Review in Advance first posted online on November 14, 2016. (Changes may still occur before final publication online and in print.)

Transcatheter Aortic Valve Replacement: State of the Art and Future Directions

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Annu. Rev. Med. 2017. 68:1.1–1.14

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-101615-020427

Keywords

TAVR, transcutaneous aortic valve replacement, aortic valve disease, percutaneous therapy

Abstract

Transcatheter aortic valve replacement (TAVR) is a transformational and rapidly evolving treatment for patients with aortic stenosis who require valve replacement. Novel technological advancements have made this percutaneous minimally invasive therapy a first-line treatment for many patients at extreme risk for conventional cardiac surgery. New devices and improvements in existing devices have reduced procedural complications, and scientific trials are investigating the role of TAVR in lower-risk aortic stenosis populations, in patients with aortic regurgitation, and in patients with bicuspid aortic valve disease. Finally, there is intense interest in identifying patients in whom the risk-benefit ratio of TAVR is not favorable and should not be performed.

INTRODUCTION

Aortic valve replacement (AVR) was first introduced in 1960 as a surgical treatment for severe aortic regurgitation (AR) (1) and has become the gold-standard treatment for patients with both severe aortic valve stenosis (AS) and AR (2, 3). During the past decade, transcatheter aortic valve replacement (TAVR), also called transcutaneous aortic valve replacement, has emerged as an effective minimally invasive treatment for aortic valve disease for patients at high risk for surgical AVR. Since its first description in 2002 by Cribier (4), TAVR has undergone a rapid evolution as a result of groundbreaking technological advances and robust clinical research to become a safe and common procedure across the developed world. Since its approval in the United States in 2011, 45,000 TAVR procedures (commercial as well as research) have been performed. Current clinical trials are investigating the role of TAVR for AS patients at low and intermediate risk for conventional surgery, which will have implications for professional societal guidelines and more importantly for patient-specific care. Multiple new TAVR devices have been developed to minimize complication rates and to simplify the procedure and patient recovery. TAVR as a treatment for native AR, bicuspid aortic valve disease, and degenerated bioprosthetic valves is also under active investigation. This review covers the current state of TAVR clinical practice and research as well as the future of this transformational therapy.

In surgical AVR, native aortic valve leaflets are excised under direct visualization and the new prosthesis is sewn into the native aortic annulus using a prosthetic sewing ring. By contrast, TAVR typically involves a tissue prosthesis that is folded inside a metallic stent, which is positioned over a guidewire in the native aortic valve using fluoroscopic guidance. The transcatheter prosthesis (whether balloon expandable, self expanding, or mechanically expanding) is anchored using radial force within the existing valve, thereby displacing and trapping the native leaflets between the prosthesis stent and native aortic valve annulus. Various methods of transcatheter valve delivery and expansion exist and are detailed below (**Table 1**). Several improvements in newer devices reduce complications and enhance ease of use.

DEVICES

Sapien Balloon-Expandable Prosthesis

The SAPIEN valve (Edwards Lifesciences, Irvine, CA) is one of two commercially approved devices for percutaneous treatment of AS in the United States, having received approval by the US Food and Drug Administration (FDA) in 2011. The SAPIEN 3 valve is typically delivered transfemorally through a 14F (20-, 23-, and 26-mm valve) or 16F (29-mm valve) sheath over a guidewire after retrograde crossing of the stenotic aortic valve and is the only FDA-approved balloon-expandable valve (**Figure 1*a***). Alternative approaches for patients with unfavorable iliofemoral anatomy include transapical, trans-subclavian, and transaortic approaches. The radiopaque valve is carefully positioned using aortic cineangiography and then expanded against the aortic annulus by positioning and deploying the prosthesis during rapid ventricular pacing (**Figure 1*a***). Transesophageal or transthoracic echocardiography is used to determine the presence and severity of paravalvular leak and exclude complications. In the PARTNER (Placement of AoRtic TraNscathetER Valves) trial, the first randomized controlled trial performed in valvular heart disease, TAVR with the SAPIEN valve was compared to surgical AVR and to medical management in a group of patients at prohibitive risk for surgery (5, 6). Compared to standard medical therapy, TAVR significantly and markedly reduced mortality, improved symptoms, and reduced hospitalizations, albeit at the incumbent cost of higher risk of stroke and vascular events related to an invasive therapy (6). Compared to surgical AVR, TAVR was associated with similar one-year

Table 1 Transcatheter aortic valve replacement device characteristics

Device (manufacturer)	Expansion method	Delivery routes	Femoral sheath size	Unique features	Therapeutic roles	Level of evidence
SAPIEN 3 (Edwards Lifesciences)	balloon expansion	TF TA TAo	14F	sealing cuff	AS VIV	strong moderate
Evolut R (Corevalve, Medtronic)	self expansion	TF TAo	14F	supraannular, retrievable	AS AR VIV	strong weak moderate
Lotus (Boston Scientific)	mechanical expansion	TF	18F	sealing cuff, retrievable	AS VIV	moderate weak
Portico (St. Jude Medical)	self expansion	TF	18F	sealing cuff, retrievable	AS VIV	moderate weak
Direct Flow (Direct Flow Medical)	mechanical expansion	TF	18F	non-metallic polymer-injectable frame, retrievable	AS AR	moderate weak
JenaValve (JenaValve)	self expansion	TA	NA	active valve fixation, retrievable	AS AR VIV	weak weak weak
ACURATE TA (Symetis)	self expansion	TA	NA	active valve fixation, sealing cuff	AS AR VIV	weak weak weak

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; TA, transapical; TAo, transaortic; TF, transfemoral; VIV, valve in valve.

survival rates in the high-risk AS population (5). Recently, longer-term results have become available and are discussed below.

Balloon-expandable prostheses continue to evolve. The third-generation SAPIEN 3 valve consists of a bovine pericardial tissue valve within a cobalt chromium alloy stent frame and allows for low-profile crimping and radial strength once expanded to maintain a circular shape. The ventricular side of the stent is covered by a polyethylene terephthalate outer skirt designed to minimize the risk of paravalvular leak. An upcoming new version (SAPIEN 3 Ultra) will feature a simpler on-balloon delivery system (thus eliminating several steps to device deployment) and a new 14F sheath that will accommodate all valve sizes.

Corevalve Self-Expanding Prosthesis

The Corevalve (Medtronic, Minneapolis, MN) is the other commercially available device for percutaneous treatment of AS, having received FDA approval in 2013 after the US Corevalve Pivotal Trial demonstrated superior survival compared to surgical AVR in high-risk patients with AS at one year (7). The Evolut R is the most recent version of Corevalve and is made of a nitinol self-expanding frame housing a supra-annular porcine tissue valve that is delivered through a 14F in-line sheath (**Figure 1*b***). Because the valve is self-expanding, it does not require balloon expansion or rapid ventricular pacing and is typically delivered via a transfemoral approach. An advantage of the Evolut R device is that the valve can be recaptured after partial deployment

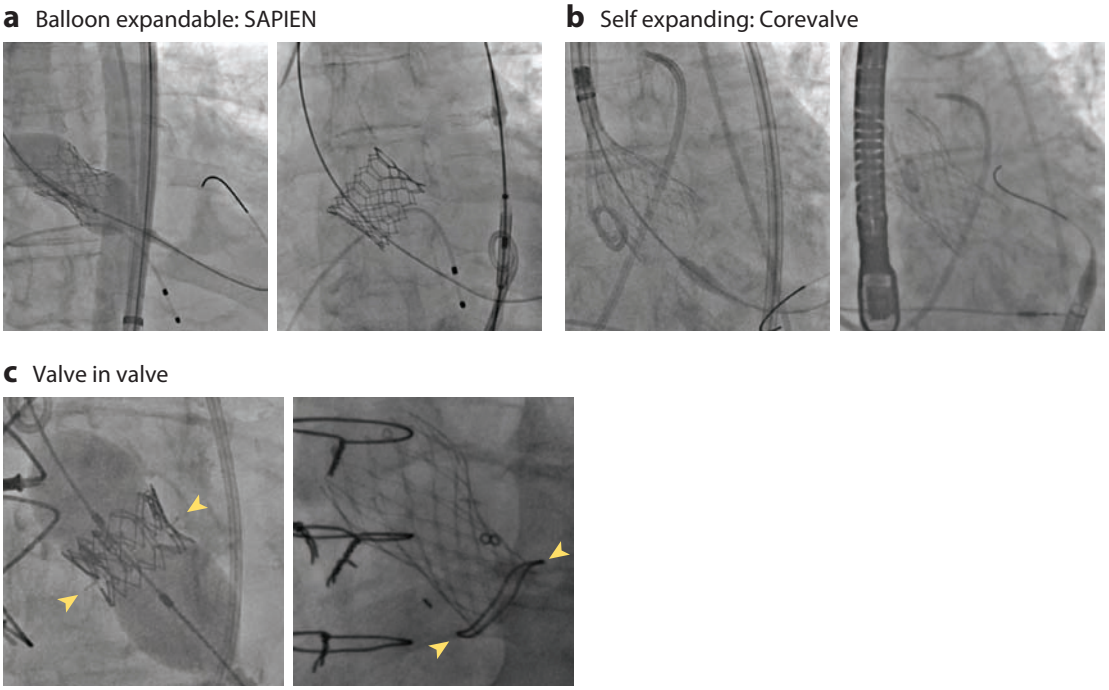

Figure 1

Cinefluoroscopic views of transcatheter aortic valve implantation. (*a*) A 29-mm SAPIEN 3 device during (*left*) and after (*right*) balloon expansion in a patient with severe aortic stenosis. (*b*) A self-expanding 29-mm Evolut R device during (*left*) and after (*right*) deployment in a patient with severe aortic stenosis. (*c*, *left*) A 23-mm SAPIEN XT device during balloon-expanded deployment within a severely regurgitant 23-mm St. Jude Biocor bioprosthesis; (*right*) a 23-mm Evolut R device within a severely regurgitant 23-mm Hancock bioprosthesis (*yellow arrowheads* correspond to radiopaque sewing ring of the surgical bioprosthesis).

if repositioning is desired. Alternative access approaches for Corevalve delivery include transsubclavian and transaortic.

Other Devices

Improvements in newer TAVR devices include small profile, repositionability, and sealing to reduce paravalvular leak.

The Lotus valve (Boston Scientific, Marlborough, MA) is a mechanically expanded bovine pericardial nitinol prosthesis with an adaptive outer seal designed to prevent paravalvular regurgitation. The system is delivered with an 18F (23-mm valve) or 20F (27-mm valve) system via a transfemoral approach. The most innovative feature of this device is the ability to be fully recaptured after deployment but before release. Furthermore, the valve leaflets are fully functional at 50% deployment. This allows a slower and more controlled deployment without hemodynamic instability and avoids the need for rapid pacing. Initial registry data from REPRISE II (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System—Evaluation of Safety and Performance) have demonstrated the safety and effectiveness of this device (8). The most recent randomized trial, REPRISE III, is the first trial to compare two TAVR devices against each other (Lotus versus Corevalve). Recruitment of this noninferiority trial is complete, and final results are anticipated in early 2017 (NCT02202434). A forthcoming

iteration (Lotus Edge) will be deliverable with a 14F overlapping sheath and will feature a simpler locking mechanism.

The Direct Flow valve (Direct Flow Medical, Santa Rosa, CA) is a bovine pericardial prosthesis with a unique, inflatable, Dacron polyester scaffold. It is delivered through an 18F transfemoral sheath and available in four valve sizes (23, 25, 27, and 29 mm). The valve is initially positioned while deflated in the left ventricular outflow tract, then retracted upward toward the aortic valve and inflated with a saline contrast mixture to anchor the device in place. Once a satisfactory position and hemodynamic result is confirmed, the saline contrast mixture is removed and a polymer is injected into the scaffold to permanently deploy the valve (9). Two-year data from the initial experience of Direct Flow in high-risk AS patients suggests very good results, similar to those of surgical AVR, with a low rate of paravalvular leak (14.9% mild and 85% none/trace). The SALUS pivotal trial, which randomizes extreme-risk AS patients to Direct Flow or other TAVR devices, has nearly completed enrollment (NCT02163850).

The Portico valve (St. Jude Medical, Minneapolis, MN) is a bovine pericardial valve with a porcine pericardial sealing cuff attached to a nitinol self-expanding frame delivered via an 18F transfemoral sheath (10). Although early feasibility results of the Portico valve were promising, a randomized trial comparing Portico to other TAVR devices was halted due to an unexpected finding of reduced prosthesis leaflet motion on computed tomography (CT) in a patient who had a stroke after TAVR. This finding suggested subclinical valve thrombosis requiring further investigation (11). The trial was resumed after FDA approval because reduced leaflet motion is not unique to the Portico valve and typically is not associated with adverse outcome. Additional TAVR devices are described below in the section on AR.

COMPLICATIONS

Paravalvular Leak

Paravalvular leak, defined as AR occurring between the prosthesis and the native aortic annulus, is the most common complication of TAVR. It is intuitive that paravalvular leak is more common in TAVR, where native calcific aortic valve tissue is displaced but not removed, and the prosthesis is anchored against the annulus by radial force, which may lead to incomplete sealing between the prosthesis and native annulus. Paravalvular leak may also be due to a mismatch between the circular shape of many transcatheter valves and the elliptical shape of the aortic annulus. In the Corevalve Pivotal US trial (12), paravalvular leak was considerably more common in TAVR cases than in surgical AVR cases at hospital discharge (mild 34.4% versus 3.0%, $\geq$ moderate 7.8% versus 0.3%, $p < 0.001$). In a meta-analysis of the first-generation Corevalve and SAPIEN valves, moderate or severe AR was more common with Corevalve than SAPIEN (16.0% versus 9.1%, $p = 0.005$) (13). Importantly, the presence of moderate or severe paravalvular leak is associated with increased mortality (13, 14), although the degree of leak appears to diminish somewhat over time (12). Study of the mechanisms, effects, and treatment of paravalvular leak after TAVR is hampered by variations in grading of severity and lack of validated criteria. Recent efforts have aimed to standardize the definitions of paravalvular leak and improve measurement techniques (15, 16). When moderate or severe paravalvular leak is recognized after TAVR, further interventions can be performed, including balloon postdilation of the prosthesis, valve in valve, or percutaneous device closure of the paravalvular leak (17). Newer TAVR devices include features to minimize paravalvular leak, such as an outer skirt to provide a better seal between the prosthesis and native annulus (**Figure 2**). The Lotus valve appears to have the lowest incidence of moderate or severe paravalvular leak—only 1% in the REPRISE II study (8)—and unpublished results on the Evolut

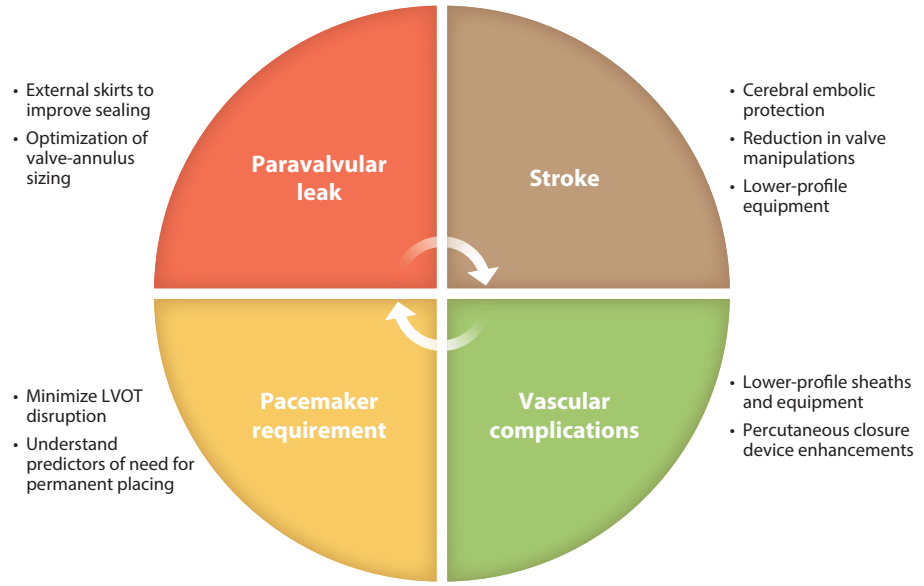

Figure 2

Paravalvular leak, stroke, pacemaker requirement, and vascular complications are the key areas in need of further research and improvement in device and procedural technology. LVOT, left ventricular outflow tract.

R and SAPIEN 3 valves suggest a significant reduction in the rates of paravalvular leak in these newer devices.

Pacemaker Implantation

Given the close proximity of the cardiac conduction tissue to the aortic valve, TAVR is associated with the development of left bundle branch block and varying degrees of AV block. The risk varies by device; the Lotus and Corevalve devices are associated with the highest risk of permanent pacemaker implantation, approaching 30% (7, 8). With the SAPIEN valve, according to the PARTNER trial, permanent pacemaker implantation occurred at rate of ~9% and was associated with increased length of hospital stay, higher rates of repeat hospitalization, and higher one-year mortality (18). However, analysis of a larger number of patients has suggested that permanent pacemaker implantation after TAVR is not associated with increased mortality (19). Understandable concerns exist, however, regarding the potential impact a permanent pacemaker may have on a younger population, given the potential for detrimental long-term effects of RV pacing on ventricular function (19). Procedural factors that may predict increased risk of heart block include the depth of implantation within the left ventricular outflow tract and higher-percent oversizing of the valve to the native annulus (20, 21). Patient-related factors including advanced age, male sex, baseline right bundle branch block, QRS duration, and intraprocedural AV block are all associated with higher risk of permanent pacemaker requirement (22). Several uncertainties exist as to the optimal indications for permanent pacemaker implantation after TAVR and best methods to identify patients at risk for heart-block related sudden death. Methods include measurement of H-V (His-Ventricular) intervals using invasive electrophysiologic testing (23) and the use of implantable loop recorders post TAVR in selected patients (NCT02153307).

Vacular Complications

Major vascular complications, including iliofemoral dissection or rupture, have declined considerably with the iterative reduction in TAVR sheath sizes. Initial studies reported a 5–20% risk of vascular complications with transfemoral TAVR, typically due to arterial sheath insertion. With the sheath-size reduction in newer devices (e.g., the original 22F SAPIEN device has declined to 14F in SAPIEN 3), better preprocedural identification of ileofemoral anatomy, and improved percutaneous closure techniques, the rate of vascular complications has declined to 8% in the PARTNER continued access registry (24) and 4% in the Transcatheter Valve Therapies (TVT) registry (25). Technological advances including newer sheaths, innovative vascular closure devices, and smaller devices may help to further lower the rate of vascular complications. With the increasing use of percutaneous technique over surgical femoral cut-down approach, rehospitalizations for wound complications such as infections and seromas requiring drainage may decline.

Cerebral Embolization

Initially, stroke was believed to be more frequent with TAVR compared to surgical AVR, but the Corevalve Pivotal trial showed 30-day rigorously adjudicated clinical stroke rates were similar with TAVR (4.9%) and surgical AVR (6.2%) in high-risk AS patients ($p = 0.46$) (7). More recent data from the TVT registry has shown that 30-day stroke rates after TAVR have now declined to 2% with newer devices (25). Closer examination of cerebral embolization using transcranial Doppler assessment of high-intensity transient signals during TAVR and now diffusion-weighted magnetic resonance imaging (MRI), however, has revealed that virtually all patients experience silent microembolic events that are believed to be related to embolization of material primarily during valve deployment (26). Concerns exist that increasing the number of manipulations to the aortic valve complex, such as device repositioning, balloon predilatation, and balloon postdilatation may increase the risk and burden of cerebral embolization. In up to 86% of patients undergoing TAVR, debris in the form of fibrin/thrombotic, calcium, tissue-derived, and polymer material can be collected with embolic protection filters positioned in the aortic arch (27, 28). It remains unclear whether diffusion-weighted MRI abnormalities that are present in up to 98% of patients undergoing TAVR (NCT01833052) are predictive of subsequent clinical events or more subtle neurocognitive impairment such as changes in ability to perform activities of daily living. Complicating factors also include development of postoperative atrial fibrillation and delirium. Several cerebral embolic protection devices have shown a reduction in the number and volume of MRI-detected lesions after TAVR in initial safety and feasibility trials (29) and are currently being investigated in clinical randomized trials (NCT02214277, NCT02536196) to determine whether cerebral embolic protection is associated with a reduction in clinical stroke rates and/or improved neurocognitive function after TAVR. Similar devices are also being tested in surgical AVR given the heightened interest in and recognition of arterial embolization that has occurred with the advent of TAVR.

Subclinical Valve Thrombosis

Recent reports have raised concern over the unexpected observation of early subclinical prosthetic valve leaflet dysfunction visualized by 4D CT believed to be mediated by thrombosis (11). In an investigation of 55 patients enrolled in the Portico IDE trial who underwent contrast CT 30 days after TAVR, reduced aortic valve leaflet motion was present in 40%, including 16/37 (43%) with Portico valves, 6/14 (43%) with SAPIEN XT valves, and 0/4 with Corevalve valves.

The prevalence of reduced leaflet motion was lower among patients who received therapeutic anticoagulation with warfarin after TAVR than among those without therapeutic anticoagulation [0/8 patients on warfarin versus 21/41 (51%) not receiving therapeutic anticoagulation, $p = 0.007$] (11). Furthermore, dual antiplatelet therapy did not appear to protect against reduced leaflet motion. On follow-up CT six months later, normal leaflet motion recovered in patients treated with anticoagulation, but abnormal leaflet motion persisted in the majority of those not treated with anticoagulation (11). Although the number of patients is very small, the data are persuasive that abnormal leaflet motion early after TAVR may not be detected by transthoracic echocardiography and may be a result of subclinical thrombosis that can be prevented with vitamin K antagonist therapy. Two current trials in lower-risk patients include subsets in whom 4D CT is performed sequentially to better define the scope of this phenomenon (NCT02426307, NCT02318342). Randomized trials of various anticoagulation strategies in TAVR are also planned (NCT02556203, NCT02664649, NCT02247128).

THERAPEUTIC ROLE

Treating Aortic Stenosis

TAVR is the recommended first-line treatment for severe, symptomatic AS in patients at high risk for surgery [Society for Thoracic Surgery (STS) risk score ≥ 8%] who have a reasonable life expectancy (2) (**Figure 3**). This recommendation has been supported primarily by the superior observed versus expected mortality ratio of TAVR (0.21) compared to surgical AVR (1.05) in high-risk patients (30). Post-market analysis of "real-world" data from the TVT registry using first-generation devices has demonstrated similar outcomes to those demonstrated in randomized controlled trials, with one-year mortality and stroke rates of 23.7% and 4.1% in the high-risk TAVR population (25). The high one-year mortality rates after successful TAVR, however, highlight the need to improve current risk prediction tools above and beyond the STS risk score and to better quantify frailty in order to improve patient selection for TAVR. Temporal trends of TAVR practice in the United States between 2012 and 2014 show an increase in the use of percutaneous transfemoral techniques, reducing vascular complication rates, and an increase in the

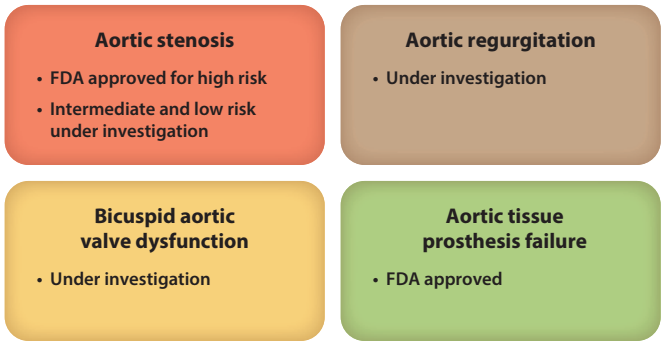

Figure 3

Transcatheter aortic valve replacement (TAVR) is a first-line treatment for patients with severe, symptomatic aortic stenosis (AS) at high risk for surgery. Low-risk AS, intermediate-risk symptomatic AS, and asymptomatic AS are currently under investigation. The role of TAVR in bicuspid aortic valve disease and noncalcified aortic regurgitation is actively being studied. TAVR is also a first-line treatment for aortic tissue prosthesis failure in patients at high risk for surgery.

use of moderate sedation (31), as well as improved survival. Several studies are investigating the role of TAVR in intermediate-risk patients (STS risk score 4–8%), including the PARTNER 2 Intermediate Risk trial and the randomized SURTAVI trial comparing TAVR (with Corevalve) to surgical AVR (32). A recent Scandinavian trial of low-risk patients undergoing TAVR was underpowered to establish superiority but provided a promising initial glimpse of how TAVR may perform in a low-risk population (33). Two separate randomized controlled trials of TAVR with SAPIEN 3 (NCT02675114) and Evolut R (NCT02701283) in low-risk patients will begin soon. Given the very favorable results of newer TAVR devices in the high-risk population, similar or even better results are expected in lower-risk patients. It is anticipated that trials of low-risk patients with TAVR will provide important data regarding the durability, morbidity, and mortality of TAVR compared to surgical AVR.

Other AS populations of interest include patients with low-flow, low-gradient, severe AS with preserved and reduced ejection fraction. Although the adverse prognosis of low flow and low gradient can be improved with AVR (34), these factors predict subsequent mortality even after TAVR (35), and it is unknown whether TAVR is preferable to surgical AVR in this population. TAVR for treatment of low-flow, low-gradient AS with reduced ejection fraction has recently received FDA approval. Another randomized trial is also forthcoming to address whether TAVR improves outcomes in patients with moderate aortic AS and concomitant left ventricular systolic dysfunction (NCT02661451), given the susceptibility to afterload that occurs in the setting of left ventricular dysfunction. Patients with asymptomatic but severe AS comprise another population for which management is controversial and randomized controlled trials are needed (36).

Treating Aortic Regurgitation

The diverse etiologies and pathophysiology of pure aortic regurgitation (AR) present a challenge for transcatheter device treatment. In patients with aortic root and annular enlargement as the primary mechanism, larger devices may be required, and the large regurgitant volume combined with lack of leaflet calcification increase the risk of device embolization. In the developing world, rheumatic AR represents an important and undertreated problem. In contrast, in the developed world, the smaller population of patients with pure severe AR relative to the large AS population has resulted in slower development of dedicated devices. Nevertheless, several TAVR devices (Direct Flow, Corevalve) have been used successfully off-label for treatment of pure severe AR in both calcified and noncalcified valves. Primarily self-expanding valves have been used because they provide greater oversizing with a lower risk of damage to the aortic annulus. In 43 patients with severe native AR (60% without significant valve calcification), Corevalve valves were implanted in 98%, but 19% required a second "valve in valve" for significant residual AR (37). A study of 26 patients with severe native AR similarly showed high rates of moderate or severe paravalvular leak, a 19% rate of valve in valve requirement, and a higher mortality rate compared to AS patients treated with TAVR (38). In 11 patients with noncalcified severe AR, the Direct Flow valve was initially successfully implanted, with no patient having more than mild paravalvular leak following the procedure; however, two patients subsequently experienced device embolization requiring reintervention (39).

Jenavalve and ACURATE TA are second-generation TAVR devices whose specific design features allow active fixation of the aortic valve. They may be more suited to treatment of noncalcified AR. Jenavalve is a trileaflet porcine tissue valve secured to a nitinol stent that is inserted transapically. The unique aspect of this device is the presence of positioning feelers that are seated in the native aortic root sinuses, which enables "clipping" and a secure attachment of noncalcified aortic valve leaflets (40). In an initial experience of five patients with moderate to severe

noncalcified AR, results were excellent, with no more than trace residual AR and no procedural mortality. In another series, Jenavalve demonstrated procedural success in 10 of 10 patients with pure AR, and no patient had greater than mild residual AR (41). The ACURATE TA (Symetis, Ecublens, Switzerland) system is a porcine tissue valve housed within a self-expanding nitinol stent that is implanted via a transapical mini-thoracotomy technique. The device uniquely consists of an upper crown that provides stabilization and allows "capping" and compression of the native leaflets from a supra-annular position, sealing cuffs to minimize paravalvular leak, and is repositionable until final release. Short-term results have shown safety and efficacy with very low rates of paravalvular leak in patients with AS (42), and early data in small numbers of patients with pure AR have suggested favorable short-term safety and efficacy (43).

Treating Bicuspid Aortic Valve Disease

The role of TAVR in the treatment of bicuspid aortic valve disease is an area of active investigation. Bicuspid aortic valve disease was uncommonly treated with TAVR until recently, owing to concerns about the asymmetry of the bicuspid aortic valve resulting in inadequate transcatheter valve expansion or apposition and potentially higher rates of complications including paravalvular leak. In the US TVT registry, only 2% of patients treated with TAVR had bicuspid aortic valve disease (44). A recent meta-analysis comparing outcomes of TAVR in bicuspid and nonbicuspid aortic valve disease showed no difference in device success rates, paravalvular leak, pacemaker rates, or 30-day or one-year mortality between the groups (45). However, a recent multicenter registry study not included in this meta-analysis has demonstrated that although 30-day and one-year mortality were favorable, there was a high incidence of post-TAVR AR (moderate or severe regurgitation in 28.4%) that seemed to be reduced by using multi-slice CT-based transcatheter valve sizing (46). Data from the Bicuspid Aortic Stenosis Following Transcatheter Aortic Valve Replacement Registry (Bicuspid TAVR) are expected to provide further insight into the clinical outcomes of TAVR in this population (NCT02394184). Randomized trials of TAVR in the bicuspid aortic valve disease population are lacking and are currently being planned. Specific challenges of studying this population include the heterogeneity and broad spectrum of bicuspid aortic valve subtypes (including those with a complete or partial raphe and those with no raphe at all) and variability of coronary versus noncoronary cusp fusion. A CT imaging–based classification scheme has recently been proposed to help guide the study of TAVR in this population (47). Studies are needed to better understand how the concomitant aortopathy that exists in many patients with bicuspid aortic valve disease may impact the use of TAVR in this group.

Treating Aortic Bioprosthesis Failure (Aortic Valve in Valve)

Structural failure of surgical aortic valve bioprostheses occurs in ~30% of patients by 15 years after surgery, and redo AVR carries considerable risk (48–51). The higher risk of the population with failed surgical bioprostheses and the growing number of patients selecting bioprostheses over mechanical prostheses have prompted the search for a lower-risk treatment option. Multiple TAVR valves have been used with high success for this indication (**Table 1**), and a growing experience has helped to develop optimal methods of implantation. The Valve in Valve International Data (VIVID) Registry has demonstrated safety and effectiveness of TAVR for treatment of failed surgical aortic valve prostheses with a low procedural mortality and stroke rate (52). Patient factors that predicted higher one-year mortality in the VIVID Registry included the presence of prosthetic stenosis (as opposed to regurgitation) and a 21-mm or smaller valve, likely because of a less favorable hemodynamic result with higher residual gradients. As a result of good observational

data, aortic valve-in-valve therapy was FDA approved for treatment of failed surgical prostheses in 2015. The valve-in-valve app by Bapat is a useful resource for clinicians to guide transcatheter valve selection and implantation based on the type and size of the failed prosthesis (53).

Complications such as paravalvular leak and heart block are less common with valve in valve than with TAVR in native AS. Annular rupture, although uncommon in conventional TAVR, does not occur at all in valve in valve because of device anchoring on the prosthetic sewing ring. However, in certain valve types such as those with leaflets sewn outside the stent frame, and in patients with smaller aortic root sizes, the risk of coronary occlusion is high, so alertness to this potential complication with valve in valve is necessary.

Long-Term Durability

Five-year outcomes from the PARTNER trial have confirmed similar valve hemodynamics between TAVR and surgical AVR (prosthesis effective orifice area was 1.6 cm^2 with TAVR versus 1.5 cm^2 with surgical AVR, $p = 0.29$, and mean valve gradients were 10 ± 7 mm Hg versus 10 ± 6 mm Hg, $p = 0.92$) with no reported incidence of structural valve deterioration in either group (54). A recent study found a 4.5% annual incidence of transcatheter valve hemodynamic deterioration (defined as absolute change in gradient $\geq$ 10 mm Hg during follow-up) that was more common in patients without anticoagulation, patients with large body mass index, patients undergoing valve in valve, and patients with a 23-mm prosthesis (55). No studies have systematically investigated the prevalence of structural prosthesis failure after TAVR in the postmarket approval setting, and registries are expected to provide these data in the future.

THE FUTURE

The future of TAVR is bright and is supported by a foundation of rigorous and groundbreaking clinical trials that now show identical five-year outcomes between TAVR and surgical AVR in high-risk patients. Advancements in the field include the study of the role of TAVR in expanded patient populations (low- and intermediate-risk AS, asymptomatic AS, bicuspid aortic valve disease, and AR) and the reduction of complications. TAVR is already a first-line treatment for patients with AS at high risk for surgery, and in the future its indication will likely be expanded to intermediate-risk and potentially low-risk patients. The role of cerebral embolic protection devices is actively being investigated, as are enhanced valve designs and CT-based valve sizing to minimize the incidence of paravalvular leak. The optimal indications for and prognostic significance of permanent pacemaker implantation also requires further study. The durability of TAVR will also become evident in the years to come, particularly with its use in the low-risk population. Ultimately the relative effectiveness, advantages, and disadvantages of the multiple devices under investigation will determine which devices are best suited to each specific patient population.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Harken DE, Soroff HS, Taylor WJ, et al. 1960. Partial and complete prostheses in aortic insufficiency. *J. Thorac. Cardiovasc. Surg.* 40:744–62

2. Nishimura RA, Otto CM, Bonow RO, et al. 2014. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:e521–643
3. Vahanian A, Alfieri O, Andreotti F, et al. 2012. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. J. Cardiothorac. Surg.* 42:S1–44
4. Cribier A, Eltchaninoff H, Bash A, et al. 2002. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 106:3006–8
5. Smith CR, Leon MB, Mack MJ, et al. 2011. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N. Engl. J. Med.* 364:2187–98
6. Leon MB, Smith CR, Mack M, et al. 2010. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N. Engl. J. Med.* 363:1597–607
7. Adams DH, Popma JJ, Reardon MJ, et al. 2014. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N. Engl. J. Med.* 370:1790–98
8. Meredith Am IT, Walters DL, Dumonteil N, et al. 2014. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. *J. Am. Coll. Cardiol.* 64:1339–48
9. Lefevre T, Colombo A, Tchetche D, et al. 2016. Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve system: 12-month outcomes of the Evaluation of the Direct Flow Medical Percutaneous Aortic Valve 18F System for the Treatment of Patients with Severe Aortic Stenosis (DISCOVER) Study. *JACC Cardiovasc. Interv.* 9:68–75
10. Willson AB, Rodes-Cabau J, Wood DA, et al. 2012. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. *J. Am. Coll. Cardiol.* 60:581–86
11. Makkar RR, Fontana G, Jilaihawi H, et al. 2015. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N. Engl. J. Med.* 373:2015–24
12. Reardon MJ, Adams DH, Kleiman NS, et al. 2015. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J. Am. Coll. Cardiol.* 66:113–21
13. Athappan G, Patvardhan E, Tuzcu EM, et al. 2013. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J. Am. Coll. Cardiol.* 61:1585–95
14. Kodali SK, Williams MR, Smith CR, et al. 2012. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N. Engl. J. Med.* 366:1686–95
15. Kappetein AP, Head SJ, Genereux P, et al. 2012. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J. Am. Coll. Cardiol.* 60:1438–54
16. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. 2015. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. *JACC Cardiovasc. Imaging* 8:340–60
17. Eleid MF, Cabalka AK, Malouf JF, et al. 2015. Techniques and outcomes for the treatment of paravalvular leak. *Circ. Cardiovasc. Interv.* 8:e001945
18. Nazif TM, Dizon JM, Hahn RT, et al. 2015. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc. Interv.* 8:60–69
19. Urena M, Webb JG, Tamburino C, et al. 2014. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation* 129:1233–43
20. Kim WJ, Ko YG, Han S, et al. 2015. Predictors of permanent pacemaker insertion following transcatheter aortic valve replacement with the Corevalve revalving system based on computed tomography analysis: an asian multicenter registry study. *J. Invasive Cardiol.* 27:334–40
21. Maan A, Refaat MM, Heist EK, et al. 2015. Incidence and predictors of pacemaker implantation in patients undergoing transcatheter aortic valve replacement. *Pacing Clin. Electrophysiol.* 38:878–86
22. Siontis GC, Juni P, Pilgrim T, et al. 2014. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J. Am. Coll. Cardiol.* 64:129–40

23. Rivard L, Schram G, Asgar A, et al. 2015. Electrocardiographic and electrophysiological predictors of atrioventricular block after transcatheter aortic valve replacement. *Heart Rhythm* 12:321–29
24. Beohar N, Kirtane AJ, Blackstone E, et al. 2016. Trends in complications and outcomes of patients undergoing transfemoral transcatheter aortic valve replacement: experience from the PARTNER continued access registry. *JACC Cardiovasc. Interv.* 9:355–63
25. Holmes DR Jr., Brennan JM, Rumsfeld JS, et al. 2015. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 313:1019–28
26. Erdoes G, Basciani R, Huber C, et al. 2012. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *Eur. J. Cardiothorac. Surg.* 41:778–83
27. Van Mieghem NM, Schipper ME, Ladich E, et al. 2013. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation* 127:2194–201
28. Van Mieghem NM, El Faquir N, Rahhab Z, et al. 2015. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. *JACC Cardiovasc. Interv.* 8:718–24
29. Lansky AJ, Schofer J, Tchetche D, et al. 2015. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur. Heart J.* 36:2070–78
30. Thourani VH, Suri RM, Gunter RL, et al. 2015. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. *Ann. Thorac. Surg.* 99:55–61
31. Holmes DR Jr., Nishimura RA, Grover FL, et al. 2015. Annual outcomes with transcatheter valve therapy: from the STS/ACC TVT Registry. *J. Am. Coll. Cardiol.* 66:2813–23
32. van Mieghem NM, Head SJ, van der Boon RM, et al. 2012. The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis. *EuroIntervention* 8:258–66
33. Thyregod HG, Steinbruchel DA, Ihlemann N, et al. 2015. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J. Am. Coll. Cardiol.* 65:2184–94
34. Eleid MF, Sorajja P, Michelena HI, et al. 2013. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: clinical characteristics and predictors of survival. *Circulation* 128:1781–89
35. Eleid MF, Goel K, Murad MH, et al. 2015. Meta-analysis of the prognostic impact of stroke volume, gradient, and ejection fraction after transcatheter aortic valve implantation. *Am. J. Cardiol.* 116:989–94
36. Eleid MF, Pellikka PA. 2015. Asymptomatic severe aortic stenosis: What are we waiting for? *J. Am. Coll. Cardiol.* 66:2842–43
37. Roy DA, Schaefer U, Guetta V, et al. 2013. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J. Am. Coll. Cardiol.* 61:1577–84
38. Testa L, Latib A, Rossi ML, et al. 2014. CoreValve implantation for severe aortic regurgitation: a multicentre registry. *EuroIntervention* 10:739–45
39. Schofer J, Nietlispach F, Bijuklic K, et al. 2015. Transfemoral implantation of a fully repositionable and retrievable transcatheter valve for noncalcified pure aortic regurgitation. *JACC Cardiovasc. Interv.* 8:1842–49
40. Treede H, Mohr FW, Baldus S, et al. 2012. Transapical transcatheter aortic valve implantation using the JenaValve system: acute and 30-day results of the multicentre CE-mark study. *Eur. J. Cardiothorac. Surg.* 41:e131–38
41. Schlingloff F, Schafer U, Frerker C, et al. 2014. Transcatheter aortic valve implantation of a second-generation valve for pure aortic regurgitation: procedural outcome, haemodynamic data and follow-up. *Interact. Cardiovasc. Thorac. Surg.* 19:388–93
42. Kempfert J, Holzhey D, Hofmann S, et al. 2015. First registry results from the newly approved ACURATE TA TAVI system. *Eur. J. Cardiothorac. Surg.* 48:137–41
43. Wendt D, Kahlert P, Pasa S, et al. 2014. Transapical transcatheter aortic valve for severe aortic regurgitation: expanding the limits. *JACC Cardiovasc. Interv.* 7:1159–67
44. Mack MJ, Brennan JM, Brindis R, et al. 2013. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 310:2069–77
45. Phan K, Wong S, Phan S, et al. 2015. Transcatheter aortic valve implantation (TAVI) in patients with bicuspid aortic valve stenosis—systematic review and meta-analysis. *Heart Lung. Circ.* 24:649–59

46. Mylotte D, Lefevre T, Sondergaard L, et al. 2014. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J. Am. Coll. Cardiol.* 64:2330–39
47. Jilaihawi H, Chen M, Webb J, et al. 2016. A bicuspid aortic valve imaging classification for the transcatheter aortic valve implantation era. *JACC Cardiovasc. Imaging.* In press
48. Cohn LH, Collins JJ Jr., Rizzo RJ, et al. 1998. Twenty-year follow-up of the Hancock modified orifice porcine aortic valve. *Ann. Thorac. Surg.* 66:S30–S34
49. David TE, Ivanov J, Armstrong S, et al. 2001. Late results of heart valve replacement with the Hancock II bioprosthesis. *J. Thorac. Cardiovasc. Surg.* 121:268–77
50. Gao G, Wu Y, Grunkemeier GL, et al. 2004. Durability of pericardial versus porcine aortic valves. *J. Am. Coll. Cardiol.* 44:384–88
51. Glower DD, Landolfo KP, Cheruvu S, et al. 1998. Determinants of 15-year outcome with 1,119 standard Carpentier-Edwards porcine valves. *Ann. Thorac. Surg.* 66:S44–S48
52. Dvir D, Webb JG, Bleiziffer S, et al. 2014. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA* 312:162–70
53. Bapat V. 2014. Valve-in-valve apps: why and how they were developed and how to use them. *EuroIntervention* 10(Suppl. U):U44–51
54. Mack MJ, Leon MB, Smith CR, et al. 2015. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 385:2477–84
55. Del Trigo M, Munoz-Garcia AJ, Wijeysundera HC, et al. 2016. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. *J. Am. Coll. Cardiol.* 67:644–55