Transcatheter Aortic Valve Replacement

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George S. Hanzel

Abstract

Aortic stenosis is a common disease with a prevalence of approximately 5 % in elderly patients. The population of people in the United States older than 65 is expected to increase from 40 million in 2010 to nearly 80 million by 2050. With this demographic shift, the burden of valvular heart disease will increase as well. Surgical aortic valve replacement (SAVR) has long been the standard of care for the treatment of severe aortic stenosis. Multiple studies however, have documented that nearly 40 % of elderly patients with severe symptomatic aortic stenosis do not undergo surgery; mainly because of advanced age and comorbidities. This unmet clinical need was the impetus for the development of transcatheter aortic valve replacement (TAVR). Since Cribier treated the first patient in 2002, great strides have been made in the technology and TAVR has become the standard of care for appropriately selected inoperable patients and it is an alternative to surgery for high-risk patients.

Keywords

Transcatheter aortic valve replacement (TAVR) • TAVR outcomes • TAVR complications • Valve-in-valve replacement • Bicuspid aortic valve • Pure aortic regurgitation

Introduction

Aortic stenosis is a common disease with a prevalence of approximately 5 % in elderly patients [1]. The population of people in the United States older than 65 is expected to increase from 40 million in 2010 to nearly 80 million by 2050 [2]. With this demographic shift, the burden of valvular heart disease will

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increase as well. Surgical aortic valve replacement (SAVR) has long been the standard of care for the treatment of severe aortic stenosis. Multiple studies however, have documented that nearly 40 % of elderly patients with severe symptomatic aortic stenosis do not undergo surgery; mainly because of advanced age and comorbidities [3–8]. This unmet clinical need was the impetus for the development of transcatheter aortic valve replacement (TAVR). Since Cribier treated the first patient in 2002 [9], great strides have been made in the technology and TAVR has become the standard of care for appropriately selected inoperable patients and it is an alternative to surgery for high-risk patients.

Commercially Approved Transcatheter Heart Valves in the United States

The Edwards Sapien XT (Edwards Lifesciences Inc., Irvine, California) and the Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) transcatheter heart valves (THV) are the two currently commercially available THVs in the United States (Figs. 15.1 and 15.2). The Edwards Sapien XT THV, an iteration of the original Edwards Sapien THV, is a balloon expandable prosthesis with a cobalt chromium stent frame and bovine pericardial leaflets. The Edwards Sapien XT can be implanted via the

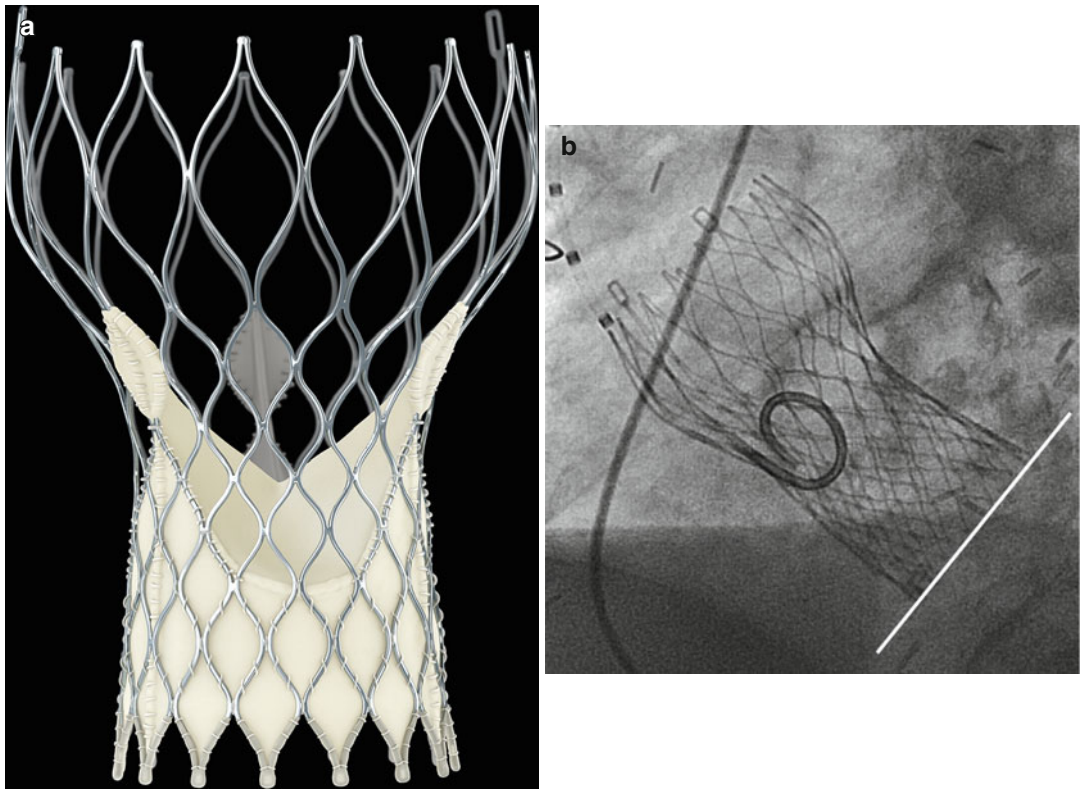

Fig. 15.1 Medtronic core valve, prosthesis diagram and under fluoroscopy in place (**a**, **b**) and (**a** copyright 2015 Medtronic, Inc.)

transfemoral approach with either a 16-French, 18-French, or 20-French expandable sheaths for the 23 mm, 26 mm, or 29 mm Sapiens XT, respectively. Alternate access routes include transaortic, transapical, and caval-aortic approaches [10]. The Medtronic CoreValve THV has a self-expanding nitinol frame and porcine pericardial leaflets. The CoreValve anchors both in the annulus as well as the proximal ascending aorta. The CoreValve can be implanted via an 18-French sheath in the femoral artery or subclavian artery. Additionally, CoreValve can be implanted via caval-aortic access or transaortic access.

Clinical Outcomes

The PARTNER (Placement of Transcatheter Aortic Valves) and CoreValve trials are the landmark randomized trials that established TAVR as a transformative technology for the treatment of aortic stenosis in high-risk and inoperable patients [11–14]. The PARTNER trial was the first randomized study to evaluate TAVR and it utilized the Edwards Sapien balloon expandable THV. It was a two-arm trial in which patients who were high risk for SAVR were randomized to TAVR vs SAVR and patients who were deemed inoperable were randomized to TAVR vs medical therapy. The CoreValve trial was also a two-armed trial which evaluated the Medtronic CoreValve self-expanding THV. High risk patients were randomized to SAVR vs TAVR and all inoperable patients were treated with CoreValve.

Survival

The PARTNER 1B trial randomized 358 inoperable patients to TAVR with Edwards Sapien THV versus medical therapy [11]. The 30 day mortality rate was 6.4 % compared with a

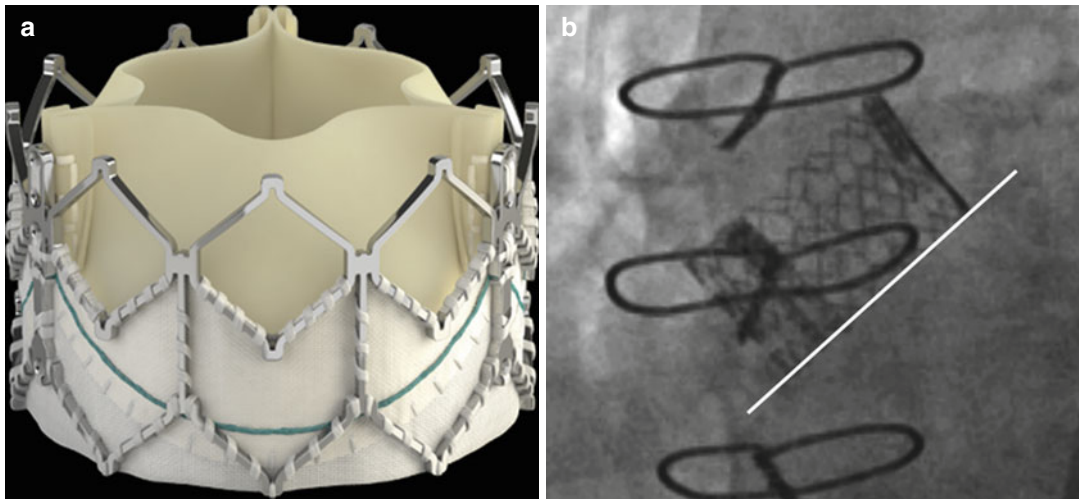

Fig. 15.2 Edwards Sapien XT valve prosthesis diagram and under fluoroscopy in place (**a**, **b**) (**a** courtesy of Edwards Lifesciences, Irvine, CA. Edwards, Edwards Lifesciences, Edwards SAPIEN, Edwards SAPIEN XT, SAPIEN, and SAPIEN XT are trademarks of Edwards Lifesciences Corporation)

Society of Thoracic Surgery (STS) predicted rate of mortality of 11.6 % for surgery. At 1 year the all-cause mortality rate, the primary endpoint of the trail, was 30.7 % for TAVR versus 50.7 % for medical therapy ($p < 0.0001$) with a number needed to treat (NNT) of 4.0 to save one life. By 3 years the mortality rate was 54.1 % vs 80.9 % ($p < 0.0001$) with NNT of 3.7 (Fig. 15.3) [15, 16]. This profound reduction in mortality led to the approval for the Edwards Sapien THV in inoperable patient in November 2011.

In the PARTNER 1A trial 699 high-risk patients were randomized to TAVR vs SAVR [12]. The mean STS score was nearly 12 % and TAVR could be performed via the transfemoral or transapical approach. The 30 day mortality rate was 3.4 % for TAVR vs 6.5 % for SAVR, $p = 0.07$. At 1 year the all-cause mortality rate, the primary endpoint of the trail, was 24.2 % vs 26.8 % for TAVR and SAVR, respectively, $p = 0.44$ (Fig. 15.4). By 3 years the mortality rate was 44.2 % vs 44.8 % (p=NS) [17, 18]. This suggests that TAVR is noninferior to SAVR in

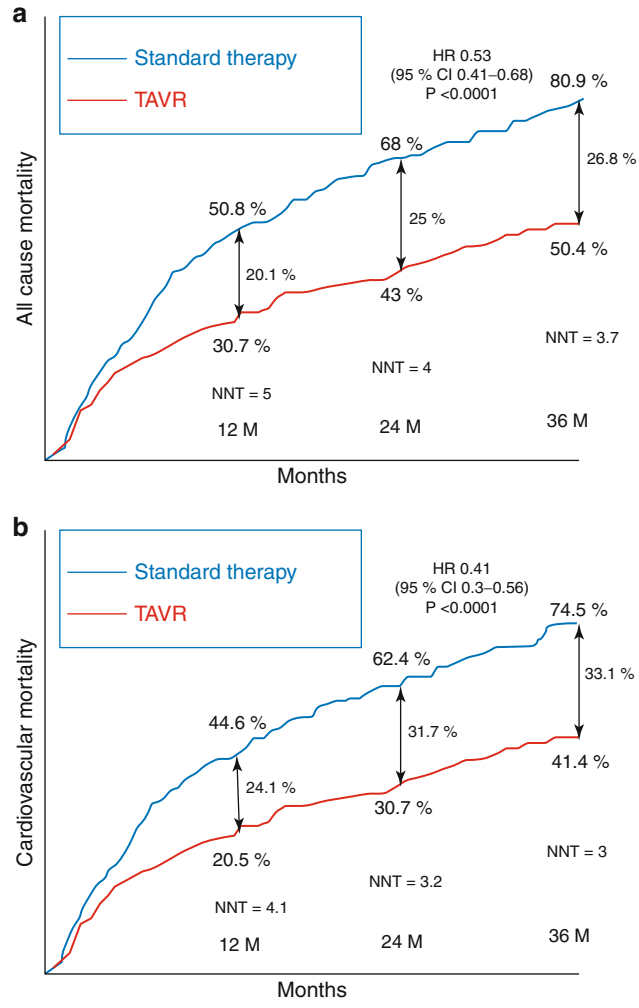

Fig. 15.3 PARTNER 1B: 3-year survival. Long-term outcomes of inoperable patients with aortic stenosis randomized to either transcatheter aortic valve replacement (*TAVR*) with Edwards Sapien valve or standard therapy revealing TAVR is superior to medical treatment in inoperable patients (**a**) reflects all cause mortality, (**b**) reflects cardiovascular mortality

high-risk patients. Interestingly, in an as treated analysis the 30 day mortality rate was 3.7 % for transfemoral TAVR, 8.7 % for transapical TAVR, and 8.2 % for SAVR. It is not clear to what extent the increased mortality seen in the transapical group was attributable to the procedure itself versus the selection of higher risk patients (i.e., severe peripheral arterial disease). However, this raises the question as to whether TAVR outcomes can continue to improve as sheath profile size decreases and more patients are treated via the transfemoral route. The Edwards Sapien valve was approved as an alternative to surgery for high-risk patients in October 2011.

In the inoperable arm of the US CoreValve trial 489 patients were treated with the CoreValve THV [13]. Patients were included in the trial if it was estimated that they had a 50 % risk of mortality or irreversible morbidity at 30 days with SAVR. The primary endpoint was the composite of all-cause mortality and stroke at 1 year compared with an objective performance goal. At 1 year all-cause mortality and stroke was 26.0 % compared with an objective performance goal of 43.0 % ($p<0.0001$) (Fig. 15.5). The 30 day and 1 year morality rates were 8.4 % and 24.3 %, respectively. This trial confirms the findings of PARTNER 1B: TAVR is superior to medical therapy in inoperable patients.

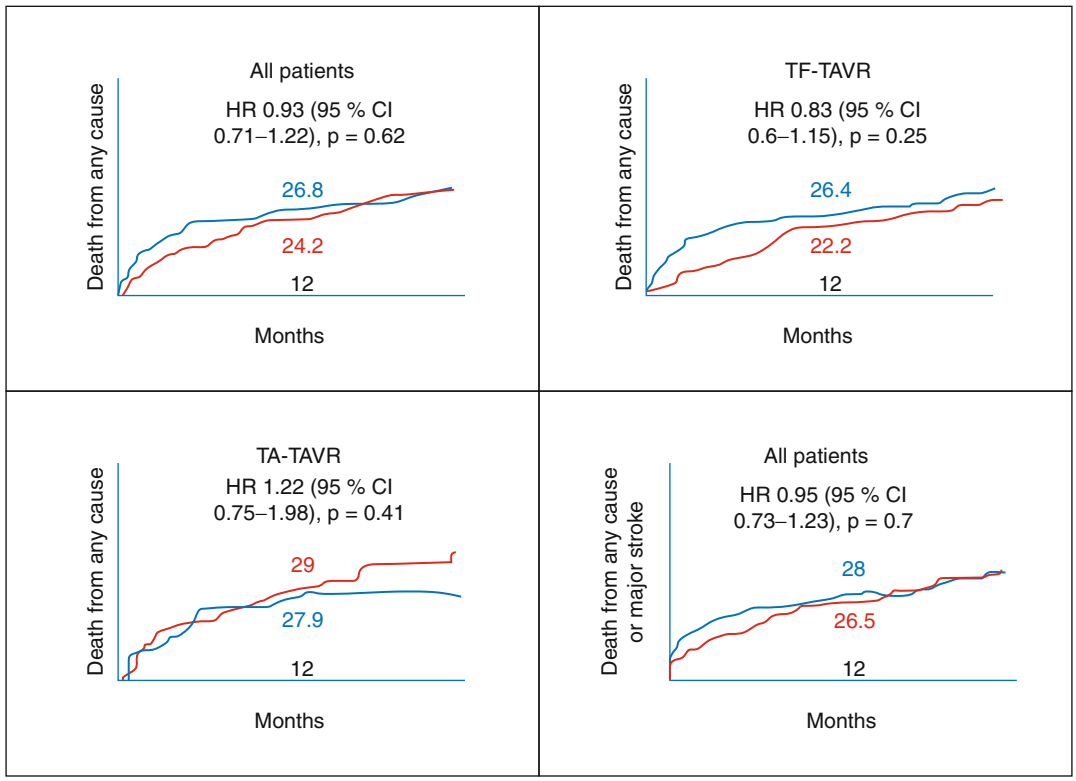

Fig. 15.4 (PARTNER 1A: 1-year outcomes. Transcatheter (*TAVR*) with Edwards Sapien valve versus surgical aortic-valve replacement (*SAVR*) in high-risk patients revealing that TAVR was non-inferior to SAVR in this cohort

In the high-risk arm of the US CoreValve trial the 795 patients were randomized to TAVR vs SAVR [14]. The primary endpoint was all-cause mortality at 1 year and the mean STS score was 7.3 %. The 30 day mortality rates were 3.3 % vs 4.5 % for TAVR and SAVR, respectively (p=0.43). The 1 year mortality rates were 14.2 % vs 19.1 % for TAVR vs SAVR, respectively (p<0.001) (Fig. 15.6). These findings of superiority of TAVR vs SAVR suggest that for high-risk patients TAVR may offer a survival advantage over conventional SAVR. Additional studies are needed to confirm these findings.

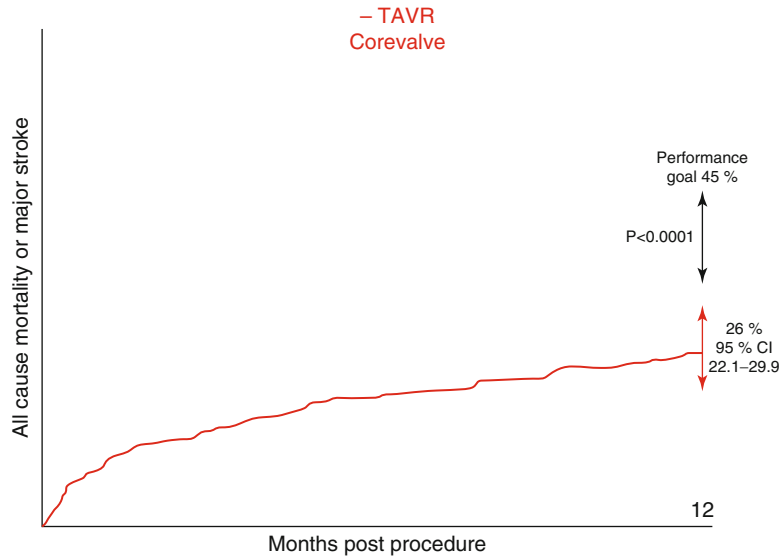

Fig. 15.5 Core valve extreme risk: all cause mortality and stroke. Transcatheter aortic valve replacement (*TAVR*) using a self-expanding Core Valve in patients with severe aortic stenosis at extreme risk for surgery revealing the outcomes were superior to the performance goal and confirming PARTNER 1B results

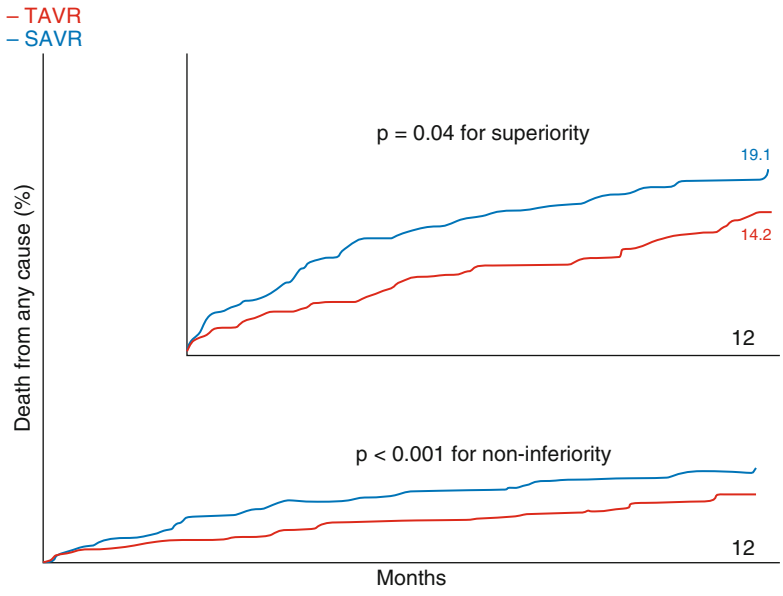

Fig. 15.6 Core valve high-risk cohort: all cause death at 1 year. Transcatheter aortic-valve replacement (TAVR) with a self-expanding Core Valve versus surgical aortic valve replacement (SAVR) in high-risk patients. Rate of death was non-inferior with TAVR versus SAVR and at 1 year a test for superiority demonstrated that TAVR was superior to SAVR. The inset shows same data with enlarged Y-axis

Functional Outcomes

TAVR with both the Sapien THV and CoreValve THV significantly improves functional capacity whether measured by New York Heart Association (NYHA) functional class, 6 min walk test or Kansas City Cardiomyopathy Quality of Life Questionnaire (KCCQ). In PARTNER 1B, >90 % of patients had NYHA class three-fourth symptoms at baseline. By 1 year less than 20 % of TAVR patients had NYHA class three-fourth symptoms compared with 60 % of medically treated patients [11]. At 1 year there was a 24.5 point improvement in KCCQ score (a 20 point change is considered a large improvement) in TAVR patients compared with no significant change in medically treated patients [19]. In CoreValve extreme risk, >90 % of patients had NYHA class three-fourth symptoms at baseline compared with <10 % of survivors at 1 year [13]. In PARTNER 1A and the CoreValve high-risk trial there was a similar improvement in NYHA class and KCQ scores in both the TAVR and SAVR arms. [12, 14, 20] The PARTNER trial also evaluated 6 min walk test. In PARTNER 1B, the TAVR arm had a significant increase in walk distance compared with medical therapy while in PARTNER 1A the TAVR and SAVR arms witnessed identical improvements in walk distance. Repeat hospitalization was evaluated in PARTNER 1B. At 2 years repeat hospitalization was decreased from 72.5 % in the medically treated arm to 35.5 % in the TAVR arm, HR 0.41 (95 % CI, 0.20–0.58) [16]. This has important implications for not just quality of like but also healthcare costs. By whichever metric is analyzed, TAVR confers significant improvements in functional outcomes and quality of life.

Valve Function and Durability

Sapien THV and CoreValve THV both have excellent valve performance. This has been demonstrated in multiple registries as well as the landmark clinical trials. The mean gradients and effective orifice area are even slightly superior to surgically implanted valves (PARTNER 1A: mean gradient 10.2 ± 4.3 mmHg vs 11.5 ± 5.4 mmHg, $p = 0.008$ and effective orifice area 1.6 ± 0.5 cm^2 vs 1.4 ± 0.5 cm^2, $p = 0.002$ for Sapien vs surgical valve, respectively; CoreValve: mean gradient 9.09 ± 3.49 mmHg vs 12.40 ± 7.38 mmHg, $p < 0.001$, and effective orifice area 1.91 ± 0.51 cm^2 vs 1.57 ± 0.49 cm^2, $p < 0.001$ for CoreValve vs surgical valve, respectively) [12, 13]. The durability of THVs is not well characterized since there is only intermediate-term follow-up of well-designed studies. Nonetheless, there appears to be excellent valve function at 5-year follow-up for the Sapien THV and 2-year follow-up for the CoreValve. Longer term follow-up will more completely define valve durability.

Complications

Neurological Events

Stroke is a devastating complication of both TAVR and SAVR. The etiology of periprocedural stroke is primarily atheroembolism from the aortic arch and the aortic valve. The incidence of silent embolic events assessed by diffusion weighted magnetic resonance imaging (MRI) is extremely high, nearly 85 % with TAVR and 75 % with SAVR, and similar between the transfemoral and transapical approaches [21–23]. Surprisingly, and contrary to the atrial fibrillation literature, silent cerebral infarcts in TAVR patients does not seem to affect intermediate term neurological and cognitive outcomes. Transcranial Doppler has been used to evaluate the timing of embolic events during TAVR. These transcranial Doppler studies have detected high-intensity transient signals (HITS) throughout all stages of the procedure: wire manipulation across the aortic arch and valve, valve implantation, and post-dilation [24, 25].

Fortunately the clinical stroke rate is significantly lower than could be expected from MRI studies. However, in many studies there seems to be a higher stroke risk associated with TAVR compared with SAVR. The PARTNER and CoreValve trials had rigorous neurological assessment and shed important light on the risk of stroke in TAVR. In the PARTNER 1A trial the

30 day total stroke rate was 4.6 % vs 2.4 % (p = 0.12) and the major stroke rate was 3.8 % vs 2.1 % (p = 0.20) for TVAR and SAVR, respectively. Although not statistically significant, the trend towards higher stroke rates with TAVR is concerning. By 2 years there was no difference in stroke. In the CoreValve trial the 30 day rate of total stroke was 4.9 % vs 6.2 % (p = 0.46) and the rate of major stroke was 3.9 % vs 3.1 % (p = 0.55) for TAVR and SAVR, respectively [12]. At 1 year there were, numerically, more strokes in the surgical arm. Approximately, half of all strokes are early, by 48 h. The remainder of strokes occur from day 2 through 30 [26, 27]. Early strokes are likely due to embolization of valvular calcification and aortic atheroma. Late stroke risk may be due to atrial fibrillation and atherosclerotic burden. Although the stroke risk is justified based on the dramatic reduction in mortality in inoperable patients, it is imperative to reduce the stroke risk if TAVR is to be performed in lower risk patients. Anecdotally it appears that stroke risk is decreasing with smaller profile devices [19]. Additionally, embolic protection devices may reduce the early stroke risk following TAVR. Lastly, refinement and optimization of anticoagulation strategy is also of critical importance to the reduction of stroke risk.

Access Site Complications and Bleeding

Major vascular access site complications and major bleeding are the most frequent complications of TAVR and are associated with a twofold increase in mortality [28]. In PARTNER 1 larger bore sheaths, 22-French and 24-French, were required leading to high access complication rates. These complications included dissection in 63 %, perforation in 31 %, hematoma in 22 %, and retroperitoneal bleed in 10 %. Predictors of vascular complications include significant tortuosity, moderate to severe calcification, and small arterial diameter (sheath to artery ratio of >1.1:1).

In PARTNER 1A and 1B the risk of access site complications was 11.0 % and 16.2 % and major bleeding rates were 9.3 % and 16.8 % [29]. In PARTNER 2 the risk of both access site complications and bleeding were both significantly reduce (11.3 % and 7.8 % respectively) with reduction in sheath size (16F, 18F and 20F for 23 mm, 26 mm and 29 mm Sapein XT, respectively) [30]. In the high risk CoreValve trial, which required 18-French sheath, the rates of access site complications were 5.9 % vs 1.9 % (p = 0.003) for TAVR and SAVR, respectively. The risk of bleeding was 28.1 % vs 35.4 % (p = 0.05) for TAVR and SAVR respectively [14]. Both the reduction in sheath size and well as improved patient selection, guided by CTA, are responsible for the reduction in these complications. Additionally, operators have become more adept at treating access site complications. With further reduction in sheath size and use of expandable sheaths it is anticipated that these risks will continue to decrease [31, 32].

Paravalvular Aortic Regurgitation

Significant paravalvular aortic regurgitation is a rare finding after SAVR however it is relatively common after TAVR [33]. Intuitively this makes sense, as the native valve is not resected there can be malapposition of the prosthesis with the annulus, particularly at the commissures. Additional causes of paravalvular aortic regurgitation include undersizing of the valve prosthesis and either high or low deployment of the THV [34]. Preliminary studies suggested that the CoreValve device may be associated with higher rates of paravalvular aortic regurgitation [35]. However, the US CoreValve trial demonstrated lower rates of paravalvular aortic regurgitation that seemed to decrease with time, possibly due to continued expansion of the nitinol frame. The risk of mild, moderate, and severe aortic regurgitation is 52 % and 41.5 %, 12 % and 10.9 %, and 1 % and 0.5 % for Sapien and CoreValve, respectively [11, 13]. Aortic regurgitation, even of mild degree, seems to be associated with worse outcomes, both in terms of functional recovery and survival [17]. In PARTNER 1A the mortality rates were 26.3 %, 33.4 %, and 50.7 % for none to trace, mild, and moderate or severe aortic regurgitation, respectively. Optimal THV sizing

(with judicious oversizing protocols), guided by CTA, significantly reduced the risk of paravalvular aortic regurgitation [36–41]. The assessment of paravalvular aortic regurgitation severity can be challenging as there are no validated echocardiographic parameters. Thus, it is often necessary to integrate echocardiography, aortography, and hemodynamics to determine aortic regurgitation severity [42–44]. If significant aortic regurgitation is seen after valve implant then redilation, or even implantation of a second THV, should be considered. New THV designs with fabric cuffs at the inflow portion of the valve, such as the Edwards Sapien 3 and Boston Scientific Lotus THVs will likely further decrease the risk of paravalvular aortic regurgitation and improve clinical outcomes.

Conduction Disturbances and Atrial Fibrillation

The bundle of His lays on the left ventricular septum immediately distal to the membranous septum. The proximity of the conduction system to the aortic annulus and the possibility of collateral damage during valve intervention is the basis for the development of left bundle branch block (LBBB) and complete heart block [45–47]. LBBB develops in 25–35 % of TAVR patients [48–51]. Interestingly, nearly 50 % of new LBBBs resolve by 1 year and it does not seem that pre- or post-procedural LBBB predicts the need for a permanent pacemaker. Patients who develop LBBB do not realize the same increase in left ventricular systolic function as do patients who do not develop a LBBB. There are mixed results regarding survival in patients who develop a new LBBB but most data would suggest that it does not impact long-term survival [48–51].

Complete heart block is seen in approximately 5 % of patients who undergo SAVR. Similarly, Edwards Sapien THV is associated with an approximately 5 % risk for heart block requiring permanent pacemaker implantation [11, 12]. The permanent pacemaker requirement is higher for Medtronic CoreValve THV, approximately 20–25 % [13, 14, 50]. The increased rate of complete heart block is likely due to lower implant in the left ventricular outflow tract and continued expansion of the nitinol frame. Preliminary data suggests that the Boston Scientific Lotus THV is also associated with higher risk of complete heart block (28 %) [52]. Risk factors for complete heart block requiring pacemaker implantation include baseline first degree AV block, left anterior fascicular block, and right bundle branch block and intra-procedural complete heart block [53]. Pacemaker requirement is associated with lack of improvement in left ventricular systolic function following TAVR but there does not appear to be an increase in mortality [54–56].

Atrial fibrillation is common after surgical aortic valve replacement and has been reported to have an incidence of up to 10–60 % [57, 58]. In surgical patients post-operative atrial fibrillation is associated with prolonged hospital stay, stroke, and mortality. The risk of atrial fibrillation is much lower, but still important, after TAVR. In the PARTNER and CoreValve trials the rate of new onset atrial fibrillation ranged from 12 to 15 % [12, 14].A Canadian registry suggests a higher rate of new onset atrial fibrillation after TAVR (31.9 % overall, 16 % for transfemoral and 38 % for transapical approaches, $p=0.47$) [57]. In this study, new onset atrial fibrillation significantly increases the risk for stroke at 1 year (13.6 % for new onset atrial fibrillation vs 3.8 % for no atrial fibrillation). Another study suggests a graded risk for the development of atrial fibrillation depending upon the approach used (SAVR = 60 %, transapical TAVR = 53 %, transaortic TAVR = 33 %, and transfemoral TAVR 14 %) [58]. Most of this difference is presumed to be related to pericardial access although patient characteristics may play a role as well. Additional studies will be required to determine the new onset atrial fibrillation rates as more and more patients are treated via the transfemoral approach.

Acute Kidney Injury

Many patients with aortic stenosis also have chronic kidney disease and are at risk for developing acute kidney injury following TAVR or SAVR. The causes of acute kidney injury include

contrast nephropathy, hypoperfusion, bleeding, atheroembolism [59]. The risk of acute kidney injury following TAVR ranges from 5.0 to 15.0 % and the risk of renal replacement therapy is approximately 1 % [11–14]. In a meta-analysis of over 16,000 patients, acute kidney injury was the third most common complication of TRV, after heart block and vascular access complications, occurring in 4.9 % of patients [50]. Acute kidney injury is a strong predictor of poor outcomes following TAVR and strategies to minimize acute kidney injury (such as hydration, contrast reduction strategies, bleeding avoidance strategies, and avoidance of nephrotoxic agents) are of utmost importance to optimize outcomes [59].

Annular Rupture

Annular rupture is a rare but devastating, and frequently fatal, complication of TAVR. It is thought to have an incidence of <1 % but is associated with a 50 % mortality rate. With balloon expandable THVs the three predictors of rupture are moderate to severe sub-annular calcification, area oversizing of the THV by >20 %, and post-dilation [60]. Pre-procedural CT imaging is critical to mitigate the risk of rupture [36–41]. Optimal THV size selection is essential to avoid significant oversizing to reduce the risk of rupture. Perhaps in the setting of severe sub-annular calcification some devices may offer specific advantages. For instance, with the Sapien 3 or Lotus THVs oversizing may be minimized due to the fabric cuff or adaptive seal. Alternatively, self-expanding devices such as CoreValve or Protico may be advantageous.

Coronary Occlusion

The risk of coronary occlusion is <1 % but associated with a 35–50 % mortality rate. Occlusion results from the displacement of bulky, calcified native leaflets that covers the coronary ostia and is rarely related to the stent frame of fabric cuff covering the coronaries. Risk factors for coronary occlusion include low coronary height (especially <10 mm from the annulus), bulky native leaflets, narrow sinus of Valsalva, and high THV implant [61]. Pre-procedural CT imaging may help predict patients who may be at risk for coronary occlusion. Rarely a patient with low coronary ostia and small sinus of Valsalva dimensions could be excluded from TAVR. In patients thought to be at higher risk for coronary occlusion it may be prudent to place a coronary guidewire, and even a balloon, in the coronary artery at the time of TAVR.

Patient Selection

There are numerous anatomical factors, specifically annulus size, access site, and prediction of complications, that are critical to assess when planning TAVR. In general CT imaging has become the accepted modality to make these assessments [36–41]. However, transesophageal echocardiography and magnetic resonance imaging have been evaluated and may be useful in select situations, such as patients with advanced chronic kidney disease [62].

Valve selection and sizing are based on annular area and perimeter (for Sapien XT and CoreValve, respectively), sinus of Valsalva dimensions, and diameter of the sinotubular junction. CT assessment of iliofemoral size, calcification, and tortuosity is useful in selecting access route. Noncalcified or minimally calcified vessels are frequently compliant and accommodate sheaths minimally larger than their nominal size. For instance, a noncalcified vessel may accommodate a sheath 1–2 mm larger. However, heavily calcified vessels may not accommodate sheaths of the same size. Experience is required to integrate vessel size, calcification, and tortuosity permitting optimal patient selection for the femoral approach. Fortunately with the lower profile of the current generation of THVs and expandable sheaths the vast majority of patients can be treated via the transfemoral approach. In the rare patient who requires an alternate access route, CT imaging can assess subclavian size and calcification as well as aortic calcification and distance from proposed aortic entry point to the annulus.

The patients treated in the PARTNER and CoreValve trials were of advanced age, had multiple comorbidities and were often frail. Although TAVR dramatically extends survival the 1 year mortality for PARTNER A, PARTNER B, CoreValve high risk, and CoreValve extreme risk was 24.3 %, 30.7 %, 14.2 %, and 26.0 %, respectively [11–14]. In fact, in PARTNER B at 6 months approximately 40 % of patients had either died or had not realized improvement in quality of life [63]. These findings highlight the importance of appropriate patient selection. Therefore, beyond the technical feasibility of performing TAVR, it is critical to select patients who will likely benefit in terms of survival and functional recovery and avoid those patient in which any procedure may be futile. Although it is difficult to turn down an individual patient based on any single comorbidity it is important to consider burden of comorbidities (particularly O_2 dependent COPD, severe left ventricular systolic dysfunction with low gradient, severe mitral regurgitation, advanced chronic kidney disease, malignancy, and neurological disorders such as dementia, advanced Parkinson's disease, or debilitating stroke) and frailty (conventionally measured by 5 m walk test, grip strength, albumin, and Katz activities of daily living scale) [64–72]. The assistance of geriatric medicine is often helpful in evaluating these patients and determining which patients likely will benefit from TAVR and who might not. Hopefully in the future TAVR specific risk score will be developed to help predict benefit and futility.

New Devices

Next generation THV device designs have been developed to address TAVR complications and improve ease of use (Fig. 15.7). In particular, some of the newer THVs are designed to minimize paravalvular arotic regurgitation which is associated with increased mortality and has been described as the "Achilles Heel" of TAVR. Some THVs can be recaptured, repositioned, and even fully retrieved to ensure optimal implant position in every case. The Sapien 3 (Edwards Lifesciences

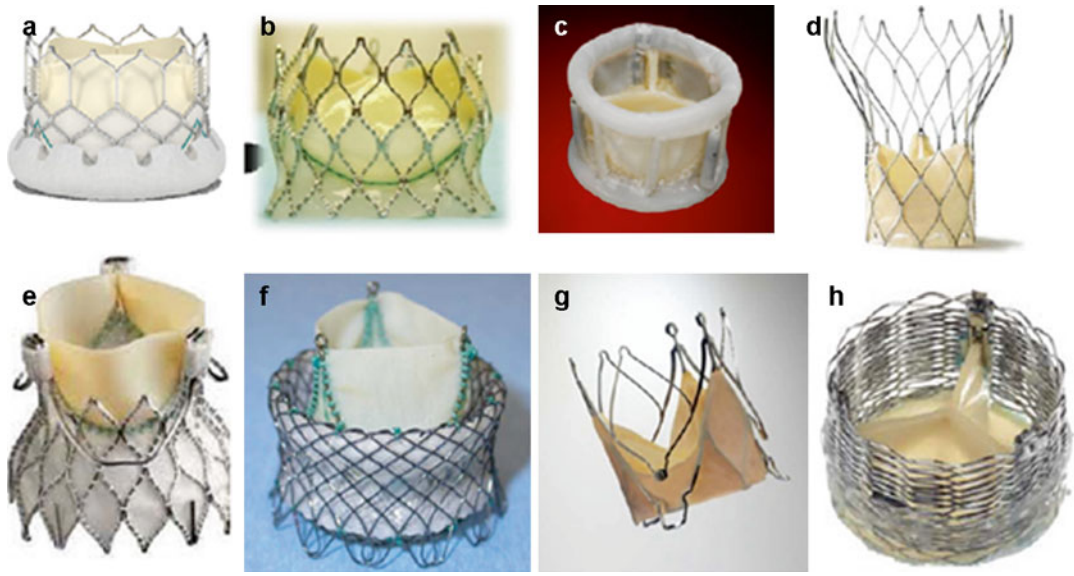

Fig. 15.7 Next generation transcatheter heart valve designs (**a**) SAPIEN 3, (Edwards Lifesciences, Irvine, California), (**b**) CENTRA, (Edwards Lifesciences), (**c**): Direct Flow Medical, (Direct Flow Medical, Santa Rosa, California), (**d**) Portico, (St. Jude Medical, St. Paul, Minnesota), (**e**) Engager, (Medtronic, Minneapolis, Minnesota), (**f**) Heart Leaflet, Heart Leaflet Technologies, Maple Grove, Minnesota), (**g**) JenaValve, (JenaValve Technology, Germany), (**h**) Sadra Lotus Medical (Boston Scientific Scimed Inc., Maple Grove, Minnesota) (From Genereaux et al. [90] with permission)

Inc., Irvine, California) THV has a fabric cuff at the inflow segment of the stent frame designed to reduce paravalvular aortic regurgitation and the 14 French expandable sheath will hopefully reduce vascular complications [73, 74]. In the first multicenter prospective registry of 150 patients with an STS risk score of 7.4 % the 30 day event rates were: death 2.1 %, moderate aortic regurgitation 3.5 %, severe aortic regurgitation 0 %, access site complications 4.2 %, stroke 2.7 %, and new pacemaker requirement 13.3 % [74]. These promising results suggest that Sapien 3 attains its intended goal of a significant reduction in paravalvular aortic regurgitation and access site complications. However, there seems to be a trade-off for greater heart block requiring pacemaker implantation from the fabric cuff impinging on the conduction system. The CoreValve Evolut R (Medtronic, Minneapolis, Minnesota) and PORTICO THVs have self-expanding stent frames that are fully recapturable, repositionable, and retrievable [75]. Unlike all other THVs the Direct Flow THV (Direct Flow Medical, Santa Rosa, California) has a non-metallic frame [76]. Dacron polyester rings in the aortic and ventricular position are inflatable and deflatable to allow precise positioning and reduce paravalvular aortic regurgitation. A multicenter study of 75 patients demonstrated a high procedural success rate, low paravalvular aortic regurgitation (1.4 % moderate, 0 % severe), and a pacemaker rate of 17 % [76]. Larger studies are required to confirm these promising results. The Lotus THV (Boston Scientific Corporation, Marlborough, Massachusetts) combines features of Sapien 3 as well as CoreValve Evolut R and PORTICO [52]. It is constructed from bovine pericardial leaflets and a nitinol frame. Rather than a self-expanding nitinol frame, during deployment the single nitinol element is shortened resulting in radial expansion. It is recapturable, repositionable, and retrievable and there is an adaptive seal on the inflow segment of the nitinol frame. In the 120 patient REPRISE II trial (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System) there was a 100 % procedural success rate, 1.9 % of patients with moderate or severe paravalvular aortic regurgitation, and a 28.6 % new pacemaker rate. This preliminary data suggests that Sapien 3 and Lotus THVs dramatically reduce paravalvular aortic regurgitation but at a cost of a higher rate of pacemaker implantation [52, 74]. Whether this is confirmed in future trials and how this affects long-term outcomes will be important subject of additional studies. Whether repositionable THVs improve outcomes or conversely increase atheroembolic events will also need to be evaluated in clinical trials.

Adjunctive devices may also help minimize major risks related to TAVR. Embolic protection devices such as Claret Medical Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, California) and Embrella (Edwards Lifesciences Inc., Irvine, California) are currently being studied to determine whether they reduce the incidence of new stroke following TAVR (Fig. 15.8).

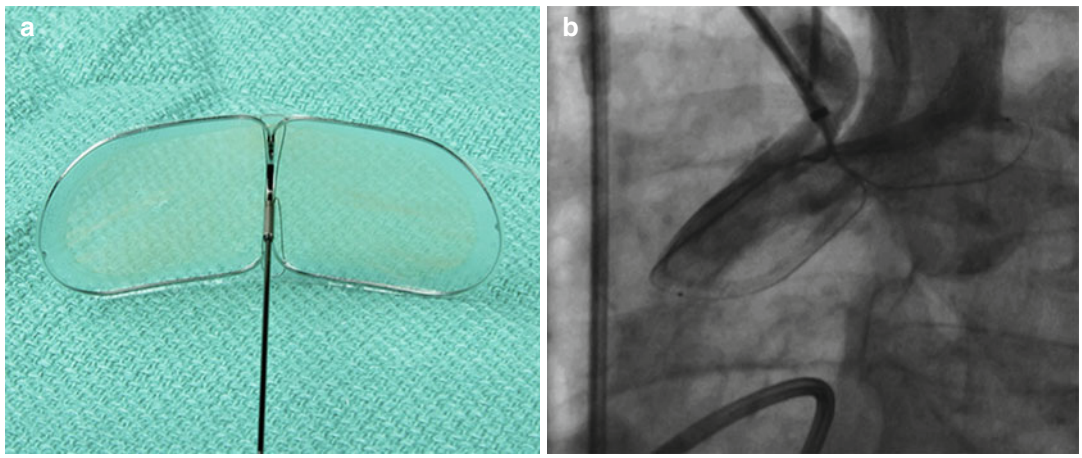

Fig. 15.8 Edwards Lifesciences embrella embolic protection device (**a**). The device in place under angiographic guidance, (**b**) (From Rodes-Cabau et al. [78] with permission)

Intuitively, embolic protection devices should reduce stroke rate. However, the current data is sparse and mixed. The recently presented CLEAN TAVI study (Claret Embolic Protection and TAVI) randomized 100 patients to TAVR with embolic protection versus TAVR alone. Diffusion weighted MRI at 7 days demonstrated a significant reduction the median number of new lesions (3 vs 7) and median lesion volume (101 mm^3 vs 292 mm^3) in patients treated with embolic protection [77]. However, in the small PROTAVI-C Pilot Study the Embrella did not reduce embolic events [78]. Diffusion weighted MRI was performed at 7 days in 36 patients treated with Embrella embolic protection and 6 control patients. There was no difference in median number of new lesions (7.5 with Embrella vs 4.0 for control) or median lesion volume (305 mm^3 with Embrella vs 180 mm^3 for control). Much more work is required to determine whether embolic protection devices truly reduce stroke rates.

New Patient Populations

TAVR is expanding into new anatomical subsets such as valve-in-valve replacement, bicuspid aortic valve, and pure aortic regurgitation. TAVR is an attractive treatment alternative for degenerated bioprosthetic valves. The circular, rigid, radiopaque ring provides a discrete landmark to aid in optimal THV positioning, nearly eliminates the concern for paravalvular aortic regurgitation, and mitigates against the risk of annular rupture and conduction disturbances [79–81]. The risk of coronary occlusion may be greater in patients with narrow sinuses of Valsalva and coronary ostia below bioprosthetic valve post. Additionally, patients with small bioprosthetic valves (less than 21 mm) may have unacceptably high gradients. The Valve-In-Valve International Data Registry (VIVID) which included 459 patients there was a 5 % rate of moderate or greater arotic regurgitation, a mean gradient of 16.1 mmHg, and a 1 year survival of 83.2 % [82]. Interestingly patients with degenerated bioprosthetic due to aortic regurgitation had better outcomes than patients with bioprosthetic aortic stenosis. PARTNER and CoreValve registries are being conducted to validate these promising results.

Unlike aortic stenosis, a regurgitant aortic valve does not typically have thickened leaflets and a calcified annulus to anchor to during deployment. As such, the risk of embolization and migration may be higher. Although specifically designed to address aortic stenosis, Edwards Sapien and Medtronic CoreValve have been used to treat pure aortic regurgitation in a limited number of patients [83]. It has been shown that these devices requires significant oversizing and there is a higher need for a second THV. Recently, two small case series employing Symetis ACURATE TA (Symetis, Ecublens, Switzerland) and JenaValve (JenaValve Technology, Munich, Germany) have demonstrated very high procedural success rates [84, 85]. Further studies of these THVs as well as other platforms such as the Helio system (Edwards Lifesciences) are required to define the role of TAVR in aortic regurgitation [86].

There has been concern that bicuspid valves may not be ideally treated by TAVR due to the elliptical orifice, highly asymmetric calcification, and frequently associated aortic root enlargement. This could lead to inadequate apposition of the THV to the commissures resulting in significant paravalvular aortic regurgitation. As a consequence, bicuspid aortic valves were excluded from the major clinical trials. Several case series suggest that TAVR is feasible for bicuspid valve disease [87, 88]. However, there is a greater risk for moderate or greater paravalvular aortic regurgitation, 28.4 % in one study [89]. For TAVR to have a role bicuspid disease the rates of aortic regurgitation must be improved whether by better patient selection and valve sizing by CT or new device iterations to specifically address the anatomical challenges of bicuspid valves.

Currently TAVR is approved in the United States only for high-risk and inoperable patients. Most patients who undergo surgical aortic valve replacement are low risk and only approximately 25 % of these patients have an STS risk score of ≥4 %. The PARTNER S3i (Sapien 3) and SURTAVI (CoreValve) trials are studying intermediate patients with an STS risk score of 4–8 %. These studies will define the role of TAVR in this relatively large population of patients.

Conclusions

TAVR has become the standard of care for high risk and inoperable patients with severe aortic stenosis owing to its dramatic improvement in patient survival and quality of life. However, many serious complications have come to light as TAVR has been rigorously studied over the last decade. Additionally, many of the initial patients treated were either too frail or had too many comorbidities to gain any significant improvement in survival or quality of life. With improved device design attributes and improved patient selection, based on imaging and clinical factors, the frequency of these complications are decreasing and patient outcomes are improving. As patient outcomes continue to improve, and if valve durability is proven, TAVR will likely gain expanded indications to treat ever larger populations of patients.

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