Current Cardiology Reports (2019) 21:161
https://doi.org/10.1007/s11886-019-1250-5

VALVULAR HEART DISEASE (TL KIEFER, SECTION EDITOR)

Should All Low-risk Patients Now Be Considered for TAVR? Operative Risk, Clinical, and Anatomic Considerations

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Abstract

Purpose of Review This article reviews the current data on TAVR in low-risk patients with severe, symptomatic aortic stenosis, highlights the results of the recently published Medtronic Low Risk Randomized Study and PARTNER 3 trials, and describes specific clinical, anatomic, and procedural considerations regarding the optimal treatment choice in this population.

Recent Findings In low-risk patients, the Medtronic Low Risk Randomized Study demonstrated TAVR to be non-inferior to surgery with respect to the composite endpoint of death or disabling stroke while PARTNER 3 trial proved TAVR to be superior to surgery with regard to the composite endpoint of death, stroke, or rehospitalization.

Summary Recent trials demonstrate the safety and efficacy of TAVR in low-risk patients and have led to an FDA indication for the use of TAVR in these patients. However, the lack of long-term data on the rate of transcatheter valve deterioration in the younger population, higher incidence of paravalvular leak and pacemaker implantation following TAVR, along with certain intrinsic anatomic factors remain potential challenges to generalize TAVR in all low surgical risk patients. We describe specific clinical, anatomic, and procedural considerations regarding the optimal treatment choice for low-risk patients with severe, symptomatic AS.

Keywords TAVR · TAVI · SAVR · Low risk · Severe aortic stenosis

Introduction

In the past decade, TAVR rapidly gained widespread popularity as an alternate treatment modality in patients with severe symptomatic aortic stenosis (AS). The technology was initially indicated for patients considered to be inoperable [1,2] but FDA-approval has since been expanded to include patients with high [3,4] and intermediate surgical risk [5,6]. Given the iterative technological advancements in transcatheter heart valve platforms, increased operator experience, and minimalist procedure approaches, TAVR has rapidly complemented traditional surgical aortic valve replacement (SAVR) and the number of TAVR procedures carried out per year in the USA has now surpassed SAVR [7].

Until very recently, traditional SAVR remains the standard of care for patients at low surgical risk, but there has been escalating interest in this patient population. Based on the most recent data of TAVR in low-risk patients, the FDA has approved TAVR for this patient population. This paper will review early studies on TAVR in low-risk patients, summarize the two largest clinical trials in these patients, and highlight future directions for the optimal treatment of these patients.

Early Studies

The LRT Trial [8, 9] was an FDA-approved trial in the USA to evaluate the feasibility of TAVR in low-risk patients. The study enrolled 200 low-risk patients (STS score ≤ 3%), and 88.2% of patients received the balloon-expandable Edwards

This article is part of the Topical Collection on *Valvular Heart Disease*

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Published online: 28 November 2019

Sapien S3 valve. At 1 year, mortality was 3.0%, stroke rate was 2.1%, and permanent pacemaker implantation rate was 7.3%. Importantly, the LRT trial was a non-randomized study; there was no direct comparison between TAVR and SAVR, with the SAVR cohort being a historical control from the STS database.

The NOTION (Nordic Aortic Valve Intervention) trial was the first randomized trial to compare TAVR using the earlier generation Medtronic CoreValve device with SAVR in predominantly low-risk patients. NOTION enrolled 280 patients, and 82% had STS-Predicted Risk of Mortality (PROM) < 4%. The trial demonstrated no significant difference between TAVR and SAVR in terms of composite rate of all-cause mortality, stroke, or MI at 1 year (13.1 vs. 16.3%, $p = 0.43$) [10] and at 5 years (38.0 vs. 36.3%, $p = 0.86$) [11]. The rate of all-cause mortality also did not differ between the two groups at 1 year (4.9 vs 7.5%, $p = 0.38$) [10] and at 5 years (27.6 vs 28.9%, $p = 0.75$) [11•]. Although these early results demonstrated the feasibility of TAVR in lower-risk patients, widespread extrapolation of TAVR in this population based on this study may be limited in the current era due to a small study population, earlier generation valve, and high pacemaker implantation rates.

The most current evidence demonstrating the safety and efficacy of TAVR in patients of low surgical risk comes from the recent Medtronic Low Risk Randomized study [12••] and PARTNER 3 [13••] trial, two large-scale multi-center randomized trials comparing TAVR with SAVR in low-risk patients.

Low-risk Randomized Study

Study Population

The Medtronic Low Risk Randomized Study [12••] randomized 1403 patients to undergo either TAVR ($n = 725$) or SAVR ($n = 678$). The mean age of the patients in the trial was 74 years with median STS PROM at 30 days of 1.9%. Patient characteristics were well-balanced between study arms. Among patients undergoing TAVR, 3.6% of patients received the first-generation CoreValve, 74.1% received Evolut R, and 22.3% received the third-generation Evolut PRO, which has an outer pericardial wrap that is designed to minimize incidence of paravalvular leak.

Primary Endpoint

The primary safety and effectiveness endpoint was a composite of all-cause mortality or disabling stroke in TAVR vs. SAVR at 24 months, which was shown to be 5.3 vs. 6.7% ($p < 0.05$ for non-inferiority, $p > 0.05$ for superiority). The 24-month estimated incidence of death from any cause was 4.5% in both TAVR and surgery groups. The 24-month estimated incidence of disabling stroke was 1.1 vs. 3.5%.

Secondary Endpoints

Among secondary endpoints, all-cause mortality or disabling stroke at 30 days was shown to be lower in TAVR compared to SAVR (0.8 vs. 2.6%). TAVR patients also experienced lower rates of bleeding complications (2.4 vs. 7.5%), acute kidney injury (0.9 vs. 2.8%), and atrial fibrillation (7.7 vs. 35.4%) at 30 days but higher rates of moderate and severe paravalvular regurgitation (3.5 vs. 0.6%) and pacemaker implantation (17.4 vs. 6.1%). Comprehensive data regarding primary and secondary endpoints at 30 days and 1 year are provided in Table 1.

The Low Risk Study demonstrated the non-inferiority of TAVR with a self-expanding supraannular bioprosthesis compared to surgery with respect to death or disabling stroke at 24 months in patients with severe symptomatic aortic stenosis who were at low surgical risk. TAVR patients had a better recovery rate at 30 days as indicated by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, which estimates quality of life. Patients undergoing TAVR also had superior valvular hemodynamics: lower aortic valve gradients and larger effective orifice area. However, patients undergoing SAVR had lower incidence of pacemaker implantation and aortic valve regurgitation.

PARTNER 3 Trial

Study Population

In the PARTNER 3 trial [13••], a total of 1000 patients were enrolled and the assigned procedure was performed in 950 patients. The patients were randomized to undergo either TAVR with the balloon expandable Edwards SAPIEN 3 valve ($n = 496$) or SAVR ($n = 454$). The patients enrolled in the trial had a mean age of 73 years and a mean STS-PROM at 30 days of 1.9%.

Primary Endpoint

The primary endpoint was a composite of death, stroke, or rehospitalization (defined as any hospitalization related to the procedure, valve, or heart failure) at 1 year. It was observed to be 8.5% in the TAVR group compared with 15.1% in the surgery group ($p < 0.001$ for non-inferiority, $p = 0.001$ for superiority).

Secondary Endpoints

At 30 days, TAVR resulted in a similar rate of all-cause mortality compared to SAVR (0.4 vs. 1.1%, $p < 0.05$), lower rate of stroke than surgery (0.6 vs. 2.4%), lower rate of new-onset atrial fibrillation (5.0 vs. 39.5%), shorter index hospitalization

Table 1 Medtronic Low Risk Trial—clinical endpoints at 30 days and 1 year

Endpoint	30 days			1 year		
	TAVR % of patients	SAVR % of patients	Difference, TAVR-surgery (95% BCI) percentage points	TAVR % of patients	SAVR % of patients	Difference, TAVR-surgery (95% BCI) percentage points
Death from any cause or disabling stroke	0.8	2.6	− 1.8 (− 3.2 to − 0.5)	2.9	4.6	− 1.8 (− 4.0 to 0.4)
Death from any cause	0.5	1.3	− 0.8 (− 1.9 to 0.2)	2.4	3.0	− 0.6 (− 2.6 to 1.3)
Death from cardiac cause	0.5	1.3	− 0.8 (− 1.9 to 0.2)	1.7	2.6	− 0.9 (− 2.7 to 0.7)
All stroke	3.4	3.4	0.0 (− 1.9 to 1.9)	4.1	4.3	− 0.2 (− 2.4 to 1.9)
Disabling stroke	0.5	1.7	− 1.2 (− 2.4 to − 0.2)	0.8	2.4	− 1.6 (− 3.1 to − 0.3)
TIA	0.6	0.8	− 0.2 (− 1.2 to 0.7)	1.7	1.8	− 0.2 (− 1.6 to 1.3)
Hospitalization for heart failure	1.2	2.5	− 1.3 (− 2.8 to 0.1)	3.2	6.5	
Major vascular complication	3.8	3.2	0.6 (− 1.4 to 2.5)	3.8	3.5	0.3 (− 1.7 to 2.3)
Life threatening or disabling bleeding	2.4	7.5	− 5.1 (− 7.5 to − 2.9)	3.2	8.9	− 5.7 (− 8.4 to − 3.1)
Myocardial infarction	0.9	1.3	− 0.4 (− 1.5 to 0.7)	1.7	1.6	0.1 (− 1.3 to 1.5)
Permanent pacemaker implantation	17.4	6.1	11.3 (8.0 to 14.7)	19.4	6.7	12.6 (9.2 to 16.2)
Atrial fibrillation	7.7	35.4	− 27.7 (− 31.8 to − 23.6)	9.8	38.3	− 28.5 (− 32.8 to − 24.1)
Acute kidney injury stage 2 or 3	0.9	2.8	− 1.8 (− 3.4 to − 0.5)	0.9	2.8	− 1.8 (− 3.4 to − 0.5)
Coronary artery obstruction	0.9	0.4	0.5 (− 0.3 to 1.4)	0.9	0.4	0.5 (− 0.3 to 1.4)
Aortic re-intervention	0.4	0.4	0.0 (− 0.8 to 0.7)	0.7	0.6	0.0 (− 1.0 to 0.9)
Endocarditis	0.1	0.2	− 0.1 (− 0.7 to 0.3)	0.2	0.4	− 0.2 (− 0.9 to 0.5)
Valve thrombosis	0.1	0.1	0.0 (− 0.4 to 0.4)	0.2	0.3	− 0.1 (− 0.9 to 0.5)

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(3 vs. 7 days), and a lower risk of a poor treatment outcome (death or low KCCQ score) at 30 days (3.9 vs. 30.6%). There were no significant differences in the rate of pacemaker implantation at 30 days (6.5 vs. 4.0%, p = NS) or in the rate of moderate to severe paravalvular aortic regurgitation at 1 year (0.6% TAVR vs. 0.5% for SAVR, p = NS). At 1 year, the rate of death or disabling stroke was 1.0% in the TAVR group compared with 2.9% in the surgery group. Comprehensive data regarding primary and secondary endpoints of the trial at 30 days and 1 year are provided in Table 2.

The results of the PARTNER 3 trial concluded superiority of TAVR over SAVR in terms of the primary composite endpoint of preventing death, stroke, or rehospitalization at 30 days and 1 year. TAVR was also associated with significantly lower rates of atrial fibrillation at 30 days, a shorter index hospitalization, and lower risk of poor treatment outcome (death or low KCCQ score) at 30 days than surgery. TAVR patients also had more rapid improvements in the NYHA class, 6-min walk-test distance, and KCCQ score than those who underwent surgery.

Though the two trials differed in their composite endpoints, the rates of severe adverse events were comparable between the two trials. The Medtronic Low Risk study reported a lower rate of all-cause mortality with TAVR vs. SAVR (0.5 vs. 1.3%, $p < 0.05$) at 30 days while no significant difference was noted between the two groups in the PARTNER 3 trial (0.4 vs. 1.1%, respectively). In the Medtronic Low Risk study, the rate of stroke was observed to be 3.4% in both groups at 30 days, whereas it was found to be lower with TAVR vs. SAVR in the PARTNER 3 trial (0.6 vs. 2.4%, $p = 0.02$). The results of the two trials demonstrate overall similar rates of death and stroke in TAVR compared to SAVR. The rate of new onset atrial fibrillation was observed to be higher among SAVR patients than TAVR in both the Medtronic Low Risk study (7.7 vs. 35.4%, $p < 0.05$) and PARTNER 3 trial (5.0 vs. 39.5%, $p < 0.001$). The rate of pacemaker implantation, however, was significantly higher among patients undergoing TAVR in Medtronic Low Risk study as compared to those undergoing TAVR in the PARTNER 3 trial (17.4 vs. 6.1%, $p < 0.05$).

General Considerations—Is TAVR as Good as SAVR?

The results of both the landmark trials—Medtronic Low Risk and PARTNER 3—have been encouraging and demonstrate the short-term safety and efficacy of TAVR compared with SAVR. In the Medtronic Low Risk study, TAVR was non-inferior to SAVR with respect to mortality and disabling stroke. The incidence of stroke, in fact, remained higher in the SAVR arm at 2-year follow-up. The PARTNER 3 trial provided substantial evidence to suggest superiority of

Table 2 PARTNER 3 Trial—clinical endpoints at 30 days and 1 year

Endpoint	30 days			1 year		
	TAVR % of patients	SAVR % of patients	Treatment Effect [95% CI]	TAVR % of patients	SAVR % of patients	Treatment effect [95% CI]
Death, stroke or rehospitalization	4.2	9.3	0.45 [0.27, 0.76]	8.5	15.1	0.54 [0.37, 0.79]
Death from any cause	0.4	1.1	0.37 [0.07, 1.88]	1.0	2.5	0.41 [0.14, 1.17]
Death from cardiac cause	0.4	0.9	0.46 [0.08, 2.49]	0.8	2.0	0.40 [0.12, 1.30]
Any stroke	0.6	2.4	0.25 [0.07, 0.88]	1.2	3.1	0.38 [0.15, 1.00]
Disabling stroke	0.0	0.4	0.00 [NA]	0.2	0.9	0.22 [0.03, 2.00]
Death or stroke	1.0	3.3	0.30 [0.11, 0.83]	1.8	4.9	0.36 [0.17, 0.79]
TIA	0.0	0.7	0.00 [NA]	1.0	1.1	0.89 [0.26, 3.06]
Rehospitalization	3.4	6.5	0.53 [0.29, 0.97)	7.3	11.0	0.65 [0.42, 1.00]
Major vascular complications	2.2	1.5	1.44 [0.56, 3.73]	2.8	1.5	1.83 [0.74, 4.55]
Life-threatening/disabling, or major bleeding	3.6	24.5	0.12 [0.07, 0.21]	7.7	25.9	0.25 [0.17, 0.37]
Life-threatening/disabling bleeding	1.2	11.9	0.09 [0.04, 0.22]	2.8	12.8	0.20 [0.11, 0.36]
Myocardial infarction	1.0	1.3	0.76 [0.23, 2.50]	1.2	2.2	0.54 [0.20, 1.49]
New permanent pacemaker	6.5	4.0	1.66 [0.93, 2.96]	7.3	5.4	1.39 [0.83, 2.33]
New onset atrial fibrillation	5.0	39.5	0.10 [0.06, 0.16]	7.0	40.9	0.13 (0.09, 0.20]
Requirement for renal replacement	0.2	0.7	0.30 [0.03, 2.93]	0.2	0.7	0.30 [0.03, 2.93]
Coronary obstruction requiring intervention	0.2	0.7	0.30 [0.03, 2.93]	0.2	0.7	0.30 [0.03, 2.93]
Aortic valve re-intervention	0.0	0.0	N/A	0.6	0.5	1.33 [0.22, 7.95]
Endocarditis	0.0	0.2	N/A	0.2	0.5	0.44 [0.04, 4.89]
Asymptomatic valve thrombosis	0.2	0.0	N/A	1.0%	0.2%	4.47 [0.52, 38.24]

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TAVR over SAVR in preventing death, stroke, or rehospitalization at 1-year follow-up. The evidence from both these trials is compelling to believe that TAVR is equally safe and effective as SAVR among patients of low surgical risk, at least in the short term. Nevertheless, there are still a number of unanswered questions with respect to the long-term safety and durability of these valves.

SAVR has been the gold standard for AVR, and SAVR valve durability remains an important benchmark while determining application of TAVR to younger patients [14]. Though there has been significant heterogeneity in the data regarding the definition and rate of structural valve deterioration (SVD) of surgical bioprostheses across different studies [14], in general, SVD is not common (≤ 15%) during the first decade post-SAVR [15]. Age at implantation has been identified as one of the most important predictors of surgical bioprosthetic valve durability and is inversely associated with greater SVD; at younger age of implantation, the rate of SVD has been shown to be higher [16]. With TAVR being a relatively young technology, the data are scarce on long-term durability of TAVR valves. The 5-year results of the PARTNER 1A trial reported no significant incidence of SVD in either TAVR or SAVR arms, though long-term follow-up is challenging given the high overall mortality rates in this high-risk population [17]. Toggweiler et al. [18] reported a 3.4% incidence of SVD at the end of 5 years in a cohort of 88 patients who received Edwards SAPIEN valve. In another study of 353 patients who underwent implantation of the Medtronic CoreValve, the incidence of significant prosthetic valve failure was reported to be 1.4% at the end of 5-year follow-up [19]. In all these studies, the mean age of patients at implantation was > 80 years [17–19]. In the NOTION trial through 6 years, the rate of SVD was reported to be 4.8% and the mean age of patients at implantation was 79.1 years [20]. Though the rate of SVD in these studies has been satisfactory, long-term follow-up is essential to assess the durability of TAVR valves if they were to be implanted in a much younger patient population with longer life-expectancy. Both the Medtronic Low Risk study and PARTNER 3 trial will provide annual follow-up for 10 years and consequential data on long-term durability of valves should become evident over the course of follow-up of these low surgical risk patients.

Peri-procedural Complications of TAVR Impacting Long-term Outcomes

Paravalvular Leak

Historically, there has been a higher incidence of paravalvular leak (PVL) associated with TAVR [3–6], and this has been associated with higher mortality [5,6]. Mismatch of the valve annulus and prosthesis diameter sizes, device landing zone calcification, and suboptimal device implantation have been identified as the major predictors of PVL [21,22]. With implementation of pre-procedural multidetector computed tomography imaging and more accurate sizing of transcatheter heart valve sizes, the incidence of PVL has been significantly reduced [23]. Also, while the incidence of PVL was observed to be higher in early generation valves, the rate has improved with the availability of a wider range of valve sizes and with the development of newer generation valves that have been engineered to provide better sealing mechanisms [24]. The PARTNER 3 trial reported similar rates of moderate to severe PVL with the balloon-expandable transcatheter valve as compared to SAVR (0.6 vs. 0.5%) [13••]. However, the incidence of moderate to severe PVL remained higher with self-expanding valves as seen in Medtronic Low Risk study (3.5 vs. 0.55%) [12••]. This has been consistent with prior studies reflecting higher incidence of moderate to severe PVL with self-expanding valves compared to balloon-expandable valves. Importantly, calcification of the device-landing zone, particularly if located in the left ventricular outflow tract, has been identified as an independent predictor of residual PVL [22] and continues to be a technical issue with TAVR. It would be reasonable to consider SAVR in low surgical risk patients with high LVOT calcium burden until there is convincing evidence to suggest heightened efficacy of novel generation valves in reducing PVL in highly calcified anatomies.

Vascular Complications

Vascular complications have been recognized as an important cause of morbidity and mortality in patients undergoing TAVR [25]. Early trials of TAVR reported vascular complications in 11–18% of patients. Those platforms utilized very large delivery systems (22–24 Fr) [26]. With the introduction of lower-profile, 14 to 18 Fr delivery sheaths, there has been a sharp drop in rate of vascular complications following TAVR [26]. The PARTNER 3 trial reported no difference in major vascular complications between TAVR and SAVR whereas the Medtronic Low Risk study demonstrated lower rate of vascular complications in TAVR patients. These results reflect that TAVR has dramatically improved its safety profile in terms of vascular complications. There is, however, limited data on non-transfemoral access in low surgical risk patients. The PARTNER 3 trial exclusively utilized iliofemoral access and the Medtronic Low Risk study consisted of attempted iliofemoral access in 99.0% of the TAVR patients. Both trials excluded patients with illiofemoral vessel characteristics that would preclude safe passage of the introducer sheath. In such patients with severe peripheral vascular disease and unfavorable iliofemoral access, with otherwise low surgical risk, SAVR may remain a better option.

Pacemaker Implantation

Another important complication associated with TAVR has been the higher rate of permanent pacemaker implantation (PPI) compared to SAVR. PPI has been associated with significantly longer post-procedure hospitalization and higher rates of repeat hospitalization [27]. A study analyzing the clinical outcomes of PPI post-TAVR from STS/ACC TVT registry reported a 31% increased risk for 1-year mortality and a 33% increased risk for a composite of mortality or heart failure admission at 1 year [28]. Incidence of PPI was higher among early generation valves, especially with the self-expanding Medtronic CoreValve [29]. With newer generation valves and strategies targeting shallower implantation depth, the PPI rate has declined in both balloon-expandable [30] and self-expanding valves [31,32]. The incidence of PPI, however, still remains higher in self-expanding valves compared to SAVR, as highlighted in Medtronic Low Risk study (17.4 vs. 6.1%) and this continues to be a potential challenge when considering expanding TAVR to low-risk and younger patients. Pre-existing RBBB, left coronary cusp calcium burden, and trans-apical or trans-aortic access have been identified as predictors of PPI [28,33]. Given higher mortality associated with PPI following TAVR, low surgical risk patients with these characteristics are likely better candidates for SAVR than TAVR.

Anatomic and Procedural Considerations

Bicuspid Aortic Valves

Bicuspid aortic valves (BAV) are frequently associated with premature aortic stenosis and regurgitation. The more elliptical nature of the aortic annulus and enlarged anatomy of the aortic root can make positioning and anchoring of a transcatheter valve more challenging than for a typical trileaflet aortic valve. TAVR is also associated with increased risk of asymmetric and incomplete valve expansion and injury to the aortic root and ascending aorta during the procedure [34]. Owing to these anatomic challenges, BAV have been largely treated with SAVR and have been excluded from all large-scale clinical trials comparing TAVR to SAVR. The use of TAVR in BAV has been reported in some recent studies. Though TAVR in BAV does not seem to cause excess mortality, it is

associated with higher rates of PVL and PPI [35]. Given the higher prevalence of bicuspid AS in a younger population, expanding the use of TAVR to this group warrants longer-term durability data and a randomized trial. A current multicenter, prospective, single-arm clinical trial (Medtronic Transcatheter Aortic Valve Replacement Low Risk Bicuspid Study; NCT03635424) is evaluating the procedural safety and efficacy of the Medtronic CoreValve Evolut platform in patients with bicuspid aortic anatomy and severe AS at low risk for SAVR and will provide further insight into device success in this subgroup of patients.

Aortic Valve Calcification

The severity and location of aortic valve calcification are important contributors to post-TAVR PVL [36] and conduction disturbances [37]. Calcification has been thought to impair the seal of the THV to the aortic annulus and LVOT, resulting in PVL. Some calcium patterns may promote injury to the conduction pathways. Fujita et al [33] identified pre-existing RBBB and elevated LCC calcification > 209 mm^3 as significant predictors of PPI. The risk for PPI was calculated to be 53.8% in patients who had both pre-existing RBBB and an elevated LCC calcium burden. Given higher mortality associated with PVL and PPI, it is of paramount importance to stratify low surgical risk patients according to their risk of developing these long-term adverse complications.

Low Coronary Height

TAVR has been associated with a rare, but life threatening complication, of coronary obstruction. The incidence has been reported to be < 1%. The left coronary ostium has been noted to be more prone to occlusion due to its significantly lower height as compared to the right coronary ostium in most patients. The most frequent mechanism described has been the displacement of a calcified native cusp over a coronary ostium. A coronary ostium height of ≤ 12 mm and aortic sinus of valsalva diameter < 30 mm have been identified as important risk factors for coronary obstruction [38]. Emergent percutaneous coronary intervention (PCI) for post-TAVR coronary obstruction, though feasible, has been shown to increase mortality. Pre-emptive coronary protective measures [39,40] and more recently BASILICA (Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction), an investigational procedure that utilizes an electrified catheter-based technique to lacerate the aortic cusps prior to TAVR, still under clinical trial [ClinicalTrials.gov Identifier: NCT03381989], are being explored to mitigate the incidence of coronary obstruction. However, these investigational procedures currently remain limited to high or extreme surgical risk patients. Patients with low surgical risk, identified to have low coronary ostia height and small SOV on MDCT, should be considered for SAVR to prevent coronary obstruction.

Concomitant Coronary Artery Disease

Coronary artery disease (CAD) often co-exists in patients with severe symptomatic AS. Surgical series have demonstrated that untreated significant coronary artery stenoses increase postoperative mortality, and therefore, the standard of care in this population has been coronary artery bypass grafting at the time of surgical valve replacement. A recent systemic review and meta-analysis that studied the outcomes in patients undergoing TAVR with concomitant CAD demonstrated that PCI before or during TAVR conferred no clinical benefit, and in fact increased the risk of major vascular complications and 30-day mortality [41]. The approach to the treatment of concomitant untreated CAD in patients with severe symptomatic AS remains controversial. In younger and low surgical risk patients with a greater impact of CAD on long-term mortality and quality of life, justification of TAVR would require larger randomized control trials to determine the best therapeutic approach to treat concomitant significant coronary artery disease.

Poor Transfemoral Access

Transfemoral access remains the preferred route for TAVR as multiple studies have demonstrated lesser morbidity, shorter hospitalizations, and more rapid recovery compared to non-femoral approaches [42,43]. Current commercial TAVR sheath sizes range from 14 to 18 Fr. Despite reduction in sheath size and improvement in delivery systems, there remains a portion of patients with iliofemoral calibers that are too small for safe transfemoral TAVR. Alternative access routes such as subclavian, direct aortic, or transapical require a surgical cut-down and have been associated with increased mortality in a higher-risk population. Although this should be decided on a case-by-case basis, patients with poor transfemoral access that are otherwise low risk for surgery may benefit more from traditional SAVR. However, the volume of low-risk patients considered unsuitable for TAVR due to narrow vascular access is likely low and will continue to become smaller with further reduction in sheath size. Table 3 highlights specific considerations for SAVR compared with TAVR among low-risk patients.

Subclinical Valve Thrombosis

The LRT Trial reported 14.0% incidence of subclinical valve thrombosis [8,9], also referred to as hypo-attenuating leaflet thickening (HALT) as detected on MDCT imaging. The incidence of HALT is observed to be higher in TAVR compared to SAVR [44]. Subclinical valve thrombosis is often an

Table 3 Considerations for SAVR preference in low-risk patients

Young age (< 60 years)
Anatomy concerning for significant paravalvular leak
Poor transfemoral access
Extensive conduction system disease
Bicuspid aortic valve (studies ongoing) and aortopathy
Low coronary height(s)
Significant concomitant coronary artery disease
Additional significant mitral or tricuspid valve disease

incidental finding and does not cause any significant valvular dysfunction. However, there have been concerns that subclinical valve thrombosis might progress towards clinical valve thrombosis, increase the risk of TIA/stroke, and/or negatively impact the long-term durability of the aortic bioprosthetic valve [45]. The LRT Trial proposes a potential mechanistic link between subclinical valve thrombosis and stroke. At 1-year follow-up, LRT reported a numerically higher rate of stroke in subjects with HALT (3.8 vs. 1.9%, $p = 0.53$), although the absolute number of events was small in both groups (1/27 with HALT vs. 4/166 with no HALT) [9]. In the SAVORY/RESOLVE registry [44], reduced leaflet motion was associated with increased incidence of TIA; however, in this registry, the status of the leaflet was not known at the time of TIA [45]. On the other hand, despite the known higher incidence of subclinical valve thrombosis in TAVR, the short- and mid-term data do not demonstrate cerebrovascular events to be occurring at higher rates following TAVR compared to SAVR [17,46]. Of the 14% of TAVR subjects in the LRT study who had evidence of leaflet thickening at 30 days, there was no impact on valve hemodynamics at 1 year [9]. Whether subclinical valve thrombosis/HALT leads to increased risk of clinical valve thrombosis or premature structural valve deterioration would become more evident as long-term data becomes available from the Low Risk Medtronic Trial and the PARTNER 3 trial.

Cost-effectiveness OF TAVR

A cost-effectiveness analysis from PARTNER 1A demonstrated that TAVR was cost-effective compared with SAVR among patients treated via the transfemoral approach [47]. In a more recent economic analysis among intermediate-risk patients on the basis of PARTNER 2A trial and S3i registry, TAVR was projected to be economically more favorable over a life-time horizon owing to the shorter length of stay during the index hospitalization, less resource utilization during follow-up, and fewer rehabilitation and skilled nursing facility days [48]. Considering fewer co-morbidities in low surgical risk patients, if long-term data reveals comparable clinical benefits between TAVR and SAVR, TAVR may ultimately prove a societally cost-effective option in this group as well.

FDA Indication

In August 2019, the US FDA approved an expanded indication for the Medtronic Corevalve Evolut R/Pro and Sapien 3 platforms for patients with severe symptomatic AS at low surgical risk for traditional surgery, primarily based on the two landmark clinical trials that demonstrated their safety and efficacy compared with SAVR. As part of the approved indication, the manufacturers will be required to continue to follow patients enrolled in the randomized studies for 10 years, as specified in their respective protocols. Additionally, manufacturers will be required to participate in the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy Registry.

Conclusion

Both PARTNER 3 and Medtronic Low Risk Randomized trials have demonstrated excellent safety results in low surgical risk patients and have led to expanded FDA indication for TAVR in this patient population. The Low Risk Randomized trial revealed that TAVR was non-inferior to SAVR with regard to death or disabling stroke as compared to SAVR while the PARTNER 3 trial validated superiority of TAVR over SAVR in preventing death/disabling stroke/rehospitalization. While 5-year data from earlier studies on TAVR reveal favorable valve durability, the long-term SVD rate following TAVR, particularly in younger patients, remains unknown and will become more evident with continued follow-up. Technological innovations and technical modifications addressing the PVL and PPI observed with self-expanding valves are necessary when contemplating TAVR in low-risk patients, given associated increase in morbidity and mortality with these complications. Low-surgical risk patients with bicuspid aortic valves, low-coronary heights, concomitant CAD, and those with poor transfemoral access offer procedural challenges that may render traditional SAVR a better option in the current era.

Compliance with Ethical Standards

Conflict of Interest Saima Siddique has no relevant disclosures.

Hemal Gada reports consulting for Medtronic, Bard Inc., Abbott Vascular, and Boston Scientific Corp.

Mubashir A. Mumtaz reports consulting and proctoring for Abbott, Edwards Lifesciences, Medtronic, Atricure, Medtronic, Z-Medica, and JOMDD.

Amit N. Vora reports consulting for Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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