The implications and requirements of transcatheter aortic valve replacement in low-risk patients

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Abstract

Transcatheter aortic valve replacement (TAVR) is a transformative technology that has changed the management of patients with severe, symptomatic aortic stenosis. The use of TAVR in intermediate- to high-risk patients has been validated in several rigorously performed, randomized clinical trials. Recent studies using newer generation devices have demonstrated the noninferiority of TAVR as compared with surgical aortic valve replacement in low-risk patients, supporting the increased utilization and expansion of TAVR. The use of TAVR in low-risk patients has important implications and requires a multifaceted approach that includes a highly functional multidisciplinary heart team for careful patient selection; a need to understand and help mitigate certain key complications, such as stroke, paravalvular regurgitation, and conduction disturbances; careful data collection for continual outcome assessment and improvement; and the necessary expertize and procedural volume to maintain excellent outcomes and ensure optimal clinical care pathways. *(Anatol J Cardiol 2020; 23: 2-9)*

Keywords: transcatheter aortic valve replacement, surgical aortic valve replacement, aortic valve stenosis, risk factors, postoperative complications, treatment outcome

Introduction

Transcatheter aortic valve replacement (TAVR) is a transformative technology that has changed the management of patients with severe, symptomatic aortic stenosis (AS). It has allowed patients who were previously not considered candidates for surgical aortic valve replacement (SAVR) or those who are deemed high risk to undergo a potentially life-saving procedure as demonstrated in rigorously performed, randomized clinical trials (1–3). Over the last decade, many of the initial obstacles and complications encountered with TAVR were addressed, and lessons learned were quickly disseminated in the community of practitioners. Better patient selection and meticulous procedural planning taking full advantage of multimodality imaging, together with advances in device development and accumulating operator and site experience, have resulted in steady improvements in outcomes and allowed for the expansion of TAVR to lower risk patients. Recent randomized controlled trials using newer generation devices have demonstrated noninferiority of TAVR as compared with SAVR, expanding the indication for low-risk patients (Fig. 1) (4, 5). Two recent meta-analyzes of randomized clinical trials have even shown that TAVR yields superior results compared with SAVR (Fig. 2) (6, 7). It appears that TAVR will be the treatment of choice for most patients with severe AS. With this remarkable opportunity comes an equally great responsibility of achieving and maintaining the safety, effectiveness and quality at levels that place TAVR where it is today.

Patient selection

The expansion and increased utilization of TAVR in lower risk and younger patients require a multifaceted approach with an understanding of key factors that have had the most impact on improved outcomes. Iterative advances in device development and operator and procedural team experience partially explain the rapid improvement in TAVR outcomes over the last 15 years. An equally important factor has been the steady improvement in patient selection. In contemporary practice, a highly functional, multidisciplinary heart team integrates clinical and multimodality imaging data to select patients who will most benefit from TAVR. Integration of patient functional status and frailty assessment has led to more accurate risk prediction. Careful clinical assess-

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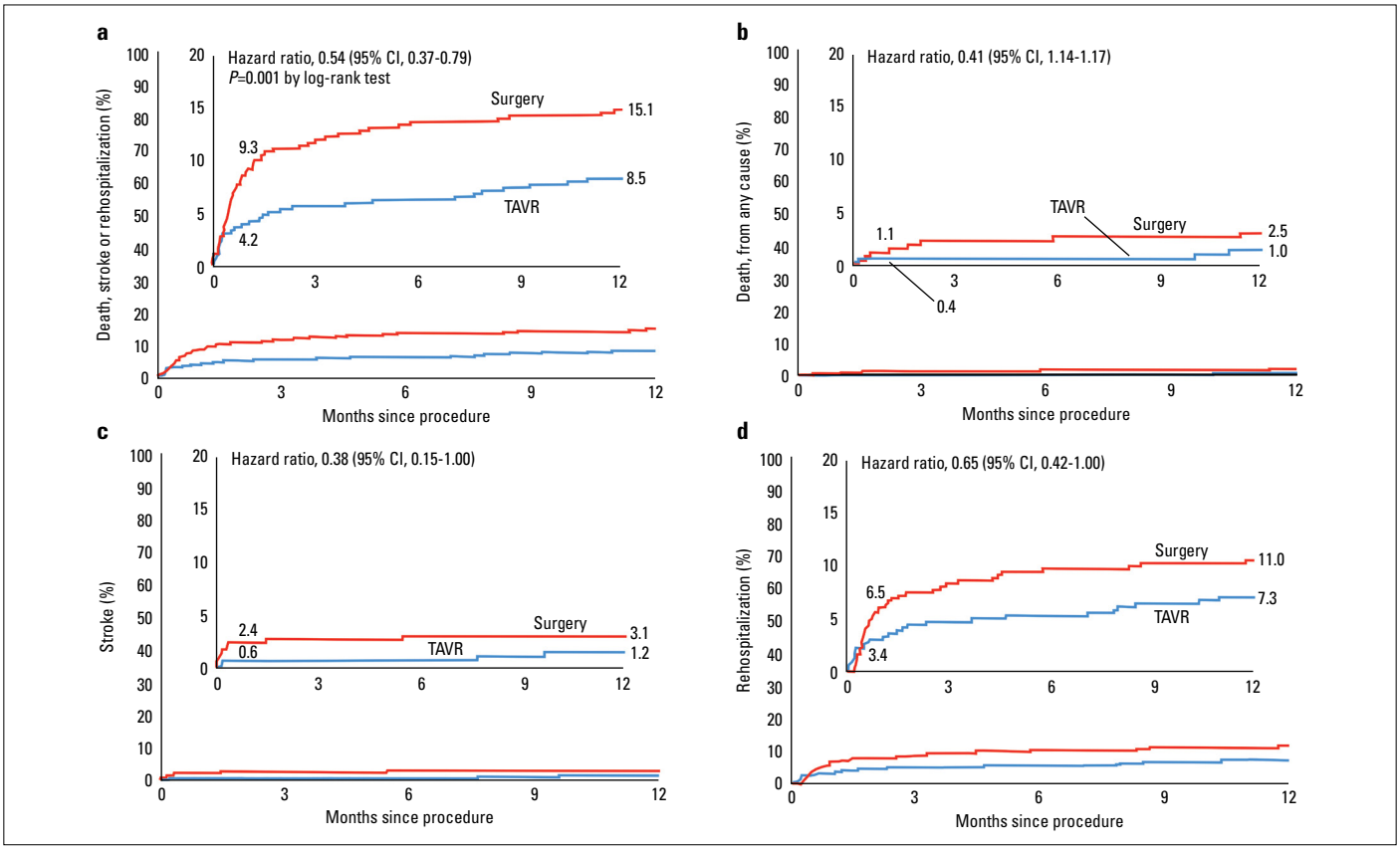

Figure 1. Kaplan–Meier estimates of the rate of the primary composite end point (a) and the individual components of the primary end point, which are death from any cause (b), stroke (c), and rehospitalization (d), in patients who underwent transcatheter aortic-valve replacement and those who underwent surgical aortic-valve replacement. Adapted from Mack et al. (4)

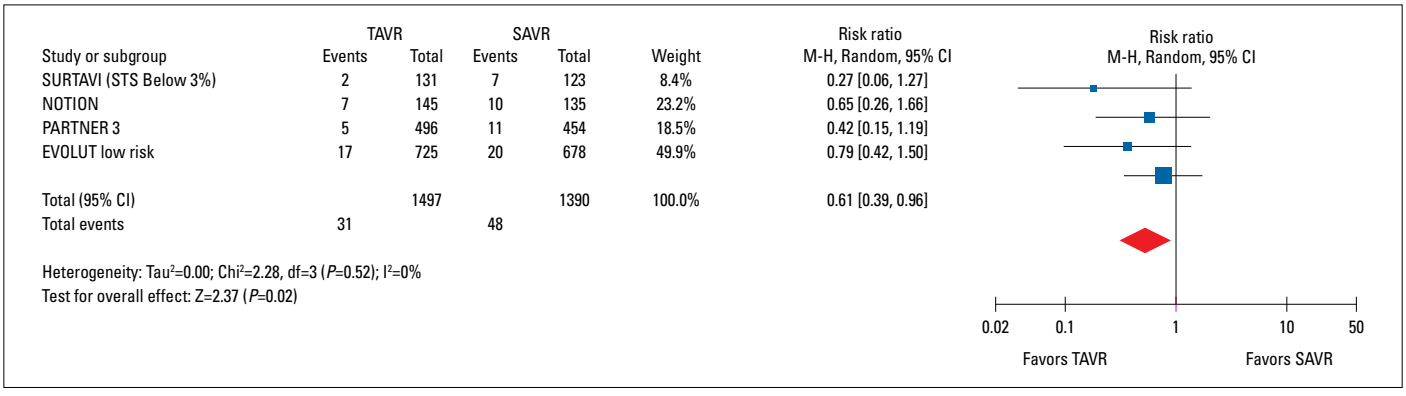

Figure 2. All-cause death at 1 year after TAVR versus SAVR in low-risk patients is shown. TAVR was associated with significantly lower risk of all-cause death (2.1% vs. 3.5%, RR: 0.61, 95% CI: 0.39–0.96, *P*=0.03, I^2=0%) at 1 year than SAVR in low-risk patients with severe aortic stenosis. Adapted from Kolte et al. (6)

CI - confidence interval; M–H - Mantel–Haenszel; NOTION 1 - Nordic Aortic Valve Intervention Trial; PARTNER - Placement of Aortic Transcatheter Valves; RR - risk ratio; SAVR - surgical aortic valve replacement; STS - Society of Thoracic Surgeons; SURTAVI - Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVR - transcatheter aortic valve replacement

ment not only helps in counseling patients regarding the risk of TAVR but also guides the heart team to steer away from referring patients to procedures unlikely to be helpful. Although the early TAVR trials in high-risk patients showed TAVR to be safe and as effective as SAVR, approximately a quarter of these patients died within 1 year, mostly due to non-cardiovascular causes (1-3). In addition, many of these patients did not receive an appreciable improvement in their quality of life. These findings in early randomized trials and subsequent large registry studies led heart teams to examine their approach to high-risk patients with multiple comorbidities and poor functional status. It became important to identify patients best served and likely to benefit from TAVR with an understanding of its limitations as certain patients had poor outcome irrespective of any intervention (8, 9). Mul-

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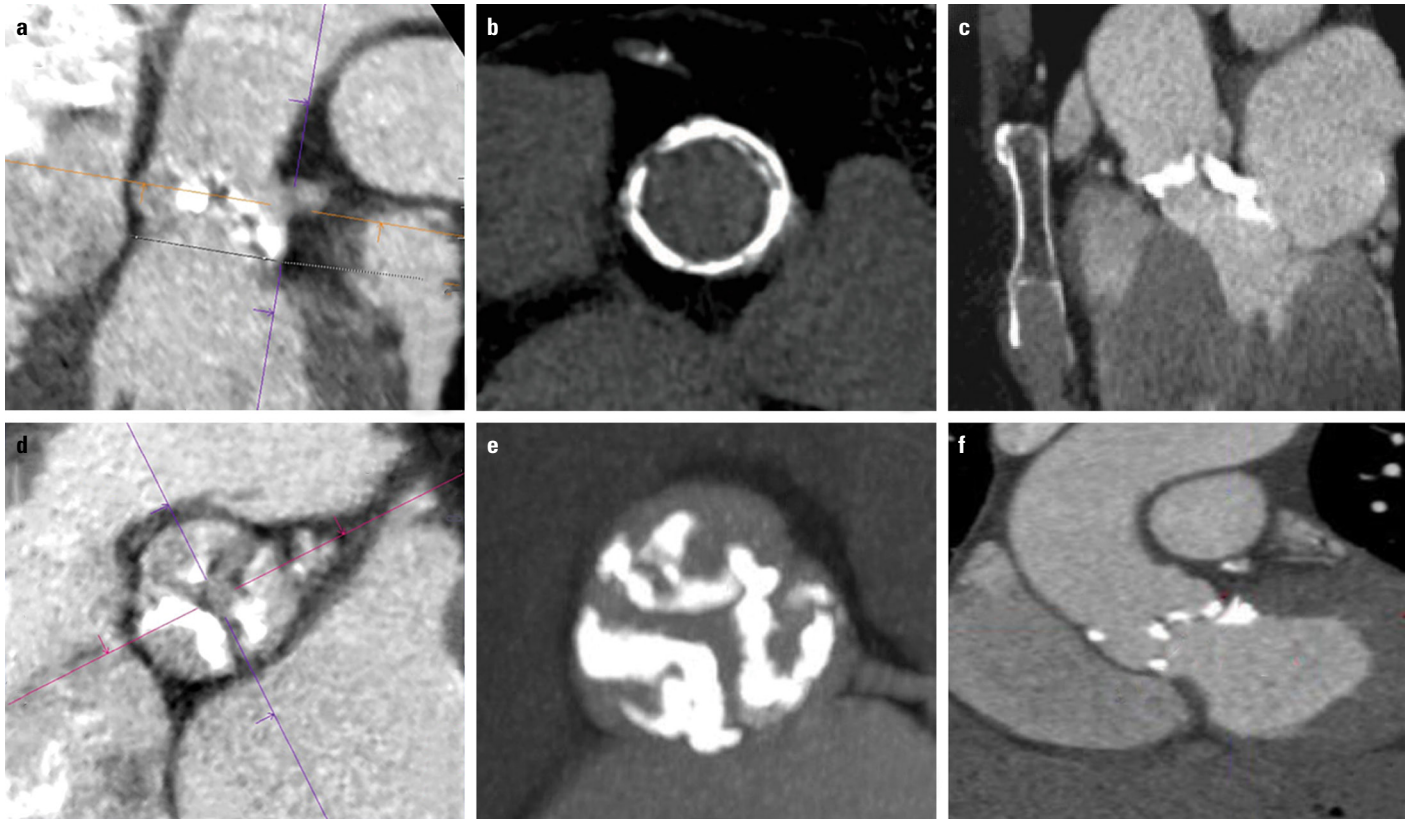

Figure 3. Multidetector computed tomography images of high-risk anatomical features relevant to transcatheter aortic valve replacement (TAVR). (a) Calcified left coronary cusp with short left coronary artery height <12 mm with increased risk for coronary obstruction. (b) Circumferential calcification of sinotubular junction with increased risk for aortic disruption or dissection or asymmetric valve expansion. (c) Heavily calcified left ventricular outflow tract with calcium extending from aortic to mitral valve annulus. (d) Narrow and deficient sinus of Valsalva concerning for coronary obstruction due to sequestration of the sinus after valve deployment. (e) Heavily calcified bicuspid aortic stenosis including calcification of the raphe. (f) Nodular calcification of left ventricular outflow tract and ventricular septum concerning for annular rupture

tidisciplinary heart teams have now incorporated a structured assessment of patients, including quantified frailty status and geriatric risk assessment (10). In addition to clinical risk assessment, integration of standardized multimodality imaging focusing on specific anatomical characteristics has led to better risk stratification.

Surgical risk scores are widely used but have proven to be poor predictors of TAVR-related outcomes. Certain high-risk anatomical features relevant to TAVR are not part of surgical risk calculators and may be prohibitive to the safe performance of the procedure (Fig. 3). Severely calcified and bulky valve leaflets with low (<12 mm) coronary ostia height combined with a narrow sinus of Valsalva may result in coronary artery obstruction. This frequently lethal complication occurs when the transcatheter heart valve (THV) displaces the native aortic valve leaflets outward and obstructs the coronary artery ostia, directly or by sequestering the sinus of Valsalva at the sinotubular junction. In addition to low coronary ostia and deficient sinus of Valsalva, several factors can contribute to coronary obstruction, including low sinotubular junction height, native valve leaflets longer than coronary ostia height, and leaflets with large calcific mass that can be displaced into the coronary ostium. Heavy calcium involving other parts of the aortic-valvular complex is an additional high-risk anatomical characteristic. Particularly asymmetrical heavy calcifications and those extending into the left ventricular outflow tract (LVOT) may lead to incomplete valve expansion, severe paravalvular regurgitation (PVR), and disruption of the annulus or aorta during THV deployment. Atherosclerotic plaque with mobile thrombi in the ascending aorta or arch increases the risk of stroke. In addition, bicuspid aortic valve (BAV) stenosis with asymmetric cusps and heavily calcified raphe may result in incomplete valve expansion and severe PVR.

Bicuspid AS can be seen in the elderly but is more common in younger patients aged 60–70 years who are usually low risk for SAVR (11). This fact has important implications for the expansion of TAVR to these patients while maintaining excellent outcomes. Although the rate of all-cause mortality has been shown to be comparable between bicuspid and tricuspid AS in registry studies, patients with TAVR with bicuspid AS had more frequent aortic root injury and more moderate and severe PVR (12). In addition, the anatomical features of a BAV may not allow full THV expansion, resulting in asymmetric leaflets. This may potentiate hypo-attenuated leaflet thickening or subclinical leaflet thrombosis with an undetermined effect on long-term du-

rability (13). Heart teams should take these caveats into account before referring a younger patient with AS with low surgical risk to TAVR. The BAV pathology is a spectrum rather than a single anatomic abnormality (Fig. 4). Some of these patients may very well be good TAVR candidates. Nevertheless, a low-risk patient with reasonably TAVR-suitable bicuspid AS should still have another reason to have TAVR rather than SAVR. Substudies of the PARTNER 3 and Evolut TAVR Low Risk patient trials in patients with bicuspid AS are ongoing. Results of these studies will help in the decision making in this patient population; however, this issue will unlikely be completely resolved without a randomized clinical trial. In the interim, the role of a highly functional, multidisciplinary heart team that includes imaging specialists, interventional cardiologists, and cardiac surgeons cannot be overemphasized in reaching the right decision by integrating clinical characteristics, imaging data, and specific TAVR risk assessment criteria.

There are several other examples of high-risk anatomy that highlight the importance of careful patient selection. The heart team plays a critical role by referring patients with high-risk anatomical characteristics to SAVR rather than TAVR unless the risk of SAVR is also prohibitively high. It is important to note that the PARTNER 3 and Evolut TAVR Low Risk trials excluded such patients, as well as those aged <65 years and those with poor transfemoral access, BAVs, or clinical features that significantly increased the risk of complications associated with either TAVR or SAVR. A similarly robust patient selection process is necessary to achieve outcomes comparable with randomized trials. A highly functional multidisciplinary heart team needs to be guided by national and global data, as well as carefully collected outcome data from individual centers. In addition, it is becoming increasingly clear that TAVR programs become consistently successful if they are functioning in the larger valve center environment rather than an isolated targeted procedure program.

Complications

The frequency of certain key procedural complications has declined in conjunction with improved patient selection, contributing to better outcomes. First, stroke can have potentially devastating consequences, including higher 30-day and 1-year mortalities (14). Early TAVR trials involving high-risk patients showed higher stroke rates with TAVR than SAVR (1-3). However, subsequent randomized trials of intermediate- and low-risk patients, incorporating independent routine pre- and post-pro-

Classification	Characteristics
Sievers Type 0/bicommisural non-raphe type	Two fairly symmetric cusps and two commissures Each cusp has one most basal insertion point; therefore, there are a total of two most basal insertion points
Siever Type 1/bicommisural raphe type	Two of three cusps are conjoined by a raphe Asymmetric cusp sizes with the cusp opposing the raphe (i.e cusp not participating in raphe formation) being larger than in a tricuspid aortic valve Raphe does not extend to the level of the ST junction which is the distinguishing characteristic to a non-opening commissure Size of the raphe and degree of calcification can vary. Upper row: non-calcified raphe Middle row: moderately calcified raphe Lower row: severely calcified raphe
Acquired/functional bicuspid valve (underlying tricuspid anatomy)	Underlying tricuspid anatomy with symmetric Sinus of Valsalva Non-opening commissure due to degenerative changes (fusion of right and left commissure in example) Non-opening commissure reaches ST junction, which is a distinguishing feature compared to a raphe

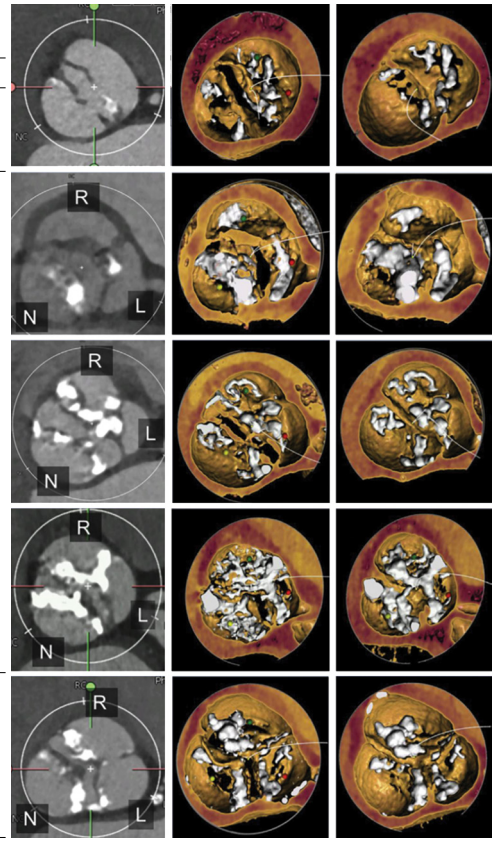

Figure 4. Variability and heterogeneous spectrum of bicuspid aortic valve morphology. Sievers bicuspid valve classification and characteristics with multidetector computed tomography imaging. Imaging shows double oblique transverse multiplanar reformat (column 1), volume rendered en face view in systole (column 2), and volume rendered en face view in diastole (column 3). Variability in bicuspid aortic stenosis with high-risk bicuspid anatomy identified with Sievers type 1 with severely calcified raphe. Adapted from Blanke et al. (32)

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cedure neurologic evaluation, demonstrated lower stroke rates after transfemoral TAVR (15). Successive improvements in THV technology with lower profile and flexible delivery systems, periprocedural anesthesiology, increasing operator experience, and better patient selection may have contributed to improvements in stroke rates in the preapproval stage of TAVR. Interestingly, real-world Transcatheter Valve Therapy (TVT) registry data have demonstrated no significant change in stroke rates between 2011 and 2017 (16). Nevertheless, the recent low-risk TAVR trial has shown a remarkably low stroke rate (4). The totality of the data suggests that patient risk profile is an important determinant of stroke risk and may explain these findings. As important as understanding the cause, further mitigation of stroke may be possible with the use of cerebral embolic protection devices. The use of a cerebral embolic protection device demonstrated a significantly higher rate of stroke-free survival than that of unprotected TAVR in a propensity-matched cohort study in patients undergoing TAVR (17). It is currently unclear whether embolic protection devices will have a benefit in low-risk patients. It will be important to define the role of these devices in this population and the effect of TAVR on harder to define outcomes, such as cognitive decline that may be associated with debris embolization and not immediately clinically apparent.

Second, PVR is a common complication of TAVR and is a product of malapposition or insufficient contact of the circular transcatheter valve prosthesis to the often eccentric and calcified aortic annulus. Several mechanisms play a role in the incidence and severity of PVR, such as heavy localized calcification, undersizing of the prosthesis, incorrect positioning of the THV, and acute aorta-LVOT angle affecting the proper seating of the THV. Despite improvement in the valve area and gradient after TAVR, increasing grades of PVR adversely impacts ventricular function and ultimately survival (18). Multidetector computed tomography has become the standard method for the accurate measurement of the aortic-valvular complex, resulting in better valve sizing and a reduction in PVR (19). PVR has also been improved by the development of new transcatheter valves with outer sealing skirts or cuffs or other abluminal sealing mechanisms. This has been so effective that the presence of moderate or greater PVR at 30 days was seen in only 0.8% of patients treated with the SAPIEN 3 valve in the PARTNER 3 trial (4). However, mild PVR was seen in 29.4% of patients at 1-year follow-up. Most studies have failed to demonstrate a relationship between mild PVR and 1–2-year mortality, although a meta-analysis showed the opposite (20). In view of the considerably longer expected survival of low-risk and particularly younger patients, even mild PVR after TAVR may be consequential. Therefore, more work is needed to completely abolish TAVR-related PVR.

Finally, conduction disturbances requiring permanent pacemaker implantation occur more frequently after TAVR, particularly when self-expanding or mechanically expandable valves are used. Permanent pacemaker implantation exposes patients to specific complications, such as infections, lead fractures, vein thrombosis, endocarditis, and secondary tricuspid regurgitation. Continuous right ventricular pacing may not be innocuous. Although studies with relatively short-term follow-up did not show a survival disadvantage, data from the TVT registry (21) and a recent report from a Canadian registry (22) have shown an increase in mortality and heart failure in those patients who require a pacemaker after TAVR. Left bundle branch block (LBBB), which occurs more frequently after TAVR than SAVR, is another concerning conduction abnormality. Although earlier studies did not show an association with 1–2-year mortality, a recent analysis of pooled data of 2043 patients from the PARTNER 2 trial and S3 intermediate-risk registry demonstrated that new LBBB is associated with adverse clinical outcomes at 2 years, including all-cause and cardiovascular mortalities, rehospitalization, new pacemaker implantation, and worsened left ventricular systolic function (23). The risks posed by these conduction abnormalities become even more relevant when TAVR is considered in younger patients with AS who have a longer life expectancy. There may be an association between lower THV implantation depth (percent of frame height below the annulus) and greater device oversizing and new conduction abnormality and permanent pacemaker implantation (24). A higher implantation height and less oversizing may decrease the incidence of conduction abnormalities after TAVR and potentially improve long-term outcomes.

When considering TAVR in lower risk and younger patients, a longer life expectancy has important implications for valve durability and future treatment options. There are limited long-term data on THV durability in low-risk and younger patients. Although a 5-year echocardiographic follow-up of high-risk patients who underwent TAVR with first generation devices did not show significant structural valve deterioration (SVD), there is a need to provide definitive long-term data on valve durability (25). In this regard, the PARTNER 3 and Evolut R Low Risk randomized trials will provide 10-year echocardiographic data assessing the incidence of SVD in low-risk patients. Data from these systematic follow-up examinations will define the patient and valve characteristics that may be associated with limited valve durability in transcatheter and surgical valves. Treating younger patients will also require better long-term planning as bioprosthetic valves by their nature will ultimately fail. The choice of treatment strategy and implanted valve size will have an effect on future treatment options and specifically valve-in-valve procedures for senescent bioprosthetic valves.

Training and procedural volume

There are several other conceptual and difficult to measure factors that contributed to the successful introduction and implementation of TAVR and may have had a significant effect on outcomes. The collaborative efforts of the medical community, professional societies, regulators, and device manufacturers initially restricted the use of TAVR to high-volume centers with significant expertize to ensure high-quality outcomes. The addition

of new TAVR sites was methodical, providing time to respond to device limitations and implement iterative improvements. Training centers were created that provided didactic as well as simulation and live case experience. Proctors were assigned to new centers to help buffer the learning curve before allowing sites to be independent. There was dissemination of knowledge via international valve conferences, allowing for shared experience and learning. Most importantly, there were carefully staged, large randomized trials in different risk groups that provided invaluable data, informing the responsible dispersion of the technology. Equally informative studies originating from various registries allowed careful and complete collection, rapid analysis, and widespread distribution of real-world data. Initial industry sponsored registries after the completion of randomized trials, followed by regional and national registries, played a pivotal role in this process. It is impossible to develop and sustain a successful TAVR program without being informed by prospectively collected and properly analyzed data. This measured and rigorous approach should serve as an example for other transcatheter devices and for future expansion of TAVR and increased utilization in low-risk and younger patients.

A similar careful approach is necessary when starting new TAVR programs that may not initially meet the same characteristics and outcomes of programs participating in the major clinical trials. TAVR procedures display important learning curve characteristics with both greater procedural safety and a lower mortality when performed by experienced operators in high-volume centers. TAVR performed at low annual volume (<50 procedures) institutions is associated with decreased procedural safety and higher patient mortality (26). An analysis of 113,662 patients in the TVT registry showed higher mortality at 30 days and more variability at hospitals with low procedural volume. This was even true after exclusion of the first 12 months of TAVR procedures at each hospital (27). These findings have important implications for operator training and patient care at centers performing TAVR. TAVR programs will have to meet the performance standards of excellent surgery for TAVR to be an acceptable alternative for low-risk patients. Critical determinants of high performance include a well-functioning multidisciplinary heart team, clinical outcomes and device characteristics that meet benchmark standards, carefully collected data to guide improvement in quality, and operator and site volume and program expertize (transcatheter and surgical) to ensure optimal clinical care pathways.

Surgical aortic valve replacement

Having discussed the advances and gaps in contemporary TAVR practice, we would be remiss if the relative shortcomings of SAVR are not briefly discussed. Recent meta-analyzes of randomized trials (6, 7), as well as previous reports from nonrandomized studies (28), suggest that transfemoral TAVR results in lower 30-day and 2-year mortality rates than SAVR. Randomized trials have also consistently demonstrated higher rates of all, as well as disabling, strokes after SAVR compared with TAVR (6, 7). This consistent finding should be taken into account during decision making and discussion with the patient. Much higher rates of atrial fibrillation, bleeding, and transfusion rates and more frequent kidney injury after SAVR are other worrisome issues. Rapid improvement of the quality of life, resumption of normal daily activities, and return to work within days to a few weeks are obvious advantages of TAVR and should be among the factors considered in deciding the mode of aortic valve replacement. Another important point is gaps in the SAVR data. There is no long-term SAVR study with independent clinical event adjudication and complete echocardiogram follow-up with core lab readings. Although surgical heart valves are considered the gold standard for valve durability, a close examination of the literature reveals marked variability in reporting of SAVR deterioration, inconsistency in the definition of SVD, and lack of systematically collected long-term data (29). Rigorously collected long-term data with standardized definitions for surgical valves are needed to provide a benchmark for the durability of rapidly evolving transcatheter valves.

Conclusion

Although several challenges remain for the continued global expansion and increased utilization of TAVR for most patients with AS, the paradigm is slowly shifting from "SAVR if possible, TAVR if necessary" to "TAVR if possible, SAVR if necessary." Recent data in low-risk patients have demonstrated that TAVR performed by experienced operators using a transfemoral approach in patients without high-risk clinical or anatomic factors was associated with lower rates of major clinical events than SAVR (Table 1) (4, 5, 30, 31). TAVR performing centers will have to meet the same benchmark standards as programs involved in these randomized trials to replicate similar results in low-risk patients. This requires a highly functional, multidisciplinary heart team that integrates clinical and multimodality imaging data to select patients who will most benefit from TAVR with an understanding of its limitations. Certain high-risk anatomical features relevant to TAVR may be prohibitive to the safe performance of the procedure. Bicuspid AS becomes an important factor as TAVR is performed in younger patients and may have a significant impact on outcomes and long-term THV durability. Although the incidence and severity of PVR has significantly improved, it is still unclear what effect even mild PVR has on long-term survival, and every measure should be taken to eliminate this complication. In addition, conduction disturbances are associated with adverse clinical outcomes and require further device development and other mitigation strategies. The expansion of TAVR will also require the necessary expertize and procedural volume to maintain excellent outcomes, as well as participation in registries for continual outcome assessment and improvement. Interventional cardiologists and cardiac surgeons need to cooperate at each center and work together to make the best decision for each patient

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Table 1. Major clinical events at 30 days after transcatheter aortic valve replacement as reported in the low-risk transcatheter aortic valve replacement trials

Outcome	PARTNER 3[4] (n=496)	Evolut low risk[5] (n=725)	NOTION[30] (n=142)	Low-risk TAVR[31] (n=200)
All-cause death – no. (%)	2 (0.4)	4 (0.5)	3 (2.1)	0 (0)
Stroke – no. (%)	3 (0.6)	25 (3.4)	2 (1.4)	0 (0)
Life threatening or major bleeding – no. (%)	18 (3.6)	17 (2.4%)	16 (11.3)	5 (2.5)
Major vascular complication – no. (%)	11 (2.2)	28 (3.8)	8 (5.6)	5 (2.5)
Paravalvular regurgitation moderate or severe – no. (%)	4 (0.8)	25 (3.5)	22 (15.3)	2 (1.0)
Permanent pacemaker implantation – no. (%)	5 (6.1)	126 (17.4)	46 (34.1)	10 (5.0)
Left bundle branch block – no. (%)	118 (23.7)	-	-	-
New atrial fibrillation – no. (%)	25 (5.0)	56 (7.7)	24 (16.9)	6 (3.0)
Coronary artery obstruction – no. (%)	1 (0.2)	7 (0.9)	-	1 (0.5)
Implantation of a second valve – no. (%)	1 (0.2)	9 (1.2)	4 (2.8)	4 (2.0)
Annulus rupture – no. (%)	1 (0.2)	-	-	-
Ventricular perforation – no. (%)	1 (0.2)	-	2 (1.4)	-

whether it be transcatheter or surgical to deliver the best treatment result. The expansion and increased utilization of TAVR require this understanding, as well as continued research and careful data collection, to guide process improvement and outcomes.

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