Journal of the American Heart Association

ORIGINAL RESEARCH

Age-Related Outcomes of Valve-in-Valve Transcatheter Aortic Valve Replacement for Structural Valve Deterioration

Takashi Nagasaka, MD; Vivek Patel, MS; Kazuki Suruga, MD; Alon Shechter, MD, MHA; Ofir Koren, MD; Tarun Chakravarty, MD; Wen Cheng, MD; Hideki Ishii, MD; Hasan Jilaihawi, MD; Mamoo Nakamura, MD; Raj R. Makkar, MD

BACKGROUND: Valve-in-valve transcatheter aortic valve replacement (TAVR) is a recognized alternative for treating the structural valve deterioration of bioprosthetic valves. Recent guidelines and trials have expanded the indications for TAVR to include younger patients with structural valve deterioration. In this study, we aimed to examine the outcomes of valve-in-valve TAVR across different age groups to understand the age-related clinical outcomes of treating structural valve deterioration following surgical aortic valve replacement and TAVR.

METHODS AND RESULTS: In this retrospective study, we included patients who underwent valve-in-valve TAVR at our center. We compared procedural complications and clinical outcomes among patients <75 years of age (n=99), those 75 to 84 years of age (n=103), and those ≥85 years of age (n=71). Echocardiography and computed tomography were used for follow-up evaluations. This study included 273 patients and revealed a low in-hospital complication rate across all age groups. Although the 3-year risk of all-cause mortality was higher in patients >85 years of age, no significant differences in the incidence of stroke/transient ischemic attack were observed among age groups. All groups exhibited significant improvements in valve hemodynamics that persisted for 3 years. Although leaflet thrombosis assessed using computed tomography imaging 30 days post-TAVR was more prevalent in the older group, age was not an independent predictor of this outcome.

CONCLUSIONS: Valve-in-valve TAVR was associated with an increased 3-year mortality risk among older patients despite consistent hemodynamic benefits across all age groups. Age-related differences in leaflet thrombosis did not predict hypoattenuated leaflet thickening, indicating that further studies are necessary to elucidate its implications.

Key Words: aortic valve ■ functional status ■ heart valve prosthesis ■ hemodynamics ■ transcatheter aortic valve replacement

Valve-in-valve (ViV) transcatheter aortic valve replacement (TAVR) has emerged as an effective alternative to repeat surgical aortic valve replacement (SAVR) for treating the structural valve deterioration (SVD) of bioprosthetic valves. ViV-TAVR reportedly yields more favorable outcomes than repeat SAVR.[1–3] Although SVD is a considerable concern post-SAVR, the use of bioprosthetic valves is becoming increasingly prevalent among patients <60 years of age in the United States and Europe, primarily to avoid the need for lifelong anticoagulation treatment.[4–6] Notably, although the 2014 American Heart Association/American College of Cardiology guidelines recommended mechanical valves for patients <60 years of age,[7] the 2020 update shifted this recommendation to patients <50 years of age.[8] Moreover, the PARTNER

Correspondence to: Mamoo Nakamura, MD, Cedars-Sinai Medical Center Smidt Heart Institute, 127 S. San Vicente Boulevard, Advanced Health Sciences Pavilion, Third Floor, Suite A3100, Los Angeles, CA 90048. Email: mamoo.nakamura@cshs.org

This article was sent to Nadia R. Sutton, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.037168

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Among patients undergoing valve-in-valve transcatheter aortic valve replacement, those ≥85 years of age exhibited higher 3-year all-cause mortality compared with younger patients, although age was not a significant predictor of hypoattenuated leaflet thickening.
- Improvements in functional status and hemodynamic performance after valve-in-valve transcatheter aortic valve replacement were evident across all age cohorts and persisted for the 3-year follow-up, reinforcing the procedure's value in enhancing quality of life.

What Are the Clinical Implications?

- This study highlights the need for careful patient selection and individualized risk assessment in older patients undergoing valve-in-valve transcatheter aortic valve replacement, while emphasizing the sustained hemodynamic and functional benefits of the procedure across all age groups.

Nonstandard Abbreviations and Acronyms

HALT	hypoattenuated leaflet thickening
HAM	hypoattenuation affecting motion
SAVR	surgical aortic valve replacement
STS	Society of Thoracic Surgeons
SVD	structural valve deterioration
TAVR	transcatheter aortic valve replacement
THV	transcatheter heart valve
ViV	valve-in-valve

3 (Placement of Aortic Transcatheter Valves 3) trial demonstrated lower rates of all-cause mortality, disabling stroke, and rehospitalization among low-risk patients with severe symptomatic aortic stenosis who underwent TAVR than those among patients who underwent SAVR, potentially expanding TAVR indications to younger patients with aortic stenosis.[9]

Considering these trends, the demographic profile of patients eligible for ViV-TAVR for SVD after SAVR or TAVR is expected to broaden to include younger patients. Recognizing the importance of age-related clinical outcomes for patients undergoing ViV-TAVR is crucial, particularly for the treatment of SVD after SAVR or TAVR. Therefore, this study aimed to compare the outcomes of ViV-TAVR across different age groups.

METHODS

Study Design and Patient Population

This retrospective observational study was conducted at the Cedars-Sinai Medical Center. Overall, 313 consecutive patients ≥18 years of age underwent ViV-TAVR for SVD from April 2015 to February 2021. We maintained the specificity of our study outcomes by excluding patients who underwent TAVR concurrently with other heart valve interventions, thereby mitigating the effects of potential confounding factors. However, patients who underwent coronary revascularization procedures in conjunction with TAVR were considered eligible for inclusion. We categorized the patients into 3 age groups: <75 years of age, 75 to 84 years of age, and ≥85 years of age.

Data Follow-Up

Patient data were retrospectively obtained from an established interventional cardiology laboratory database, outpatient visits, and telephonic interviews. All of the patients underwent transthoracic echocardiography 30 days after the procedure as part of a standard valvular functional assessment. Subsequent transthoracic echocardiography was conducted at 1 and 3 years post-ViV-TAVR. This study adhered to the ethical standards of the Declaration of Helsinki (1975) and was approved by the institutional review board of Cedars-Sinai Medical Center. Informed consent was obtained from all of the patients. The data that support the findings of this study are available upon reasonable request from the corresponding author.

Procedural Details

The indications for ViV-TAVR were determined by a multidisciplinary heart team at the Cedars-Sinai Medical Center. The decision on the appropriate device and access site for each procedure was based on a thorough analysis of preprocedural images, including computed tomography (CT) and transesophageal echocardiographic images. All ViV-TAVR procedures were performed under general anesthesia and guided by fluoroscopy and echocardiography.

Outcomes

In this study, we evaluated the 3-year incidence of key clinical outcomes, with all-cause mortality as the primary outcome. Other outcomes were all-cause stroke (a composite of disabling or nondisabling stroke and transient ischemic attack), and a

composite outcome comprising all-cause mortality, all-cause stroke, reintervention, major bleeding, major vascular complications, new-onset atrial fibrillation, pacemaker implantation, and rehospitalization for heart failure. We also assessed in-hospital complications and clinical assessments, such as the New York Heart Association functional class, along with echocardiographic features, including valve hemodynamics and paravalvular leak. The assessment of clinical outcomes was based on the Valve Academic Research Consortium criteria.[10] Paravalvular leak severity was classified according to the recommended echocardiography criteria as none, trace, mild, moderate, or severe.[11]

Additionally, certain patients (n=137) underwent repeat CT examinations 30 days post-ViV-TAVR as part of the RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment With Anticoagulation) registry (NCT02318342). A 4-dimensional multidetector CT scan was performed to detect leaflet thrombosis after ViV-TAVR. Hypoattenuated leaflet thickening (HALT) was defined as an observable increase in leaflet thickness during diastole. In cases in which HALT was detected, a detailed assessment of leaflet motion was conducted using 4-dimensional multidetector CT. The reduction in the motion of each leaflet was evaluated using a multiphase, volume-rendered, en face cine projection. A reduction in a leaflet's motion >50% compared with the radius of the bioprosthetic frame was classified as a hypoattenuation affecting motion (HAM).

Statistical Analysis

Continuous variables are presented as mean±SD or median and interquartile range. Categorical variables are presented as frequency and percentage. One-way ANOVA was applied to normally distributed continuous data, whereas the Kruskal-Wallis method was used for nonnormally distributed continuous data. Categorical variables were assessed using the χ^2 test. Cumulative event rates were estimated using Kaplan-Meier survival analysis, and the log-rank test was used to compare the groups. Cox regression models were used to analyze clinical outcomes at 3 years across age categories, adjusting for Society of Thoracic Surgeons (STS) scores, $P2Y_{12}$-inhibitor use, and anticoagulant use. Logistic regression analysis was used to determine the predictors of HALT 30 days post-TAVR. The presented model consisted of the following variables: age, sex, redo transcatheter heart valve (THV) size, anticoagulation status, preprocedural left ventricular ejection fraction, and atrial fibrillation with their respective odds ratios (ORs) and 95% CIs. Two-sided *P* values <0.05 were considered statistically significant. All analyses were performed using SPSS (version 24.0; IBM) and R software (version 4.3.2; R Foundation for Statistical Computing).

RESULTS

Baseline Patient and Echocardiographic Characteristics

In this study, 273 patients were included: 99 (36.3%) <75 years of age, 103 (37.7%) 75 to 84 years of age, and 71 (26.0%) ≥85 years of age (Figure 1). The mean age of the participants was 76.3±11.9 years, of whom 56.8% were men (Table 1). Increased age was correlated with higher incidences of dyslipidemia, atrial fibrillation, coronary artery disease, and previous permanent pacemaker implantation. Older patients exhibited significantly higher STS scores, and older patients were more likely to be men. Conversely, the younger group had a higher body mass index and a more frequent occurrence of bicuspid aortic valves.

Procedural Data/In-Hospital Complications

The mean time since prior SAVR or TAVR was 8.61 years overall (Table 2). Overall, 262 patients (96.0%) underwent ViV-TAVR via the femoral approach, and 219 patients (80.2%) underwent ViV-TAVR with a balloon-expandable TAVR valve. Younger patients tended to require larger THVs. Additionally, the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique was used in 3 younger patients during ViV-TAVR. The length of hospital stay did not differ among the groups (*P*=0.37). The risk of in-hospital complications is presented in Table 3. The cumulative incidence of in-hospital complications did not differ among the 3 groups. No in-hospital deaths, infections, or cerebrovascular accidents were recorded.

Clinical Outcomes

In terms of the 3-year clinical outcomes among different age cohorts post-ViV-TAVR, a significantly elevated risk of all-cause mortality was observed in the older cohort, as evidenced by both the crude and adjusted hazard ratios, compared with that in the younger group (Table 4, Figure 2). No statistically significant difference was noted in the incidence of stroke/transient ischemic attacks among the age groups. Although the crude risk for valve reintervention seemed higher among older participants, the difference was not statistically significant before or after adjustment. Other outcomes, including permanent pacemaker implantation, major vascular complications, major bleeding, hospitalization due to heart failure, and new-onset atrial fibrillation,

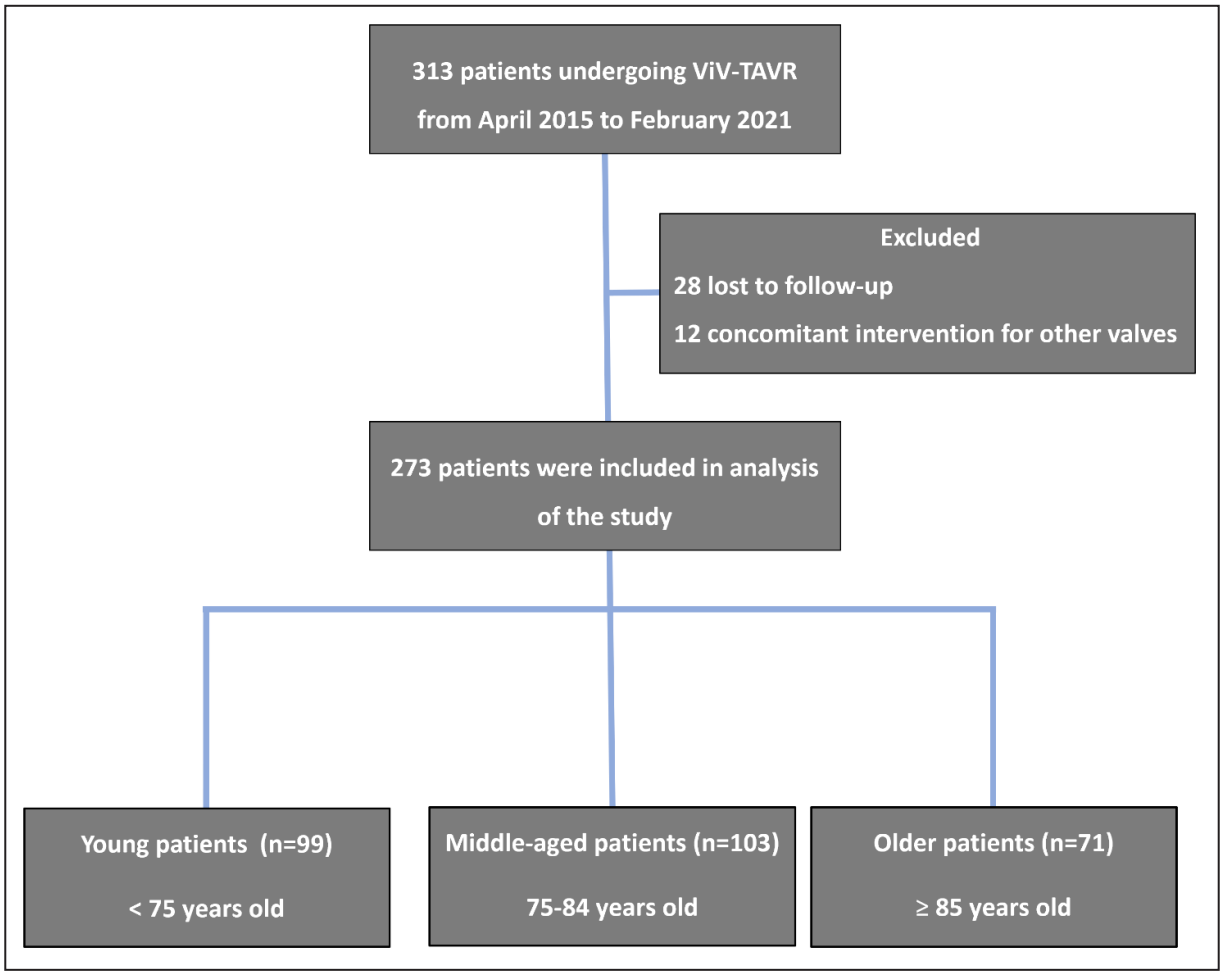

Figure 1. Study flowchart.
The total number of enrolled patients in the study and their inclusion and exclusion criteria are shown. ViV-TAVR indicates valve-in-valve transcatheter aortic valve replacement.

also did not exhibit statistically significant variations across age groups (Table S1).

Echocardiographic Follow-Up Data

Figure 3A illustrates that the mean aortic valve pressure gradient decreased significantly 30 days post-ViV-TAVR across all age groups compared with baseline. This improvement was maintained over the 3-year follow-up period, with no significant differences among the groups. Figure 3B reveals that the aortic valve area had significantly increased from baseline by 30 days, 1 year, and 3 years post-ViV-TAVR in all cohorts.

Assessment of Leaflet Thrombosis Via CT 30 Days Post-TAVR

Among patients with recorded CT data, HALT and HAM were assessed 30 days after TAVR (Figure 4). HALT was observed more frequently in the older group than in the middle-aged and younger groups (46.8% versus 28.8% versus 19.6%; P=0.004). Furthermore, the incidence of HAM was significantly higher in the older group than in the younger group (15.6% versus 5.3%; P=0.014). Upon multivariable logistic regression analysis, anticoagulation (OR, 0.24 [95% CI, 0.06–0.91]; P=0.036) was identified as a factor associated with HALT (Table 5). However, factors such as age (OR, 1.04 [95% CI, 0.99–1.08]; P=0.11) and aspirin use (OR, 1.13 [95% CI, 0.41–3.09]; P=0.81) were not independently associated with HALT.

DISCUSSION

In our study, we compared clinical outcomes following ViV-TAVR across predefined age groups. To the best of our knowledge, this is the first detailed comparison of clinical outcomes across different age groups among patients who underwent ViV-TAVR, including functional outcomes, echocardiographic findings, and follow-up CT imaging. Our major results were as

Table 1. Baseline Patient Characteristics Among Age Groups

		Age groups			
Characteristic	Overall, N=273*	Younger, n=99*	Middle-aged, n=103*	Older, n=71*	*P* value†
Age, y	76.29±11.88	63.84±9.69	79.65±2.89	88.79±3.15	<0.001
Sex, men	155 (56.8)	69 (69.7)	49 (47.6)	37 (52.1)	0.004
BMI, kg/m^2	26.65±6.83	27.83±6.23	27.17±8.31	24.24±4.24	<0.001
Hypertension	227 (83.2)	77 (77.8)	88 (85.4)	62 (87.3)	0.191
Hyperlipidemia	192 (70.3)	63 (63.6)	70 (68.0)	59 (83.1)	0.019
Prior CVA/TIA	53 (19.4)	18 (18.2)	22 (21.4)	13 (18.3)	0.819
Porcelain aorta	18 (6.6)	9 (9.1)	6 (5.8)	3 (4.2)	0.478
Smoker	57 (20.9)	23 (23.2)	24 (23.3)	10 (14.1)	0.262
Diabetes	53 (19.4)	18 (18.2)	27 (26.2)	8 (11.3)	0.046
Current dialysis	13 (4.8)	6 (6.1)	6 (5.8)	1 (1.4)	0.338
Chronic lung disease	45 (16.5)	14 (14.1)	17 (16.5)	14 (19.7)	0.627
Prior PAD	36 (13.2)	8 (8.1)	19 (18.4)	9 (12.7)	0.093
Previous PPI	48 (17.6)	8 (8.1)	22 (21.4)	18 (25.4)	0.006
Afib	91 (33.3)	22 (22.2)	40 (38.8)	29 (40.8)	0.013
CAD	122 (44.7)	35 (35.4)	47 (45.6)	40 (56.3)	0.024
Prior MI	31 (11.4)	8 (8.1)	12 (11.7)	11 (15.5)	0.321
CKD ≥III	62 (22.7)	20 (20.2)	18 (17.5)	24 (33.8)	0.031
Prior CABG	86 (31.5)	24 (24.2)	36 (35.0)	26 (36.6)	0.146
Prior PCI	45 (16.5)	15 (15.2)	18 (17.5)	12 (16.9)	0.914
NYHA class					0.975
1	0 (0)	0 (0)	0 (0)	0 (0)	
2	22 (8.1)	9 (9.1)	8 (7.8)	5 (7.0)	
3	147 (53.8)	53 (53.5)	54 (52.4)	40 (56.3)	
4	104 (38.1)	37 (37.4)	41 (39.8)	26 (36.6)	
NYHA class at 30 d					0.016
1	106 (38.8)	38 (38.4)	37 (35.9)	31 (43.7)	
2	118 (43.2)	51 (53.0)	43 (41.7)	24 (33.8)	
3	44 (16.1)	7 (7.1)	22 (21.4)	15 (21.1)	
4	2 (0.7)	0 (0)	1 (1.0)	1 (1.4)	
NYHA class at 1 y					0.063
1	85 (31.1)	32 (32.3)	31 (30.1)	22 (31.0)	
2	128 (46.9)	53 (53.5)	46 (44.7)	29 (40.8)	
3	46 (16.8)	7 (7.1)	22 (21.4)	17 (23.9)	
4	11 (4.0)	4 (4.0)	4 (3.9)	3 (4.2)	
NYHA class at 2 y					0.532
1	96 (35.2)	37 (37.4)	32 (31.1)	27 (38.0)	
2	115 (42.1)	43 (43.4)	47 (45.6)	25 (35.2)	
3	45 (16.5)	11 (11.1)	19 (18.4)	15 (21.1)	
4	14 (5.1)	5 (5.1)	5 (4.9)	4 (5.6)	
STS score	7.13±6.71	5.26±7.25	7.25±5.40	9.58±6.94	<0.001
Aspirin use (any)	173 (63.4)	61 (61.6)	65 (63.1)	47 (66.2)	0.827
$P2Y_{12}$ use (any)	60 (22.0)	13 (13.1)	28 (27.2)	19 (26.8)	0.029
Anticoagulant use	91 (33.3)	23 (23.2)	39 (37.9)	29 (40.8)	0.026
DOAC use	54 (19.8)	13 (13.1)	24 (23.2)	17 (23.9)	0.923
Bicuspid aortic valve	44 (16.1)	28 (28.3)	11 (10.7)	5 (7.0)	<0.001
Aortic insufficiency	57 (20.9)	19 (19.2)	21 (20.4)	17 (23.9)	0.760
Preoperative LVEF	55.10±14.49	52.85±15.68	55.89±14.41	57.08±12.52	0.144

(*Continued*)

Table 1. Continued

		Age groups			
Characteristic	Overall, N=273*	Younger, n=99*	Middle-aged, n=103*	Older, n=71*	*P* value†
Preoperative mean PG	52.86±25.81	54.20±26.83	51.06±25.73	53.60±24.63	0.602
Preoperative AVA, cm^3	0.76±0.29	0.77±0.35	0.76±0.25	0.73±0.25	0.648
Concomitant severe MR or TR	13 (4.8)	5 (5.1)	5 (4.9)	3 (4.2)	>0.999

Afib indicates atrial fibrillation; $P2Y_{12}$ indicates platelet receptor involved in ADP-mediated platelet activation and aggregation; AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; DOAC, direct oral anticoagulant; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PG, pressure gradient; PPI, permanent pacemaker implantation; STS, Society of Thoracic Surgeons; and TR, tricuspid regurgitation.

*Mean±SD or n (%).

†Kruskal-Wallis rank sum test, Pearson χ^2 test, or Fisher exact test.

follows: (1) In-hospital complications of ViV-TAVR were infrequent across all age cohorts. (2) Being ≥85 years of age was associated with a higher rate of all-cause mortality compared with being younger. (3) HALT and HAM 30 days after ViV-TAVR were observed more frequently in the older group than in the other 2 groups.

Table 2. Procedural Data of ViV-TAVR According to Age Groups

		Age groups			
Previous procedural data	Overall, N=273*	Younger, n=99*	Middle-aged, n=103*	Older, n=71*	*P* value†
Time from first SAVR/TAVR	8.61±4.66	9.18±4.93	8.19±5.02	8.41±3.60	0.157
First valve size (mm)	23.43±3.12	24.77±2.86	22.75±2.30	22.66±3.76	<0.001
TAVR devices					
Core valve	6 (2.2)	4 (4.0)	0 (0)	2 (2.8)	
Evolute Pro	8 (2.9)	2 (2.0)	4 (3.9)	2 (2.8)	
Evolute R	36 (13.2)	12 (12.1)	10 (9.7)	14 (19.7)	
Portico	2 (0.7)	1 (1.0)	1 (1.0)	0 (0)	
Resilia	1 (0.4)	0 (0)	0 (0)	1 (1.4)	
S3	117 (42.9)	47 (47.5)	45 (43.7)	25 (35.2)	
Sapien	6 (2.2)	1 (1.0)	1 (1.0)	4 (5.6)	
Ultra	43 (15.8)	16 (16.2)	17 (16.5)	10 (14.1)	
XT	54 (19.8)	16 (16.2)	25 (24.3)	13 (18.3)	
Approach					0.393
Femoral	262 (96.0)	93 (93.9)	100 (97.1)	69 (97.2)	
Carotid	1 (0.4)	0 (0)	0 (0)	1 (1.4)	
Subclavian	4 (1.5)	2 (2.0)	1 (1.0)	1 (1.4)	
Apical	6 (2.2)	4 (4.0)	2 (1.9)	0 (0)	
Balloon-expandable valve	219 (80.2)	79 (79.8)	88 (85.4)	52 (73.2)	0.138
THV size of ViV-TAVR (mm)	24.48±2.47	25.36±2.75	23.90±1.96	24.07±2.42	<0.001
Predilatation	20 (7.3)	6 (6.1)	11 (10.7)	3 (4.2)	0.229
Postdilatation	55 (20.1)	19 (19.2)	20 (19.4)	16 (22.5)	0.843
Cerebral embolic protection	58 (21.2)	20 (20.2)	26 (25.2)	12 (16.9)	0.397
Total amount of contrast (mL)	82.84±66.41	77.34±64.11	86.51±63.37	85.18±73.93	0.438
Total fluoroscopic time (min)	19.33±13.61	18.94±14.84	18.93±10.56	20.46±15.75	0.276
BASILICA	3 (1.1)	3 (3.0)	0 (0)	0 (0)	0.064
Concomitant PCI	39 (14.3)	9 (9.1)	19 (18.4)	11 (15.5)	0.155
LOH (d)	3.68±3.62	3.99±4.61	3.46±3.07	3.56±2.69	0.365

BASILICA indicates bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction; LOH, length of hospital stay; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve; and ViV-TAVR, valve-in-valve transcatheter aortic valve replacement.

*Mean±SD or n (%).

†Kruskal-Wallis rank sum test, Pearson χ^2 test, or Fisher exact test.

Table 3. In-Hospital Complications of Valve-in-Valve Transcatheter Aortic Valve Replacement Stratified by Age

In-Hospital complications of valve-in-valve transcatheter aortic valve replacement	Age groups			*P* value
	Younger, n=99	Middle-aged, n=103	Older, n=71	
Acute coronary obstruction	1 (1.0)	5 (4.9)	3 (4.2)	0.2
In-hospital AKI	2 (2.0)	0 (0)	0 (0)	NA
Cardiac arrest	2 (2.0)	1 (1.0)	3 (4.2)	0.5
In-hospital death	0 (0)	0 (0)	0 (0)	NA
CVA/TIA	0 (0)	0 (0)	0 (0)	NA
Infection	0 (0)	0 (0)	0 (0)	NA
Major bleeding	0 (0)	1 (1.0)	2 (2.8)	>0.9
Major vascular complications	4 (4.0)	4 (3.9)	3 (4.2)	0.8
Permanent pacemaker implantation	1 (1.0)	5 (4.9)	3 (4.2)	0.2
Cumulative outcomes	10 (10.1)	12 (11.7)	12 (16.9)	0.8

Data are expressed as n (%). AKI indicates acute kidney injury; CVA, cerebrovascular accident; NA, not applicable; TIA, transient ischemic attack.

However, multivariable analysis revealed that age was not a significant predictor of HALT.

In our cohort, 36.3% of the patients were <75 years of age, and the overall median age was younger than a real-world population of patients who underwent TAVR in a previous study.[12] In the PARTNER 2 (Placement of Aortic Transcatheter Valves 2) trial, the median age of patients with ViV-TAVR cases was lower than that of patients undergoing native TAVR, and the STS score of patients with ViV-TAVR was significantly higher than that of patients who underwent TAVR of the native aortic valve.[13] Our results support the understanding that, regardless of age, patients who have undergone prior SAVR or TAVR and are experiencing SVD have an elevated surgical risk, rendering them appropriate candidates for ViV-TAVR. Therefore, age-related outcomes in the ViV-TAVR cohort need to be studied, because they differ in terms of age distribution from patients undergoing native TAVR.

Few in-hospital complications occurred across all age groups compared with those in previous studies,[14,15] and hospital stays were shorter. We hypothesize that these favorable outcomes are related to the use of newer-generation devices, the transfemoral approach, and the experience of the operators. In regard to permanent pacemaker implantation after ViV-TAVR, results have been varied. In one study, the permanent pacemaker implantation rate was lower among such patients than that among patients undergoing native TAVR.[16] In contrast, Deharo et al reported that the rate of pacemaker implantation in the ViV-TAVR group was 18.4%, significantly higher than in the redo-SAVR group.[2] Nevertheless, the pacemaker implantation rate was low across all age groups in this study, potentially owing to the lower mean age and frequent use of balloon-expandable prosthetic valves.

Table 4. Clinical Outcomes 3 Years After Valve-in-Valve Transcatheter Aortic Valve Replacement

	Younger group	Middle-aged group, crude HR (95% CI)	*P* value	Middle-aged group, adjusted HR (95% CI)	*P* value	Older group, crude HR (95% CI)	*P* value	Older group, adjusted HR (95% CI)	*P* value
All-cause mortality	Reference	1.14 (0.51–2.55)	0.7	1.10 (0.49–2.47)	0.8	2.76 (1.32–5.76)	0.007	2.41 (1.17–5.12)	0.018
Stroke/TIA	Reference	NA	>0.9	NA	>0.9	1.84 (0.41–8.21)	0.4	2.53 (0.47–13.72)	0.3
Composite outcome	Reference	0.67 (0.39–1.16)	0.2	0.63 (0.37–1.10)	0.1	1.42 (0.85–2.37)	0.2	1.32 (0.72–2.22)	0.3
Valve reintervention	Reference	0.29 (0.06–1.43)	0.13	NA	>0.9	0.20 (0.04–1.05)	0.058	NA	>0.9
Permanent pacemaker implantation	Reference	0.9 (0.06–14.38)	>0.9	1.25 (0.07–21.58)	0.9	4.1 (0.43–39.41)	0.2	6.43 (0.57–72.01)	0.13
Major vascular complication	Reference	1.83 (0.17–20.21)	0.6	1.7 (0.14–20.12)	0.7	NA	>0.9	NA	>0.9
Major bleeding	Reference	0.58 (0.10–3.49)	0.6	0.53 (0.09–3.32)	0.5	0.98 (0.16–5.88)	>0.9	0.92 (0.14–5.89)	>0.9
Severe paravalvular leak	Reference	NA	>0.9	NA	>0.9	NA	>0.9	NA	>0.9
Hospitalization for heart failure	Reference	0.88 (0.25–3.03)	0.8	0.91 (0.25–3.28)	0.9	1.45 (0.42–5.02)	0.6	1.39 (0.39–5.01)	0.6
New onset of atrial fibrillation	Reference	1.74 (0.16–19.08)	0.7	1.69 (0.15–18.71)	0.7	NA	>0.9	NA	>0.9
Acute coronary syndrome	Reference	NA	>0.9	NA	>0.9	NA	>0.9	NA	>0.9

HR indicates hazard ratio; NA, not available; and TIA, transient ischemic attack.

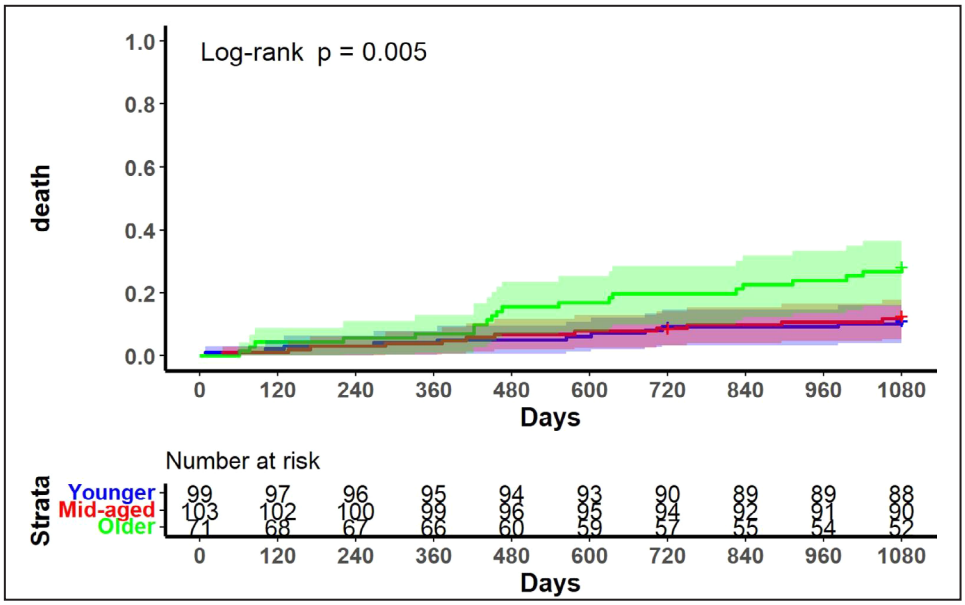

Figure 2. Age-related clinical outcome after valve-in-valve transcatheter aortic valve replacement.
Kaplan-Meier survival curves depicting the cumulative incidence of death over time for 3 age groups: younger (blue), middle-aged (red), and older (green). Shaded areas represent the 95% CIs for each group. The number at risk for each age group at different time points is shown below the *x* axis. The log-rank test indicates a significant difference between the groups (*P*=0.005).

Furthermore, coronary obstruction remains a serious concern in ViV-TAVR. However, recent studies have revealed a low incidence of 30-day myocardial infarction. In our study, coronary obstruction was observed in 8 patients (2.9%) during their hospital stay. Additionally, percutaneous coronary intervention was performed in conjunction with ViV-TAVR in 39 patients (14.3%), and the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique was used in 3 cases to mitigate the risk of coronary obstruction. These results revealed that appropriate analysis of preprocedural CT images may play a crucial role in predicting the coronary obstruction risk and accordingly determining the optimal management strategy. Further studies are warranted to explore the procedural electrocardiographic and CT data to identify the risk of in-hospital complications associated with ViV-TAVR.

Echocardiographic data revealed that ViV-TAVR significantly improved the hemodynamic status of all patients in this study, regardless of age. A trend toward implantation of larger THVs was observed in younger patients with larger body mass indices (Table 2). Notably, among older patients, despite the use of smaller THVs, significant improvements in both aortic valve pressure gradient and aortic valve area were evident after TAVR, persisting beyond 3 years. In the PARTNER 2 trial that included patients with STS scores similar to those of our patients, the 3-year echocardiographic follow-up of enrolled patients who underwent ViV-TAVR demonstrated excellent durability.[17] Our study similarly confirmed the favorable 3-year durability of ViV-TAVR across different age groups. Still, further research is warranted to thoroughly assess the long-term valve performance. In the present study, patients ≥85 years of age showed a higher all-cause mortality than in younger groups despite similar THV performance, which persisted even after adjusting for parameters such as the STS score. Perhaps this increased mortality risk is likely attributable to the presence of additional comorbidities, frailty, and other age-related conditions that are more prevalent in an older population.

Additionally, we investigated leaflet thrombosis 30 days after ViV-TAVR. Notably, 29.9% of patients had early HALT upon CT, which was higher than that previously reported.[18,19] ViV-TAVR was previously reported as likely associated with leaflet thrombosis.[20] A previous study reported that HALT may be more frequently observed with balloon-expandable valves, possibly due to their design and deployment mechanism.[21] In the current study, 219 patients (80.2%) underwent ViV-TAVR with a balloon-expandable TAVR valve, which might have contributed to the higher rate of early leaflet thrombosis. Despite this result, the overall stroke rate at 3 years was only 2.6%. In the present study, approximately 20% of patients undergoing ViV-TAVR were treated with cerebral embolic

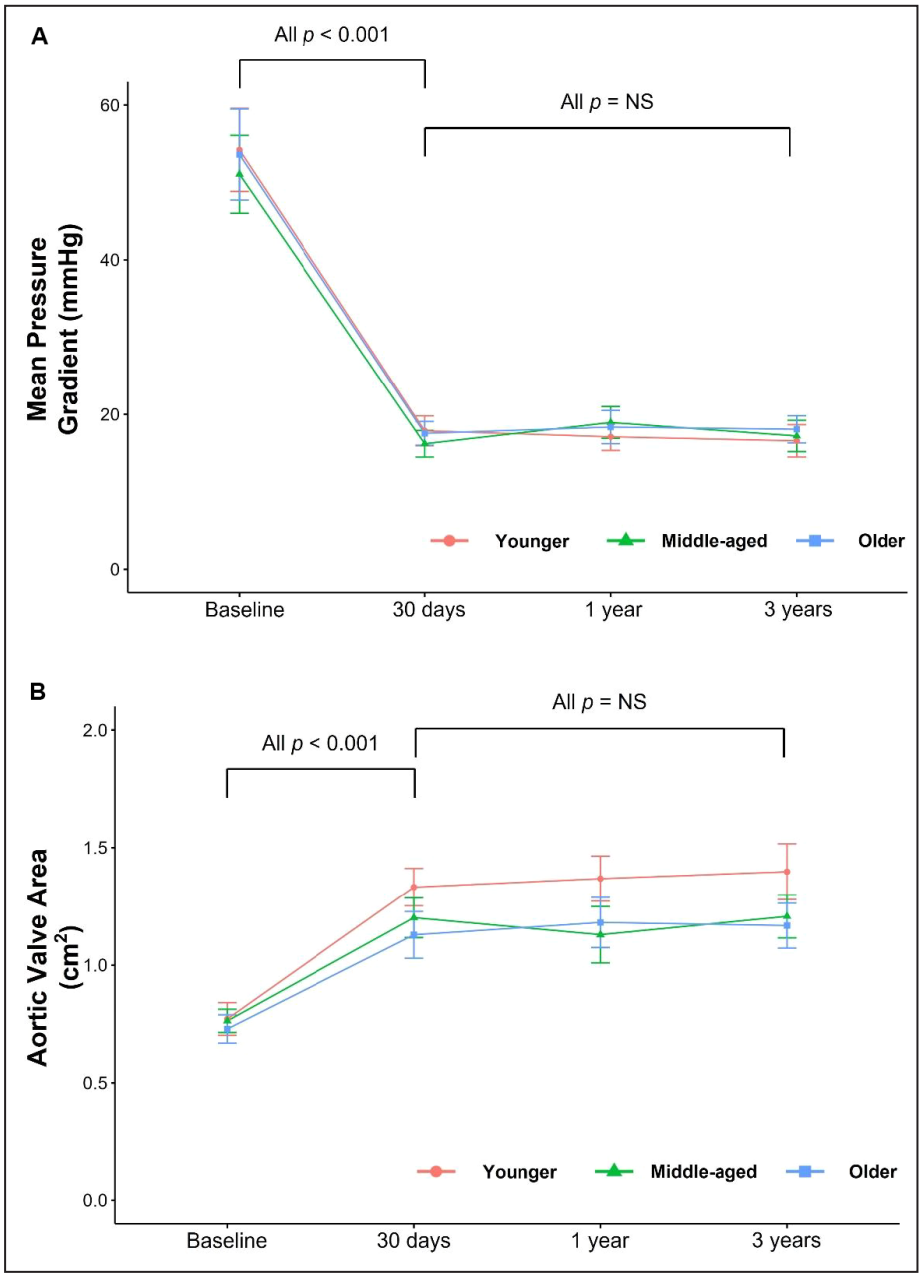

Figure 3. Echocardiographic data postprocedure during the follow-up period.
The figure illustrates the changes in mean pressure gradient (**A**) and aortic valve area (**B**) according to age groups from baseline to follow-up. NS indicates not significant.

protection. Considering its low usage rates and the ongoing debate on its usefulness, the specific contribution of cerebral embolic protection to the observed favorable outcomes remains uncertain. Nonetheless, an association between cerebral embolic protection use and reduced stroke rates has been reported in patients undergoing ViV-TAVR.[22] Further investigation is therefore warranted to determine the definitive benefits of cerebral embolic protection in this patient population. Moreover, our results revealed that HALT was not associated with cerebrovascular events, which is consistent with the results of previous studies.[23] HALT and HAM were significantly more frequently observed in the older group than among younger and middle-aged patients. However, after multivariable analysis, the use of anticoagulation therapy remained a significant factor but age did not. Therefore, the use of anticoagulation therapy may have a greater impact on thrombosis than age. However, the use of anticoagulation therapy to prevent HALT in patients

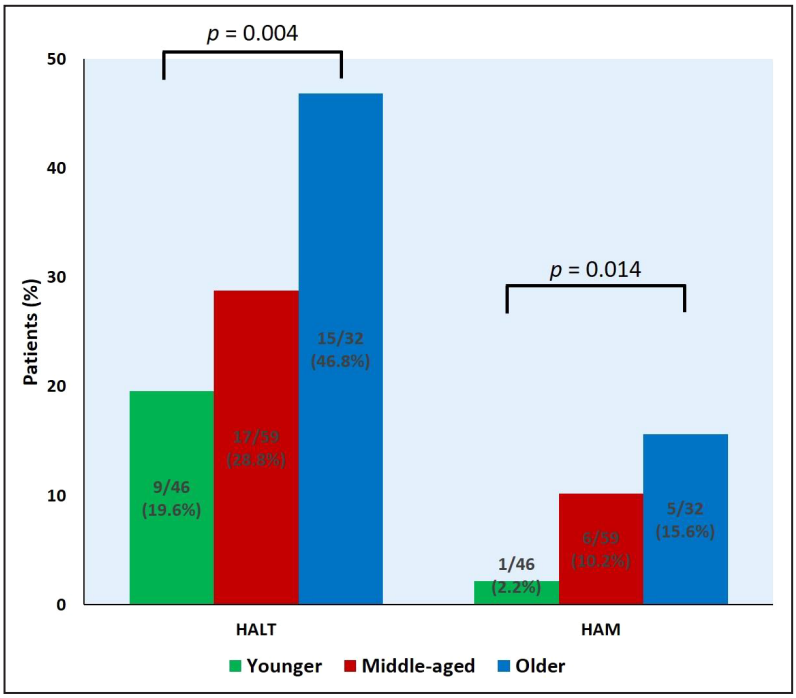

Figure 4. Evaluation of hypoattenuated leaflet thickening and hypoattenuation affecting motion.
The bar graphs show the assessment of hypoattenuated leaflet thickening and hypoattenuation affecting motion at 30 days after valve-in-valve transcatheter aortic valve replacement. HALT indicates hypoattenuated leaflet thickening; and HAM, hypoattenuation affecting motion.

post-ViV-TAVR remains controversial. In addition, the prognostic implications of HALT post-ViV-TAVR remain inadequately elucidated. Furthermore, factors such as optimal valve expansion and deployment technique may also contribute to HALT development. The decision to implement anticoagulation therapy is particularly critical for older patients and those with high bleeding risk. Thus, we believe the present study provides valuable insights by presenting age-stratified outcomes of ViV-TAVR and HALT incidence.

Table 5. Multivariable Predictors of Leaflet Thrombosis After ViV-TAVR

Multivariable predictors of leaflet thrombosis after ViV-TAVR	Univariable model		Multivariable model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.02 (0.98–1.06)	0.23	1.04 (0.99–1.08)	0.11
Male sex	0.91 (0.44–1.91)	0.81	1.46 (0.61–3.53)	0.4
BMI	0.97 (0.91–1.03)	0.34		
Hypertension	2.06 (0.82–5.18)	0.13		
Diabetes	2.02 (0.7–5.78)	0.19		
Prior CVA/TIA	0.61 (0.23–1.65)	0.33		
Prior atrial fibrillation	0.26 (0.1–0.68)	0.006	0.5 (0.16–1.57)	0.24
CKD	2.34 (0.64–8.59)	0.2		
Aspirin use	0.42 (0.18–1.02)	0.054	1.13 (0.41–3.09)	0.81
Anticoagulant use	0.17 (0.057–0.52)	0.002	0.24 (0.06–0.91)	0.036
LVEF, per 10% increase	1.01 (0.98–1.04)	0.51		
THV size (ViV-TAVR)	0.98 (0.85–1.14)	0.82		

BMI indicates body mass index; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; LVEF, left ventricular ejection fraction; OR, odds ratio; THV, transcatheter heart valve; and ViV-TAVR, valve-in-valve transcatheter aortic valve replacement.

Limitations

This study has several limitations. First, it was a single-center study with a relatively small sample, which might have limited the generalizability of the results. Second, the retrospective and observational design of the study introduced the possibility of selection bias for the ViV-TAVR procedure. Although a multivariable analysis was conducted to adjust for confounding factors, we might not have adjusted for all potential factors that affected clinical outcomes. Moreover, certain patient characteristics, such as frailty or anatomical constraints, might have precluded the feasibility of ViV-TAVR in some cases. Third, our study's follow-up duration was relatively long at 3 years; however, a longer follow-up period is necessary to discern the outcomes more accurately across different age groups. Fourth, there was a potential bias, because only a subset of patients underwent postprocedural CT as part of the RESOLVE study, which might have affected the assessment of leaflet thrombosis and other related outcomes.

CONCLUSIONS

Our study indicates that patients ≥85 years of age who underwent ViV-TAVR had an increased risk of all-cause mortality over the next 3 years compared with their younger counterparts. Improvements in functional status and hemodynamic performance post-ViV-TAVR were evident across all age cohorts and persisted for the 3 years of follow-up. Age did not emerge as a significant predictor of HALT among the population of patients undergoing ViV-TAVR.

ARTICLE INFORMATION

Received June 18, 2024; accepted December 31, 2024.

Affiliations

Cedars-Sinai Medical Center, Smidt Heart Institute, Los Angeles, CA (T.N., V.P., K.S., A.S., O.K., T.C., W.C., H.J., M.N., R.R.M.); Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan (T.N., H.I.); Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (A.S.); and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel (O.K.).

Sources of Funding

None.

Disclosures

Dr Makkar received grant support from Edwards Lifesciences; he is a consultant for Abbott Vascular, Cordis, and Medtronic and holds equity in Entourage Medical. Dr Chakravarty is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic; he is a consultant for Abbott Lifesciences and a consultant and speaker for Boston Scientific. The remaining authors have no disclosures to report.

Supplemental Material

Table S1

REFERENCES

1. Spaziano M, Mylotte D, Thériault-Lauzier P, De Backer O, Søndergaard L, Bosmans J, Debry N, Modine T, Barbanti M, Tamburino C, et al. Transcatheter aortic valve implantation versus redo surgery for failing surgical aortic bioprostheses: a multicentre propensity score analysis. *EuroIntervention*. 2017;13:1149–1156. doi: 10.4244/EIJ-D-16-00303
2. Deharo P, Bisson A, Herbert J, Lacour T, Etienne CS, Porto A, Theron A, Collart F, Bourguignon T, Cuisset T, et al. Transcatheter valve-in-valve aortic valve replacement as an alternative to surgical re-replacement. *J Am Coll Cardiol*. 2020;76:489–499. doi: 10.1016/j.jacc.2020.06.010
3. Tam DY, Dharma C, Rocha RV, Ouzounian M, Wijeysundera HC, Austin PC, Chikwe J, Gaudino M, Fremes SE. Transcatheter ViV versus redo surgical AVR for the management of failed biological prosthesis: early and late outcomes in a propensity-matched cohort. *JACC Cardiovasc Interv*. 2020;13:765–774. doi: 10.1016/j.jcin.2019.10.030
4. Caus T, Chabry Y, Nader J, Fusellier JF, De Brux JL. Trends in SAVR with biological vs. mechanical valves in middle-aged patients: results from a French large multi-centric survey. *Front Cardiovasc Med*. 2023;10:1205770. doi: 10.3389/fcvm.2023.1205770
5. Jiménez-García R, Perez-Farinos N, Miguel-Díez J, Hernández-Barrera V, Méndez-Bailón M, Jimenez-Trujillo I, de Miguel-Yanes JM, López-de-Andrés A. National trends in utilization and in-hospital outcomes of surgical aortic valve replacements in Spain, 2001–2015. *Braz J Cardiovasc Surg*. 2020;35:65–74. doi: 10.21470/1678-9741-2019-0181
6. Schnittman SR, Adams DH, Itagaki S, Toyoda N, Egorova NN, Chikwe J. Bioprosthetic aortic valve replacement: revisiting prosthesis choice in patients younger than 50 years old. *J Thorac Cardiovasc Surg*. 2018;155:539–547.e539. doi: 10.1016/j.jtcvs.2017.08.121
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, et al. 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 practice guidelines. *Circulation*. 2014;129:2440–2492. doi: 10.1161/CIR.0000000000000029
8. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000923
9. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052
10. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77:2717–2746. doi: 10.1016/j.jacc.2021.02.038
11. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. *JACC Cardiovasc Imaging*. 2015;8:340–360. doi: 10.1016/j.jcmg.2015.01.008
12. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595
13. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *New Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
14. Ahmad D, Yousef S, Kliner D, Brown JA, Serna-Gallegos D, Toma C, Makani A, West D, Wang Y, Thoma FW, et al. Outcomes of valve-in-valve transcatheter aortic valve replacement. *Am J Cardiol*. 2024;215:1–7. doi: 10.1016/j.amjcard.2023.12.061
15. Hirji SA, Percy ED, Zogg CK, Malarczyk A, Harloff MT, Yazdchi F, Kaneko T. Comparison of in-hospital outcomes and readmissions for valve-in-valve transcatheter aortic valve replacement vs. reoperative surgical aortic valve replacement: a contemporary assessment of real-world outcomes. *Eur Heart J*. 2020;41:2747–2755. doi: 10.1093/eurheartj/ehaa252

16. Paradis JM, Del Trigo M, Puri R, Rodés-Cabau J. Transcatheter valve-in-valve and valve-in-ring for treating aortic and mitral surgical prosthetic dysfunction. *J Am Coll Cardiol*. 2015;66:2019–2037. doi: 10.1016/j.jacc.2015.09.015
17. Webb JG, Murdoch DJ, Alu MC, Cheung A, Crowley A, Dvir D, Herrmann HC, Kodali SK, Leipsic J, Miller DC, et al. 3-year outcomes after valve-in-valve transcatheter aortic valve replacement for degenerated bioprostheses: the PARTNER 2 registry. *J Am Coll Cardiol*. 2019;73:2647–2655. doi: 10.1016/j.jacc.2019.03.483
18. Chakravarty T, Søndergaard L, Friedman J, Backer OD, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abramowitz Y, Jørgensen TH, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–2392. doi: 10.1016/S0140-6736(17)30757-2
19. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Higashimori A, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2019;12:e007349. doi: 10.1161/CIRCINTERVENTIONS.118.007349
20. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, Becker B, Landt M, Kebernik J, Schwarz B, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–697. doi: 10.1016/j.jcin.2017.01.045
21. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, Arai T, Kawakami T, Maekawa Y, Tsuruta H, et al. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. *JACC Cardiovasc Imaging*. 2017;10:1–11. doi: 10.1016/j.jcmg.2016.11.005.
22. Shekhar S, Krishnaswamy A, Reed G, Puri R, Yun J, Kapadia S. Cerebral embolic protection in valve-in-valve transcatheter aortic valve replacement. *Am J Cardiol*. 2024;216:110–111. doi: 10.1016/j.amjcard.2024.02.013
23. Hein M, Schoechlin S, Schulz U, Minners J, Breitbart P, Lehane C, Neumann FJ, Ruile P. Long-term follow-up of hypoattenuated leaflet thickening after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2022;15:1113–1122. doi: 10.1016/j.jcin.2022.04.018