



Transcatheter Aortic Valve Replacement: A Review Article

Juan A Siordia*, Rinku Skaria, Sreekumar Subramanian

Department of Surgery, University of Arizona Medical Center, University of Arizona, 1501 N Campbell Ave., Tucson, AZ 85719, United States

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) is a novel therapeutic intervention for the replacement of severely stenotic aortic valves in high-risk patients for standard surgical procedures. Since the initial PARTNER trial results, use of TAVR has been on the rise each year. New delivery methods and different valves have been developed and modified in order to promote the minimally invasive procedure and reduce common complications, such as stroke. This review article focuses on the current data on the indications, risks, benefits, and future directions of TAVR.

Recently, TAVR has been considered as a standard-of-care procedure. While this technique is used frequently in high-risk surgical candidates, studies have been focusing on the application of this method for younger patients with lower surgical risk. Moreover, several studies have proposed promising results regarding the use of valve-in-valve technique or the procedure in which the valve is placed within a previously implemented bioprosthetic valve. However, ischemic strokes and paravalvular leak remain a matter of debate in these surgeries. New methods and devices have been developed to reduce the incidence of post-procedural stroke. While the third generation of TAVR valves (i.e., Edwards Sapien 3 and Medtronic Evolut R) addresses the issue of paravalvular leak structurally, results on their efficacy in reducing the risk of paravalvular leak are yet to be obtained. Furthermore, TAVR enters the field of hybrid methods in the treatment of cardiac issues via both surgical and catheter-based approaches. Finally, while TAVR is primarily performed on cases with aortic stenosis, new valves and methods have been proposed regarding the application of this technique in aortic regurgitation, as well as other aortic pathologies.

TAVR is a suitable therapeutic approach for the treatment of aortic stenosis in high-risk patients. Considering the promising results in the current patient population, recent studies have been conducted to evaluate the efficacy of this approach as a standard-of-care procedure.

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Introduction

Transcatheter aortic valve replacement (TAVR) is a cardiac intervention first introduced in 2002 to provide treatment for high-risk patients requiring standard surgical interventions (1). Extensive research has been conducted on TAVR, including the invention of effective imaging modalities to determine the aortic annular size and development of potential percutaneous valves. TAVR could be implemented as a standard-of-care protocol for patients with severe aortic stenosis and other

valvular diseases in low-risk populations requiring surgical interventions.

TAVR vs. Medical and Surgical Therapy Comparison of TAVR with medical therapy

Ever since TAVR was initiated, researchers have been concerned whether this method of treatment would prevail in comparison with standard medical therapy, such as balloon aortic valvuloplasty. In one study, 358 patients with

*Corresponding author: Juan A Siordia, 329 N. Norris Ave., Tucson, Arizona 85719. Tel/Fax: (520) 223-5713; Email: jas@email.arizona.edu

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severe aortic stenosis who could not receive surgical therapy were evaluated to compare the efficacy of TAVR with medical therapy. According to the results, mortality rates associated with TAVR and standard medical therapy after one year were 30.7% and 50.7%, respectively (TAVR hazard ratio: 0.55; 95% confidence interval: 0.40-0.74; $P<0.001$) (2-6). On the other hand, rate of cardiac symptoms among surviving patients, especially those with class III and IV heart failure (based on the classification of New York Heart Association (NYHA), was significantly lower in TAVR compared to medical therapy (25.2% vs. 58.0%; $P<0.001$).

With respect to the limitations of TAVR, related studies have reported major strokes (5.0% vs. 1.1%; $P=0.06$) and vascular complications (16.2% vs. 1.1%; $P<0.001$) (6,7). On the other hand, TAVR was observed to reduce aortic pressure gradient significantly, which resulted in symptom improvement, higher functional capacity, and favorable long-term outcomes (5). Given that the benefits of TAVR far outweighed the associated risks, this procedure could be used as a new standard treatment for severe aortic stenosis in high-risk, non-surgical candidates.

Comparison of TAVR with surgical therapy

After proven superior to medical therapy, efficacy of TAVR was compared with surgical intervention. Placement of aortic transcatheter valve (PARTNER) trial indicated that after one year, surgical aortic valve replacement (SAVR) and TAVR had similar mortality rates (26.8% and 24.2%, respectively) and symptomatic relief in high-risk patients. One of the major differences between these two modalities was the incidence of stroke. In the PARTNER trial cohort group A, incidence rate of stroke in TAVR patients was twice higher than SAVR (6.1% vs. 3.0%; $P=0.07$) (8). In addition, after a 30-day postoperative follow-up, strokes were more prevalent in patients receiving TAVR (4.6% vs. 2.4%; $P=0.12$) (9).

Considering the total incidence rates of stroke and transient ischemic attacks, prevalence of cerebrovascular accidents associated with TAVR has been shown to be significantly higher compared to SAVR ($P=0.04$) (8). Furthermore, five-year follow-up of patients has revealed that risk of mortality was higher in treatment with TAVR compared to SAVR (67.8% vs. 62.4%; $P=0.76$). It is also noteworthy that no structural valve deterioration requiring surgical valve replacement was reported in these groups. Other results indicated that the rate of moderate or severe aortic regurgitation was higher in the TAVR group compared to SAVR (14% vs. 1%; $P<0.0001$).

In the TAVR group, five-year mortality rate was estimated at 72.4% for moderate or severe aortic regurgitation and 56.6% for mild aortic regurgitation ($P=0.003$) (10). Among other complications of TAVR during the PARTNER trial were valve embolization (1.7%) and need for valve-in-valve procedure for TAVR complications or the malpositioning of the aortic valve (2.3%) (8). Moreover, paravalvular regurgitation was observed to be more apparent with TAVR ($P<0.001$) (9). Additionally, new lesions occurred in 60-90% of the patients undergoing TAVR, which was twice higher than the frequency of these lesions in patients receiving treatment with SAVR (8).

In this regard, another study was performed on 699 high-risk patients randomly scheduled for SAVR or TAVR procedures. According to the results, strokes were more prevalent with TAVR compared to SAVR (5.1% vs. 2.4%) (11); however, the difference was not statistically significant. Although vascular complications were more common with TAVR, SAVR was associated with more episodes of major postoperative hemorrhage (5,11). In terms of mortality rate, TAVR and SAVR had no statistically significant difference.

Comparison of TAVR and SAVR is indicative of advantages and limitations for both procedures. While TAVR is associated with higher rate of postoperative strokes compared to SAVR, the surgical approach may lead to other complications, such as hemorrhage and pain. In addition, mortality rates are similar in these approaches as the PARTNER trial estimated the two-year mortality rate at 33.9% with TAVR and 35.0% with SAVR (9).

Preoperative Considerations for TAVR

Types of percutaneous aortic valves

Edwards SAPIEN XT transcatheter heart valve (Edwards Lifesciences Inc., Irvine, California) is the most frequently used valve in TAVR. SAPIEN valve is made of stainless steel, while SAPIEN XT valve is a balloon-expandable stent with a cobalt-chromium alloy tubular frame, which allows insertion over the diseased aortic valve. Typically, the SAPIEN XT valve is introduced into the patient with low-profile NovaFlex delivery catheter (Edwards Lifesciences) via the femoral artery. However, it is possible to implement this valve via the left ventricular apex (i.e., transapical TAVR) or ascending aorta (transaortic TAVR) (12).

CoreValve Revalving System (Medtronic Inc., Minneapolis, Minnesota) utilizes a self-expanding nitinol, which is malleable at low temperatures and becomes rigid at body temperature. Leaflets and annular seals are constructed with porcine pericardium, unlike bovine pericardium, which is seen with the SAPIEN valve. Similar to the SAPIEN

valve, CoreValve could be delivered via the transfemoral or transaortic routes; to do so, it utilizes the AccuTrak delivery catheter (Medtronic). However, unlike the SAPIEN valve, CoreValve could be transported via the subclavian artery in case of extensive peripheral artery diseases that affect femoral arteries or cause severe pathology in the femoral, iliac or abdominal aorta (i.e., calcification). Once positioned over the diseased valve, the catheter is removed. Afterwards, a long multi-staged frame is anchored over the aortic annulus, which is supported by the superior extension of the stent so as to be anchored in the supracoronary aorta (12).

Both the aforementioned valves require conventional cardiac catheterization under general anesthesia for high-risk patients in order to be inserted via the femoral artery. However, in case of severe peripheral artery diseases, each valve has an alternative route. The SAPIEN valve could be implemented transapically through the left ventricular apex, avoiding not only the peripheral arteries, but also the commonly-calcified aortic arch. However, transapical deployment of this valve requires surgical intervention.

CoreValve could be transported via the subclavian artery; however, this access point may be affected by peripheral artery diseases. Moreover, the catheter would need to travel through the aortic arch in a retrograde fashion, and at any rate, the patient could still be at the risk of strokes caused by calcium emboli.

The CoreValve device could be repositioned or removed surgically, similar to SAPIEN valve (12-14). CoreValve is known to cause atrioventricular blocks, which require a pacemaker for up to three times more than the SAPIEN valve (12,15,16). According to the studies conducted in the U.K. and France, persistent heart blocks are rare complications associated with the SAPIEN valve. Therefore, pacemakers are occasionally implemented permanently (6,11,17).

Over seven new valves have been developed in order to improve deliverability and outcomes (5), most of which incorporate self-expanding nitinol stents that are detected with the CoreValve. For instance, the Lotus Valve System (Boston Scientific Inc., Natick, Massachusetts, USA) has been designed to open longitudinally, and Direct Flow Valve (Direct Flow Medical Inc., Santa Rosa, California, USA) incorporates a tubular fabric frame inflated with a rapid-setting polymerizing agent.

Acurate (Symetis Inc., Ecublens, Switzerland) and Portico (St. Jude Medical Inc., St. Paul, Minnesota, USA) valves are also similar to CoreValve since they contain a superior-extending meshwork, which allows for supracoronary aortic positioning and support.

Moreover, Engager (Medtronic), JenaClip (JenaValve Inc., Munich, Germany), and Acurate valves house features that allow for anatomic implantation in alignment with native valve commissures and coronary openings. Several of these valves are constructed using new and improved sealing mechanisms in order to reduce the occurrence of paravalvular leaks after implantation (12,18).

Third-generation valves have been developed by Medtronic and Edwards. Medtronic developed the Evolut R, which is a new TAVR valve that keeps the same nitinol stent frame as the predecessors, while it has been associated with a 10% reduction in length on the portion of the stent that settles on the outflow tract. The sealing skirt remains unchanged in order to reduce paravalvular leak, and catheter sizes include a smaller 14-18 F sheath. Edwards developed the SAPIEN 3 valve, which differs from the previous versions due to its newly developed cobalt chromium stent frame. The lower part of the stent frame is covered similar to the SAPIEN XT, while it also includes a polyethylene terephthalate skirt to reduce paravalvular leak. As delivered with 14-16 F catheter sizes, this valve has been shown to be more effective in the reduction of vascular complications compared to its predecessors. However, it has been associated with the increased incidence of permanent pacemaker placement after TAVR deployment (19).

Modes of delivery

Currently, there are six main routes for the insertion of TAVR, as follows: transfemoral, transapical, trans-subclavian, transaortic, trans-carotid, and transcaval routes. Approximately 10-20% of patients have small or tortuous femoral arteries due to peripheral vascular diseases, precluding the use of 18-25 F delivery systems. While the CoreValve could be inserted via the subclavian artery, the SAPIEN valve should bypass the calcified aortic arch by transapically moving through the left ventricular apex. However, since this procedure requires surgical intervention, it has been associated with higher risk of other complications, such as postoperative hemorrhage (5).

Patients undergoing treatment with the transapical approach normally cannot receive intervention via peripheral arteries. These high-risk patients are considered to have lower health compared to those receiving treatment with the transfemoral approach. On the other hand, patients treated with transapical TAVR tend to suffer more comorbidities compared to transfemoral patients, which result in higher euroSCORE (29.1% vs. 25.7%; $P < 0.001$) (20). Furthermore, transapical TAVR patients have higher hospitalization rates compared to those

receiving other modes of TAVR (21).

Although the transapical approach avoids traversing through the calcified aortic arch, incidence of strokes remains similar for both transfemoral and transapical approaches. Nevertheless, the 30-day mortality rate has been estimated at 10.3% in transapical patients and 6.3% in transfemoral patients (20).

Transapical patients are already deemed critically ill to receive treatment with the transfemoral approach. This may falsely distort data towards the conception that the transapical method is not as safe as the transfemoral approach. In this regard, continued access cohort studies have obtained more successful outcomes in the transapical approach compared to the PARNTER trial. This could be due to the fact that physicians are beginning to comprehend this technique more clearly, and therefore, have higher knowledge in this regard (8).

According to the literature, CoreValve is the only valve currently approved to be used with the trans-subclavian approach if the transfemoral method is not allowed. Complications associated with the subclavian approach are similar to those of the CoreValve in the femoral approach, including left bundle branch block (27.8%) and need for a pacemaker (18.5%), which account for nearly the same rate as femoral transport. Moreover, the six-month mortality rate has been estimated at 9.4%, while the rate of valve-related complications has been reported to be 13.6% (22).

Transaortic TAVR was proposed as a treatment method to avoid the complications associated with transapical TAVR (23). This approach could be a proper alternative for introduction through tortuous peripheral arteries. Furthermore, incidence of strokes, hemorrhage and other complications is significantly lower in transaortic TAVR compared to transfemoral and transapical approaches.

In a pilot study performed on 13 patients undergoing transaortic TAVR, improved mean pressure gradient was observed in all the patients at five days postoperatively (14.8 mmHg vs. 48 mmHg pre-operatively). In addition, no cerebrovascular accidents were reported, and only one patient required a pacemaker implantation due to heart block (24). However, further studies are required in order to evaluate the efficacy of the transaortic approach and compare it with other delivery modalities. In this regard, initial studies have yielded promising results for future therapeutic interventions.

A recent study assessed the feasibility and safety of TAVR with left transcarotid approach in patients previously operated for ipsilateral carotid endarterectomy. Mortality rate and relief from major TAVR-related complications were evaluated

within a 30-day follow-up, and it was concluded that this technique was feasible and safe (25). This finding was confirmed in another study, which also reported that the left transcarotid approach allowed neurological status monitoring with lower risk of stroke, hemorrhage, and immediate patient ambulation (26).

Transcaval TAVR is another new approach used for aortic valve replacement. Percutaneous transcaval TAVR was first performed in Europe using an expandable introducer sheath for the implantation of Edwards SAPIEN 3 aortic valve. Due to severe peripheral artery disease, chronic obstructive pulmonary disease, and renal insufficiency, the patient was not considered a candidate for transfemoral or transapical treatments. Once the eSheath (Edwards Lifesciences, Irvine, CA, USA) was introduced into the abdominal aorta via the femoral and inferior vena cava, TAVR was initiated in accordance with standard procedures. Based on these results, the study concluded that transcaval venous access to the aorta could be a new strategy for TAVR in otherwise ineligible patients as a safe approach using expandable sheath technology (27).

In one research, Rodes-Cabau et al. stated that 51.3% of patients were unable to undergo TAVR via the femoral route (28). Therefore, cardiovascular health centers must be well aware of the most appropriate time to use each mode of delivery. Severe peripheral vascular disease marked with heavy calcification and tortuosity of the iliofemoral vasculature eliminates the treatment option via transfemoral approach. Moreover, similar implications in subclavian vasculature render the subclavian route obsolete. Factors such as severe pulmonary disease, previous or current disease of the descending and abdominal aorta, and diminished left ventricular function are likely to make the apical approach inadvisable.

Porcelain ascending aorta and high-arched or near-sternum vein grafts from previous coronary artery bypass are usually contraindications of direct aortic approach. Transcarotid and transcaval insertion sites are typically used when other routes are inadvisable, and no obvious contraindications are available for the respective introduction sites (29,30).

While several studies have assessed the outcomes of single modes of delivery, some studies have compared the outcomes of each TAVR approach separately. For instance, one research performed at Emory University (Georgia, USA) compared the outcomes of transfemoral and non-transfemoral TAVR. Although patients undergoing non-transfemoral TAVR had more comorbidities, no significant difference was observed in the mortality rate of

the two study groups after a 30-day follow-up (11.1% in transfemoral and 3.9% in non-transfemoral approaches) (29).

In another study, Bapat et al. reported the 30-day mortality rate to be 7.7% for transapical patients and 11.8% for transaortic patients (31), while Svensson et al. reported this rate to be 17.5% in the transapical approach (32). Moreover, Pasic et al. estimated the 30-day mortality rate at 5.7% in patients undergoing transapical TAVR only (33). These results suggest that the 30-day mortality rate associated with any mode of TAVR is superior to medical therapy (6), as well as the fact that all access routes lead to similar outcomes.

Imaging Modalities in Preoperative TAVR

High-quality imaging is essential for measuring the size of the aortic annulus. Proper measurements could prevent complications such as dislodgement and significant paravalvular aortic insufficiency (5).

To date, three imaging modalities have been evaluated in order to accurately determine the size of the aortic annulus, as follows: transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI). Comparison of these modalities indicates that TEE is used more commonly in the preparation for the procedure and accurate selection of the prosthetic valve. Studies suggest that MRI, and especially CT, are more detailed and reliable for the assessment of the size of the annulus (5,34).

Currently, CT is considered as the "gold standard" procedure. CT scanning allows for measuring the distances between the valve plane and origin of the coronary arteries, dimensions of the aortic root, and determining the presence and severity of valve calcification. Furthermore, these findings contribute to the prediction paravalvular leak (34,35).

In another study conducted on 34 patients, only one patient experienced severe paravalvular aortic regurgitation, and other procedures were reported to be successful (34). In addition, some studies have suggested that preparations based on CT and TEE may lead to different modified TAVR strategies in similar patients (34,35).

In this regard, the results of another study indicated that CT angiography overestimated the aortic annulus size, while two-dimensional (2D) TEE underestimated the size. Therefore, it was concluded that these modalities could be used simultaneously (36). Three-dimensional (3D) imaging modalities, particularly 3D-TEE, are preferred over 2D imaging modalities in the preparation for TAVR (35,37). This could be due

to the fact that height, width and depth are required for the successful implantation of the valves, and 2D imaging modalities provide insufficient data to manage the intervention.

Postoperative TAVR Outcomes

Possible complications

According to the definition proposed by the Valve Academic Research Consortium (VARC), causes of the mortality associated with TAVR are life-threatening hemorrhage, myocardial infarction, sudden death, multi-organ failure, stroke, and severe respiratory dysfunction. In addition, VARC denotes major TAVR-related complications as myocardial infarction due to left-coronary ostial occlusion, life-threatening hemorrhage, stroke, and acute renal failure requiring dialysis (8,21,38).

Most of the complications caused by TAVR are associated with cardiovascular disorders, especially strokes. Moreover, cerebrovascular accidents typically occur due to TAVR procedure, particularly with transverse retrograde through the calcified aortic arch. Calcification debris that originates from the aortic arch or diseased valve could give rise to embolism, which travels into the cerebral vasculature causing ischemic strokes. However, it has been noted that avoidance of aortic arch could still lead to high-frequency postoperative stroke (20), which is suggestive of the fact that diseased aortic valve and annulus debris could be significant contributing factors to stroke.

In a study on the comparison of TAVR with standard medical therapy, TAVR was reported to impose a high risk of stroke (5.0% vs. 1.1%; $P=0.06$), as well as major vascular complications, in the patients (16.2% vs. 1.1%; $P<0.001$) (5-7).

Another study in this regard evaluated the outcomes of 3,195 patients in the medical registries of France, and the incidence rate stroke at one year was reported to be 4.1% (39). Although it is relatively rare, hemorrhagic strokes have also been reported following TAVR procedures. TAVR-related strokes frequently occur within 2-15 days postoperatively (8).

One of the common consequences of TAVR is postoperative paravalvular leak. According to the medical registries of France, paravalvular regurgitation occurred in 64.5% of patients within one year after TAVR (39), which contributed to the long-term postoperative mortality of these patients. In the PARTNER trial, paravalvular regurgitation was more prevalent in TAVR compared to SAVR ($P<0.001$), while paravalvular insufficiency was associated with higher long-term mortality rate ($P<0.001$) (9). However, studies have indicated certain durability for the TAVR valve, which was

evidenced by the lack of progression to moderate or severe paravalvular aortic insufficiency if not presenting immediately after surgery (40).

Previous research suggests that framework or even tissue of valves might cover coronary ostia, which causes relative stenosis or obstruction leading to iatrogenic myocardial ischemia. In the literature, coverage of entries to coronary arteries is often attributed to the insertion of the SAPIEN valve rather than the CoreValve (12).

Atrioventricular heart block has been noted to occur after TAVR procedure. In this condition, the conduction system passes below the aortic annulus above the interventricular septum, and manipulation of this area with foreign materials could potentially cause partial or complete heart block.

Previous studies have demonstrated that age of patients is significantly correlated with the need for pacemaker after TAVR (17). Furthermore, the PARTNER trial has indicated that after one year, the SAPIEN valve and medical therapy had no significant difference regarding the number of the required pacemakers (4.5% vs. 7.8%; $P=0.27$) (5,6,11,12). However, 20-30% of patients receiving CoreValve acquired conduction abnormalities that warranted the insertion of pacemakers (5).

Given the possibility of conduction return in some patients, more conservative approaches are required for the placement of pacemakers. In one study performed to compare the necessity of permanent pacemaker implantation after transapical TAVR, no significant difference was observed in the survival rate of patients who used a pacemaker and those without a pacemaker. In addition, survival rate of the patients was similar after a one-year follow-up (84% with pacemaker, 80.9% without pacemaker) ($P=0.3$). Even at 30 days after the surgery, no significant difference was reported in the survival rates of the studied patients (95% vs. 93.6%) (17). However, it is noteworthy that the aforementioned results were obtained with the SAPIEN valve, and CoreValve was not used in that study. Post-TAVR renal impairment has been reported in less than 3% of patients in the PARTNER trial (41), while a meta-analysis of 13 studies performed on more than 1,900 patients reported acute kidney injury (AKI) in 8.3-57% of patients after TAVR (42). Accordingly, contributing factors to AKI were blood transfusion, transapical approach, preoperative creatinine levels of >1.1 mg/dL, peripheral vascular diseases, hypertension, and hemorrhage (42-44). Moreover, AKI was associated with increased mortality rate within 30 days postoperatively (45,46), while post-TAVR dialysis increased this rate by 10% (42). Moreover, it was

noted that the level of contrast-induced nephropathy had no correlation with the incidence of post-TAVR AKI (42,44,45).

With the rising trend of TAVR, other postoperative complications caused by this procedure have also been brought to the attention of medical experts. One of these complications is endocarditis after TAVR. This condition is similar to prosthetic valve endocarditis (PVE) accompanied by heart failure (33% for TAVRE, 42% for PVE) and cerebral embolism (18% and 10%, respectively) (47,48). Endocarditis tends to occur within 2-12 months after TAVR. Coagulase-negative *Staphylococcus* and *S. aureus* have been reported as the most common bacteria cultured from the presentations of TAVR-related endocarditis (48).

On echocardiography, 15% of patients with TAVR-related endocarditis have been reported to develop fistulas (48), while only 3% of PVE patients develop fistulas (47). According to the literature, complications associated with TAVR-related endocarditis have led to in-hospital deaths in 23% of PVE patients and 19-44.8% of TAVR patients (47-51).

In the Endocarditis-Pro prospective Cohort Study (ICE-PCS), surgery was shown to yield significantly better outcomes (47), while other studies have reported no significant association between the surgical treatment and survival rate of the patients with TAVR-related endocarditis (47-50). Immediate post-TAVR complications are relatively minor. In a pilot study, it was reported that 87% of patients experienced pain, 62% of whom were restricted by pain, and 44% had discomfort mainly in the femoral insertion site (51).

To sum up, all-cause mortality in TAVR patients at one, two, and three years postoperative has been estimated at 23.6%, 30.3%, and 34.8%, respectively, while the mortality rate associated with cardiovascular episodes was 11.2%, 12.1%, and 13.5%, respectively (40). Regardless of cardiovascular deaths, survival rate of TAVR in patients with myocardial infarction, major strokes, and life-threatening hemorrhage was calculated at 69.6% at one year, 63.5% at two years, and 59.7% at three years postoperatively (40). Although cardiovascular death is highly prevalent in TAVR, patients undergoing this procedure tend to present with many prior comorbidities, such as cardiovascular, respiratory, and neurological disorders.

Predictors of mortality in patients undergoing TAVR

In four studies, 30-day mortality rate predictors were assessed and reported as age above >90 years, need for dialysis, and use of

transapical TAVR approach (39,52-54).

In 663 high-risk patients for surgical intervention aged 81 years, the mortality rate associated with TAVR procedure was followed-up within 30 days and one year after the intervention. After 30 days of follow-up, the mortality rate was estimated at 5.4%, while it was 12.2% after six months, and 15.0% after one year. Predictors of mortality at 30-day and one-year follow-ups were determined as prior stroke, moderate or severe postoperative paravalvular leak, prior acute pulmonary edema, and chronic renal failure (54).

In this regard, a three-year follow-up in Italian CoreValve registry reported major postoperative or life-threatening hemorrhage to be associated with higher mortality rates among patients undergoing TAVR. Moreover, renal insufficiency was noted to cause high mortality during three years of follow-up ($P=0.007$) (40). Postoperative paravalvular leak was also established as a predictor for long-term mortality in these patients (54).

TAVR Outcomes in Patients with Comorbidities

Severe left-ventricular dysfunction

One study was performed on 384 patients to assess the improvement of the left-ventricular ejection fraction (LVEF) in patients with severe aortic stenosis and left-ventricular dysfunction (LVD). Group A consisted of patients with LVEF of $<35\%$, and group B included those with LVEF of $>35\%$. After TAVR, group A had an earlier, more significant improvement in LVEF compared to group B ($P<0.0001$). In addition, patients in group A were reported to have increased postoperative periprosthetic leak. However, all other complications were similar between the two groups. In total, 30-day mortality rate was higher in patients of group A compared to group B (10% vs. 3%) ($P=0.010$) (55).

Results of another study conducted on 140 patients indicated that long-term survival rate of the patients with LVEF of $<50\%$ was similar to those with normal ejection fractions. Interestingly, use of TAVR showed a reverse remodeling of the left ventricle resulting in the improvement of ejection fractions (from $37\pm8\%$ to $51\pm11\%$) (56).

Mitral regurgitation

Mitral regurgitation is a common phenomenon in severe aortic stenosis. Patients presented with aortic stenosis and mitral regurgitation obtain higher scores in euroSCORE and Society of Thoracic Surgeons (STS). Moreover, these patients tend to have echocardiographic findings suggestive of lower

LVEF, larger left-ventricle volumes, smaller aortic valve areas, and higher pulmonary artery systolic pressure. Also, higher incidence of atrial fibrillation and myocardial infarction has been reported in these patients (57).

Patients with mitral regurgitation who undergo TAVR have higher mortality rates compared to those presented with aortic stenosis only. As such, 30-day mortality rate is doubled in patients with moderate or severe mitral regurgitation compared to those with mild or no regurgitation (57,58). One-year mortality rates are classified in a stepwise fashion in patients with mitral regurgitation, as follows: none to mild: 10%, moderate: 12%, and severe: 17% (57).

Considering the aforementioned results, correction of mitral regurgitation is well advisable while fixing the aortic valve stenosis. If both these procedures are performed simultaneously in one operation, survival rate of the patient is likely to increase significantly (59).

Future Direction

Possible standard of care

TAVR has proven as a successful therapeutic intervention for high-risk patients presented with severe aortic stenosis. Some studies have suggested that TAVR is not only an alternative for patients who cannot undergo conventional surgeries, but it also is a potential standard-of-care procedure for all the patients requiring aortic valve replacement.

In this regard, the PARTNER trial has provided a landmark in patients who are extremely high-risk for surgical interventions for severe aortic stenosis. Currently, STS mortality score of the patients undergoing TAVR has been calculated at $14.0\pm11.8\%$ (52). However, STS mortality score might be affected by the complications caused by the diseased aortic valve. Potentially, eliminating some of the factors that could be ameliorated with the insertion of a new valve could lower the risk of mortality in some patients (2).

In a study performed in Munich, Germany on 420 patients with low STS mortality scores, 4.8-7.1% of the patients had a 30-day mortality rate of 3.8% and six-month mortality rate of 12.4% (Mack, 2012). The PARTNER II trial will be focusing on patients with STS mortality scores of $>4\%$, which represents the upper 25% of the patients undergoing SAVR (8).

Unresolved issues

According to the literature, younger patients tend to have lower STS mortality scores. When discussing the future of TAVR for this population, a number of obstacles require particular attention. The first concern in this regard will be post-procedural outcomes in young patients.

Aortic stenosis before the age of 60 is usually due to a congenital bicuspid aortic valve in the majority of the patients. However, the calcification caused by these valves is eccentric and extensive, which commonly proves unstable for percutaneous valve replacement (18).

If the valve is not inserted correctly, paravalvular regurgitation becomes a major issue. This outcome could contribute to post-procedural morbidity of the patients, while acting as a long-term predictor of mortality. Furthermore, if a replacement valve is deployed in a young patient, the necessity and outcomes of valve-in-valve procedures become a major issue.

Another concern in this regard revolves around the occurrence of stroke. Since the outcome is already statistically significant in high-risk patients, implementation of TAVR valves in patients who are expected to live longer may increase the risk of stroke. To address this issue, carotid embolic protection devices have been designed in order to reduce the risk of postoperative cerebrovascular accidents (2,18). Currently, four devices are available for this purpose, which are able to deflect or capture the embolism moving into the cerebral vasculature.

Two of these deflector devices are the Embrella Embolic Deflector (EED) (Edwards Lifesciences) and TriGuard Embolic Deflector Device (Keystone Heart, Herzliya, Israel). Both these devices are used to block the passage of embolism to cerebrovasculature during TAVR (18). Although EED detects smaller stroke lesions with diffusion-weighted brain magnetic resonance imaging (DW-MRI), it is able to identify more ischemic lesions compared to TAVR alone (60,61). Similar results have been reported for TriGuard Embolic Deflector Device (62-65).

The Montage Dual Filter System (Claret Medical Inc., Santa Rosa, California, USA) is deployed within the carotid and innominate arteries in order to capture embolism during TAVR (18). Although this device has not been studied extensively, the Montage Dual Filter System is reported to capture embolic debris in 75-86% of cases (65,66).

In the review of literature, no studies were found regarding the incidence of postoperative stroke with and without a filter system. As such, use of Embol-X intra-aortic filters (Edwards Lifesciences) seems to be more effective in cerebral embolic protection. In cases with standard cardiac surgery, this device is installed on the ascending aorta with aortic cannula of the cardiopulmonary bypass and is normally associated with 74% reduction of cerebral injury in high-risk patients. Furthermore, it could diminish renal complications from 24% to 14%;

however, the Embol-X device is not able to reduce the rate of postoperative stroke (66).

While the rate of postoperative cerebral lesions has been estimated at 7% in conventional SAVR via MRI, TAVR has an incidence rate of 84-90% for new cerebral lesions (68,69). In one research, Etienne et al. recommended the use of Embol-X device with transaortic TAVR (69) since it could detect the presence of embolism within the filter in 96.8% of cardiac surgery cases (67). Therefore, it could be concluded that this device is theoretically capable of capturing clinically significant cerebral embolisms (69,70).

Although Banbury et al. reported no significant reduction in the incidence rate of postoperative stroke with this device (67), Etienne et al. hypothesized that use of filters in transaortic TAVR could cause a significant reduction since the rate of postoperative stroke is normally high after the implementation of catheter-based techniques (69).

Based on the new data on the latest iteration of SAPIEN S3 (Edwards Lifesciences) balloon-expandable transcatheter valve, researchers at the American College of Cardiology (ACC) in 2015 reported historically lower rates of mortality and disabling stroke at 30 days postoperative among the patients with variable degrees of surgical risk (70,71).

According to the literature, among high-risk or inoperable patients requiring aortic valve replacement, 2% who underwent transfemoral TAVR with the SAPIEN 3 device died at 30 days postoperatively, and 1% had strokes (71). In comparison, 30-day mortality rate of the PARTNER cohort A study in high-risk surgical patients was 5.2%, while the incidence rate of stroke was 5.6%. Lower incidence of stroke could be attributed to smaller French-sized catheters (14 F rather than 22-24 F) (70,71). This emphasizes the fact that even in the high-risk cohort, mortality rate was significantly lower compared to previous studies (8).

Another obstacle to overcome is extensive peripheral vascular diseases that may occur in patients undergoing TAVR. To solve this issue, catheters with smaller sizes could be used for the procedure. In the United States, 18 F/19 F SAPIEN XT and 18 F CoreValve are commonly used for TAVR patients. If the catheter is extremely large or the vessel is tortuous, another approach should be selected. To date, two methods have been proposed to address this problem. One option is to develop smaller French-sized catheters (2,18), and the other is to perfect the transaortic TAVR approach so that it could be performed easily using minimally invasive methods with limited mortality (72).

Current data justifies the use of TAVR for patients who are considered high-risk for conventional surgeries. However, further investigation is required as to evaluate the durability and long-term complications associated with the aortic valve, especially in younger patient populations (18).

In one study, researchers used the Italian CoreValve registry consisting of 181 patients who were followed-up for three years postoperatively. According to the findings, size of the aortic valve area increased from $0.6 \pm 0.2 \text{ cm}^2$ (before TAVR) to $1.8 \pm 0.4 \text{ cm}^2$ (one year after TAVR). Furthermore, results obtained after the one-year follow-up remained unchanged for the next three years. Also, there was no evidence of moderate or severe aortic regurgitation postoperatively. Therefore, it could be concluded that CoreValve is able to withstand structural deterioration after three years (40). Future research is required in order to assess the structural durability of TAVR valves after three years of follow-up.

Ongoing research for low- or medium-risk patients for TAVR

In Switzerland, one study was performed to assess the clinical outcomes of low- or medium-risk patients for TAVR. After categorizing 389 patients based on STS scores into low-risk (STS<3%), medium-risk (STS 3-8%), and high-risk (STS>8%) groups, statistically significant differences were observed in terms of all-cause mortality at 30 days (2.4%, 3.9%, and 14.9%, respectively) ($P=0.001$) and one year of follow-up (10.1%, 16.1%, and 34.5%, respectively) ($P=0.0003$). However, no significant differences were reported in terms of stroke and myocardial infarction after the one-year follow-up. As such, researchers concluded that in contemporary practice, TAVR should not be limited to inoperable or STS-defined high-risk patients, but rather directed by the decision of the interdisciplinary cardiac team. Furthermore, well-selected patients with medium- or low-risk STS scores appeared to have more favorable outcomes compared to high-risk patients (73).

The results proposed by the PARTNER II S3 trial using the new SAPIEN 3 transcatheter valve are also promising in terms of patient outcomes, including low rates of 30-day cerebrovascular accidents and mortality. The trial was conducted on 1,076 medium-risk (STS score: 5.3%) and 583 high-risk patients (STS score: 8.6%) for valve replacement surgery.

Despite the comparable mean age of medium-risk (82 years) and high-risk (83 years) groups, all-cause and cardiovascular mortality rates at 30 days were 1.1% and 0.9% in the medium-risk group, respectively. Moreover, 2.6% of these

patients reported strokes at 30 days postoperatively, while disabling stroke was reported in only 1.0%. Low incidence rate of 30-day stroke might be due to better patient selection, use of imaging modalities, improved implantation techniques, and use of the new SAPIEN 3 valve (71,74).

Hybrid approach: TAVR with multi-vessel stenting

Approximately 40-75% of the patients who undergo TAVR are presented with significant coronary artery disease (CAD) (75). According to a comprehensive review by Goel et al., not all patients require revascularization before initiating TAVR, and percutaneous coronary intervention (PCI) should be considered for patients with acute stenotic lesions in proximal coronaries (75).

On the other hand, some studies have suggested simultaneous use of PCI and TAVR as a combined procedure. Furthermore, the findings indicated concomitant PCI and TAVR as a safe, feasible procedure recommended for all patients when PCI is necessary (75,76).

Extensive research is underway to identify the management options for CAD in patients with severe aortic stenosis requiring TAVR. Moreover, the ongoing ACTIVATION trial focuses on understanding whether pre-TAVR PCI has a favorable impact on patient outcomes after TAVR (77,78). In this regard, SURTAVI and PARTNER II trials have focused on patients with severe aortic stenosis and significant CAD requiring revascularization (79). These trials could be used to compare the efficacy of PCI in the treatment of aortic stenosis and CAD through surgical procedures.

Minimally invasive coronary artery bypass grafting (CABG) with TAVR

TAVR has been performed with minimally invasive CABG, which is also considered a valid option for myocardial revascularization in patients with critical stenosis on the anterior descending coronary artery. This procedure has been performed through the left mini-thoracotomy without cardiopulmonary bypass, aortic cross-clamp, and cardioplegic arrest (79).

Another study evaluated the outcomes in high-risk octogenarians undergoing minimally invasive aortic valve replacement and were also candidate for percutaneous or transapical aortic valve replacement. According to the findings, patients who were classified as high-risk for SAVR had remarkable outcomes after a minimally invasive surgery. Moreover, no significant difference was observed in the long-term survival rates of these patients compared to those

matched in terms of age and gender with the USA population (80).

TAVR with valve-in-valve technique

Valve-in-valve techniques are typically used in case of significant paravalvular leak, incomplete stent expansion or if a calcified leaflet overhangs into the orifice due to low TAVR placement.

A recent meta-analysis of 2,208 patients included only 38 cases of TAVR with valve-in-valve techniques (18,81). In the PARTNER trial, 7 out of 348 patients (2%) underwent valve-in-valve TAVR, three of whom died afterwards (10). For patients with degenerative aortic bioprosthesis, surgical treatment is associated with increased risk of mortality and morbidity. Therefore, performing TAVR with valve-in-valve techniques could be an alternative treatment option for these patients.

In a case series, seven patients with dysfunctional bioprosthetic aortic valves undergoing TAVR were followed-up using Edwards SAPIEN XT valve via the transfemoral approach. TAVR was successfully performed under local anesthesia with mild analgesic medication in all the cases. Although three patients had mild aortic regurgitation, no permanent pacemaker implantation was required. Moreover, no cardiac events or cerebrovascular accidents occurred, while one case of aneurysm requiring blood transfusion was reported. All seven patients improved in at least one of the NYHA classifications within 30 days postoperatively. Overall, the study concluded that TAVR with valve-in-valve techniques was a feasible option for patients with degenerative aortic bioprosthetic valves (82).

Valve-in-Valve International Data registry provided preliminary data indicating that although procedural success was achieved in 93.1% of patients, valve-in-valve procedure involved several concerns in terms of safety and efficacy. In this registry, patients who underwent transcatheter valve-in-valve implantation for degenerative bioprosthetic aortic valves had an overall one-year survival rate of 83.2%. However, this rate was reported to be lower in patients with small bioprosthesis and those with severe surgical valve stenosis (83).

Another study in this regard addressed the prosthetic mismatch of valve-in-valve technique, and evaluation of premade sizing tables including no patient dimensions was reported as the main obstacle against this approach. Therefore, the researchers concluded that prosthesis-patient mismatch was more likely to occur in patients who receive a TAVR valve-in-valve technique after conventional aortic valve replacement. In addition, 15% of currently published valve-in-

valve procedures were reported to result in the minimal reduction of pressure gradients (84).

Fixing other aortic valve pathologies

Although TAVR is a suitable intervention for the treatment of aortic stenosis, it may not be effective in repairing aortic regurgitation. TAVR is not considered a potential therapeutic intervention in these cases since the patients do not typically present with sufficient calcification or fibrosis that would necessitate the stabilization of the inserted valve (18). Rheumatic aortic insufficiency may be accompanied by fibrosis and occasional calcification of the aortic leaflets and cuff.

In Europe, use of JenaValve through the transapical route has been approved for the treatment of severe native aortic valve regurgitation in high-risk patients requiring open surgical therapy. Severe native aortic regurgitation (>3+) is generally considered an exclusion criterion for TAVR. Nevertheless, the JenaValve has CE mark approval in Europe and is the only valve approved for this purpose (85). Furthermore, the CENTERA valve (Edwards Lifesciences) has been designed specifically for high-risk patients with aortic regurgitation to benefit from a TAVR-like intervention (18).

Conclusion

TAVR is a new method of aortic valve replacement when it meets the criteria of severe aortic stenosis. Since the initial investigation in the PARTNER trial, TAVR has been shown to play a pivotal role in aortic stenosis therapy. Various methods are available for the deployment of a valve, including trans-femoral, trans-apical, and trans-aortic approaches. In addition, multiple valves could be selected depending on the necessity and mode of delivery (e.g., Edwards Sapien and CoreValve). While the main limitation of TAVR compared to surgical aortic valve replacement was increased risk of stroke, the incidence rate was found to decrease after the reduction of catheter diameters and development of new TAVR valves. Future directions of TAVR involve usage in patients with lower STS risk scores, those requiring valve-in-valve techniques, and employment of this modality in hybrid procedures. However, further trials and studies are required in order to support these new therapeutic indications and interventions.

Conflicts of interest

The authors declare no conflicts of interest.

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