Outcomes of Transcatheter Aortic Valve Implantation in Patients With Low Versus Intermediate to High Surgical Risk

Ariel Finkelstein, MD[a,1], Zach Rozenbaum, MD[a,1], Amir Halkin, MD[a], Shmuel Banai, MD[a], Samuel Bazan, MD[a], Israel Barbash, MD[b], Amit Segev, MD[b], Paul Fefer, MD[b], Elad Maor, MD[b], Haim Danenberg, MD[c], David Planner, MD[c], Katia Orvin, MD[d], Hana Vaknin Assa, MD[d], Abid Assali, MD[d], Ran Kornowski, MD[d], and Arie Steinvil, MD[a,*]

Referral of low surgical risk (LSR) patients for transcatheter aortic valve implantation (TAVI) becomes common in multiple tertiary centers, and clinical trial data for this population are not available to date. We performed a retrospective analysis on an Israeli multicenter registry. LSR and intermediate-high surgical risk (I-HSR) were defined by a Society of Thoracic Surgery score of <4% and ≥4%, respectively. The cohort included 2336 patients (LSR n = 1198, I-HLR n = 1138). As compared with LSR, patients with I-HSR were older and had significantly higher rates of baseline comorbidities. Although devices success rates (94% vs 96%), paravalvular leak (3.5% vs 5.2%), and permanent pacemaker implantation (17.2 vs 18%) were comparable (p >0.05 for all comparisons), the safety outcome at 1 month (12.7% vs 9.8%), procedural mortality (1.9% vs 0.6%), and mortality at 3 years (30.1% vs 16.1%) were higher in patients with I-HSR (p <0.05 for all comparisons). In a subanalysis of patients with very LSR, comparable rates of device success and safety outcomes were observed, whereas mortality at 1 to 3 years was lower. In conclusion, although procedural outcomes were comparable between LSR and I-HSR TAVI patients, the rates of short- and long-term mortality, as well as the safety outcome, were lower in LSR patients. **© 2018 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:644−649)**

Transcatheter aortic valve implantation (TAVI) is currently recommended in practice guidelines for patients who are at intermediate to high surgical risk (I-HSR) for surgical aortic valve replacement (SAVR).[1,2] Whereas ongoing randomized control trials aim to evaluate the safety and efficacy of TAVI in low surgical risk (LSR) patients[3,4] previous registry data and 1 multicenter randomized trial had already shown comparable outcomes between LSR and I-HSR patients who were referred to either TAVI or SAVR.[5−7] As the referral of LSR patients for TAVI becomes common in multiple tertiary centers, and until clinical trial data becomes available it is imperative to evaluate the outcomes of this procedure in LSR patients in clinical practice. The relatively high amount of patients in the current multicenter registry and the temporal trend for lower surgical risk TAVI candidates enabled us to perform more accurate and specific analyses. We therefore aim to compare the efficacy and safety of TAVI in LSR versus I-HSR patients. In addition, in order to evaluate whether a reduced surgical risk results in better patients outcomes, we further analyze our data in a subset of patients defined as very LSR (VLSR).

Methods

The study was based on a retrospective analysis of an Israeli multicenter registry comprised of 4 tertiary centers.[6,8,9] Patients who underwent TAVI between 2009 and 2016 were grouped according to preprocedural surgical risk. Parameters influencing decision of the Heart Team were left to the discretion at each center in accordance to practice guidelines published at the time of procedure.[1,2] LSR was defined a Society of Thoracic Surgery (STS) score of <f. I-HSR was defined as a STS score of 4 and above. Further division of LSR patients was set according to classification and regression trees (CART) modeling with 1 month mortality as the dependent variable.[10] The CART algorithm is a type of recursive partitioning which enables classification of cohorts into categories of a predefined risk. The algorithm is meant to maximize sensitivity and specificity, thereafter providing dichotomous splits. The dichotomous splits enable to create an output which consists of a decision tree with apt cut points.

Patients included in the registry had severe aortic stenosis, defined by echocardiography and practice guidelines

[a]The Cardiology Department, Tel Aviv Sourasky Medical Center, Israel, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [b]Leviev Heart Center, Chaim Sheba Medical Center, Ramat Gan, Israel, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [c]The Cardiology Department, Hadassah Medical Center, Jerusalem, affiliated to the Hebrew University of Jerusalem, Jerusalem, Israel; and [d]The Cardiology Department, Rabin Medical Center, Petach Tikva, Israel, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.. Manuscript received September 19, 2018; revised manuscript received and accepted November 15, 2018.

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[1]Dr. Ariel Finkelstein and Dr. Zach Rozenbaum equally contributed to the study.

*Corresponding author: Tel: +97236973332.

E-mail address: arikst@tlvmc.gov.il (A. Steinvil).

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(valvular orifice area <1.0 cm^2 or <0.6 cm^2/m^2 and/or a mean transaortic valvular gradient >40 mm Hg and/or jet velocity >4.0 m/s).[1,2] Patients who were included underwent a thorough baseline assessment process. Data regarding laboratory tests, calculation of the STS score predicted risk of mortality (STS-PROM) were collected, in addition to history-taking, physical examination, and a comprehensive echocardiographic assessment. All collected data were pooled into a dedicated multicenter database.

The analysis outcome measures were defined according to the Valve Academic Research Consortium-2 (VARC-2)[11] consensus definitions. In brief, device success was defined according to procedural mortality, correct positioning of the valve, mean aortic valve gradient <20 mm Hg, or peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation. The safety outcome at 30 days was defined as a composite of all-cause mortality, stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure. Other complications during hospitalization were noted. Mortality data were retrieved for all patients from the Israeli Ministry of Health via identification number.

All procedural aspects including valve selection, anesthesia, and access site were determined by operator discretion and were based on clinical, anatomical, and angiographic characteristics. Access routes for TAVI included transfemoral, transapical, transaxillary, or direct aortic approach. By default, the transfemoral access was preferred in all centers, providing anatomic limitations were not present.

Categorical variables were reported as numbers and percentages, and continuous variables were reported as mean and standard deviation (SD) or as medians and interquartile range (IQR). Continuous variables were tested for normal distribution using histograms and Q-Q plots. Continuous variables were compared between groups using independent samples *t* test or Mann-Whitney test and categorical variables were compared using Pearson's chi-test or Fisher's exact test. CART models were used to define VLSR patients. Kaplan-Meier survival curves with the Mantel-Haenszel log-rank test was used to compare survival. A two tailed p value ≤0.05 was considered as statistically significant. All statistical analyses were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

The study population included 2336 patients at a median age of 83 years (IQR 79 to 87), 55% females. The median STS score for mortality of 1198 patients at LSR was 2%, and 6% for 1138 at I-HSR. The mean STS score along the study period dropped significantly from 7.4 in 2009 to 4.1 in 2017 ($p < 0.001$ for trend). As compared with LSR, I-HSR patients had significantly higher rates of baseline comorbidities and were more likely to be frail. LSR patients were less likely to present with classic symptoms (effort angina pectoris and dyspnea). A detailed description of baseline characteristics is presented in Table 1.

Table 1.
Baseline characteristics according to preprocedural risk assessment

Variable	High-risk patients (STS ≥4) (n = 1138)	Low-risk patients (STS <4) (n = 1198)	p Value
STS mortality (%)	6 (5-9)	2 (1-3)	<0.001
Age (years)	85 (81-88)	81 (77-85)	<0.001
Women	60%	51%	<0.001
BMI >25 (kg/m^2)	56%	71%	<0.001
Prior thoracotomy	22%	13%	<0.001
Ischemic heart disease	57%	50%	0.001
Systolic dysfunction	21.5%	14.4%	<0.001
Atrial fibrillation	34%	26%	<0.001
Pacemaker/ICD	11%	11%	0.903
Diabetes mellitus	44%	32%	<0.001
Hyperlipidemia	80%	76%	0.016
Hypertension	89%	85%	0.003
CVA/TIA	17%	13%	0.003
Peripheral vascular disease	18%	8%	<0.001
Porcelain aorta	5%	5%	0.619
COPD	21%	11%	<0.001
Renal dysfunction eGFR <60 ml/min/1.73m^2)	86%	63%	<0.001
Dialysis	4.1%	0.2%	<0.001
Liver disease	0.6%	1.3%	0.206
Prior malignancy	12%	13%	0.293
Frailty	31%	18%	<0.001
LBBB	10.7%	8.4%	0.094
RBBB	11.6%	11.3%	0.808
Symptom at presentation			
Syncope	9%	8%	0.404
Effort angina pectoris	21%	15%	0.007
Effort dyspnea	83%	69v	<0.001

LSR patients had higher preprocedural aortic valve gradients compared with patients with I-HSR and higher ejection fraction. I-HSR patients had higher rates of preprocedural mitral regurgitation, tricuspid regurgitation, and higher systolic pulmonary artery pressures compared with LSR. Other echocardiographic parameters are presented in Table 2.

Procedural characteristics are presented Table 3. The femoral approach was more likely to be used in LSR patients compared with I-HSR patients. As compared with LSR, urgent TAVI was performed more often in I-HSR patients.

Procedural outcomes are presented in Table 4 and Figure 1. Device success was comparable between the groups. However, procedural mortality (Figure 1) was higher in I-HSR, as well as the 1-month safety outcome. In addition, acute kidney injury and the need for dialysis were more prevalent in in I-HSR patients. Length of stay in the cardiac intensive care unit and the length of hospitalization were longer for I-HSR patients. Mortality differed between the groups as well. Rates of 1, 2, and 3-year mortality were higher for I-HSR ($p < 0.001$ for all).

Following CART modeling an STS score of 2.7% further divided the LSR group into groups: group 1 and group 2 that were defined by and STS score of <2.7 and ≥2.7, respectively (group 1 n = 529; group 2 n = 669). Rate of device success and safety outcome at 1 month were comparable for patients with between these 2 groups. Outcomes which were

Table 2.
Echocardiographic characteristics according to preprocedural risk assessment

Variable	High-risk patients (STS ≥4) (n = 1138)	Low-risk patients (STS <4) (n = 1198)	p Value
	Baseline echocardiography		
Aortic valve peak pressure (mm Hg)	70 (57-86)	73 (60-89)	0.002
Aortic valve mean pressure (mm Hg)	43 (34-55)	45 (37-56)	0.005
Aortic valve area (cm^2)	0.7 (0.5-0.8)	0.7 (0.6-0.8)	<0.001
Ejection fraction (%)	50 (50-60)	60 (55-60)	<0.001
Diastolic dysfunction grade ≥2	19.2%	19.9%	0.819
Mitral regurgitation ≥moderate	15.9%	8.3%	<0.001
Tricuspid regurgitation ≥moderate	14.8%	8.6%	<0.001
Right ventricle dysfunction ≥moderate	3.9%	2.5%	0.246
Systolic pulmonary artery pressure (mm Hg)	41 (32-53)	37 (29-47)	<0.001
Left ventricle end diastolic diameter (mm)	46 (42-51)	46 (42-51)	0.464
Left ventricle end systolic diameter (mm)	29 (25-35)	28 (25-33)	0.025
Interventricular septal diameter (mm)	13 (12-14)	13 (12-14)	0.582
Posterior wall thickness (mm)	11 (10-12)	11 (10-12)	0.174
Left ventricular outflow tract diameter (mm)	20 (19-22)	21 (19-22)	0.125
Left atrial diameter (mm)	44 (40-49)	44 (40-48)	0.023
Left atrial area (cm^2)	24 (21-28)	23 (21-27)	
	Echocardiography at 1 month		
	n = 53	n = 231	
Aortic valve peak pressure (mm Hg)	13 (10-18)	14 (11-20)	0.002
Aortic valve mean pressure (mm Hg)	7 (5-10)	8 (6-11)	0.001
Ejection fraction (%)	60 (50-60)	60 (55-60)	<0.001
Systolic dysfunction (%)	16	9	0.001
Delta mitral regurgitation grade	0 (-1-0)	0 (0-0)	0.048
Systolic pulmonary artery pressure (mm Hg)	35 (25-45)	33 (26-42)	0.208
Left ventricle end diastolic diameter (mm)	45 (41-50)	28 (25-33)	0.756
Left ventricle end systolic diameter (mm)	46 (42-50)	28 (24-32)	0.014
Left atrial diameter (mm)	43 (39-48)	43 (39-46)	0.054
Left atrial area (cm^2)	24 (21-28)	23 (21-27)	0.474

Table 3.
Procedural characteristics according to preprocedural risk assessment

Variable	High-risk patients (STS ≥4) (n = 1138)	Low-risk patients (STS <4) (n = 1198)	p Value
Procedure time frame	2009-2016	2009-2016	
General anesthesia	42%	40%	0.282
Femoral access	87%	95%	<0.001
Urgent procedure	5.4%	2.5%	0.001
Valve size, mm			
23	19%	13%	0.004
25	0.5%	1.5%	
26	48%	42%	
27	0.5%	0.5%	
29	30%	41%	
31	2%	1.5%	
New generation valves	31.1%	20.9%	<0.001
S3	5%	9%	
XT	28%	23%	
Corevalve	50%	42%	
Evolut-R	16%	22%	
Other	1%	4%	
Predilatation	62.4%	63.1%	0.707
Postdilatation	15.2%	17.1%	0.205
Contrast volumes	152 (112-196)	155 (125-197)	0.023
Fluoroscopy time	17 (14-22)	16 (13-21)	0.016
Paravalvular leak ≥moderate per angiography	1.7%	2%	0.701

less prevalent in patients with very VLSR (group 1) were acute kidney injury, length of hospitalization, and mortality. Table 5 presents additional comparisons between these 2 groups.

Discussion

The present results demonstrate comparable procedural outcomes between LSR and I-HSR patients referred to TAVI in a large multicenter registry. Although the safety outcome was more frequent in I-HSR patients, its components were comparable between groups. Procedural mortality was lower in patients with LSR; however, at 1-month mortality rates did not differ significantly according to STS score. In addition, there was no difference in device success and the safety outcome between patients within the low-risk subgroups. Our findings support the notion that early procedural outcomes are similar across surgical risk groups. Long-term outcomes and mortality may be affected by the baseline individual clinical characteristics and surgical risk. The results are in line with international clinical trends in TAVI of divergence toward lower surgical risk patients.

A high proportion of low-risk TAVI patients was observed in the present analysis. As clinical real-life practice often exceeds practice guidelines based on delay from trial data to guidelines publications, physician experience and patient's choice, a clear trend toward treatment of lower STS populations was observed in our cohort. Similar

Table 4.
Outcomes and complications according to preprocedural risk assessment

Variable	High-risk patients (STS ≥4) (n = 1138)	Low-risk patients (STS <4) (n = 1198)	p Value
Device success	94%	96%	0.379
Valve malposition	2.1%	3.2%	0.248
Procedural mortality	1.9%	0.6%	0.003
Mean aortic valve gradient >20 mm Hg or peak velocity >3 m/s	0%	0%	n/a
Paravalvular leak ≥moderate per echo post procedure, %	3.5%	5.2%	0.057
Safety outcome at 1 month	12.7%	9.8%	0.032
Mortality	3.9%	1.9%	0.378
Stroke	2.5%	1.9%	0.378
Life-threatening bleeding	2.1%	2.3%	0.811
Acute kidney injury stage 2 or 3	2.6%	2.3%	0.622
Coronary artery obstruction requiring intervention	0.7%	0.4%	0.513
Major vascular complication	4.7%	4.2%	0.568
Valve-related dysfunction requiring repeat procedure	3.5%	3.3%	0.792
Other in-hospital complications			
Conversion to surgery	0.4%	0.5%	>0.999
Septal perforation	0.1%	0%	0.434
Mitral apparatus damage	0.1%	0.2%	>0.999
Tamponade	1.3%	2%	0.204
Annular rapture	0.2%	0.5%	0.654
Valve migration	1.9%	2.1%	0.688
Procedure CPR	2.6%	1.6%	0.381
Procedure VT/VF	1%	0.4%	0.272
Periprocedural (72 hours) myocardial infarction	1.3%	0.6%	0.12
In hospital bleeding			
Minor	4.5%	4.9%	0.901
Major	6%	5.8%	
New postprocedure LBBB	24.4%	27%	0.169
Permanent pacemaker implantation	17.2%	18%	0.616
New atrial fibrillation	6.7%	6.2%	0.7
Infection	9.3%	6.3%	0.017
Heart failure post procedure	6.1%	5.6%	0.667
Acute kidney injury (any)	15.2%	11%	0.002
Dialysis	1.3%	0.1%	0.002
Length of stay, days			
CICU	1(1-3)	1(1-2)	<0.001
Hospitalization	5(4-7)	5(4-6)	<0.001
Long-term mortality			
1-year mortality	14.5%	6.9%	<0.001
2-year mortality	20.7%	12.2%	<0.001
3-year mortality	30.1%	16.1%	<0.001

trends have been seen in previous real-life reports[12] even before intermediate risk trials have been published,[13,14] or the eventual publication of the clinical studies which include lower-risk patients.[3,4] In pivotal TAVI trials, the mean STS score was 4.5%[13] and 5.8%.[14] Over 70% of patients had an STS score ≤5%, and >15% with had an STS score of <3%.[13] In a second trial, 81.3% of patients had a score in 4.0% and 8.0%, whereas 6.7% of the patients had an STS score ≤4.0%.[14] Notable outcomes in the present study aside from those which were mentioned above, were renal failure, need for dialysis, length of hospitalization, length of stay in the cardiac intensive care unit, and long-term mortality. Patients at LSR demonstrated favorable rates in each of these outcomes. Patients at VLSR demonstrated even lower rates of each of these outcomes.

Currently, 4 trials are underway in the LSR patient population: PARTNER 3, Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients, NOTION 2, and the LRT study. Until results are published, available registry data have shown comparable outcomes for LSR patients referred for TAVI with matched patients who underwent SAVR.[5,15] In spite of these encouraging results, a recent meta-analysis[16] on 6 studies published between 2012 and 2017 revealed that short-term mortality after TAVR and SAVR was similar, but by 2 years the mortality rate was 17.2% for TAVR and 12.7% for SAVR.

We report lower prevalence of overall complications compared with the TAVI arm of previous trials.[17,18] Low surgical risk patients demonstrated low rates of permanent pacemaker (PPM) implantation (18%) as compared with other LSR TAVI reports: 34%,[5] 24%.[7] One possible mechanism for PPM implantation is pre-existing bundle branch block. However, multiple factors may also play a role.[19] The lower rate of PPM use may be a result of better patient selection, experience gained both by operators as well as EP consultants following the procedure, and the use of novel devices.[20,21] Additional differences in outcomes were life-threatening bleeding – 2.3% in the present cohort compared with 14.6%[7] and 4.4%,[18] paravalvular leak (PVL) 5.2% vs 10%[7] and 9.5%,[18] 1-month safety end point 9.8% vs 17.1%,[7] and 1-year mortality 6.9% vs 10.1%.[7] Of note, there was higher a trend for a higher proportion of patients with ≥moderate PVL in the low-risk cohort (5.2 vs 3.5%, p = 0.057). The gap may be explained by the differences in rates of implantation of newer generation valves, which were designed for lower risk of postprocedure PVL. Renal failure was more prevalent in our cohort: 2.3% compared with 0.7%[5] and 0%,[7] although a rate of 7.5% was also reported.[18] As expected, mechanical complications, such as valve malposition, coronary obstruction, septal perforation, mitral apparatus damage, stroke, and vascular complications, did not show a predilection according to preoperative surgical risk. Thus, a reduction in rates of such complications would not result from selection of lower risk candidates, but from operative and device improvement and innovations.

Several limitations should be regarded. The relatively long duration of the registry duration raises potentially 2 biases. First, outcome data is representative for both new and old generation valves. Moreover, newer valves which have not been used throughout the centers of the registry are available in some countries. Nevertheless, reported outcome rates are generally low even with the inclusion of old generation valves. Second, currently available risk scores, including the currently used STS score, have been originally proposed for patients undergoing surgery and not percutaneous interventions, and have not been validated statistically. A prominent discrepancy is the fact that included among patients who were considered low risk for surgery in our cohort were very elderly patients with co-morbidities and frailty characteristics. Nevertheless, currently there are no other universally used alternative risk scores available. Moreover, elderly patients with low surgical risk were presently shown to

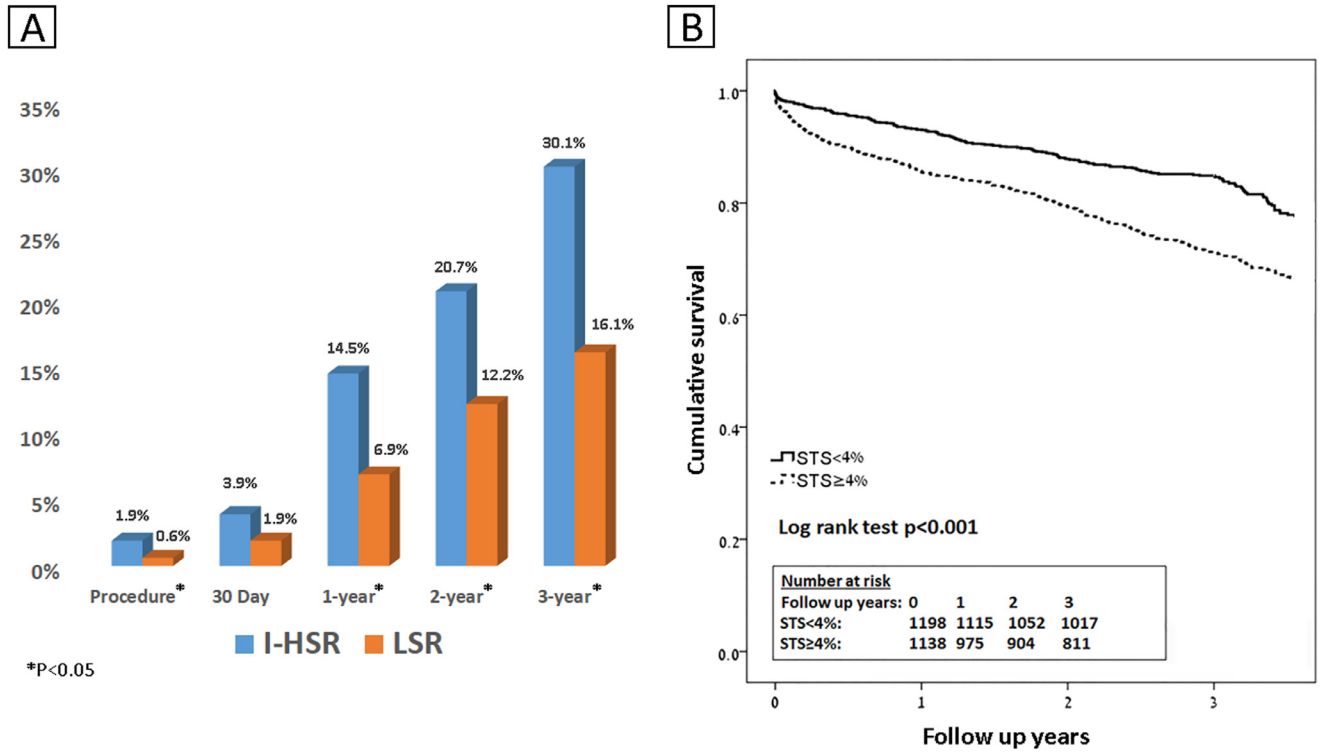

Figure 1. All-cause mortality following transcatheter aortic valve implantation in low versus intermediate to high surgical risk patients. *(A)* Time specific all-cause mortality rates following transcatheter aortic valve implantation (TAVI) in univariate models for low surgical risk (LSR, defined as STS score<4%), versus intermediate to high surgical (I-HSR, defined as STS≥4%). *(B)* Kaplan-Meyer curve for cumulative survival following TAVI in LSR versus I-HSR patients.

benefit from TAVI. However, the question of whether low risk younger patients are appropriate candidates for TAVI remains unanswered. A decision for treatment strategy in such patients should require a comprehensive discussion with the patient on the potential limitations. The possibility for the need of repeated valve-in-valve procedure or future surgical repair should be acknowledged.[22] Third, our analysis is also limited by the definition of low-risk TAVI. The STS score alone does not truly reflect the true TAVI risk,[9] as is was not formulated for TAVI patients and neglect multiple unknown factors in this population (frailty, bundle block, LV remodeling, etc.). Fourth, operator experience is changing throughout the time frame. Additionally, follow-up was available up to 3 years. Valve durability is a matter of concern in the long term of TAVI patients, especially among those with longer life expectancy as expected with low surgical risk patients. Finally, although data were collected prospectively, analyses were performed retrospectively, which may be a source of bias.

Table 5.
Outcomes and complications for patients with low and very low according to surgical 1 month mortality risk

Variable	Low-risk patients (STS 2.7-4) n = 669	Very low risk† patients (STS<2.7) n = 529	p Value
Device success	97%	96%	0.289
Safety outcome at 1 month	10.3%	9.4%	0.602
Paravalvular leak ≥moderate (per echo post procedure)	5.7%	4.6%	0.429
In-hospital stroke	1.9%	2%	0.828
Life-threatening bleeding	2.6%	1.8%	0.372
Major vascular complication	4%	4.4%	0.736
Permanent pacemaker implantation	16.6%	19.7%	0.169
Acute kidney injury (any)	13.1%	8.3%	0.009
Procedural mortality	0.9%	0.2%	0.135
1-month mortality	2.6%	1.1%	0.059
1-year mortality	8.6%	5%	0.014
2-year mortality	14.2%	9.7%	0.017
3-year mortality	19%	12.7%	0.003
CICU length of stay, days	1 (1-2)	1 (1-2)	0.658
Hospitalization length of stay, days	5 (4-6)	4 (3-6)	0.029

† According to CART analysis.

Conflict of interest

Prof. Ariel Finkelstein receives proctor fees from Medtronic and Edwards life-sciences.

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