.2 ± 11.1     |
| CRP (mean ± SD)             | 1.7 ± 0.46      |

**Medical history**

| Hypertension (%)            | 57 (54.3)       |
| Smoking (%)                 | 26 (24.8)       |
| Acute coronary syndromes (%)| 62 (59)         |
| Diabetes mellitus (%)       | 54 (51.4)       |
### Table 2. Comparison of the study parameters in participants with or without acute coronary syndrome.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>History of acute coronary syndrome (ACS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACS</td>
</tr>
<tr>
<td>Mean age ± SD (yr)</td>
<td>59.9 ± 9.2</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>23 (69.7)</td>
</tr>
<tr>
<td>Mean weight ± SD (Kg)</td>
<td>75.5 ± 8.7</td>
</tr>
<tr>
<td>Mean BMI ± SD (Kg/m2)</td>
<td>26.9 ± 2.7</td>
</tr>
<tr>
<td>CMV IgG (%)</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td>CMV IgM (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CMV PCR (%)</td>
<td>13 (39.4)</td>
</tr>
</tbody>
</table>

#### Biochemical examinations

<table>
<thead>
<tr>
<th></th>
<th>ACS</th>
<th>No ACS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride (mean ± SD)</td>
<td>220.4 ± 121.7</td>
<td>178.3 ± 101.9</td>
<td>0.114</td>
</tr>
<tr>
<td>Fasting blood glucose (mean ± SD)</td>
<td>148.9 ± 57.9</td>
<td>154.5 ± 75.3</td>
<td>0.406</td>
</tr>
<tr>
<td>Fibrinogen (mean ± SD)</td>
<td>194.9 ± 57.1</td>
<td>206.7 ± 54</td>
<td>0.406</td>
</tr>
<tr>
<td>Cholesterol total (mean ± SD)</td>
<td>190.1 ± 36.9</td>
<td>171.3 ± 41.5</td>
<td>0.046</td>
</tr>
<tr>
<td>LDL cholesterol (mean ± SD)</td>
<td>108.6 ± 34.1</td>
<td>93.9 ± 39.9</td>
<td>0.05</td>
</tr>
<tr>
<td>CRP (mean ± SD)</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.4</td>
<td>0.944</td>
</tr>
</tbody>
</table>

#### Medical history

<table>
<thead>
<tr>
<th></th>
<th>ACS</th>
<th>No ACS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>22 (66.7)</td>
<td>35 (48.6)</td>
<td>0.096</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>11 (33.3)</td>
<td>15 (20.8)</td>
<td>0.223</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>20 (60.6)</td>
<td>34 (47.2)</td>
<td>0.216</td>
</tr>
</tbody>
</table>

Table 3. Multivariable logistic regression model for evaluating independent association between unstable angina and myocardial infarction and other factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>Std. Error</th>
<th>Sig.</th>
<th>Exp (B)</th>
<th>95% Confidence Interval for Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.041</td>
<td>0.030</td>
<td>0.177</td>
<td>1.042</td>
<td>0.982 - 1.106</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.421</td>
<td>0.662</td>
<td>0.525</td>
<td>1.524</td>
<td>0.416 - 5.583</td>
</tr>
<tr>
<td>BMI</td>
<td>0.028</td>
<td>0.087</td>
<td>0.746</td>
<td>1.028</td>
<td>0.868 - 1.218</td>
</tr>
<tr>
<td>Diabetes mellitus history</td>
<td>0.965</td>
<td>0.751</td>
<td>0.199</td>
<td>2.625</td>
<td>0.603 - 11.435</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>-0.003</td>
<td>0.003</td>
<td>0.388</td>
<td>0.997</td>
<td>0.991 - 1.004</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-0.013</td>
<td>0.008</td>
<td>0.084</td>
<td>0.987</td>
<td>0.973 - 1.002</td>
</tr>
<tr>
<td>FBS</td>
<td>0.010</td>
<td>0.006</td>
<td>0.064</td>
<td>1.010</td>
<td>0.999 - 1.022</td>
</tr>
<tr>
<td>Positive CMV PCR test</td>
<td>1.437</td>
<td>0.649</td>
<td>0.027</td>
<td>4.206</td>
<td>1.178 - 15.022</td>
</tr>
</tbody>
</table>

We also correlated CMV PCR test results with family history for CVD. We found that patients with a positive CMV test result performed on their atherosclerotic plaques and evaluated by PCR are significantly more likely to have high levels of triglyceride (197 ± 113 vs. 145 ± 8, respectively; P < 0.001). Then we reanalyzed data for coronary arterial atherosclerotic lesions and compared them to that of 53 mamillary artery specimens. None of the specimens from the mamillary artery was positive for CMV when it was evaluated by the PCR (P < 0.0001).

**Discussion**

The potential impact of viral pathogens on inducing endothelial injury — resulting in the exposure of underlying smooth muscle cells and development of atherosclerosis — has been studied massively, and CMV was the most commonly implicated agent investigated. Despite all the studies, however,
The role of CMV in atherosclerosis remains obscure. There are several reports indicating a potential role for CMV replication in the coronary arterial wall and atherosclerotic plaque formation in humans, while several other studies have doubted this hypothesis based on their own observations, which will be discussed shortly. Our study evaluated this association in a population of patients with CVD who have undergone CABG.

The prevalence of antibodies to CMV infection has been associated with atherosclerosis and is common in the general population, with evidence of past infection in approximately 15% of adolescents, 50% of adults by age 35, and 70% of patients older than 75 years. The rates in our study of Iranian CVD patients were also high, with 87% IgG positivity for CMV in adults ages 75 years and younger and 70% for those older than 75 years (the latter group included only seven patients). The high prevalence of CMV infection in the general population and in CVD patients coupled with the high rate of mortality from CVD in almost all parts of the world emphasizes the relevance of any potential relationship between CMV infection and CVD. In a prospective cohort of 134 age-matched pairs of male patients who underwent vascular surgery versus patients with no evidence of atherosclerosis, investigators found that patients in the surgery group are significantly more likely to have CMV antibodies than in the controls. On the other hand, investigators also followed 46 pairs of patients, one of each having undergone vascular surgery and the other having had no surgery, all with symptoms of atherosclerosis. The latter cohort showed no difference between patients with respect to CMV antibodies. Those investigators concluded that elevated levels of CMV antibodies might be associated with CMV-mediated vascular injury and subsequent atherosclerosis. In our study, we found no association between CMV antibodies and acute coronary syndromes, but anti-CMV IgM was associated with hypertriglyceridemia — although, given the limited number of CMV IgM positive patients (4 cases), this study would need to be replicated to confirm any observations.

In autopsies of young people dying of trauma, viral pathogens from the herpes family have been found in various layers of the vessel wall, including endothelial and smooth muscle cells. This observation suggests that these viral agents exist in the arterial wall of young patients with no symptoms of atherosclerosis. However, there is no consensus on the relevance of this colonization and its potential impact on the development of atherosclerosis. Several studies have investigated associations between CMV localization in the arterial walls and atherosclerosis formation; some of them were only observational studies showing a high rate of CMV DNA positivity in the atherosclerotic lesions of arteries. Despite finding some higher proportion of atherosclerotic lesions with CMV infection, they failed to reach significance level, maybe due to limited sample size or improper testing. However, after using more sensitive techniques including PCR and a large sample size, researchers found a highly significant relationship between atherosclerotic patients and CMV DNA detection compared to patients with non-significant arterial disease, although diverse results have also been reported. In our study, CMV DNA was detected in 27% of the atherosclerosis specimens from patients who had undergone CABG. However, none of the specimens from normal mammary arteries were positive for CMV DNA. The same finding was reported by Ibrahim et al., who reported an exclusive detection of CMV DNA in coronary and carotid lesions versus in the mammary artery. Nevertheless, another study found a large proportion of mammary artery specimens that were positive for CMV DNA.

The association between CMV infection and acute coronary syndromes has also been investigated. Kol et al. investigated the presence of CMV in atherectomy specimens from patients with stable versus unstable angina using southern blotting and hybridization with a specific probe for detecting the CMV major immediate-early (MIE) gene. They found no specimen with a positive hybridization signal and concluded that in patients with unstable angina, replication of CMV in coronary atherosclerotic plaques is not a major cause of plaque instability. However, Liu et al. investigated the presence of CMV in the coronary plaques of 23 patients with coronary syndromes and compared them with 17 control patients using immunohistochemical techniques; they found a significantly higher rate of infection in the acute coronary syndrome group ($P = 0.01$). In our study, using a more sensitive PCR method, we found the same results as the latter study in which patients who had positive PCR results for CMV DNA were significantly more likely to have a history of unstable angina or myocardial infarction. This finding is of utmost relevance: not only does it show a high rate of CMV infection present in atherosclerotic plaques, but it also confirms through clinical evidence a higher risk of acute coronary syndromes for CMV replication in atherosclerotic plaques. This in turn should encourage us to find preventive strategies toward a potential favorable effect of using antiviral agents to prevent ominous heart events.

A novel finding of this study is the association between a positive CMV DNA detection in the atherosclerotic plaques and a positive family history for CVD. As mentioned above, autopsy analysis of young people who died from trauma revealed positive CMV DNA in their coronary artery specimens, with no clinical evidence of CVD. Some investigators suggested that this finding implies a role for CMV infection in initiating the atherosclerosis process in the coronary arteries. However, we suggest that the higher rate of a positive family history of CVD for patients with CMV-positive atherosclerosis implies that their arterial walls have a higher sensitivity to CMV replication. This implication is also very relevant because, if proven, one may assume that such family members should begin preventive antiviral treatment.

CMV infection has also been associated with arterial hypertension, diabetes mellitus-mediated atherosclerosis, and a positive test for proliferative signals including CRP. In our current study, we did not find any relationship between CMV IgM, CMV IgG, and CMV PCR positivity and having arterial hypertension or higher systolic and/or diastolic blood pressure (data not shown). Moreover, no association was found with regard to diabetes mellitus and any of the CMV tests. The same observation was found when CMV test results were correlated with CRP.

**Conclusion**

This study confirms previous evidence about the replication of CMV virus in the atherosclerotic plaques of coronary arteries, and it brings clinical significance to this observation by showing a higher prevalence of acute coronary syndromes in the CMV-infected plaques. Moreover, patients with a positive PCR result for CMV in their atherosclerotic plaques were more likely to have a positive family history for CVD. This suggests a familial vulnerability to CMV replication in the coronary artery walls.

**Conflict of Interest Disclosure:** All authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and none were reported.

**Funding/Support:** The authors have no funding disclosures to report.

**Keywords:** cytomegalovirus, atherosclerotic plaques, acute coronary syndrome, enzyme-linked immunosorbent assay, ELISA
References


Recent studies of ancient Egyptian mummies by whole-body multislice computed tomographic scans documented the presence of atherosclerosis in their aorta, as evidenced by calcification, as well as in the femoral, iliac, carotid, and coronary arteries.\textsuperscript{1, 2} Therefore, arteriosclerosis and cardiovascular calcification are not unique to contemporary humans. Indeed, coronary atherosclerotic disease is not a modern ailment: it existed in China as far back as 2nd-century B.C.\textsuperscript{3-8} Extensive occlusive coronary atherosclerotic disease was found in a 50-year-old Chinese noblewoman — Lady Dai — who died in 163 B.C.\textsuperscript{9} She had a severely occluded left anterior descending coronary artery (Figure 1), which was responsible for her sudden death from an anterior myocardial infarction an hour or so after a meal.\textsuperscript{3-8}

Lady Dai had several risk factors. First, she had a Type A personality; 138½ musk melon seeds were found in her stomach (Figure 2), and researchers believed she must have gulped down...
the melon in a great haste.6,8 Second, she was overweight as evidenced by her appearance (Figure 1). Third, she had diabetes and hypertension.9 Fourth, as judged from her richly furnished tomb and the fact that she was a noblewoman with many servants waiting on her, she probably did not need to exert herself. Finally, packets of herbal medicines containing cinnamon, magnolia bark, and peppercorns were found in the tomb (Figure 3), suggesting that the noblewoman suffered from angina pectoris during her life.6 According to Han medical canons, these medicines were prescribed for patients with coronary heart disease as they still are by traditional Chinese doctors in China today.7

Keywords: coronary arteriosclerosis, coronary atherosclerotic disease

References
3. Hall AJ. A lady from China’s past. A noblewoman’s last day, 2100 years ago, seems to dawn again with the discovery of her richly furnished tomb. Natl Geogr. 1974;145;660-81.

Figure 3. The unearthed herbs that were buried in the noblewoman’s tomb. Courtesy of Hunan Provincial Museum, China.
CARDIAC MRI DEMONSTRATES SEVERE PARAVALVULAR AORTIC REGURGITATION

Kamran A. Shaikh, M.D.; Mahesh Ramchandani, M.D.; Dipan J. Shah, M.D.
Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

Aortic valve replacement with bioprosthesis. A 43-year-old man who had undergone aortic valve replacement with a bioprosthesis presents with worsening heart failure symptoms. Cardiac MRI revealed dehiscence along the right and noncoronary cusps, with associated severe paravalvular aortic insufficiency (regurgitant volume: 93 mL; regurgitant fraction: 53%). Still frames of peak systole and end diastole (Figures 1, 2) show extensive rocking motion of the bioprosthesis throughout the cardiac cycle. Figure 2 also shows clear discontinuity of the bioprosthesis with the aortic annulus. Images submitted by Kamran Shaikh, M.D., Dipan J. Shah, M.D., and Mahesh Ramchandani, M.D.

Figure 1. Short-axis views of a bio-prosthetic aortic valve in peak systole and end diastole showing excessive movement of the prosthesis during the cardiac cycle (arrows). To access a video of this online, visit www.debakeyheartcenter.com/journal/video

Figure 2. Apical long-axis views of a bioprosthetic aortic valve in peak systole and end diastole, again showing rocking motion of the prosthesis (dashed red lines) causing severe aortic insufficiency. Also shown is complete disconnection of the prosthesis and annulus (arrow). To access a video of this online, visit www.debakeyheartcenter.com/journal/video
Methodist Echocardiologist Miguel Quiñones Recognized by Nation’s Top Two Cardiology Societies

Miguel Quiñones, M.D., chair of the Department of Cardiology at the Methodist DeBakey Heart & Vascular Center and professor of medicine at Weill Cornell Medical College, was honored by two of the country’s most prestigious cardiology societies: the American College of Cardiology and the American Society of Echocardiography.

In March, Quiñones was named a Master of the American College of Cardiology at the college’s annual meeting in Chicago. Each year, a maximum of four cardiologists receive the title of master, which is the highest honor bestowed by the college. And in June, Quiñones was honored by the American Society of Echocardiography with the Physician Lifetime Achievement Award during the group’s 23rd Annual ASE Scientific Sessions taking place in National Harbor, Maryland. According to an ASE representative, Quiñones was recognized for a “lifetime of outstanding achievements in the field of cardiovascular ultrasound” and for having served as a role model through service, research, and teaching.

“I cannot think of anyone, anywhere who deserves these honors more than Miguel,” said Alan B. Lumsden, M.D., medical director and cardiovascular surgeon at the heart center. “Not only is he one of the pillars of the Methodist DeBakey Heart & Vascular Center, but he has also helped build our research and teaching programs over the last several years to the enviable positions they occupy today.”

As an expert in imaging and measuring heart and vascular function, Quiñones is responsible for many of the guidelines used by cardiologists and cardiovascular surgeons worldwide to interpret echocardiographic data.

Cleveland Clinic cardiologist and ASE President James D. Thomas, M.D., who nominated Quiñones, wrote that “Mike is one of the true pioneers in the field of echocardiography, having led the way in the assessment of ventricular and valvular function.”

Quiñones is the fourth recipient of the ASE Physician Lifetime Achievement award.

Coronary Aneurysm Repair without Open Surgery

Methodist DeBakey Heart & Vascular Center interventional cardiologists repaired a large coronary artery aneurysm using stent-assisted coil embolization rather than open-heart surgery. The success of this first-time procedure could signify a new option for patients, especially those for whom open surgical repair is risky.

Coronary aneurysms are believed to occur in 1–2% of American adults. In this case, the 37-year-old male patient came to the heart center with severe stable angina and underwent an exercise myocardial perfusion stress test that was strongly positive. Follow-up cardiac catheterization showed a large fusiform aneurysm of the proximal left anterior descending artery, ectasia of the proximal circumflex artery with 95% narrowing, and an occluded right coronary artery with an occluded proximal aneurysm. Traditional treatment for this type of aneurysm consists of open surgical repair, a complex and risky procedure, especially if the aneurysm is situated at the beginning of the coronary artery. The procedure often keeps patients hospital-bound for several weeks, with extensive recovery time.

Instead, interventional cardiologists Htut Win, M.D. and Neal Kleiman, M.D., in collaboration with cardiac imaging specialists Su Min Chang, M.D., and Venkateshwar Polhani, M.D., performed stent-assisted coil embolization, which was designed specifically for the patient using three-dimensional CT coronary angiograms.

The procedure consisted of percutaneous intervention of the circumflex artery using a 3.0 x 23-mm MultiLink Vision stent (Abbott Vascular) that was post-dilated progressively with noncompliant balloons. They then performed stent-assisted embolization of the aneurysm, and the patient was treated with aspirin and clopidogrel. This was the first time the technique has been used to repair a large coronary artery using percutaneous means.

According to Win, the patient walked out of the hospital the next day and ran on a treadmill, unassisted and without trouble, for 12 minutes during a follow-up visit a month later.

“Our experts routinely work in teams to come up with new ways to help our patients,” Win said. “Methodist has a strong history in heart imaging. Without the help of Dr. Chang and his team, without the eyes that allowed us to see the procedure before actually getting in, we could not have done this with such ease and, more importantly, safety. There were no surprises.”

The work is published in the February issue of Circulation: Cardiovascular Interventions, an American Heart Association journal.

Could Starving the Heart Prolong Life?

Researchers at the Methodist DeBakey Heart & Vascular Center recently tested the theory that restricting nutrient intake may prolong longevity by enhancing the body’s resistance to ischemia/reperfusion arrhythmias. The study found that starved myocytes maintain normal calcium cycling and basic mitochondrial function far longer than non-starved cells during periods of extreme stress.

These findings, which were published in Cell Calcium (Elsevier), add to a growing body of scientific evidence suggesting that the consumption of less energy, while maintaining balanced nutrition, can enhance cell performance and reduce DNA damage associated with the aging process.

Principal investigator Miguel Valderrabano, M.D., along with Sufen Wang, Ph.D., and Jiexiao Chen of The Methodist Hospital Research Institute, studied cultured heart cells originally derived from young rats. The cells were grown in a 2 cm x 2 cm monolayer, where researchers mapped intracellular calcium ions and mitochondrial membrane potential with the help of fluorescent tags. Ischemia was simulated by placing a 1.8 cm x 1.8 cm cover slip over the center of the cell culture, limiting oxygen and nutrient flow to that part of the culture, while reperfusion was simulated by removing the cover slip.

All cells were raised for 2 to 3 days in a blood-serum medium containing glucose. One group of cells was subjected to a low-nutrient medium for 24 hours prior to the ischemia-reperfusion...
experiments. These nutrient-restricted cells were more likely to maintain normal mitochondrial action potentials and normal calcium cycling across the cellular membrane than cells that had ongoing access to nutrients.

Nutrient-restricted cells maintained normal pulsing about 8 minutes longer than unrestricted cells during ischemia. They also maintained mitochondrial action potentials and calcium cycling activity throughout simulated ischemia and reperfusion events, whereas the unrestricted cells lost significant action potentials during reperfusion.

“These experiments are not yet telling us whether we can emulate the effects of nutrient restriction in humans to lessen the damage of ischemia-reperfusion,” Valderrábanosaid. “But we have shown one way in which nutrient restriction may be acting to reduce heart tissue damage, a subject of interest to many laboratories.”

William Zoghbi, M.D., at the Helm of the American College of Cardiology

Methodist DeBakey Heart & Vascular Center cardiologist William Zoghbi, M.D., became president of the world’s largest society of cardiologists last March, during the American College of Cardiology’s annual scientific sessions in Chicago.

With more than 27 years in medical practice, Zoghbi is well suited to the task. He is the director of the Methodist DeBakey Heart & Vascular Center for Cardiovascular Imaging and a professor of medicine at Weill Cornell Medical College. As the new president of the American College of Cardiology (ACC), Zoghbi plans to improve patients’ access to health information and provide new tools for providers to enhance the patient-physician relationship.

“More and more people around the world have instant access to medical information, and we want to give patients tools to educate themselves so they can fully engage in the decision-making process,” said Zoghbi. “Health literacy is so important. We want to bring all patients to the point where they are deeply interested and engaged. As physicians, we need to partner with our patients — the more involved they are in their care, the better.”

Among the new information-based ACC initiatives are expansions of CardioSmart.org, an ACC website that serves patients and their caregivers, and CardioSource.org, a portal for doctors, nurses, and other health care providers. These expansions will include a greater wealth of information about preventive measures, heart and vascular disease and treatment options, and new mobile tools for smart phones and tablets that help users find crucial information wherever they may be.

“What the ACC does is fairly unique in this country in the area of quality,” said Zoghbi. “We’re collaborating with governmental agencies such as the FDA and CMS as well as other professional societies to figure out how best to introduce new technologies, such as transaortic valve replacement, to the marketplace. We want patients to have access to the safest, most effective therapies as quickly as possible, keeping an eye on the actual delivery of quality care through registries.”

Zoghbi is the first Methodist Hospital-based physician to be president of the ACC since 1991, when William L. Winters Jr., M.D., served in that role. Zoghbi holds a chair at Methodist named in Winters’ honor — the William L. Winters Chair in Cardiac Imaging at the heart center. He has authored more than 200 peer-reviewed publications and has given invited presentations at every major cardiology conference in the world.
LITIGATION: AN OUNCE OF PREVENTION

William L. Winters, Jr., M.D.
Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

He learned the art of establishing rapport with a patient/family quickly by presenting a professional demeanor and approach that encouraged and enhanced confidence and trust. In case things didn’t go as planned, he had prepared the family and the patient for possible disappointment. His forthright and humble approach, without arrogance or a “father-knows-best” attitude, enabled him to head off disappointed or disgruntled families looking for someone to blame. They were given time to ask questions and declare their expectations. I know there are physicians and surgeons who have not been sued. They will be the first to agree that meaningful communication with a patient and family is the first step toward a trusting doctor-patient relationship.

During the past 40 years, medical malpractice costs have soared, increasing an average of 11.1% annually. Studies have shown that the primary cause of lawsuits is not negligence but ineffective communication among patients, physicians and consultants, and families of patients. A humanistic, holistic, empathetic environment has been shown to reduce litigation, reduce physician burnout, and increase patient satisfaction, patient compliance, and physician satisfaction. The tangible influence of an empathetic physician on clinical outcomes is difficult to document, but such reports have been published. A sympathetic human presence may contribute as much to healing as well-chosen words. We have all observed what appears to be a decline in empathy in medical students as they progress through medical school and residency programs, and attempts to reverse that trend are well reported. Competence is a prerequisite of professionalism, but a physician’s communication skills in a holistic environment trump all other known factors in medical litigation. Furthermore, effective physician/patient communication is a lynchpin in fostering patient safety, which in turn discourages liability. For either reason, an unhurried, open conversation among stakeholders permits them to air their concerns, questions, opinions, and prejudices and, coincidentally, exposes for physicians where their patient may be uninformed or misinformed. Patients are much more likely to be satisfied if they feel free to speak their minds and know their physician is listening.

“You are in the driver’s seat. The advent of managed care tends to cloud that concept, but only slightly. Notwithstanding the constraints of managed care, you still have the primary obligation to serve your patients, including being your patient’s keeper, at least medically and surgically. Don’t defer to a patient’s decision that contravenes your best judgment for the patient’s well being.
Be sure you explain fully; then, if the patient rejects your opinion, at least you have gone the extra mile than your responsibility requires. This is a major element in the art of self defense.7 These words, written by physician attorney Don Harper Mills during the advent of managed care, resonate equally well today.

Modern medicine, with its increasingly structured requirements and time limitations, discourages and inhibits such face-to-face discussions and augments the challenges to physicians to provide the kind of personal care we would all like to receive. But one surgeon managed for 40 years to avoid the quagmire of medical legalities. So it is possible, and it benefits both patients and physicians.

_Say it again Doc, in words that are clear,_
_To my family who are all gathered right here._
_What are my choices and chances_
_That appropriately enhances_
_An outcome to be cheered by those near and dear?8_

References

8. The movie, “Casablanca.” With apologies.
EARLY POST-OPERATIVE DYSFUNCTION OF A MECHANICAL AORTIC VALVE

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Case Report

A 49-year-old-male was referred to the Methodist DeBakey Heart & Vascular Center for evaluation of prosthetic valve endocarditis. His medical history was significant for aortic valve replacement in 2010, with a 23 mm mechanical aortic valve due to a bicuspid aortic valve with severe stenosis. Approximately 1 year later, he developed fatigue and mild dyspnea. Transesophageal echocardiography (TEE) demonstrated a large paravalvular defect with severe aortic regurgitation. Three different blood cultures were positive for Staphylococcus epidermidis. The affected mechanical valve was explanted, extensive debridement of the aortic annulus was performed, and a new 23 mm mechanical aortic valve was implanted. Intraoperative TEE revealed normal valve seating with normal leaflet mobility. The patient was extubated 4 hours after surgery and had a routine postoperative recovery. Oral and intravenous anticoagulation was initiated the day after surgery.

Four days later the patient underwent routine transthoracic echocardiogram, which demonstrated a markedly elevated transvalvular gradient across the newly implanted mechanical aortic valve (peak velocity of 5 m/s, mean gradient of 61 mmHg, peak gradient of 100 mmHg, Doppler velocity index of 0.23 [normal >0.25]) with normal left ventricular function (Figure 1). Cinefluoroscopy of the valve was performed to evaluate valve opening. Fluoroscopy showed equally reduced opening of both prosthetic leaflets (opening angle of 40-50 degrees with

Figure 1. Transthoracic Doppler study demonstrates a high pressure gradient (100 mmHg) across the prosthetic aortic valve.

Figure 2. Cinefluoroscopy demonstrates restricted leaflet function. (A) Normal diastolic leaflet closure is demonstrated. (B) During systole there is restricted mobility of both leaflets of the prosthetic mechanical aortic valve, with angulation between leaflets of 45-50 degrees. (C) A normally functioning bileaflet mechanical valve should demonstrate an opening angle of 10-12 degrees (yellow dotted lines).
normal closure) (Figure 2). For a normally functioning bileaflet mechanical valve, the angulation between the leaflets is 10-12 degrees when the valve is open and 120-130 degrees when the valve is closed.1,2 TEE was performed to assess for possible causes of acute valve obstruction, including thrombosis or vegetation; however, there was significant prosthetic valve shadowing, and a mechanism of prosthetic valve dysfunction could not be identified. A cardiac computed tomography (CT) was ordered to assess for thrombus — which would be seen as a low attenuation mass on the valve — or subvalvular tissue causing impaired leaflet motion. The CT clearly demonstrated reduced systolic leaflet motion without any evidence of subvalvular clot or restrictive tissue (Figure 3). After 1 week of anticoagulation within the therapeutic range, the transvalvular Doppler gradients remained elevated and unchanged.

Because of this acute prosthetic valve dysfunction, the patient once again underwent redo valve surgery. The mechanical valve was successfully explanted, and under direct inspection no apparent thrombus, suture, or tissue was identified on or around the valve. With manual manipulation, the explanted valve clearly demonstrated restricted leaflet opening (Figure 4). A new 21-mm bioprosthetic aortic valve was implanted, and postoperative echocardiogram demonstrated normal valve function and Doppler gradients. The patient was discharged home in stable condition.

**Comment**

We report a case of very early postoperative mechanical aortic valve obstruction. Restricted leaflet opening of prosthetic mechanical valves may be due to aberrant suture or pledget material, incomplete decalcification of the aortic annulus, thrombus (early or late), or pannus (late) formation. Any of these rare mechanisms of dysfunction tend to cause unilateral or asymmetric leaflet restriction in systole or diastole. In this case, multiple imaging modalities (echo Doppler, cinefluoroscopy, and CT) demonstrated acute systolic valve dysfunction involving both mechanical leaflets, however neither this noninvasive imaging nor direct inspection of the explanted valve could identify a macroscopic cause of the restricted leaflet motion. Possible explanations for acute mechanical valve dysfunction include mechanical valve failure (although the intraoperative TEE demonstrated normal prosthetic valve function) or possibly microthrombi at the pivot/hinges of the leaflets that could not be identified by routine imaging and visual examination. In this case, the explanted valve was returned to the valve manufacturer and thoroughly examined. That report indicated that “two of the recessed pivot areas contained thick coagulated blood,” and that after cleaning the explanted valve leaflets demonstrated normal function. In summary, we report a rare case of very early mechanical aortic valve dysfunction. The mechanism of prosthetic leaflet restriction in this case remains uncertain; however, we believe that microthrombi located within the leaflet pivot points (hinges) was likely a contributing factor.

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**Keywords:** aortic valve, prosthetic valve endocarditis, aortic valve replacement, mechanical aortic valve dysfunction

**References**


HE

He wonders why there are no tigers in the Bible.
He thinks someone should consider putting them in.
He can be the very soul of elation. Yet some days
he’s too sad to even button his coat. An impetuous man,
not entirely bound by natural laws, he never gets enough
kissing or figures out what kind of animal he is.
An impoverished doctor or handsome drifter,
when he sees a woman carrying a sick child wrapped
in an old plaid coat into the emergency room
he rushes over to help her. No coward soul is his,
though he is given to copious groaning. He once
wrote a play called Eight People Who are Really
Tired. The audience loved it. When he and his brother
were thirteen and fourteen, respectively, they took LSD
in a tree house their father had built. For seven hours
he watched his cells vibrate wildly in time with cells
in the tree’s trunk and leaves. Now, thirty years later,
he’s never entirely forgotten that feeling.
It’s been raining for days. He seems content
to stand on the covered front porch, under the dripping
eaves, smoking and petting his adoring sheepdog.
Whenever it rains like this, he remembers the one offense
his dad spanked him for when he was a kid.
He knows he deserved it. He sits down on the welcome
mat, taps off his ash, and kisses the dog’s furry head.
She wiggles her hindquarters and licks the knee of his jeans.
In gleaming moments like these, forming and falling
like raindrops, I’d give anything to be one of them,
either that man or his dog. Instead, not knowing
which end is up, or what saints to pray to,
I find myself hopelessly in love with them both.

— Amy Gerstler

Amy Gerstler is a Los Angeles-based writer who has published 11 books of poetry. She is a winner of the National Book Critics Circle Award, and The New York Times named Dearest Creature, from which “He” is taken, one of the notable books of the year for 2009.
THE COMPUTER ART OF DR. PHIL

Philip Alexander, M.D., born and raised in Conroe, Texas, is a creative genius. He thought music was to be his calling in life, so he graduated with a degree from Philadelphia’s Curtis Institute of Music. His instrument was the oboe, which he played with magnificent skill. While still in high school, he performed for President John F. Kennedy at the White House and later at the Mormon Tabernacle in Salt Lake City, Utah.

Then, in a sudden departure from his plan, he applied to medical school at Baylor College of Medicine. He had none of the academic prerequisites. To his surprise and probably everyone else’s, he was accepted. After graduation, he completed a residency in Internal Medicine at Baylor College of Medicine and has practiced in College Station for more than 25 years. Throughout this time, music continued to play a role in his life. He performed for 25 years as an oboe soloist for the Brazos Valley Symphony Orchestra. As a medical student at Baylor, he performed with the Houston Symphony Orchestra. One evening while performing, he left the stage to help a patron in the audience who was having a heart attack.

In 1980, Dr. Phil’s world took another turn after receiving a copy of a book titled, “Drawing on the Right Side of the Brain.” For 10 years, he became widely known for his pencil sketches, then switched to art drawn on the computer. The images, which we will include in each issue now and hereafter, are completely original, created from scratch with a computer mouse using no references or imported photographs.

I hope you will enjoy the talents of Dr. Phil — a native Texan, musician, physician, and artist. One of a kind.

— William L. Winters Jr., M.D.
Editor-in-Chief
Methodist DeBakey Cardiovascular Journal

Image 1. Last Shuttle mission to the International Space Station

Image 2. Sea traveler
The Methodist DeBakey Cardiovascular Journal was created in part to celebrate and perpetuate the education cornerstones of the Michael E. DeBakey legacy at The Methodist Hospital. Several significant players who participated in this education died before the creation of this journal. The memorial to the life of one of those significant players, Dr. Stanley Crawford, appeared in Volume 7, issue number 1.

In this issue, a tribute to another of Dr. DeBakey’s associates — Dr. Arthur C. Beall Jr. — is presented. Other tributes to both cardiovascular surgeons and cardiologists now deceased who played pivotal roles in the cardiovascular education and training programs at The Methodist Hospital will appear in subsequent issues.

— William L. Winters Jr., M.D.
Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

Arthur C. Beall Jr., was born in Atlanta and educated in the undergraduate and medical schools of Emory University. He completed a surgical internship at Barnes Hospital in St. Louis, Missouri, before coming to Baylor College of Medicine for a residency in general and then thoracic surgery. In 1956, Dr. Beall’s residency training was interrupted by 2 years of active duty as a naval officer and as assistant chief of Thoracic Surgery in the Naval Hospital in Oakland, California. There, he was privileged to work with Dr. Frank Gerbode at Stanford University, where he first began designing a prosthetic heart valve destined to one day be known as the “Beall Valve” — a ball valve design used extensively around the world from 1965 to 1970. When his residency was completed in 1950, he accepted an appointment as an instructor of surgery at Baylor in Houston, where he remained for the rest of his career. He was promoted in 1971 to professor of surgery, a position he held until 1999 when he became professor emeritus, a title he enjoyed until his death in 2002.

During his career, Dr. Beall was actively involved in conceptualizing improvements in cardiopulmonary bypass, priming solutions for the pump and filters to remove debris from the lines. His work resulted in more than 360 publications.

Dr. Beall served in a variety of roles during his Baylor career, including director of surgical laboratories, medical director of the Cardiovascular Perfusion Program, and physician-in-charge of the Cardiovascular Perfusion Service. He helped organize a Baylor-sponsored cardiac surgery program at the King Faisal Hospital and Research Center in Riyadh, Saudi Arabia. For 30 years, he oversaw the thoracic surgical residency program at Baylor and affiliated hospitals and served 5 years as the chief of the surgical service at the Michael E. DeBakey VA Medical Center in Houston. On the national and international fronts, he was president of the Association for the Advancement of Medical Instrumentation, the Alliance for Engineering in Medicine and Biology, the American College of Chest Physicians, and the Michael E. DeBakey International Surgical Society. He also served as vice president of the American College of Cardiology.

In his early years, Dr. Beall was active in the management of trauma at both the Jefferson Davis Hospital and Ben Taub General Hospital in Houston, introducing a number of new operative techniques. As many prominent surgeons were wont to do, he developed many cardiovascular surgical instruments and devices.

As a cardiologist, I had the privilege of working with him on several of his private patients during the 1970s. Among his many strong attributes, the one that has resonated with me long after his departure was his intense and dedicated personal care of each of his patients. He was a beloved mentor and colleague whose life achievements are well channeled in the lores of The Methodist Hospital and Baylor College of Medicine.
TRAUMATIC CORONARY ARTERY FISTULA CLOSURE WITH STENT GRAFT

Morteza Safi, M.D.; Nematollah Pour Ebrahim, M.D.; Mohammad Hasan Namazi, M.D.; Habibollah Saadat, M.D.; Hosein Vakili, M.D.; Manuchehr Hekmat, M.D.; Mohammad Reza Movahed, M.D., Ph.D.

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Abstract

We present a rare case of a symptomatic acquired large coronary fistula and aneurysm secondary to chest trauma that was successfully closed using stent graft. This case is followed by review of the literature.

Case Report

A 30-year-old man suffering from a penetrating stab wound to his mid-left-anterior chest wall underwent left lateral thoracotomy at the fourth intercostal space to repair his chest wall injury. No clear cardiac injury was identified at that time. After surgery, the patient developed increasing exertional angina that limited his activities. He was referred for further evaluation 5 months after his trauma due to persistent symptom. His physical exam was remarkable for a loud grade III/IV continuous murmur that was heard at left sternal border. ECG was normal. Chest X-ray showed mild cardiac enlargement. Coronary angiography revealed a large coronary pseudoaneurysm and fistula originating from mid left anterior descending artery (LAD) connecting to the right ventricular cavity (Figures 1 and 2). Distal LAD after the fistula was very small due to poor distal flow. The decision was made to close the fistula using a stent graft.

The left main coronary artery was engaged using a JL3.5 guiding catheter. After wiring the LAD, a 3-mm x 20-mm compliant balloon was inflated at the side of the fistula to determine successful closure with contrast injection during balloon inflation. Next, a 3-mm x 26-mm coronary GraftMaster stent was implanted at the aneurysm neck level, followed by balloon dilatation using a 3-mm x 18-mm Sapphire balloon. The aneurysm was completely sealed after stenting, with restoration of normal flow into the distal LAD (Figure 3). The patient tolerated the procedure and remains asymptomatic during follow-up visits.

Discussion

Large coronary artery fistulas are rare, and the true incidence is difficult to discern as a great number of them are asymptomatic. At least 75% of coronary artery fistulas are small and clinically silent. Most are congenital while some are acquired, as was the case presented herein. Coronary fistulas cause blood flow to be shunted into cardiac chambers, great vessels, or other structures, bypassing the myocardial capillary network. Symptoms may be caused by either coronary steal or a high left to right shunt flow. In symptomatic patients, closure of the fistula should be considered.1

Physical examination is normal in typical patients. In the case of a very large fistula, a widened pulse pressure may be detected, and a continuous murmur may be heard similar to our case. On rare occasions, thoracic trauma can lead to coronary artery fistula. In our case, coronary fistula occurred in the setting of a stab wound penetrating the chest. Trauma-related coronary fistulas usually are connected to right-sided heart structures. In large fistulas similar to our case, coronary steal is the presumed cause of symptoms.
The best management of a coronary artery fistula secondary to penetrating trauma is not known. Therapeutic options consist of surgical or endovascular repair. Although surgical approach has been described as a gold standard for coronary artery fistula closure, endovascular treatment has recently been advocated as a less invasive procedure and is more acceptable to patients. Various percutaneous devices are available including detachable balloon, coil embolization, and graft stents. Due to the presence of a large pseudoaneurysm, the use of a stent graft appeared to be the best approach in this patient.

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Keywords: coronary artery fistula

References
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ABOUT THE
METHODIST DEBAKEY HEART & VASCULAR CENTER

The Methodist DeBakey Heart & Vascular Center continues the groundbreaking work begun by famed heart care pioneer, Dr. Michael E. DeBakey, and his associates, who developed many of today’s life-saving techniques, tools and procedures at The Methodist Hospital. Located in Houston, Texas, the Methodist DeBakey Heart & Vascular Center combines research, prevention, diagnostic care, surgery and rehabilitation services in a coordinated multidisciplinary program with one focus: delivering compassionate, effective care and treatment to patients suffering from heart disease.