40 Comparison of Transcatheter Aortic Valve Implantation to Surgical Aortic Valve Replacement in Intermediate-Risk Patients

Anita W. Asgar and Nathan Messas

40.1 Introduction

Transcatheter aortic valve implantation (TAVI), also called transcatheter aortic valve replacement (TAVR), is first-line therapy for patients with severe symptomatic aortic stenosis (AS) and a prohibitive risk for standard surgical aortic valve replacement (SAVR) [1]. Accumulating clinical experience of TAVR operators and technological advances in transcatheter valve systems have led to a massive expansion of TAVR interventions worldwide. TAVR is now available in more than 65 countries around the world with over 250,000 procedures performed to date. As a result, there is now an interest to expand TAVR indications to patients at lower surgical risk such as those at intermediate or low risk. At present, SAVR remains the gold standard treatment for aortic stenosis patients at low or intermediate surgical risk; however recent evidence from observational studies and randomized trials are shifting this treatment paradigm from surgery closer to TAVR.

40.2 Defining Risk for Patients with Aortic Stenosis

Aortic stenosis (AS) is now the most common indication for valve replacement in Europe and North America, with an ever-increasing disease prevalence due to the aging population. Decision making in valvular heart disease necessitates a careful evaluation of the risk-to-benefit ratio, considering both the results of intervention and the severity-adjusted risk of adverse outcomes without intervention. Appropriate risk stratification is therefore crucial to select the optimal treatment strategy for patients with symptomatic severe AS. Factors associated with adverse clinical outcomes include poor functional capacity, advanced age, and concomitant coronary disease [2].

Evaluation of risk in AS is often focused on risk of surgical intervention or operative mortality. There are numerous clinical factors that are associated with increased operative risk including the need for emergency intervention, left ventricular dysfunction, pulmonary hypertension, advanced age, previous cardiac surgery, and comorbidities such as renal insufficiency and severe chronic obstructive pulmonary disease (COPD). To facilitate risk evaluation, multivariate risk scores have become commonplace to stratify patients into risk categories. The most commonly used scores include the Society for Thoracic Surgeons score (STS score) which calculates the predicted risk of mortality (STS-

A. W. Asgar (✉) · N. Messas
Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada
e-mail: anita.asgar@umontreal.ca

A. Giordano et al. (eds.), *Transcatheter Aortic Valve Implantation*,
https://doi.org/10.1007/978-3-030-05912-5_40

Table 40.1 Definition of operative risk

	Low risk	Intermediate risk	High risk	Prohibitive risk
Clinical characteristics	No frailty No comorbidities	No more than mild frailty Or 1 major organ system compromise not to be improved postoperatively	Moderate-severe frailty or >2 major organ system compromises not to be improved postoperatively	Severe frailty Or ≥3 major organ system compromises not to be improved postoperatively
STS-PROM	<4%	4–8%	>8%	PROM >50% at 1 year
EuroSCORE II	<10%	10–20%	>20%	

PROM) and the EuroSCORE. Both scores utilize a numeric scoring system based on clinical parameters to calculate risk using an algorithmic risk model. It should be noted that surgical risk scores share several limitations by insufficiently considering multiple factors that may increase the risk related to surgery; patient frailty, cognitive impairment, the risk of delirium, anatomical characteristics such as a porcelain aorta, and social support post-discharge are some of the factors that are not evaluated in the traditional risk scores. Finally, they do not take into account the local surgical results in a given institution, which may potentially have a lower operative risk.

Definition of risk categories in aortic stenosis has been driven by randomized control trials of TAVR which have created four risk groups: low, intermediate, high, and prohibitive risk as shown in Table 40.1. The first three groups are defined by the STS-PROM score as follows: low risk [<4%], intermediate risk [4–8%], or high risk [>8%]. Prohibitive risk is defined as risk of mortality and morbidity at 1 year >50%, compromise of ≥3 major organ systems, severe frailty, or severe procedure-specific impediments [3].

There is consensus, according to North American and European guidelines, that TAVR is a class IA recommendation for inoperable or prohibitive-risk patients with severe symptomatic AS but a life expectancy of at least 12 months [1, 4]. TAVR is an acceptable treatment option (class IA) in those patients with a high operative risk provided a multidisciplinary heart team has confirmed the TAVI indication, and there is a sufficient life expectancy. As of this writing, TAVR is also now deemed a reasonable alternative (class IIA) to SAVR in symptomatic AS patients at intermediate surgical risk [1].

Despite what has been published in the literature, the spectrum of patients with symptomatic severe aortic stenosis who require aortic valve replacement is much larger than that of patients previously studied in TAVI trials [5–9]. In fact, the high-risk population studied in the TAVI trials represents a small percentage of the total patient population needing aortic valve replacement. The Society of Thoracic Surgeons database of aortic valve disease cases during 2002–2010 (N = 141,905) shows that just 6.2% were ranked as high risk, whereas most patients (79.9%) were low risk, and 13.9% were intermediate risk [10]. In light of this distribution of patients and the focus on expanding indications for TAVR, there is increased interest to push the boundaries of the technology into the lower-risk cohorts.

40.3 Comparison of TAVR to SAVR in Intermediate-Risk Patients: Clinical Evidence

TAVR is established therapy for symptomatic severe AS in both inoperable/prohibitive-risk and high-risk patients. The journey to establishing an indication in intermediate risk began with data from cohort studies and prospective matched studies (see Table 40.2) finally culminating in data from prospective randomized trials of both balloon expandable and self-expandable transcatheter heart valves.

Table 40.2 Cohort studies (propensity match analysis) of TAVR vs. SAVR in intermediate-risk patients

Reference	# patients	Mean risk score	30-day mortality (%)	Vascular complications (%)	Permanent pacemaker (%)
Latib et al.	222	4.6 (STS)	1.8 vs. 1.8 (p = NS)	33.3 vs. 0.9 ($p < 0.001$)	11.7 vs. 2.7 ($p = 0.009$)
Fraccaro et al.	830	9.9 (EuroSCORE)	2.7 vs. 3.6 (p = NS)	6.0 vs. 0.5 ($p < 0.0001$)	13.4 vs. 3.7 ($p < 0.0001$)
Schymik et al.	432	8.7 (EuroSCORE)	1.4 vs. 4.2 (p = NS)	10.6 vs. 0.0 ($p < 0.001$)	13.9 vs. 4.6 ($p < 0.0001$)
Piazza et al.	510	17.4 (EuroSCORE)	7.8 vs. 7.1 (p = NS)	*	*
Thourani et al.	2021	5.3 (STS)	1.1 vs. 4	6.1 vs. 5.4	10.2 vs. 7.3

*Not reported

40.4 Prospective Nonrandomized Cohort Studies

Early insights into outcomes of TAVR in intermediate-risk patients were published in 2012 in a small propensity matched study of patients undergoing TAVR using either the Edwards SAPIEN XT or Medtronic CoreValve device. Latib et al. compared clinical outcomes of transfemoral TAVR vs. SAVR in 111 patients, propensity matched for clinical characteristics and risk scores, with a mean STS score of 4.6 ± 2.3 (TAVR) vs. 4.6 ± 2.6 (SAVR). There were no significant differences in all-cause mortality at 1 year (6.4% for TF-TAVR and 8.1% for SAVR; $p = 1.0$). Transfemoral TAVI was associated with a higher rate of vascular complications (33.3% vs. 0.9%, $p < 0.001$) and permanent pacemaker (11.7% vs. 2.7%, $p = 0.009$), while acute kidney injury was more frequent in the SAVR group (26.1% vs. 8.1%, $p < 0.001$) [11].

Additional prospective cohort data was available from the single-nation, multicenter cohort of patients treated with either SAVR or TAVR in Italy. The OBservational Study of Effectiveness of SAVR-TAVR procedures for severe Aortic steNosis Treatment (OBSERVANT) study enrolled 7618 consecutive patients with symptomatic severe AS who underwent SAVR or TAVI from December 2010 to June 2012 in 93 Italian participating hospitals. After excluding those patients felt to be inoperable or higher risk, due to concomitant coronary artery bypass, patients that underwent TAVR and SAVR were propensity matched. The authors found no significant difference in early mortality or myocardial infarction between TAVI and SAVR with a 30-day death of 3.6% for SAVR and 2.7% for TAVR ($p = 0.4328$). The incidence of stroke (3.0% SAVR and 0.0% TAVR; $p = 0.0455$) was slightly higher in those undergoing SAVR. There were higher rates of acute renal failure (9.6% vs. 3.6%, $p = 0.001$) and blood transfusions in the SAVR cohort (63.2% vs. 34.5%; $p < 0.001$). TAVR was however associated with increased vascular complications (6.0% vs. 0.5%; $p < 0.0001$) and new permanent pacemaker implantation (13.4% vs. 3.7%; $p < 0.0001$) [12].

More recent comparisons of intermediate-risk patients have compared newer-generation transcatheter valves with surgical aortic valve replacement. The propensity matched study of Thourani et al. compared intermediate-risk TAVR patients from the PARTNER 2 SAPIEN 3 observational study [13] with intermediate-risk SAVR patients from the PARTNER 2A randomized study using a pre-specified propensity score analysis to account for between-trial differences in baseline characteristics [14]. The primary endpoint for the propensity score analysis was the 1-year nonhierarchical composite event of death from any cause, all strokes, and posttreatment aortic regurgitation. The mean age was 81 years, and 88% underwent transfemoral

TAVR with a mean STS score of 5.3%. Compared with previously published data, the use of the SAPIEN 3 was associated with lower rates of all-cause mortality of 1.1%, disabling stroke of 1.0%, moderate or severe PVL of 4.2%, major vascular complications of 6.1%, life-threatening bleeding of 4.6%, and new permanent pacemaker implantation of 10%. Furthermore, the authors found a significant superiority of TAVR for the composite endpoint of mortality, strokes, and moderate or severe aortic regurgitation (weighted difference of proportions −9.2%, 95% CI −13.0 to −5.4; $p < 0.0001$) to surgical valve replacement.

40.5 Randomized Controlled Trial Data

To date, there have been three randomized controlled trials (RCTs) examining TAVR in intermediate surgical risk patients as shown in Table 40.3.

The Nordic Aortic Valve Intervention (NOTION) trial, a multicenter all-comers study, compared TAVR using a self-expanding prosthesis with SAVR in low- to intermediate-risk patients with severe aortic valve stenosis. A total of 280 patients were included, to be followed up for 5 years. Patients' clinical risk was estimated using both the Society of STS-PROM and EuroSCORE I and II. Around 80% of participants were considered low-risk patients. In the intention-to-treat analysis, no differences were found in the primary endpoint, a composite of death from any cause, stroke, or myocardial infarction (MI) at 1 year (13.1% for TAVI vs. 16.3% for SAVR; $p = 0.43$) [15].

In the prospective, randomized, non-inferiority PARTNER 2A trial, TAVR with the balloon-expandable SAPIEN XT valve (Edwards Lifesciences, USA) was compared with SAVR in 2032 patients with severe AS deemed to be at intermediate surgical risk, defined by a STS score of 4–8% (mean 5.8%). The primary endpoint, a composite of death from any cause or disabling stroke at 2-year follow-up, was similar between the TAVR and SAVR groups ($P = 0.001$ for meeting the non-inferiority criteria), and the 2-year survival curve event rates were not significantly different in the TAVR and SAVR cohorts (16.7% and 18.0%, respectively). Interestingly, among the 76% of patients who underwent TAVR with the use of TF access, all-cause death and disabling stroke rates were 21% lower ($P = 0.05$) than in the SAVR group. Moreover, the improvements in aortic valve areas and gradients at all time points after the procedure were significantly better with TAVR than with SAVR. Conversely, a higher rate of mild or worse paravalvular leaks was observed in the TAVR group [8].

Finally, in the prospective randomized non-inferiority SURTAVI trial of the Medtronic CoreValve, 1746 patients at intermediate surgical risk (mean STS 4.5%) were enrolled to evaluate the safety and efficacy of the self-expanding bioprosthesis CoreValve or Evolut R (Medtronic, USA) versus SAVR. At 2 years, the incidence of all-cause death or disabling stroke (the primary endpoint) was similar in the TAVR and SAVR groups, as assessed with a Bayesian analytical approach (12.6% and 14.0%, respectively). TAVR patients had lower mean transaortic gradients and larger aortic valve areas than patients who underwent SAVR, whereas TAVR was associated with a 26% rate of permanent pacemaker implantation and higher rates of moderate or severe residual paravalvular AR [9].

Taken together, these randomized trials with a non-inferiority design strongly support the safety and efficacy of TAVR for patients with severe AS whose operative risk of death is intermediate and have thus resulted in an updated indication of IIA [1].

Table 40.3 Randomized control trial data of TAVR vs. SAVR in intermediate-risk patients

Reference	# patients	Mean risk score	30-day mortality (%)	Vascular complications (%)	Permanent pacemaker (%)
PARTNER 2A	2032	5.8 (STS)	3.9 vs. 4.1 ($p = 0.78$)	7.9 vs. 5.0 ($p = 0.008$)	8.5 vs. 6.9 ($p = 0.17$)
SURTAVI	1746	4.5 (STS)	2.2 vs. 1.7	6 vs. 1.1	25.9 vs. 6.6

40.6 Meta-Analysis of Current Data

A meta-analysis by Singh et al. evaluated the results of aortic valve replacement in 2375 and 2377 intermediate-risk patients undergoing TAVI and SAVR, respectively. This analysis found similar 30-day all-cause mortality ($p = 0.07$), 30-day cardiac mortality ($p = 0.53$), and 12-month all-cause mortality ($p = 0.34$) between the two groups. However, TAVR via transfemoral access had a significantly lower mortality than SAVR (OR 0.58, $p = 0.006$). The incidence of moderate or greater aortic insufficiency ($p < 0.00001$) and new permanent pacemaker implantation ($p < 0.0001$) was higher in the TAVR group [16].

In the largest meta-analysis to date of patients with severe aortic stenosis, Gargiulo et al. compared mortality after TAVR or SAVR in 16,638 patients. Overall, there was no statistically significant difference between TAVI and SAVR in early (odds ratio [OR], 1.01 [95% CI, 0.81–1.26]) or midterm (OR, 0.96 [CI, 0.81–1.14]) all-cause mortality; however the analysis combined patients at all risk levels from prohibitive to intermediate risk. Analysis of the patient subgroup of low to intermediate risk showed statistically nonsignificant reductions in early (OR, 0.67 [CI, 0.42–1.07]) and midterm (OR, 0.91 [CI, 0.67–1.23]) mortality with TAVI. TAVR was associated with significant reductions in rates of major bleeding, acute kidney injury, and new-onset atrial fibrillation however was also associated with an increased need for permanent pacemaker implantation, vascular complications, and paravalvular leak which were significantly lower in the SAVR group. Interestingly, a significant long-term mortality benefit was found for TAVR in randomized trials within the transfemoral subgroup, $p = 0.001$ [17].

40.7 Remaining Questions

TAVR is the standard of care for high-risk or inoperable patients with symptomatic severe aortic stenosis and is now recommended in intermediate-risk patients as well. As indications widen to the lower-risk populations, remaining questions become ever more important to clarify.

Vascular complications, once the Achilles heel of the technology, are steadily decreasing with advances in transcatheter valve technology. They are however associated with significant morbidity and mortality as well as increased cost [18, 19]. The increased rates of new permanent pacemakers with TAVR vary according to the technology used but are a source of increased healthcare costs and clinical concern. Recent published work suggests that new pacemakers, although not associated with increased mortality do have an impact on increased incidence of heart failure hospitalizations and lack of improvement in left ventricular function post-intervention. Chanandi et al. performed a retrospective multicenter study to evaluate the incidence and outcomes of new permanent pacemaker implantation. In a population of over 1600 patients, approximately 20% required a new pacemaker within 30 days and up to 86% of these patients did require pacing. At follow-up, patients with new pacemaker had higher rates of rehospitalization due to heart failure (22.4% vs. 16.1%; adjusted HR 1.42; 95% CI 1.06–1.89; p 1/4 0.019) and the combined endpoint of mortality or heart failure rehospitalization (59.6% vs. 51.9%; adjusted HR 1.25; 95% CI 1.05 to 1.48; p 1/4 0.011). In addition, new pacemaker was associated with lesser improvement in LVEF over time (p 1/4 0.051 for changes in LVEF between groups), particularly in patients with reduced LVEF before TAVR (p 1/4 0.005 for changes in LVEF between groups) [20]. Further work will be required to determine whether in those patients that become pacemaker dependent if cardiac resynchronization therapy would be of potential benefit to reduce the incidence of heart failure.

The durability of transcatheter heart valves remains a question as experience is limited to the past 5–7 years. Issues regarding structural valve deterioration of both transcatheter and surgical valves are under scrutiny, and new definitions promise to create a more standardized approach to evaluation and follow-up [21]. It remains an important issue that will require rigorous follow-up however in the years to come.

40.8 Conclusions

Transcatheter aortic valve replacement has changed the treatment of aortic stenosis in those at high surgical risk, providing a less invasive treatment option with superior results. For those patients at intermediate surgical risk, TAVR is also now a non-inferior option. The pendulum is now swinging in the direction of the low-risk patient, and we anxiously await data in this population to fully comprehend the potential of this technology. Questions remain, and we must be vigilant to answer them in order to provide the best possible care for our patients.

References

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2017;70(2):252–89.
2. Vahanian A, Otto CM. Risk stratification of patients with aortic stenosis. Eur Heart J. 2010;31(4):416–23.
3. Otto CM, Kumbhani DJ, Alexander KP, Calhoon JH, Desai MY, Kaul S, et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology Task Force on clinical expert consensus documents. J Am Coll Cardiol. 2017;69(10):1313–46.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739–91.
5. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366(18):1696–704.
6. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014;63(19):1972–81.
7. Reardon MJ, Adams DH, Coselli JS, Deeb GM, Kleiman NS, Chetcuti S, et al. Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery. J Thorac Cardiovasc Surg. 2014;148(6):2869–76 e1-7.
8. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374(17):1609–20.
9. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376(14):1321–31.
10. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg. 2015;99(1):55–61.
11. Latib A, Maisano F, Bertoldi L, Giacomini A, Shannon J, Cioni M, et al. Transcatheter vs surgical aortic valve replacement in intermediate-surgical-risk patients with aortic stenosis: a propensity score-matched case-control study. Am Heart J. 2012;164(6):910–7.
12. Fraccaro C, Tarantini G, Rosato S, Tellaroli P, D'Errigo P, Tamburino C, et al. Early and midterm outcome of propensity-matched intermediate-risk patients aged >/=80 years with aortic stenosis undergoing surgical or transcatheter aortic valve replacement (from the Italian Multicenter OBSERVANT Study). Am J Cardiol. 2016;117(9):1494–501.
13. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J. 2016;37(28):2252–62.
14. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet. 2016;387(10034):2218–25.
15. Sondergaard L, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: the all-comers nordic aortic valve intervention randomized clinical trial. Circ Cardiovasc Interv. 2016;9(6):e003665.
16. Singh K, Carson K, Rashid MK, Jayasinghe R, AlQahtani A, Dick A, et al. Transcatheter aortic valve implantation in intermediate surgical risk patients with severe aortic stenosis: a systematic review and meta-analysis. Heart Lung Circ. 2018;27(2):227–34.
17. Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis. Ann Intern Med. 2016;165(5):334–44.
18. Genereux P, Cohen DJ, Mack M, Rodes-Cabau J, Yadav M, Xu K, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. J Am Coll Cardiol. 2014;64(24):2605–15.
19. Redfors B, Watson BM, McAndrew T, Palisaitis E, Francese DP, Razavi M, et al. Mortality, length of

stay, and cost implications of procedural bleeding after percutaneous interventions using large-bore catheters. JAMA Cardiol. 2017;2(7):798–802.
20. Chamandi C, Barbanti M, Munoz-Garcia A, Latib A, Nombela-Franco L, Gutierrez-Ibanez E, et al. Long-term outcomes in patients with new permanent pacemaker implantation following transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2018;11(3):301–10.
21. Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation. 2018;137(4):388–99.