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Transcatheter aortic valve implantation: State-of-the-art and future perspectives

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Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-2922-5
DOI 10.3389/978-2-8325-2922-5

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Transcatheter aortic valve implantation: State-of-the-art and future perspectives

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Citation

Tarantini, G., Tang, G., eds. (2023). *Transcatheter aortic valve implantation: State-of-the-art and future perspectives*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2922-5

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frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 16 May 2022
doi: 10.3389/fcvm.2022.876546

Assessment of New Onset Arrhythmias After Transcatheter Aortic Valve Implantation Using an Implantable Cardiac Monitor

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OPEN ACCESS

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 15 February 2022
Accepted: 14 April 2022
Published: 16 May 2022

Citation:
Nozica N, Siontis GCM, Elchinova EG, Goulouti E, Asami M, Bartkowiak J, Baldinger S, Servatius H, Seiler J, Tanner H, Noti F, Haeberlin A, Branca M, Lanz J, Stortecky S, Pilgrim T, Windecker S, Reichlin T, Praz F and Roten L (2022) Assessment of New Onset Arrhythmias After Transcatheter Aortic Valve Implantation Using an Implantable Cardiac Monitor. Front. Cardiovasc. Med. 9:876546. doi: 10.3389/fcvm.2022.876546

Background: Transcatheter aortic valve implantation (TAVI) is associated with new onset brady- and tachyarrhythmias which may impact clinical outcome.

Aims: To investigate the true incidence of new onset arrhythmias within 12 months after TAVI using an implantable cardiac monitor (ICM).

Methods: One hundred patients undergoing TAVI received an ICM within 3 months before or up to 5 days after TAVI. Patients were followed-up for 12 months after discharge from TAVI for the occurrence of atrial fibrillation (AF), bradycardia (≤30 bpm), advanced atrioventricular (AV) block, sustained ventricular and supraventricular tachycardia.

Results: A previously undiagnosed arrhythmia was observed in 31 patients (31%) and comprised AF in 19 patients (19%), advanced AV block in 3 patients (3%), and sustained supraventricular and ventricular tachycardia in 10 (10%) and 2 patients (2%), respectively. Three patients had a clinical diagnosis of sick-sinus-syndrome. A permanent pacemaker (PPM) was implanted in six patients (6%). The prevalence of pre-existing AF was 28%, and 47% of the patients had AF at the end of the study period. AF burden was significantly higher in patients with pre-existing [26.7% (IQR 0.3%; 100%)] compared to patients with new-onset AF [0.0% (IQR 0.0%; 0.06%); $p = 0.001$]. Three patients died after TAVI without evidence of an arrhythmic cause according to the available ICM recordings.

Conclusions: Rhythm monitoring for 12 months after TAVI revealed new arrhythmias, mainly AF, in almost one third of patients. Atrial fibrillation burden was higher in patients with prevalent compared to incident AF. Selected patients may benefit from short-term remote monitoring.

Trial Registration: https://clinicaltrials.gov/: NCT02559011.

Keywords: TAVI, implantable cardiac monitor (ICM), pacemaker (PM), atrial fibrillation, bundle branch block (BBB), AV block, ventricular tachycardia (VT)

INTRODUCTION

Little is known about the frequency and burden of conduction disturbances and arrhythmias directly associated with degenerative aortic valve disease. Transcatheter aortic valve implantation (TAVI) for the treatment of severe symptomatic aortic valve stenosis has been established as the treatment of choice among inoperable (1), as well as high (2–4) and intermediate risk patients (5–8) and is a valid alternative for older patients at low surgical risk (9–12). Patients with aortic valve stenosis have a high incidence of both brady- and tachyarrhythmias before and after successful valve replacement. These arrhythmias include atrial fibrillation (AF), atrioventricular (AV) conduction disorder, sick sinus syndrome, ventricular and supraventricular tachycardia and are associated with significant morbidity and mortality. The reported prevalence of pre-existing AF in patients undergoing TAVI ranges from 16 to 50% in various studies (13, 14). New-onset AF (NOAF) after TAVI has been reported in 14–18% of patients after 1 year and 25% after 2 years (13, 15). The incidence of bradyarrhythmia after discharge from TAVI is generally low (4% after 1 year) (15), but may reach 20% in patients with new-onset left bundle branch block (LBBB), including advanced atrio-ventricular (AV) block in 15% of patients, when assessed using an implantable cardiac monitor (ICM) (16). In contrast, sustained ventricular tachycardia is very rare (16). Timely diagnosis and initiation of appropriate therapy may prevent untoward sequelae of arrhythmias, like ischemic stroke, syncope or sudden cardiac death. The purpose of the present study was to investigate the incidence of brady- and tachyarrhythmias among patients with severe, symptomatic aortic stenosis before, during and after TAVI using a small ICM.

Abbreviations: AF, Atrial fibrillation; AV, Atrioventricular; ICM, Implantable cardiac monitor; LAVI, Left atrial volume index; LBBB, Left bundle branch block; NOAF, New-onset atrial fibrillation; PPM, Permanent pacemaker; RBBB, Right bundle branch block; TAVI, Transcatheter aortic valve implantation.

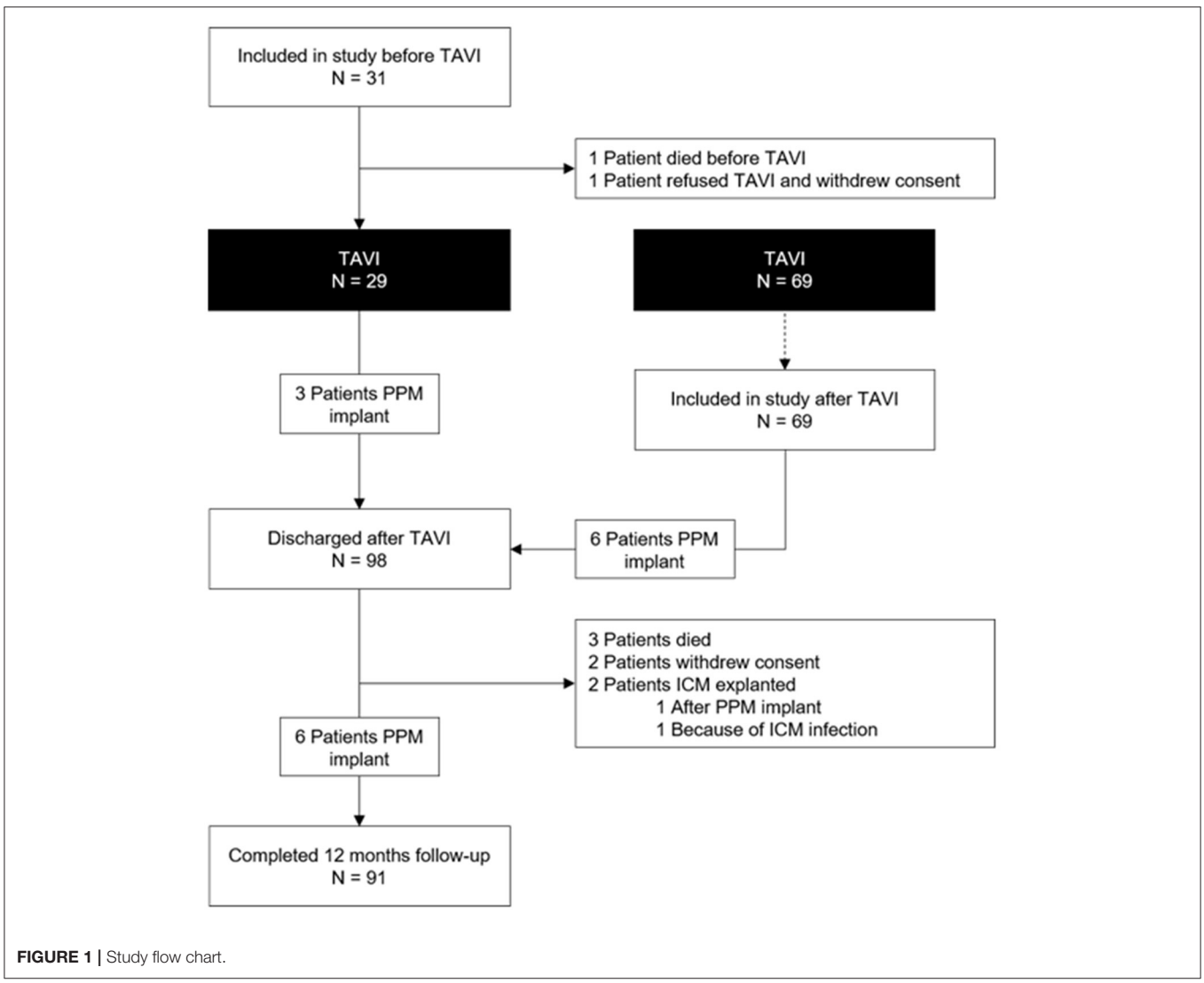

FIGURE 1 | Study flow chart.

METHODS

Study Population

In this single-center, prospective cohort study, we included 100 patients aged >18 years undergoing TAVI for the treatment of severe symptomatic aortic valve stenosis between March 2016 and October 2019. Patient inclusion was independent of the implanted valve type, access site or baseline heart rhythm. TAVI patients participating in randomized controlled trials ongoing during the same period, patients with a previously implanted permanent pacemaker (PPM) or internal cardioverter defibrillator, patients with clinical contraindications for ICM implantation, and patients unable to give informed consent were excluded from participation in the study. The study was approved by the local ethics committee (KEK-Number 281/15). All study procedures were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Study Procedures

All patients included in the study received an ICM (Reveal LINQ^{TM}, Medtronic, MN, USA) with remote monitoring capability via the Medtronic CareLink System^{TM} (Medtronic, MN, USA). Whenever possible, we implanted the ICM during pre-TAVI work-up, with the aim to screen for baseline arrhythmias. Implantation was performed subcutaneously according to standard practice in a manufacture-recommended location, as reported elsewhere (17). Details on the programming of the ICMs can be found in the **Supplementary Table**. All patients received detailed instructions on how to perform remote data transmission and were asked to perform a manual transmission once weekly, in addition to automatic, daily remote transmissions. Staff exclusively responsible for remote monitoring of patients at our institution and well-trained in electrocardiogram analysis triaged all episodes transmitted by the ICMs of study participants. Later during the study, triaging of episodes was provided by FocusOn^{TM} (Medtronic, MN, USA), a specialized triaging service for remote monitoring data. An experienced electrophysiologist adjudicated all triaged electrocardiograms with arrhythmias or unclear findings. If the diagnosis was ambiguous, a second and a third electrophysiologist were consulted and a consensus reached. Data on AF burden was retrieved as displayed in the Medtronic CareLink System.

A 12-lead ECG was recorded in all patients before TAVI, immediately after TAVI and daily thereafter until stabilization of AV conduction or permanent pacemaker (PPM) implantation. Indications for PPM implantation after TAVI were based on institutional and international recommendations (18). Study follow-up included in-office visits or phone calls at 30 days, 3 and 12 months after TAVI. At each time point, a 12-lead ECG was obtained and analyzed according to established recommendations (19). Remote monitoring of the ICM was continuously performed up to study end. If remote transmission failed for longer than 2 weeks, the patients were contacted and remote transmission issues resolved.

Outcomes

The main study outcome was the diagnosis of new onset arrhythmia within 1-year follow-up after discharge from TAVI and included: AF; sustained supraventricular tachycardia; sustained ventricular tachycardia; advanced AV block; sinus arrest with a pause ≥6 s duration; AF with a pause ≥6 s duration; and bradycardia ≤30 beats per minute for more than 30 s. 12-lead ECGs before TAVI, immediately after TAVI, on day 7 after TAVI or hospital discharge (whichever came first) and after 3 and 12 months after TAVI were analyzed according to established recommendations (19).

TABLE 1 | Clinical and procedural characteristics.

Age, years	81 ± 5
Gender, female	35 (35%)
Arterial hypertension	89 (89%)
Diabetes mellitus	23 (23%)
Dyslipidemia	71 (71%)
Coronary artery disease	60 (60%)
Peripheral artery disease	9 (9%)
Congestive heart failure	13 (13%)
History of stroke/TIA	10 (10%)
STS Score	3.4 ± 2.1
Atrial fibrillation	28 (28%)
Paroxysmal	16 (57%)
Time since atrial fibrillation diagnosis, months	24 (3; 52)
Baseline treatment	
Antiplatelet therapy	99 (99%)
Oral Anticoagulation	32 (32%)
Beta-blockers	55 (55%)
Calcium channel blockers (non-dihydropyridine type)	2 (2%)
Amiodarone	4 (4%)
Echocardiography	
LVEF, %	59 ± 10
Mean gradient, mmHg	40 ± 14
Peak aortic valve gradient, mmHg	66 ± 22
Aortic valve area, cm^2	0.7 ± 0.3
Indexed Aortic Valve Area, cm^2/m^2	0.2 ± 0.1
Left atrial volume index, ml/m^2	42 ± 14
TAVI procedure performed	98 (98%)
Access site (*n*, %)	
Right femoral artery	88 (90%)
Left femoral artery	10 (10%)
Type of valve (*n*, %)	
Self-expanding valves	41 (42%)
Balloon-expandable valves	52 (53%)
Mechanically-expandable valves	5 (5%)

Data are provided as mean ± standard deviation, as median with interquartile range (1st; 3rd) or frequencies with percentages. LVEF, left ventricular ejection fraction; STS, society of thoracic surgeons; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

TABLE 2 | ECG characteristics before TAVI, after TAVI, and during follow-up.

ECG	Before TAVI	Day 1	Discharge*	3 months	12 months
Number of patients	93 (95%)	94 (96%)	88 (90%)	89 (91%)	86 (88%)
Atrial fibrillation	14 (15%)	16 (17%)	16 (18%)	13 (15%)	13 (15%)
Higher-degree AV block	–	4 (4%)	1 (1%)	1 (1%)	–
PR interval, ms	179 ± 42	185 ± 37	193 ± 43	186 ± 44	187 ± 47
QRS width, ms	106 ± 23	121 ± 28	120 ± 28	109 ± 26	112 ± 28
RBBB	6 (7%)	7 (8%)	4 (5%)	3 (3%)	6 (7%)
LBBB	9 (10%)	34 (36%)	34 (39%)	19 (21%)	19 (22%)
UICD	5 (5%)	4 (4%)	4 (5%)	4 (5%)	5 (6%)

Data are provided as mean ± standard deviation or frequencies with percentages.
**ECG on hospital discharge or day 7, whichever came first.*
LBBB, left bundle branch block; RBBB, right bundle branch block; TAVI, transcatheter aortic valve implantation; UICD, unspecified, intraventricular conduction disorder.

TABLE 3 | Overview of patients undergoing PPM implantation.

Case #	PPM implant*	Days since TAVI	Indication of PPM implant	ICM finding	Device
11	Before discharge	0	Complete AV block; SSS	No	DDD-PM
22	Before discharge	0	LBBB and PR interval >300 ms	No	VVI-PM
23	Before discharge	2	Complete AV block	No	VVI-PM
29	Before discharge	5	LBBB, AF with pauses >3 s	No	VVI-PM
35	Before discharge	2	LBBB, 2° AV block	No	VVI-PM
40	Before discharge	2	Complete AV block	Yes	DDD-PM
42	Before discharge	0	Complete AV block	No	DDD-PM
43	Before discharge	2	LBBB and increasing PR interval	No	DDD-PM
45	After discharge	10	Complete AV block	Yes	DDD-PM
50	Before discharge	1	Complete AV block	Yes	DDD-PM
51	After discharge	14	Complete AV block	Yes	DDD-PM
53	After discharge	35	SSS	No	VVI-PM
60	After discharge	231	SSS	No	VVI-PM
64	After discharge	9	Complete AV block	Yes	DDD-PM
72	After discharge	36	SSS	No	DDD-PM

**All PPM were implanted after TAVI.*
AF, atrial fibrillation; AV, atrioventricular; ICM, implantable cardiac monitor; LBBB, left bundle branch block; PPM, permanent pacemaker; SSS, sick sinus syndrome; TAVI, transcatheter aortic valve implantation.
The symbol # indicates number.

Statistical Analysis

Continuous variables are expressed as means with standard deviations or medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. Continuous variables were compared using the Mann–Whitney *U*-test or *t*-test while differences in proportions were tested with Pearson's $\chi 2$ test or Fisher's exact test. Predictors for AF diagnosis by the ICM were assessed in uni- and multi-variable analyses. Variables with a *p*-value of <0.2 in the crude comparison were selected for adjustment and variable selection in the multiple generalized linear model. Results for survival free from AF or any new arrhythmia with time-to-event data were displayed as Kaplan-Meier curves for descriptive purposes. All tests were performed at a two-sided 5% significance level with two-sided 95% confidence intervals (CIs). All analyses were performed using Stata (StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

Among the 100 study patients, 31 received the ICM a median of 20 days (IQR 4; 29) before TAVI (**Figure 1**). In the remaining 69 patients, the ICM was inserted a median of 1 day (IQR 0; 2) after TAVI. **Table 1** shows the baseline patient characteristics. Four patients died during follow-up, three patients withdrew consent and two patients had their ICM explanted before the end of the study: one because of ICM infection 245 days after TAVI and one after PPM implantation 256 days after TAVI (**Figure 1**). TAVI was not performed in two patients who had received an ICM (one

died prior to the procedure and one withdrew consent for both TAVI and participation in the study).

The prevalence of baseline right bundle branch (RBBB) and LBBB block was 7 and 10%, respectively. The prevalence of LBBB increased to 39% after TAVI and decreased to 22% after 1 year (**Table 2**). A PPM was implanted in 15 of the 98 patients who underwent TAVI (15%; **Table 3**; **Figure 1**). Nine PPM were implanted before hospital discharge and six thereafter. No patient received a PPM prior to TAVI. Within 1 year after TAVI, a new arrhythmia was observed in 31 patients (31%; **Figure 2A**). The new arrhythmias were as follows: AF in 19 patients (19%), advanced AV block in three patients (3%), and sustained supraventricular and ventricular tachycardia in 10 (10%) and two patients (2%), respectively.

Atrial Fibrillation

Among the 28 patients with a history of AF at inclusion, 22 were asymptomatic (79%), and AF was paroxysmal in 16 (57%). Overall, AF was recorded by the ICM in 43 patients (43%). The diagnosis of NOAF was made in 19 patients (19%) and in 24 patients (24%) AF was pre-existing (**Figure 2**). Patients with NOAF initially all had paroxysmal AF. One of these patients developed persistent AF within 12 months after TAVI. Oral anticoagulation was initiated in all after NOAF diagnosis. No AF was observed in four out of the 28 patients (14%) with pre-existing AF. Median time of ICM implantation to first AF recording was 6 days (IQR 0; 93) overall, 57 days (IQR 36; 153) in patients with NOAF, and 1 day (IQR 0; 2) in patients with pre-existing AF (**Supplementary Figure**). Among the 31 patients with ICM implantation before TAVI, AF was recorded before the procedure in nine patients (29%) at a median of 19 days before TAVI (range 1–96 days before TAVI). AF was pre-existing in seven of these patients (78%) and new in two (22%). AF burden recorded by the ICM in patients with pre-existing AF was 26.7% (IQR 0.3%; 100%), and 0.0% (IQR 0.0%; 0.06%) in patients with NOAF (p for difference = 0.001). In patients with pre-existing AF, we found no difference in AF burden before vs. after TAVI [0.0% (IQR 0.0%; 4.8%) vs. 0.1% (IQR 0.0%; 6.1%); p = 0.837]. History of stroke or transient ischemic attack, prolonged PR interval or filtered P wave duration and larger left atrial volume index (LAVI) were predictors of pre-existing or new-onset AF. In multivariate analysis, larger LAVI and lower mean aortic valve gradient remained significant predictors for AF. **Tables 4**, **5** show uni- and multivariate predictors for prevalence and incidence of AF.

Bradycardia and PPM Implantation

Sinus bradycardia and/or sinus arrest were not observed by the ICM in any patient. AF with a pause lasting 8 s at night was recorded in one patient. No pacemaker was implanted in this patient because he was bedridden. Asymptomatic complete AV block was recorded in five patients with pauses lasting from 2 to 8 s. Complete AV block occurred before discharge from TAVI in two patients and after discharge from TAVI in three patients (6, 7, and 8 days after TAVI). A PPM was implanted in all five patients (**Table 3**). Second degree AV block type Wenckebach was recorded by the ICM in two additional patients 167 and 300 days after TAVI, respectively. No PPM was implanted in these patients. In three patients, a PPM was implanted during follow-up because of a clinical diagnosis of sick sinus syndrome (symptomatic bradycardia or chronotropic incompetence) 35, 36, and 231 days after TAVI. These patients did not meet bradycardia endpoint criteria defined for the ICM.

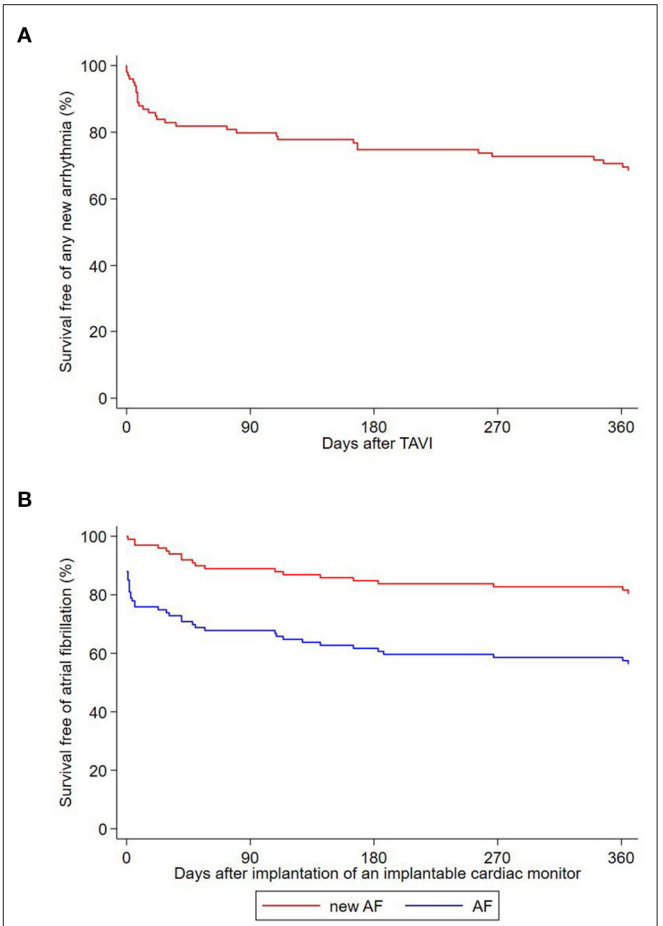

FIGURE 2 | (A) Kaplan-Meier survival curve free of any new arrhythmia recorded by the ICM after TAVI. **(B)** Kaplan-Meier survival curve free of atrial fibrillation and new-onset atrial fibrillation after implantation of an implantable cardiac monitor.

Sustained Ventricular and Supraventricular Tachycardia

Sustained ventricular tachycardias were observed in two patients (2%). One patient had three episodes of asymptomatic ventricular tachycardias lasting from 1 to 8 min. His betablocker dose was increased but he refused further therapies. Another patient had asymptomatic ventricular tachycardia lasting 1 min. After a detailed work-up showing normal left ventricular function, it was decided to continue remote monitoring of the patient without additional interventions. Ten patients (10%) had a median of one sustained supraventricular tachycardia (range 1–6) lasting from 30 s to 1 h and 12 min. All patients with a supraventricular tachycardia were asymptomatic.

TABLE 4 | Univariate predictors of atrial fibrillation.

	No AF *N* = 53	AF *N* = 47	*P*-value*	Pre-existing AF *N* = 28	New-onset AF *N* = 19	*P*-value#
Age, years	80 ± 5	82 ± 5	0.054	81 ± 5	83 ± 5	0.039
Gender, female	22 (42%)	13 (28%)	0.207	6 (21%)	7 (37%)	0.790
Arterial hypertension	45 (85%)	44 (94%)	0.210	26 (93%)	18 (95%)	0.429
Diabetes mellitus	12 (23%)	11 (23%)	1.000	6 (21%)	5 (26%)	0.759
Dyslipidemia	39 (74%)	32 (68%)	0.660	18 (64%)	14 (74%)	1.000
Coronary artery disease	33 (62%)	27 (57%)	0.685	14 (50%)	13 (68%)	0.783
Peripheral artery disease	5 (9%)	4 (9%)	1.000	2 (7%)	2 (11%)	1.000
Congestive heart failure	8 (15%)	5 (11%)	0.564	4 (14%)	1 (5%)	0.429
History of stroke/TIA	2 (4%)	8 (17%)	0.043	6 (21%)	2 (11%)	0.283
BMI, kg/m^2	27 ± 5	28 ± 5	0.292	29 ± 5	27 ± 5	0.942
Electrocardiogram						
PR interval, ms	180 ± 41	205 ± 42	0.007	223 ± 36	193 ± 43	0.235
QRS width, ms	101 ± 23	109 ± 30	0.130	117 ± 32	98 ± 23	0.596
LBBB	12 (23%)	12 (26%)	0.816	8 (29%)	4 (22%)	1.000
RBBB	–	1 (2%)	0.469	–	1 (6%)	0.257
fPWD, ms	146 ± 17	164 ± 23	<0.001	178 ± 25	156 ± 16	0.028
P wave integral, μVs	777 ± 263	665 ± 254	0.068	598 ± 247	706 ± 256	0.328
PACS per hour, number	29 ± 71	46 ± 111	0.384	69 ± 147	21 ± 40	0.658
Echocardiography						
LVEF, %	58 ± 11	59 ± 9	0.927	57 ± 9	61 ± 8	0.451
Mean gradient, mmHg	42 ± 16	38 ± 11	0.139	36 ± 11	41 ± 10	0.737
Aortic valve area, cm^2	0.6 ± 0.2	0.8 ± 0.3	0.001	0.8 ± 0.3	0.8 ± 0.3	0.003
LAVI, ml/m^2	37 ± 13	47 ± 13	<0.001	48 ± 13	47 ± 13	0.008
Laboratory						
BNP, pg/mL	331 ± 622	285 ± 228	0.638	334 ± 245	211 ± 183	0.423
hsTT, μg/L	0.1 ± 0.3	0.1 ± 0.1	0.478	0.1 ± 0.1	0.0 ± 0.0	0.523
hsCRP, mg/L	5.8 ± 6.7	7.8 ± 7.1	0.162	9.2 ± 7.3	5.7 ± 6.3	0.929
Creatinine, μmol/L	122 ± 149	115 ± 83	0.764	122 ± 104	106 ± 35	0.627

Data are provided as mean ± standard deviation or frequencies with percentages.

**Comparison of patients with AF (pre-existing and new-onset) vs. patients without AF.*

 # Comparison of patients with new-onset AF vs. patients without AF.

AF, atrial fibrillation; BNP, brain natriuretic peptide; fPWD, filtered P wave duration; hsCRP, high sensitive C-reactive protein; hsTT, high sensitive Troponin T; LAVI, left atrial volume index; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PACS, premature atrial contractions; RBBB, right bundle branch block; TIA, transient ischemic attack.

Clinical Outcomes

Table 6 shows the outcomes 30 days and 1 year after TAVI. We were able to retrieve the ICM of the three patients who died after TAVI. The recordings of the ICMs showed either artifacts or asystole, recorded after death in all three patients. No death was causally related to a recorded arrhythmia in any patient. The ICM of the patient who died before TAVI had his last transmission 2 days before death, it showed an increase in heart rate and AF burden. This patient died due to hepatocellular carcinoma and his ICM was not retrievable.

DISCUSSION

Rhythm monitoring for 1 year with an ICM in patients undergoing TAVI reveals the following arrhythmias: (1) New-onset atrial fibrillation in one quarter of patients without pre-existing atrial fibrillation; (2) sustained supraventricular tachycardia in one tenth of patients; (3) complete AV block after discharge from TAVI in 3% of patients; and (4) sustained ventricular tachycardia in 2% of patients.

In the MARE multicentric study, 103 patients received an ICM within 3–6 days after TAVI and were followed up during 12 months for relevant arrhythmias (16). In contrast to our study, all patients in the MARE study had new-onset, complete LBBB at inclusion and all patients were included after TAVI. The prevalence of pre-existing AF was 26% compared to 28% in our study. We found an incidence of NOAF of 26% compared to 17% in the MARE study. Using continuous PPM monitoring after TAVI, other authors reported a similar incidence of NOAF of 25% within 1 year (20), while it was 14% 1 year after TAVI in a pooled analysis performed by our group (15). Because the incidence of AF depends on both the screening strategy and the

TABLE 5 | Multivariate predictors of atrial fibrillation.

	Coefficient (95%-CI)	OR (95%-CI)	*p*-value
Patients with AF (pre-existing and new-onset) vs. patients without AF			
Age, years	0.08 (−0.03 to 0.19)	1.08 (0.97–1.21)	0.177
History of stroke/TIA	−0.98 (−2.70 to 0.74)	0.38 (0.07–2.10)	0.264
QRS duration, ms	−0.00 (−0.02 to 0.02)	1.00 (0.98–1.02)	0.920
Mean gradient, mmHg	−0.04 (−0.07 to 0.00)	0.96 (0.93–1.00)	0.053
LAVI (left atrial volume index), mL/m^2	0.07 (0.03–0.11)	1.07 (1.03–1.11)	0.001
High sensitive C-reactive protein, mg/L	0.04 (−0.04 to 0.12)	1.04 (0.96–1.12)	0.319
Patients with new-onset AF vs. patients without AF			
Age, years	0.11 (−0.05 to 0.28)	1.12 (0.95–1.32)	0.164
Filtered P wave duration, ms	0.01 (−0.04 to 0.05)	1.01 (0.97–1.05)	0.696
Aortic valve area, cm^2	4.06 (0.59–7.52)	57.72 (1.80–1,848.62)	0.022
LAVI (left atrial volume index), mL/m^2	0.06 (0.01–0.12)	1.07 (1.01–1.13)	0.029

AF, atrial fibrillation; CI, confidence interval; hsCRP, high sensitive C-reactive protein; fPWD, filtered P wave duration; LAVI, left atrial volume index; OR, odds ratio; TIA, transient ischemic attack.

TABLE 6 | Clinical outcomes.

30 days	
All-cause mortality	–
Cardiovascular mortality	–
Any stroke	1 (1%)
Major or life-threatening bleeding	7 (7%)
1 year	
All-cause mortality	3 (3%)
Cardiovascular mortality	–
Any stroke	1 (1%)
Major or life-threatening bleeding	10 (10%)
Structural valve deterioration	1 (1%)

patient population included, higher detection rates are expected in studies using continuous monitoring (21).

Both pre-existing AF and NOAF have been associated with higher mortality and stroke incidence after TAVI (14, 15). Screening for AF and initiation of the appropriate treatment may therefore improve outcome, while predictors of an increased risk of AF are not well investigated in this population. Our prospective study provides some answers and identifies larger LAVI and longer P wave duration as predictors of NOAF, reflecting atrial mechanical and electrical remodeling. Both LAVI and P wave duration are established predictors of AF in other populations and another group also identified left atrial size as the best predictor for NOAF in TAVI patients (22).

Despite high rates of pre-existing AF or NOAF in almost half of TAVI patients, the GALILEO trial, which investigated oral anticoagulation with Rivaroxaban at a dose of 10 mg daily after TAVI compared to antiplatelet therapy in patients without indication for oral anticoagulation, was terminated prematurely because of safety concerns (23). Anticoagulation should therefore only be initiated after unequivocal diagnosis of AF. We observed a significantly lower AF burden in patients with new-onset AF compared to patients with pre-existing AF. There is ongoing debate about the threshold of AF burden that justifies oral anticoagulation, when AF is diagnosed by continuous monitoring (24). The recently published Loop trial failed to show a benefit of oral anticoagulation in patients with screen-detected AF. Randomized trials are ongoing that will shed light onto the threshold of AF burden that justifies oral anticoagulation (25, 26).

We observed complete AV block with consecutive PPM implantation in only three patients after discharge, all within 1 week. A PPM was implanted due to clinical sick-sinus-syndrome in an additional 3% of patients after discharge amounting to a total of 6% of PPM implantation after discharge. In a larger TAVI population, we reported a similar incidence of 6% late PPM implantation after TAVI, of which 16% were due to sick-sinus-syndrome (27). In the MARE study, 10% of patients experienced severe bradycardia leading to PPM implantation, due to either advanced AV conduction impairment or sick sinus syndrome. The higher incidence in the MARE study is most likely the consequence of including a population at higher risk of conduction disturbances (new-onset LBBB after TAVI was present in all), while LBBB at discharge was only present in 39% of the patients in our study. Of note, the prevalence of LBBB decreased by over one third after 12 months, both in the MARE and in our study.

Sustained ventricular tachycardia was rare both in the MARE and the present study. No ICD was implanted in two patients experiencing asymptomatic sustained ventricular tachycardia in our study, whereas two patients received an ICD in the MARE study owing to ventricular arrhythmias. In a larger TAVI population, we have previously described a very low rate of ICD implantation after TAVI (27). With a prevalence of 10%, sustained supraventricular tachycardia were among the

most frequent arrhythmias after TAVI. However, they usually lasted only a few minutes, were asymptomatic in all patients and did not require any treatment modifications in our study.

The overall mortality and stroke rates at 12 months (3 and 1%, respectively) were rather low in this elderly population with a mean STS score of 3.4 ± 2.1%. Unfortunately, the functionality of the ICM does not allow accurate conclusions concerning the heart rhythm at the time of death, since bradyarrhythmia and sinus arrest are overwritten by subsequent asystole. Therefore, the only reliable conclusion that can be drawn concerning the occurrence of ventricular arrhythmia, is that they weren't the cause of death in any of the patients.

LIMITATIONS

The present study represents a single center experience at a tertiary care center with follow-up limited to 12 months. Transient complete AV block with a pause of <3 s or 2:1 AV block is not recorded by the ICM, and the prevalence of advanced AV block after TAVI may therefore be underestimated.

CONCLUSIONS

New arrhythmias, mainly AF, were frequent in our TAVI population. Atrial fibrillation burden was higher in TAVI patients with pre-existing AF compared to patients with new-onset AF. The incidence of advanced AV block and of ventricular tachycardia was low.

DATA AVAILABILITY STATEMENT

The data presented in this article is not readily available because included patients did not consent to share the data with our groups.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission Bern. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was supported by a grant of the Swiss National Foundation (32003B_163059) to SW. Medtronic (Minneapolis, US) provided the ICMs (REVEAL LinQ™) free of charge. Medtronic was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.876546/full#supplementary-material

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Conflict of Interest: The spouse of JS is an employee of Boston Scientific. HT reports educational grants from Biosense Webster and travel grants from Abbott. FN reports travel fees from Medtronic, Abbott, Boston Scientific and Philips Spectranetics, speaker fees from Medtronic and Abbott, educational grants from Medtronic, Abbott, Boston Scientific, Philips Spectranetics and Actinno and institutional grants from Biotronik. AH received travel/educational grants from Medtronic and Philips/Spectranetics. He is consultant/advisor for DiNAQOR and Biotronik and Co-founder/head of Act-Inno. SS reports research grants to the institution from Edwards Lifesciences, Medtronic, Boston Scientific and Abbott, as well as personal fees from Boston Scientific, Teleflex and BTG. TP reports research grants to the institution from Biotronik, Boston Scientific and Edwards Lifesciences; speaker fees from Biotronik and Boston Scientific; Clinical event committee for study sponsored by HighLifeSAS; travel reimbursement from Medira; proctoring for Medtronic. SW reports research and educational grants to the institution from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, V-Wave. He serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, Terumo, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. TR reported research grants from the Goldschmidt-Jacobson Foundation, the Swiss National Science Foundation, the Swiss Heart Foundation and the sitem-insel Support Funds, all for work outside the submitted study; advisory board membership, speaker and travel support from Abbott/SJM, Astra Zeneca, Brahms, Bayer, Biosense-Webster, Biotronik, Boston-Scientific, Daiichi Sankyo, Medtronic, Pfizer-BMS and Roche, all for work outside the submitted study and without impact on his personal remuneration; as well as support for his institution's fellowship program from Abbott/SJM, Biosense-Webster, Biotronik, Boston-Scientific and Medtronic for work outside the submitted study and without impact on his personal remuneration. FP reports travel expenses from Abbott Vascular, Edwards Lifesciences, and Polares Medical. LR received speaker honoraria from Abbott/SJM and consulting honoraria from Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 26 May 2022
doi: 10.3389/fcvm.2022.896062

Economic Evaluation of Transcatheter Aortic Valve Replacement Compared to Surgical Aortic Valve Replacement in Chinese Intermediate-Risk Patients

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OPEN ACCESS

Edited by:
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Reviewed by:
Giuseppe Santarpino, Nuremberg Hospital, Germany
Kendra Grubb, Emory University, United States

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Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *14 March 2022*
Accepted: *29 April 2022*
Published: *26 May 2022*

Citation:
Zhang W, Lou Y, Liu Y, Wang H, Zhang C and Qian L (2022) Economic Evaluation of Transcatheter Aortic Valve Replacement Compared to Surgical Aortic Valve Replacement in Chinese Intermediate-Risk Patients. Front. Cardiovasc. Med. 9:896062. doi: 10.3389/fcvm.2022.896062

Background: Aortic stenosis (AS) is a severe disease that causes heart failure and sudden death. Transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) are both recommended for patients with intermediate surgical risk, but the cost-effectiveness of TAVR compared to SAVR in China has not been investigated.

Methods: A combined decision tree and Markov model were conducted to compare the cost-effectiveness of TAVR versus SAVR with a 5-year simulation. The primary outcome was the incremental cost-effectiveness ratio (ICER), a ratio of incremental costs to incremental quality-adjusted life-year (QALY). One-way sensitive analysis and probabilistic sensitivity analysis (PSA) were conducted to test the robustness of the model.

Results: After a simulation of 5 years, the costs of TAVR and SAVR were 54,573 and 35,002 USD, respectively, and the corresponding effectiveness was 2.826 versus 2.712 QALY, respectively. The ICER for the TAVR versus SAVR comparison was 170,056 USD/QALY, which was three times higher than the per capita gross domestic product (GDP) in China. One-way sensitive analysis showed that the cost of the TAVR device impacted the ICER. The TAVR could be cost-effective only in the case where its cost is lowered to 29,766 USD.

Conclusion: TAVR is currently not cost-effective in China, but it could be cost-effective with a reduction of costs to 29,766 USD, which is approximately 65% of the current price.

Keywords: TAVR, SAVR, economic evaluation, cost-effectiveness, aortic stenosis

INTRODUCTION

Aortic stenosis (AS) is a severe disease that causes heart failure and sudden death (1, 2). A retrospective survey conducted in China showed that the prevalence of AS was 0.16% in inpatients younger than 65 years old and that it was 0.41 and 0.56% in those aged 65–74 and over 75 years old (3). Another study conducted in China found that 0.39–0.66% of outpatients aged over 65 years who received echocardiography were diagnosed with severe AS (4). As the Chinese population is entering an aging society, the burden of AS is increasing.

Surgical aortic valve replacement (SAVR) has always been the optimal treatment for patients with AS across different risk stratifications (5, 6). However, several important clinical studies regarding transcatheter aortic valve replacement (TAVR) (7–10) have demonstrated the efficacy and safety of TAVR all over the world (11, 12). It is estimated that more than 306,000 patients with AS have undergone TAVR in the United States (13). The number of patients AS who have undergone TAVR in China is much lower but is increasing at a fast rate.

In patients with AS who are at intermediate risk for surgery, it has been demonstrated that TAVR has similar efficacy as that of SAVR (9). The 2021 European Society of Cardiology (ESC) guidelines for valvular heart disease recommended that SAVR and TAVR are both first-line treatments for patients at intermediate-risk (6). In clinical practice, whether a treatment can be widely used depends not only on its effectiveness but also on whether it is cost-effective. The collective purchase policy launched by the Chinese govenment allows only cost-effective drugs or medical devices to be widely used in Chinese hospitals, but an economic evaluation comparing TAVR versus SAVR is lacking. Thus, the present study aimed to investigate the cost-effectiveness of TAVR compared to SAVR among Chinese patients at intermediate-risk.

MATERIALS AND METHODS

Overview

The basic structure of the model consisted of two parts, namely, a 30-day decision tree and a 59-month Markov model. Patients who entered the model would first enter the decision tree, and a TAVR or SAVR was performed. After 30 days, the patients would enter a Markov model with a simulation of 59 months. The summary simulation period was 60 months. The starting age was 80 years old, and the simulation cycle was 5 years, which was similar to that in the PARTNER 2 study.

Model Structure

In the 30-day decision tree model, patients allocated to the TAVR or SAVR group may experience one or several complications of the procedure, including death, disabling stroke, non-disabling stroke, myocardial infarction (MI), major vascular complication, major bleeding, acute kidney injury (AKI), permanent pacemaker implantation, and new atrial fibrillation (AF). After that, the patients would enter a Markov model with a simulation of 59 months, and every patient entering the Markov model would transit among five states, including no events, post-AF, post-disabling stroke, post-non-disabling stroke, and death. The cycle period in the Markov model was 1 month, and there were 59 cycles in summary. The detailed model is displayed in **Figure 1**.

Input Parameters

Clinical Data

The clinical data analyzed in our study was mainly derived from the PARTNER 2 study (Placement of aortic transcatheter valves II - XT intermediate and high risk) (9, 14). For periprocedural complications within 30 days, the corresponding data were directly extracted from a published article. For data between

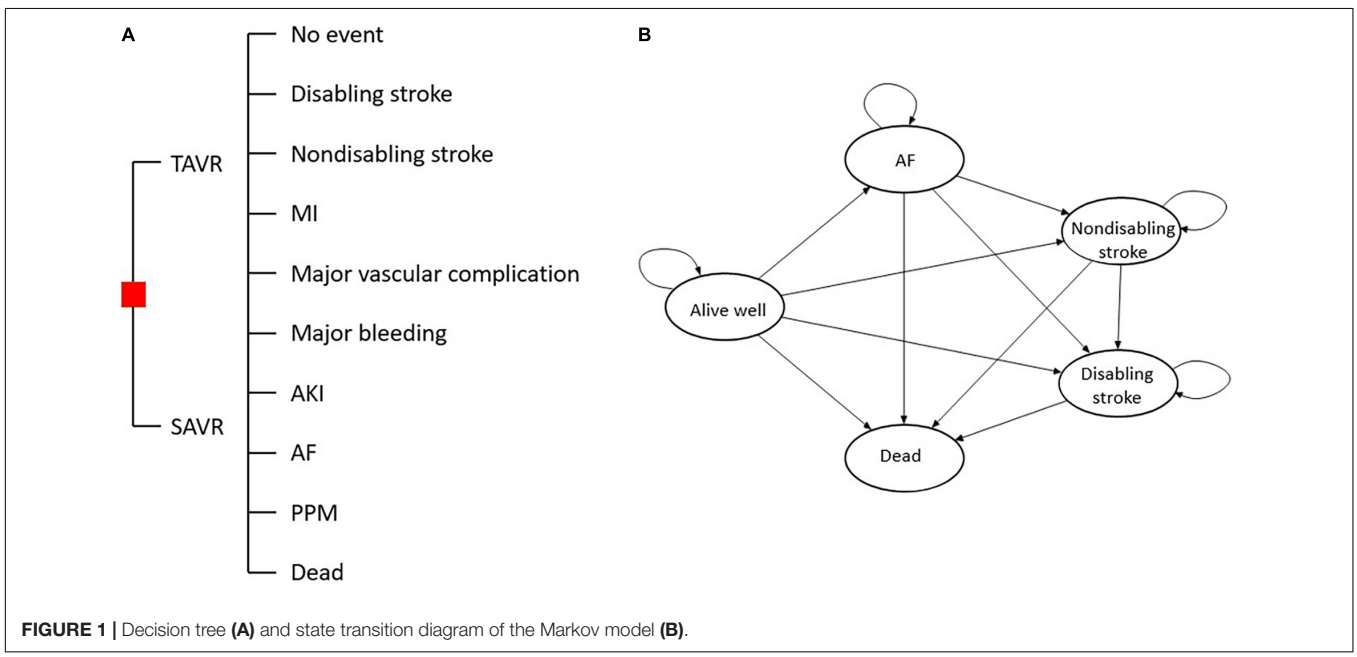

FIGURE 1 | Decision tree **(A)** and state transition diagram of the Markov model **(B)**.

1 month and 5 years post-procedure, they were transformed into probability per month. Considering that the probabilities of complications and death within 1, 2, and 5 years may vary, we separately calculated the data between these periods. The non-cardiovascular mortality in the Markov model was obtained from the China National Bureau of Statistics[1]. As the AF incidence was much higher in patients with a procedure than without a procedure, the AF incidence was accessed from the PARTNER 2 study. However, the mortality of AF was obtained from a study conducted in a Chinese population (15), and the mortality of stroke was also derived from a Chinese cohort study. The key input parameters in this study are listed in **Table 1**.

Costs

The key costs are displayed in **Table 1**. The costs of TAVR are shown in USD, including the TAVR device costs, medicine costs, diagnosis costs, and other costs, and the overall costs of SAVR are also shown in USD. Different from previous studies, the costs in the present study were derived from a domestic article, and the costs of intensive care unit (ICU) or ward stay were covered in the medicine and other costs. The costs of stroke, AF, MI, major bleeding, AKI, and permanent pacemaker were obtained from a published article. Because there are no explicit costs of major vascular complications, we consulted two experts in this field and adopted the value of 5,000 USD as its cost. All the costs were discounted at.037 annually, which was the mean medical consumer price index (CPI) in the past 5 years in China. The range of costs was extracted from a published article. If the costs could not be extracted from a published article, we adopted 0.5 fold and 2 fold as the lower and higher limits, respectively. All the costs were converted from Chinese renminbi (RMB) to USD at a ratio of 6.5, which was the mean ratio in 2021.

Utilities

If there were utilities for the Chinese population, we adopted the domestic value; otherwise, we adopted the commonly used utilities. The base utilities of post-procedure were obtained from a published article investigating the utilities of TAVR and SAVR, and we adopted the disutility for complications including AF, bleeding, major vascular complications, non-disabling stroke, and AKI. The utility for disabling stroke was a fixed value of.39, which is commonly used in published studies.

Outcomes

The primary outcome of this study was the incremental cost-effectiveness ratio (ICER), representing the incremental costs per quality-adjusted life-year (QALY). As there was no specific willing-to-pay (WTP) threshold in China, we selected three times the per capita GDP in China in 2021 as the WTP, which was 37,500 USD. The TAVR would be considered cost-effective if the ICER was less than 37,500 USD/QALY; otherwise, it would be thought as not cost-effective. In addition, if the TAVR was not cost-effective, the cost leading to cost-effectiveness would be calculated.

[1]http://www.stats.gov.cn/

Sensitive Analysis

One-way sensitive analysis was conducted to compare the effects of variables on ICER, and the result was illustrated in a tornado diagram. Probabilistic sensitive analysis (PSA) was employed using 10,000 times of Monte Carlo simulation. All the costs were assumed to follow the gamma distribution, and probabilities were assumed to follow the beta distribution. Cost-effectiveness acceptability curves and a scatter plot were used to show the uncertainty.

Given that the cost of the TAVR device may vary among different regions, we also adopted different costs for scenario analysis.

RESULTS

The periprocedural complication incidence, transition probabilities, utilities, and costs are listed in **Tables 1**, **2**. The range, distribution, and sources are also displayed in **Tables 1**, **2**. All the analyses were performed based on the above data.

Base Case

In the base case, after a simulation of 5 years, compared to SAVR, TAVR gained plus.115 QALY (2.826 vs. 2.712 QALY) but led to a higher cost of 54,573 USD, which was 35,002 USD in SAVR. The ICER of TAVR versus SAVR was 170,056 USD/QALY, which was higher than three times the per capita GDP in China (**Table 3**).

Sensitive Analysis

As shown in **Figure 2**, the cost of the TAVR device had the greatest impact on ICER. When the cost of the TAVR device fluctuated from 22,965 to 68,086 USD, the ICER ranged from –20,611 to 359,652 USD/QALY. The costs of the SAVR device also impacted the ICER. The ICER fluctuated between 39,357 and 234,602 USD/QALY when the SAVR cost decreased from 31,159 to 7,790 USD. Other variables had little impact on the ICER fluctuation. The ICER was consistently greater than 100,000 USD/QALY regardless of the changes in other variables.

The cost-effectiveness acceptability curve suggested that when the WTP threshold is 100,000 USD, the acceptability of TAVR is $< 10\%$. If the WTP is $> 160{,}000$ USD, the acceptability can exceed 50% (**Figure 3**). The scatter plot indicated that under the current context, TAVR could be cost-effective with a 5% probability (**Figure 4**).

Scenario Analysis

The current price of the imported TAVR device is approximately 45,526 USD, ranging from 17,268 to 40,975 USD in regions outside China, and the price for the domestic TAVR device is approximately 33,846 USD. We performed a scenario analysis based on the above costs and found that under the current Chinese domestic TAVR device costs, the TAVR is still not cost-effective, and the ICER is 71,813, which is 5.75 times higher than the current per capita GDP in China. However, if we adopted the price of TAVR in Canada, TAVR would be cost-effective due to its lower costs compared to SAVR. In addition, we also found that when the TAVR price is

TABLE 1 | Periprocedural complications incidence and transition probabilities in the model.

	Base	*SD*	Range low	Range high	Source
Periprocedural complications incidence in TAVR (30 days)					
AF	0.091	0.009	0.073	0.109	(14)
AKI	0.013	0.004	0.006	0.02	(14)
Bleeding	0.104	0.01	0.085	0.123	(14)
Death	0.039	0.006	0.027	0.051	(14)
Disabling stroke	0.032	0.006	0.021	0.043	(14)
Major vascular complication	0.079	0.008	0.062	0.096	(14)
MI	0.012	0.003	0.005	0.019	(14)
Non-disabling stroke	0.023	0.005	0.014	0.032	(14)
PPM	0.085	0.009	0.068	0.102	(14)
Periprocedural incidence in SAVR (30 days)					
AF	0.264	0.014	0.237	0.291	(14)
AKI	0.031	0.005	0.02	0.042	(14)
Bleeding	0.434	0.016	0.404	0.464	(14)
Death	0.041	0.006	0.029	0.053	(14)
Disabling stroke	0.043	0.006	0.031	0.055	(14)
Major vascular complication	0.05	0.007	0.037	0.063	(14)
MI	0.019	0.004	0.011	0.027	(14)
Non-disabling stroke	0.018	0.004	0.01	0.026	(14)
PPM	0.069	0.008	0.053	0.085	(14)
Transition probabilities of no event to AF in TAVR (per month)					
2–12 months	0.001	/	/	/	(14)
13–24 months	0.0011	/	/	/	(14)
25–60 months	0.0014	/	/	/	(9)
Transition probabilities of no event to AF in SAVR (per month)					
2–12 months	0.001	/	/	/	(14)
13–24 months	0.0001	/	/	/	(14)
25–60 months	0.0011	/	/	/	(9)
Transition probabilities of no event to non-disabling stroke in TAVR (per month)					
2–12 months	0.0007	/	/	/	(14)
13–24 months	0.0003	/	/	/	(14)
25–60 months	0.0005	/	/	/	(9)
Transition probabilities of no event to non-disabling stroke in SAVR (per month)					
2–12 months	0.0007	/	/	/	(14)
13–24 months	0.0003	/	/	/	(14)
25–60 months	0.0003	/	/	/	(9)
Transition probabilities of no event to disabling stroke in TAVR (per month)					
2–12 months	0.0017	/	/	/	(14)
13–24 months	0.0011	/	/	/	(14)
25–60 months	0.0011	/	/	/	(9)
Transition probabilities of no event to disabling stroke in SAVR (per month)					
2–12 months	0.0014	/	/	/	(14)
13–24 months	0.0005	/	/	/	(14)
25–60 months	0.0007	/	/	/	(9)
Cardiovascular mortality in TAVR (per month)					
2–12 months	0.0036	/	/	/	(14)
13–24 months	0.0027	/	/	/	(14)
25–60 months	0.0067	/	/	/	(9)
Cardiovascular mortality in SAVR (per month)					
2–12 months	0.0047	/	/	/	(14)
13–24 months	0.0029	/	/	/	(14)
25 and 60 months	0.0057	/	/	/	(9)
Non-cardiovascular mortality for aged 80–85 (per month)	0.0026	/	/	/	(15)
Transition probability of AF to stroke (per month)	0.0016	/	/	/	(28)
Transition probability of AF to disabling stroke (per month)	0.0011	/	/	/	(28)
Transition probability of AF to non-disabling stroke (per month)	0.0005	/	/	/	(28)
Transition probability of AF to death (per month)	0.0024	/	/	/	(28)

TABLE 2 | Utilities and costs in the model.

Utility	Base	*SD*	Range low	Range high	Sources
No event in TAVR <7 months	0.74	0.24	/	/	(19, 22)
No event in TAVR 7–12 months	0.76	0.2	/	/	(19, 22)
No event in TAVR >12 months	0.75	0.22	/	/	(19, 22)
No event in SAVR <7 months	0.68	0.24	/	/	(19, 22)
No event in SAVR 7–12 months	0.75	0.27	/	/	(19, 22)
No event in SAVR >12 months	0.74	0.23	/	/	(19, 22)
Disabling stroke	0.39	/	0.31	0.52	(29)
Disutility					
Non-disabling stroke	–0.161	0.054	/	/	(22)
AF	–0.038	/	–0.038	0	(24)
AKI	–0.177	/	–0.177	0	(24)
Bleeding	–0.447	/	–0.447	0	(24)
Major vascular complication	–0.046	/	–0.046	0	(24)
Myocardial infarction	–0.1	/	–0.1	0	(30)
Costs					
TAVR device	45526	11511	22965	68087	(21)
TAVR diagnosis	2016	721	1008	4031	(21)
TAVR medicine	2025	1163	1013	4050	(21)
TAVR others	824	112	605	1043	(21)
SAVR device	15580	15933	7790	31160	(21)
SAVR diagnosis	2076	677	749	3403	(21)
SAVR medicine	8182	5703	4091	16364	(21)
SAVR others	1401	1883	700	2801	(21)
Non-disabling stroke event	1898	/	1096	2390	(31)
Non-disabling annual cost	1349	329	404	1721	(31)
Disabling stroke event	2509	/	1379	3291	(31)
Disabling stroke annual cost	2053	516	516	2582	(31)
Myocardial infarction event	6750	/	3375	13500	(32)
Major vascular complication	5500	/	2750	11000	Calculation
Major bleeding	868	69	732	1003	(33)
AKI	1849	1176	924	3697	(34)
New permanent pacemaker	13680	4380	5094	22265	(35)
AF event	16192	/	14124	18475	(36)
AF annual cost	1891	/	945	3781	(37)
Stroke death	2151	458	1011	2843	(31)
Discount rate	0.037	/	/	/	(38)

26,794 USD, the ICER would be 12,500 USD/QALY, which is equal to the current per capita GDP in China, and the ICER would be 37,500 USD/QALY (three times greater than the current per capita GDP in China) when the TAVR price is 29,766 USD.

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the cost-effectiveness of TAVR vs. SAVR in Chinese patients with AS. We found that in the intermediate surgical risk population, TAVR is not currently cost-effective in China, and TAVR could be cost-effective only when the TAVR device cost is decreased to 29,766 USD. Thus, if the TAVR device cost is lowered to 26,794 USD, TAVR would be highly cost-effective.

Some studies have reported that TAVR is cost-effective in their countries (16–19). However, in the present study, we concluded that TAVR is not currently cost-effective in China due to several reasons. First, the costs of the TAVR device vary among different regions, ranging from 17,268 USD to 45,526 USD (20, 21). In Canada, the cost is 17,268 USD, but the cost is approximately 45,526 USD in China, resulting in an ICER of 170,056 USD/QALY, which is higher than the per capita GDP in China. However, if we adopted the Canadian TAVR device cost in our analysis, the cost of TAVR would be less but the effect would not change. Second, as China is the largest developing country, the per capita GDP is only 12,500 USD, which is lower than that in the United States, Canada, Australia, and Japan, which may cause a lower threshold of WTP. The ICER of 170,056 USD/QALY may be accepted in the United States and Australia with a per capita GDP of more than 60,000 USD, but it cannot be currently accepted in China. Third, there is a difference in the composition of surgical costs between China and other countries. In China, the TAVR device costs account for over 90% of the overall costs, and the proportion of device costs is much higher in China than in other countries (21). In the USA, the proportion of the TAVR device costs is less than 65% of the total costs, and in Australia and Canada (20, 22), the proportion of the TAVR device costs is lower than 60%. The unique situation in China leads to the fact that TAVR is not currently cost-effective in China.

Compared to SAVR, TAVR achieves similar clinical outcomes (7–9). In inoperative patients, TAVR may significantly reduce mortality and other outcomes (23), but in patients with high risk or intermediate risk, the published clinical trials have indicated that TAVR displays similar efficacy to that of SAVR (7, 14). The improvement of TAVR versus SAVR may lie in the relief of

TABLE 3 | Base case and scenario analysis based on different TAVR device cost.

	Arm	TAVR/SAVR costs (USD)	Summary Costs (USD)	Summary Effectiveness (QALY)	Incremental Cost (USD)	Incremental Effectiveness (QALY)	ICER (USD/QALY)
Base case	SAVR	15580	35001	2.71	/	/	/
	TAVR	45526	54573	2.83	19571	0.115	170056
Scenario 1	TAVR	33846	43266	2.83	8265	0.115	71813
Scenario 2	TAVR	17268	27219	2.83	–7782	0.115	–67621
Scenario 3	TAVR	26794	36439	2.83	1438	0.115	12500
Scenario 4	TAVR	29766	39316	2.83	4315	0.115	37500

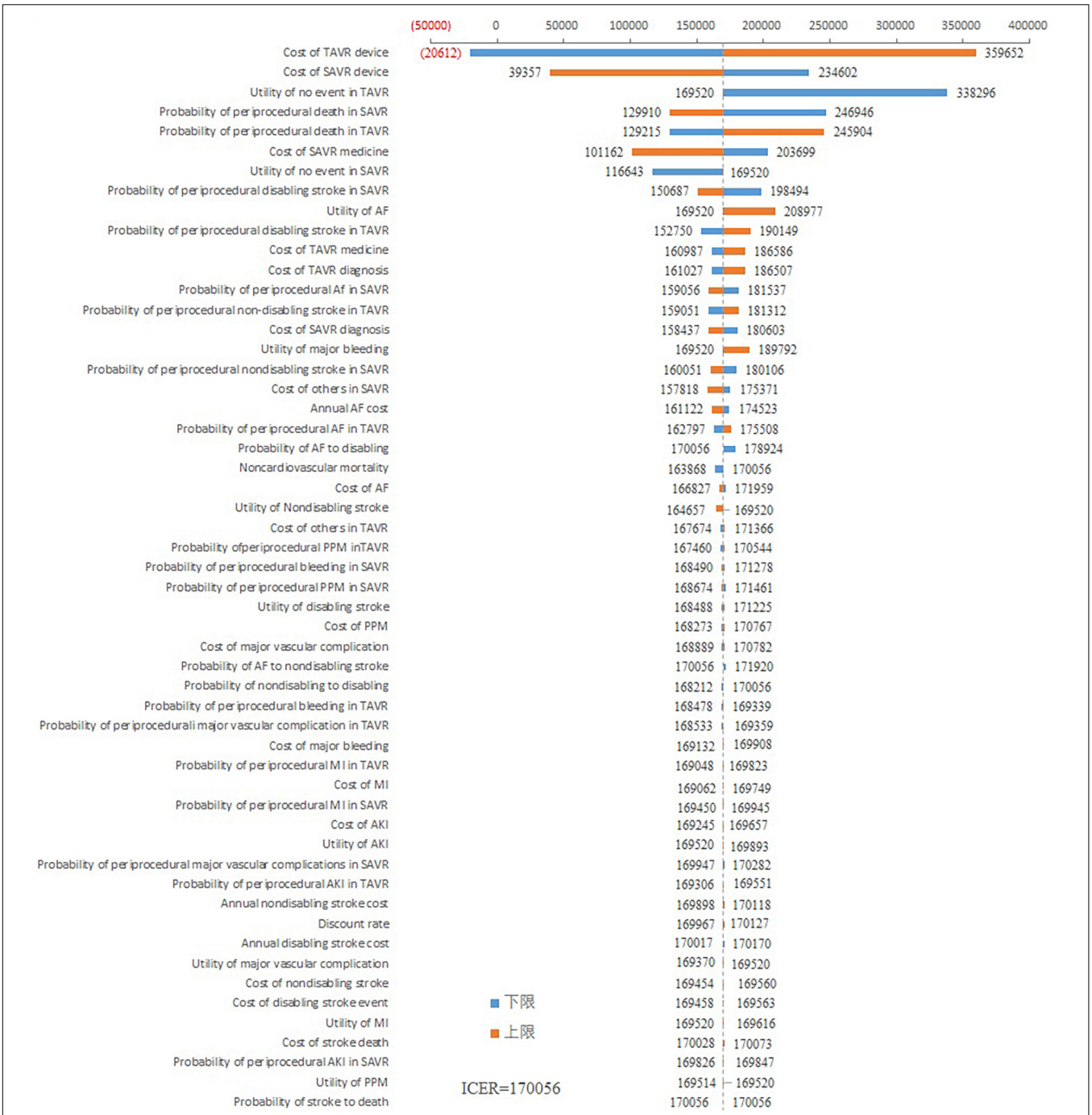

FIGURE 2 | Tornado diagram based on the one-way sensitivity analysis.

symptoms, indicating that patients who underwent TAVR may achieve higher utilities than those who received SAVR, especially in the periprocedural period (24). In the PARTNER 2 study, the periprocedural mortality is 6.1% in the TAVR group versus 8.0% in the SAVR group, but these differences are not statistically significant. When the follow-up period is extended to 5 years, the mortalities in TAVR and SAVR groups are 47.9 and 43.4%, respectively (9, 14). A previous meta-analysis conducted by our team has also demonstrated that TAVR has similar efficacy to that of SAVR regardless of the follow-up period (10). A similar efficacy but higher costs may suggest that TAVR is not cost-effective in China. In addition, the durability of TAVR should be investigated. However, studies thus far have shown that TAVR is safe. The durability of SAVR needs to be evaluated for at least 10 years of follow-up (25), but the longest reported follow-up period of TAVR is only 6 years (26).

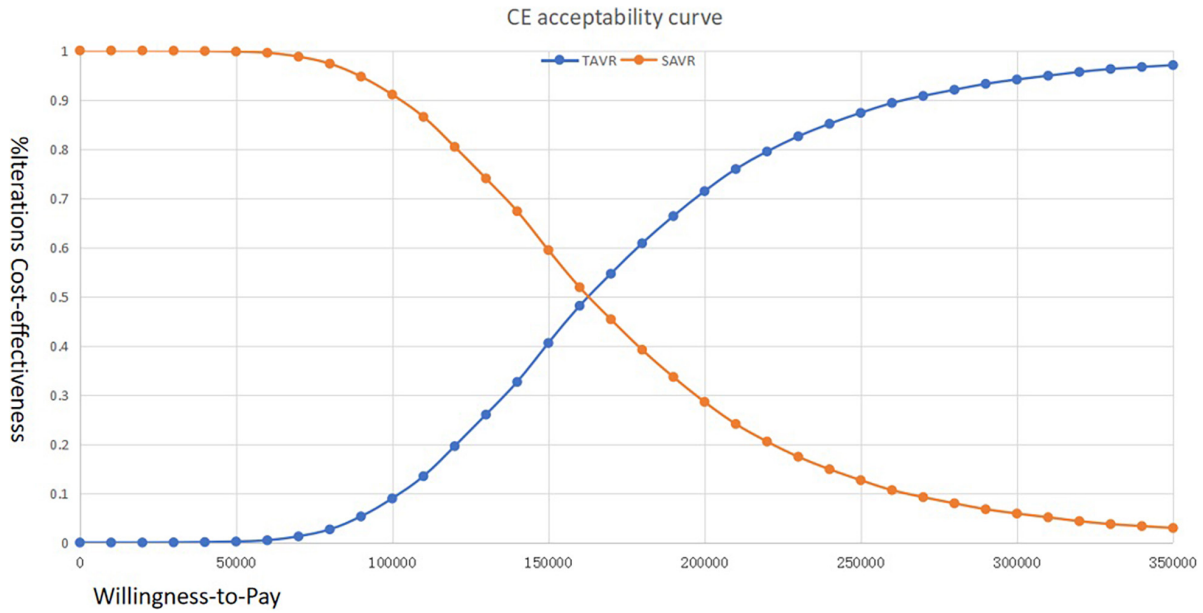

FIGURE 3 | Cost-effectiveness acceptability curve of transcatheter aortic valve replacement (TAVR) vs. surgical aortic valve replacement (SAVR) among Chinese patients with aortic stenosis (AS) who are at immediate risk.

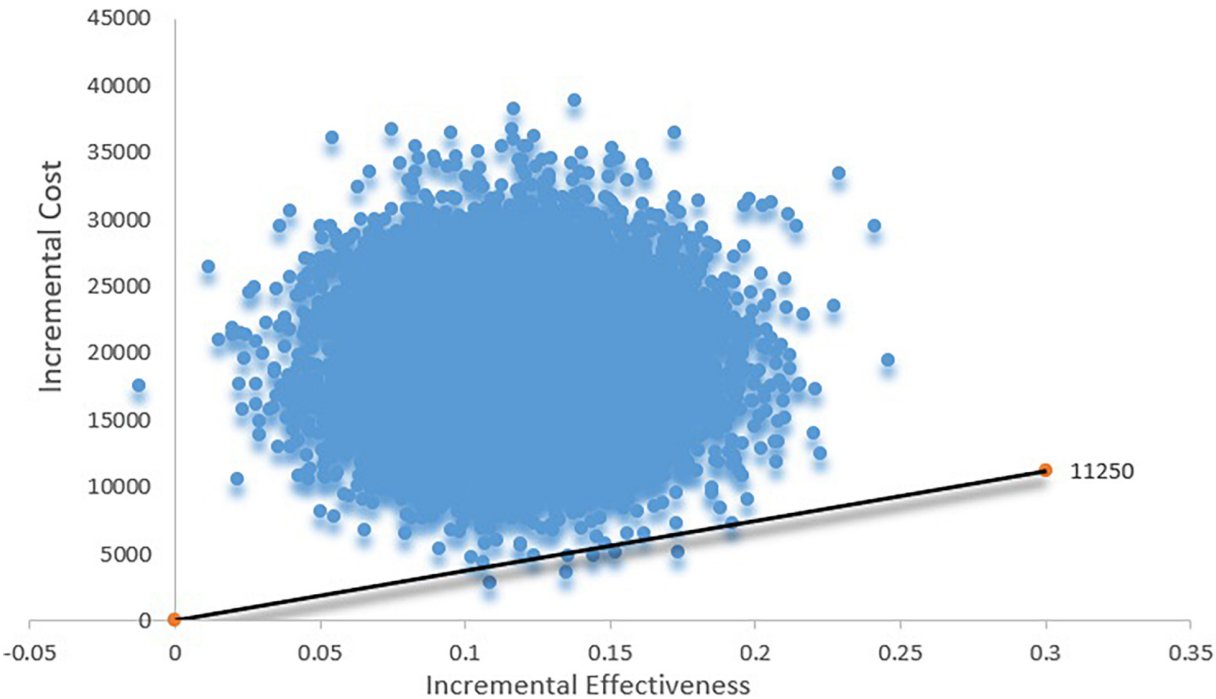

FIGURE 4 | Scatter plot based on probabilistic sensitive analysis. The probability that TAVR is cost-effective is less than 5%.

One-way sensitive analysis showed that the costs of the TAVR device had the largest impact on the ICER. The PSA showed that TAVR was cost-effective only with a 5% probability. These results indicated that under current costs, TAVR is not cost-effective. The scenario analysis showed that when the costs of the TAVR device are decreased to 29,766 USD, the TAVR could be cost-effective. If the costs of TAVR are lowered to 26,794 USD, TAVR would be highly cost-effective. The Chinese government has launched a collective purchase project, which requires that only cost-effective drugs or medical devices

can be used in public hospitals in China, indicating that only drugs or medical devices listed in the collective purchase can be widely used in China at present (27). The present study demonstrated that TAVR could be cost-effective only when the costs are lowered to 29,766 USD. Importantly, the present study provided a viewpoint for TAVR from the Chinese health care system payer's perspective.

The present study had several limitations. First, the cardiovascular mortality in our study was derived from the PARTNER 2 study with only a few Chinese patients included in the study. The cardiovascular mortality in Chinese patients who underwent TAVR may be slightly different from that in the PARTNER 2 study. Second, the simulation period in our study was 5 years, which was consistent with the PARTNER 2 study, but some studies have shown that a longer follow-up period may allow the TAVR to be cost-effective. Third, the data in our study were transformed from a published article. The inability to access the raw data limited our further analysis. Last, the present study was performed based on a published study rather than real-world data in China. Thus, real patient-level data may be more appropriate, indicating that additional studies based on the Chinese population are needed.

CONCLUSION

Transcatheter aortic valve replacement is not currently cost-effective in China. However, TAVR could be cost-effective with a reduction of costs to 29,766 USD, which is approximately 65% of the current price.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LQ and CZ came up with the idea and designed the protocol. WZ and YL synthesized the data and drafted the manuscript. YL and HW participated in the data collection and data analysis. All authors approved the final version of the manuscript.

FUNDING

This work was supported by Capital's Funds for Health Improvement and Research. No: 2020-2-1054.

ACKNOWLEDGMENTS

We thank Charlesworth Author Services for editing the English text of a draft of this manuscript.

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frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 27 May 2022
doi: 10.3389/fcvm.2022.893878

Impact of New-Onset Persistent Left Bundle Branch Block on Reverse Cardiac Remodeling and Clinical Outcomes After Transcatheter Aortic Valve Replacement

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Specialty section:
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

Received: 11 March 2022
Accepted: 03 May 2022
Published: 27 May 2022

Citation:
Kim K, Ko Y-G, Shim CY, Ryu J, Lee Y-J, Seo J, Lee S-J, Cho I, Hong S-J, Ahn C-M, Kim J-S, Kim B-K, Hong G-R, Ha J-W, Choi D and Hong M-K (2022) Impact of New-Onset Persistent Left Bundle Branch Block on Reverse Cardiac Remodeling and Clinical Outcomes After Transcatheter Aortic Valve Replacement. Front. Cardiovasc. Med. 9:893878. doi: 10.3389/fcvm.2022.893878

Background: The clinical implication of new-onset left bundle branch block (LBBB) after transcatheter aortic valve replacement (TAVR) remains controversial. We investigated the impact of new-onset persistent LBBB on reverse cardiac remodeling and clinical outcomes after TAVR.

Methods: Among 478 patients who had undergone TAVR for symptomatic severe aortic stenosis from 2011 to 2021, we analyzed 364 patients after excluding patients with pre-existing intraventricular conduction disturbance or a pacing rhythm before or during the indexed hospitalization for TAVR. Echocardiographic variables of cardiac remodeling at baseline and 1 year after TAVR were comprehensively analyzed. The primary outcome was a composite of cardiovascular death and hospitalization for heart failure. Secondary outcomes were all-cause death and individual components of the primary outcome.

Result: New-onset persistent LBBB occurred in 41 (11.3%) patients after TAVR. The no LBBB group showed a significant increase in the left ventricular (LV) ejection fraction and decreases in LV dimensions, the left atrial volume index, and LV mass index 1 year after TAVR (all $p < 0.001$). However, the new LBBB group showed no significant changes in these parameters. During a median follow-up of 18.1 months, the new LBBB group experienced a higher incidence of primary outcomes [hazard ratio (HR): 5.03; 95% confidence interval (CI): 2.60–9.73; $p < 0.001$] and all-cause death (HR: 2.80; 95% CI: 1.38–5.69; $p = 0.003$). The data were similar after multivariable regression analysis.

Conclusion: New-onset persistent LBBB after TAVR is associated with insufficient reverse cardiac remodeling and increased adverse clinical events.

Keywords: transcatheter aortic valve replacement, left bundle branch block, cardiac remodeling, prognosis, aortic stenosis

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an effective alternative to surgical aortic valve replacement (SAVR) for symptomatic severe aortic stenosis (AS) in patients with high, intermediate, or low surgical risk (1–5). However, conduction disturbances and the subsequent need for a permanent pacemaker (PPM) implantation occur more frequently after TAVR than after SAVR and remain the main complications of TAVR (6). The development of periprocedural conduction disturbances during TAVR is caused by direct mechanical insult to the conduction system, located in the proximity of the aortic valve (6). New-onset left bundle branch block (LBBB) is the most common conduction disturbance following TAVR, and its incidence varies from 4 to 30% with a balloon-expandable valve and 18–65% with a self-expandable valve (6). Despite its frequent incidence, the clinical implications of new-onset persistent LBBB after TAVR remain controversial (6–9). Several studies have reported conflicting results regarding the association between new-onset LBBB and increased cardiovascular mortality (7–10). Furthermore, limited data are available on the impact of new-onset LBBB on cardiac remodeling and function after TAVR. Because the indication for TAVR gradually expands to low-risk and younger patients, clarifying the true implication of new-onset LBBB following TAVR is crucial. Thus, the present study aimed to investigate the clinical impact of new-onset LBBB after TAVR on clinical outcomes and cardiac remodeling.

MATERIALS AND METHODS

Study Population

A total of 478 consecutive patients who had undergone TAVR for symptomatic severe AS at Severance Cardiovascular Hospital from June 2011 to May 2021 were retrospectively reviewed. We excluded patients with pre-existing intraventricular conduction disturbances ($n = 77$) (QRS >120 ms, LBBB, and right bundle branch block) before TAVR and patients who had received permanent pacemaker implantation before or during the index hospitalization for TAVR ($n = 34$). There was no patient with previously implanted intracardiac cardioverter-defibrillator or cardiac resynchronization therapy. The present study also excluded three patients who did not survive immediately after TAVR. Thus, 364 patients were included in the final analysis in this study.

Surgical risk was estimated using the European System for Cardiac Operative Risk evaluation (EuroSCORE II) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score (11, 12). The decision to use TAVR as the treatment modality was made by a multidisciplinary heart team, as previously reported (13, 14). The transcatheter aortic valve type was chosen at the discretion of the operators based on the anatomical characteristics of the aortic valve, aortic root, and vascular access. The Institutional Review Board of Severance Hospital approved this study, which was conducted in compliance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design.

LBBB was defined as a QRS duration > 120 ms, delayed onset of intrinsicoid deflection in leads V5 and V6, broad monophasic R waves that are usually notched in leads I, V5 and V6, and secondary ST- and T-wave changes opposite in direction to the major QRS deflection (15). In this study, new-onset LBBB was defined as persistent LBBB developed during or after the TAVR procedure and documented on the electrocardiogram (ECG) at hospital discharge or 7 days after TAVR.

Echocardiography

All echocardiographic studies were performed using commercially available equipment and were reviewed by imaging cardiologists without knowledge of the clinical data. Standard measurements were performed according to current guidelines (16). LV EF was measured using linear measurement or biplane methods. The LV mass index was calculated using the Devereux formula. The left atrial volume index (LAVI) was calculated using the biplane method. Pulmonary artery systolic pressure and right atrial pressure were estimated using tricuspid regurgitation jet velocity and inferior vena cava (16). Right ventricular (RV) systolic dysfunction was defined as in case of tricuspid annular plane systolic excursion <17 mm, tricuspid pulsed Doppler S wave <9.5 cm/s, or fractional area change <35% (16). Preprocedural and postprocedural AV hemodynamic parameters such as the AV peak flow velocity, transaortic pressure gradient, and aortic valve area were calculated using Doppler echocardiography (17). Concomitant at least moderate mitral or tricuspid regurgitation was defined as other valve pathology. The severity of paravalvular regurgitation was semi-quantitatively assessed according to recent recommendations (17). Patients underwent baseline echocardiography before TAVR and regular planned examinations annually after TAVR, according to standard institutional follow-up protocol. To investigate the impact of LBBB on reverse cardiac remodeling, baseline and 1-year echocardiographic parameters were compared according to the presence of LBBB.

Clinical Outcomes

The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. Secondary outcomes included all-cause death, cardiovascular death, hospitalization for heart failure, number of hospitalizations for heart failure event, and permanent pacemaker implantation. All clinical outcomes were analyzed according to the Valve Academic Research Consortium-3 consensus (18).

Statistical Analysis

Categorical variables were presented as numbers (percentages) and were compared using chi-squared test or Fisher's exact test. Continuous variables were presented as means ± standard deviation and compared using Student's *t*-test or the Wilcoxon rank-sum test. Time-to-event variables were presented as

Abbreviations: AS, Aortic stenosis; AV, Aortic valve; EF, Ejection fraction; LBBB, Left bundle branch block; LV, Left ventricle; NYHA, New York Heart Association; PPM, Permanent pacemaker; SAVR, Surgical aortic valve replacement; TAVR, Transcatheter aortic valve replacement.

Kaplan-Meier event rates and were compared using the log-rank test. The total number of hospitalizations for heart failure was calculated and compared using Poisson regression. Multivariable analysis for clinical outcomes was performed using a multivariable Cox proportional hazard regression model. The covariates included in the adjusted models were variables with clinical relevance, such as age, sex, New York Heart failure Association (NYHA) functional class, comorbidities such as chronic lung disease, end-stage renal disease, coronary artery disease, peripheral artery disease, prior cardiac surgery, atrial fibrillation, EuroSCORE II, STS-PROM score, baseline LV EF, RV systolic dysfunction, pulmonary artery systolic pressure and moderate or severe paravalvular regurgitation. The baseline and 1-year echocardiographic parameters were compared using paired *t*-test or the Wilcoxon signed-rank test as appropriate. Two-way repeated ANOVA was used to determine differences between the baseline and 1-year echocardiographic parameters according to the study groups. Missing data of 1-year echocardiographic data was not imputated. As sensitivity analysis, baseline and 1-year echocardiographic data was compared with multiple imputation of missing data. All the tests were two-tailed, and p-values < 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.1.0 (The R Foundation for Statistical Computing; www.R-project.org).

RESULTS

Baseline Characteristics

Of the 364 patients, 41 (11.3%) had new-onset persistent LBBB after TAVR. The baseline clinical characteristics are shown in **Table 1.** The two groups, new LBBB group and no LBBB group, were similar in sex distribution, symptom severity, comorbidities, and the surgical risk score. The new LBBB group was younger than the no LBBB group, but the difference did not reach statistical significance. The new LBBB group had a higher prevalence of prior cardiac surgery. The choice of transcatheter aortic valve was not statistically different between the two groups; however, the new LBBB group had a trend toward more frequent use of self-expandable valves than the no LBBB group. Predilation rate was low in the new LBBB group, and the degree of paravalvular regurgitation was comparable in both groups.

TABLE 1 | Baseline characteristics.

	New LBBB ($N = 41$)	No LBBB ($N = 323$)	p-value
Age, years	79.7 ± 6.0	81.3 ± 5.3	0.080
Male sex, *n* (%)	17 (41.5)	149 (46.1)	0.690
NYHA class III-IV, *n* (%)	25 (61.0)	186 (57.6)	0.805
Hypertension, *n* (%)	37 (90.2)	268 (83.0)	0.334
Diabetes mellitus, *n* (%)	20 (48.8)	131 (40.6)	0.402
End-stage renal disease	5 (12.2)	21 (6.5)	0.312
Chronic lung disease	7 (17.1)	51 (15.8)	0.999
Cerebrovascular accident	8 (19.5)	45 (13.9)	0.472
Coronary artery disease	24 (58.5)	175 (54.2)	0.718
Previous myocardial infarction	5 (12.2)	24 (7.4)	0.450
Prior coronary intervention	11 (26.8)	75 (23.2)	0.751
Prior cardiac surgery	6 (14.6)	17 (5.3)	0.047
Coronary artery bypass	5 (12.2)	14 (4.3)	0.079
Mitral valve surgery	1 (2.4)	3 (0.9)	0.937
Atrial fibrillation	7 (17.1)	50 (15.5)	0.971
Peripheral artery disease	9 (22.0)	38 (11.8)	0.113
Concomitant other valve pathology	1 (2.4)	33 (10.2)	0.184
Mitral regurgitation	0 (0.0)	18 (5.6)	0.243
Tricuspid regurgitation	1 (2.4)	18 (5.6)	0.633
EuroSCORE II	4.7 ± 4.2	5.2 ± 8.0	0.474
STS-PROM, %	6.1 ± 5.3	5.8 ± 5.9	0.731
Valve			0.137
Corevalve	9 (22.0)	38 (11.8)	
Evolut Pro	5 (12.2)	52 (16.1)	
Evolut R	16 (39.0)	112 (34.7)	
LOTUS	2 (4.9)	6 (1.9)	
Sapien3	9 (22.0)	115 (35.6)	
Valve type			0.118
Balloon-expandable	9 (22.0)	115 (35.6)	
Self-expandable	32 (78.0)	208 (64.4)	
Predilatation	13 (31.7)	178 (55.1)	0.008
Postdilatation	10 (24.4)	119 (36.8)	0.162
Paravalvular regurgitation			0.878
No, trace	25 (61.0)	210 (65.0)	
Mild	13 (31.7)	92 (28.5)	
Moderate	3 (7.3)	21 (6.5)	

LBBB, left bundle branch block; NYHA, New York Heart Association.

New-Onset LBBB and Reverse Cardiac Remodeling

The echocardiographic characteristics are summarized in **Table 2**. The baseline echocardiographic parameters were comparable between the new LBBB and no LBBB groups. One-year follow-up echocardiograms were obtained in 264 (73%) patients. At the 1-year follow-up after TAVR, both groups showed improved and similar AV hemodynamic parameters, such as the peak velocity, pressure gradient, and AV area; however, the new LBBB group showed a lower LV EF (59.1 ± 13.7 vs. 65.8 ± 9.6%; $p = 0.018$), a larger LV end-diastolic dimension (48.6 ± 5.5 vs. 46.5 ± 5.0 mm; $p = 0.037$) and end-systolic dimension (33.1 ± 6.7 vs. 30.3 ± 5.0 mm; $p = 0.035$), and higher E/e′ (28.2 ± 15.1 vs. 20.5 ± 7.9; $p = 0.029$) than the no LBBB group.

When the baseline and 1-year echocardiographic parameters were compared, the no LBBB group showed a significantly increased LV EF and a decreased LV end-systolic dimension, LV mass index, and left atrial (LA) volume index (all $p < 0.001$; **Figure 1**). However, the new LBBB group had significantly decreased LV EF (−6.0 ± 14.5%; $p = 0.038$) at the 1-year follow-up and no significant changes in the LV end-systolic dimension, LV mass index, and LA volume index. The sensitivity

TABLE 2 | Echocardiographic data.

	New LBBB (*N* = 41)	No LBBB (*N* = 323)	*p*-value
Baseline, *n*	41 (100.0)	323 (100.0)	>0.999
LBBB at 30 days, *n*(%)	36/41 (87.9)	0/323 (0)	<0.001
AV peak velocity, m/s	4.2 ± 0.7	4.5 ± 0.7	0.007
AV mean pressure gradient, mmHg	43.8 ± 17.5	51.6 ± 17.2	0.008
AV area, cm^2	0.8 ± 0.2	0.7 ± 0.2	0.123
Annulus diameter, mm	23.2 ± 2.5	23.5 ± 2.4	0.530
LV ejection fraction, %	61.9 ± 16.3	60.1 ± 14.2	0.461
LV end diastolic dimension, mm	48.2 ± 6.7	49.6 ± 6.4	0.187
Reduced LV ejection fraction (≤50%), *n* (%)	10 (24.4)	81 (25.1)	0.999
LV end systolic dimension, mm	32.6 ± 8.6	33.9 ± 7.5	0.310
LV mass index, g/m^2	135.2 ± 35.0	144.7 ± 42.1	0.166
LA volume index, ml/m^2	49.5 ± 14.0	52.3 ± 19.9	0.281
E/e′	22.3 ± 9.6	21.4 ± 9.0	0.565
Pulmonary artery systolic pressure, mmHg	36.8 ± 11.4	37.6 ± 13.8	0.735
Estimated right atrial pressure, mmHg	5.6 ± 1.7	6.3 ± 3.0	0.155
RV systolic dysfunction, *n* (%)	1 (2.4)	3 (0.9)	0.937
1-year follow up, *n*	28 (68.3)	236 (73.1)	0.646
LBBB at 1 year, *n* (%)	23/28 (82.1)	5/236 (2.1)	<0.001
AV peak velocity, m/s	2.2 ± 0.5	2.2 ± 0.5	0.882
AV mean pressure gradient, mmHg	10.3 ± 4.5	10.0 ± 4.7	0.830
Effective orifice area, cm^2	1.7 ± 0.5	1.8 ± 0.4	0.187
LV ejection fraction, %	59.1 ± 13.7	65.8 ± 9.6	0.018
LV end diastolic dimension, mm	48.6 ± 5.5	46.5 ± 5.0	0.037
LV end systolic dimension, mm	33.1 ± 6.7	30.3 ± 5.0	0.035
LV mass index, g/m^2	123.3 ± 29.5	119.2 ± 28.9	0.480
LA volume index, ml/m^2	46.1 ± 16.7	45.3 ± 18.2	0.839
E/e′	28.2 ± 15.1	20.5 ± 7.9	0.029
Pulmonary artery systolic pressure, mmHg	32.8 ± 12.5	32.8 ± 9.8	0.994
Estimated right atrial pressure, mmHg	5.4 ± 1.4	5.5 ± 1.8	0.891
RV systolic dysfunction, *n* (%)	1/28 (3.6)	3/236 (1.3)	0.901

AV, aortic valve; E/e′, ratio between the early mitral inflow velocity and mitral annular early diastolic velocity; LBBB, left bundle branch block; LA, left atrium; LV, left ventricle; RV, right ventricle.

analysis with multiple imputation for 1-year echocardiographic data showed similar results (**Supplementary Table 1** and **Supplementary Figure 1**). In the subgroup of patients with baseline LV systolic dysfunction (LV EF ≤ 50%), the new LBBB group showed no significant change in the LV EF (+8.2 ± 19.9%; $p = 0.408$), whereas the no LBBB group showed significant LV EF improvement (+20.5 ± 14.5%; $p < 0.001$) 1 year after TAVR. However, in patients with a preserved LV EF (>50%), the new LBBB group showed a significantly decreased LV EF (−9.0 ± 11.4%; $p < 0.002$) from the baseline while the no LBBB group had a similar LV EF (+1.0 ± 8.1%; $p = 0.092$) after TAVR (**Supplementary Figure 2**).

New-Onset LBBB and Clinical Outcomes

Patients were followed for a median of 18.1 months (interquartile range: 7.7–30.1). All the clinical outcomes after TAVR and hazard ratios for the adverse clinical events are described in **Table 3** and **Figure 2**. The new LBBB group showed a higher rate of primary composite outcome events (cardiovascular death or hospitalization for heart failure) than the no LBBB group (HR: 5.03; 95% CI: 2.60–9.73; $p < 0.001$). The new LBBB group had a higher risk of all-cause death (HR: 2.80; 95% CI: 1.38–5.69; $p = 0.003$), individual events of cardiovascular death (HR: 7.34; 95% CI: 2.35–22.93; $p < 0.001$), and hospitalization for heart failure (HR: 5.25; 95% CI: 2.57–10.75; $p < 0.001$). Furthermore, the new LBBB group had more hospitalizations for heart failure (29.4 vs. 5.1 events per 100-person year; $p < 0.001$) and PPM implantation than the no LBBB group (HR: 5.44; 95% CI: 1.21–24.52; $p = 0.010$). There was no post-procedural CRT implantation. After multivariable adjustment, the patients with new-onset LBBB still had a significantly higher risk for adverse clinical outcomes, with the exception of PPM implantation. In Cox multivariate regression analysis, new-onset persistent LBBB, end-stage renal disease, atrial fibrillation, and prior caridac surgery were identified as independent predictors for the composite events of cardiovascular death and hospitalization for heart failure (**Table 4**).

DISCUSSION

The major findings of the present study were as follows: 1) new-onset persistent LBBB occurred in 11.3% of patients without significant baseline conduction disturbances; 2) new-onset LBBB was associated with insufficient reverse cardiac remodeling and decline in the LV EF 1 year after TAVR; 3) new-onset LBBB was associated with increased occurrence of hospitalization for heart failure, cardiovascular death, and all-cause death.

The incidence of new-onset LBBB in previous studies varies widely because of differences in the inclusion of transient LBBB, timing of measurement, and type of transcatheter valve (6). Generally, new-onset LBBB occurs more frequently with self-expandable valves than with balloon-expanding valves (19). In the present study, the new LBBB group was also treated more frequently with self-expanding than balloon-expanding valves.

LBBB is associated with a shortening of LV diastole, abnormal septal motion with an associated decrease in the regional ejection fraction and an overall reduction in the global LV ejection fraction (20). LBBB further contributes to a vicious circle of LV wall stress, asymmetric hypertrophy, and dilatation that progressively deteriorates LV function (21).

Because concentric LV hypertrophy and reduced contractility is the main cardiac manifestation derived from pressure overload, the reversal of cardiac remodeling is a critical therapeutic

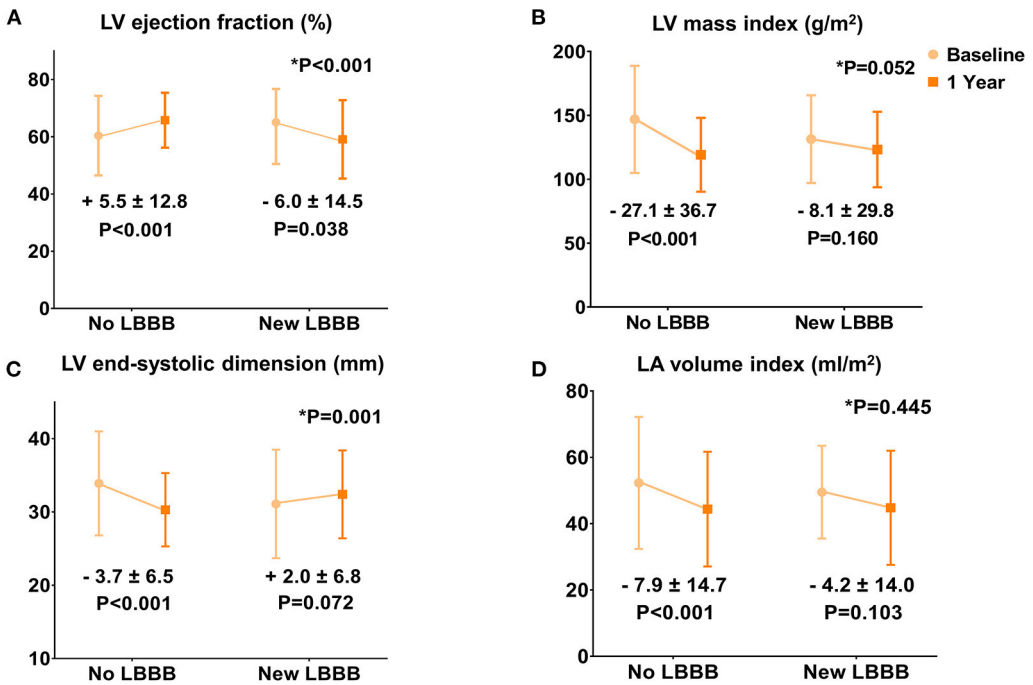

FIGURE 1 | Changes in the echocardiographic parameters 1 year after TAVR. **(A)** Left ventricular ejection fraction. **(B)** Left ventricular mass index. **(C)** Left ventricular end-systolic dimension. **(D)** Left atrial volume index.

TABLE 3 | Clinical outcomes.

Events, *n* (%/year)	New LBBB (*N* = 41)	No LBBB (*N* = 323)	Hazard ratio (95% CI), *p*-value	
			Crude	Adjusted
Primary outcome				
Cardiovascular death or hospitalization for heart failure	14 (18.9)	24 (4.2)	5.03 (2.60–9.73), $p < 0.001$	5.85 (2.87–11.95), $p < 0.001$
Secondary outcomes				
Cardiovascular death	6 (6.5)	6 (1.0)	7.34 (2.35–22.93), $p < 0.001$	7.79 (1.89–32.10), $p < 0.001$
Hospitalization for heart failure	12 (16.2)	20 (3.5)	5.25 (2.57–10.75), $p < 0.001$	5.21 (2.49–10.94), $p < 0.001$
All-cause death	11 (12.0)	27 (4.5)	2.80 (1.38–5.69), $p = 0.003$	2.47 (1.14–5.39), $p = 0.023$
Permanent pacemaker implantation	3 (3.3)	4 (0.7)	5.44 (1.21–24.5), $p = 0.010$	5.89 (0.91–38.23), $p = 0.063$
Number of heart failure hospitalization	27 (29.4)	31 (5.1)	5.91 (3.52–9.95), $p < 0.001$	5.25 (2.90–9.49), $p < 0.001$

CI, confidence interval; LBBB, left bundle branch block.

target in patients with severe AS (22). However, in the present study, new-onset persistent LBBB after TAVR was associated with insufficient reverse cardiac remodeling and decreased LV function. Although patients without conduction abnormalities after TAVR showed increased LV EF and decreased LV and LA dimensions with improved diastolic function at the 1-year follow-up, the patients with new-onset LBBB revealed declined LV EF and no significant reduction in the LV and LA dimensions. Nazif et al. (8) also reported similar findings in a retrospective analysis from the PARTNER II trial. Patients with new LBBB after TAVR demonstrated a decline in the LV EF and increased LV dimensions at 1 and 2 years. Similarly, among patients who had undergone aortic valve surgery, those with electrical dyssynchrony, such as LBBB, and those with an electrical pacing rhythm showed no significant improvement in LV EF compared with patients without conduction disturbance (23).

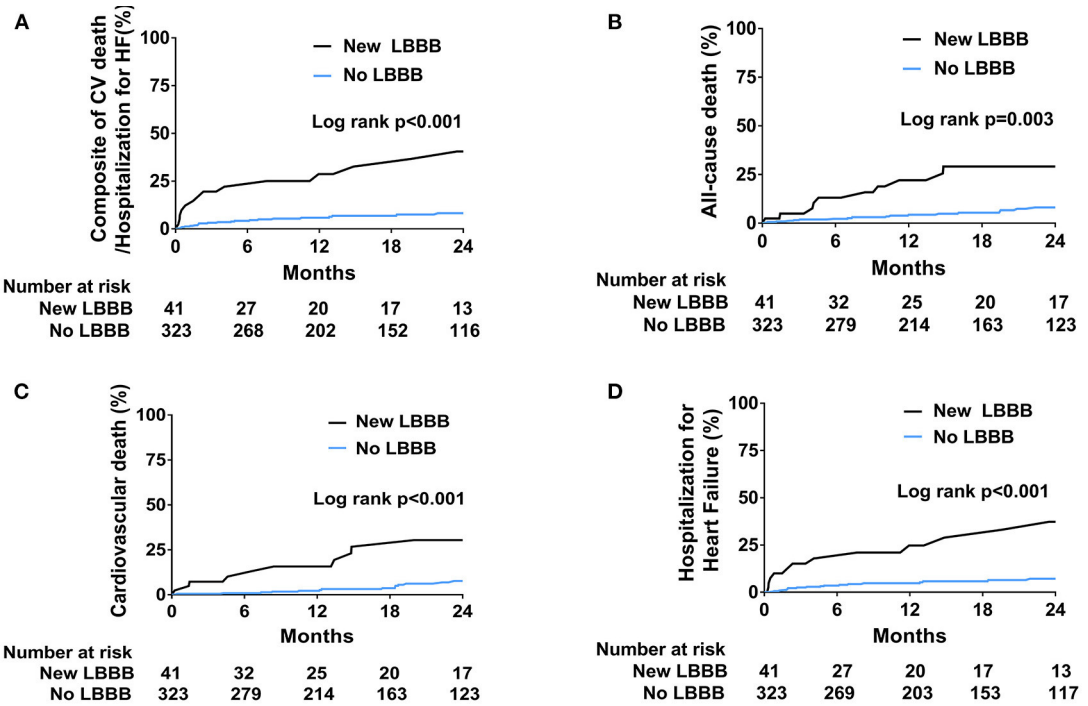

FIGURE 2 | Kaplan-Meier curves for the incidence of clinical outcomes. **(A)** Composite of cardiovascular death and hospitalization for heart failure. **(B)** All-cause death. **(C)** Cardiovascular death. **(D)** Hospitalization for heart failure.

TABLE 4 | Univariate and multivariable predictors of clinical outcomes after TAVR.

Variables	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*p*-value
New LBBB	5.03 (2.60–9.73)	<0.001	5.85 (2.87–11.95)	<0.001
Age, per year	0.95 (0.90–1.000)	0.050	1.00 (0.94–1.07)	0.941
Male sex	0.84 (0.44–1.60)	0.599	0.59 (0.27–1.25)	0.167
NYHA III-IV (vs. NYHA I-II)	1.23 (0.64–2.39)	0.533	1.24 (0.60–2.57)	0.566
Chronic lung disease	0.28 (0.07–1.17)	0.082	0.42 (0.10–1.87)	0.256
End stage renal disease	4.78 (2.18–10.47)	<0.001	5.93 (1.91–18.39)	0.002
Coronary artery disease	2.12 (1.05–4.28)	0.035	1.85 (0.86–3.99)	0.118
Peripheral artery disease	2.50 (1.22–5.15)	0.013	1.69 (0.72–3.95)	0.226
Prior cardiac surgery	3.77 (1.72–8.24)	<0.001	2.58 (1.04–6.39)	0.040
Atrial fibrillation	2.93 (1.50–5.73)	0.002	3.37 (1.57–7.25)	0.002
Euroscore II	1.02 (1.00–1.05)	0.079	0.97 (0.91–1.04)	0.429
STS-PROM	1.04 (1.01–1.07)	0.005	1.03 (0.96–1.10)	0.491
Baseline LV ejection fraction	0.97 (0.95–0.99)	<0.001	0.98 (0.95–1.01)	0.134
RV systolic dysfunction	4.64 (1.11–19.34)	<0.001	1.15 (0.22–6.01)	0.869
Pulmonary artery systolic pressure	1.03 (1.01–1.05)	0.002	1.03 (1.00–1.05)	0.080
Paravalvular regurgitation, moderate or severe	3.33 (1.39–8.00)	0.008	2.37 (0.86–6.48)	0.166

LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.

LBBB is a significant risk factor for both cardiovascular and all-cause mortality in patients with various cardiovascular diseases (24). Houthuizen et al. (25) first demonstrated the association of new-onset LBBB with increased mortality after TAVR. However, further clinical studies did not confirm this association, and the clinical implication of new-onset LBBB after TAVR remains controversial (7–9). Recently, Nazif et al. (8) also reported that new-onset LBBB after TAVR increased the incidence of adverse clinical events such as all-cause and cardiovascular mortality, rehospitalization, and

new pacemaker implantation. Additionally, a meta-analysis found an association between new LBBB and increased cardiovascular mortality (7). Our findings are consistent with those of these previous studies (7, 8). The discrepancy among study results regarding the association of LBBB with increased mortality and adverse clinical outcomes may be due to different definitions of LBBB in the different studies, characteristics of the study different populations, and variability in follow-up durations. The mechanism underlying the association of new LBBB after TAVR with a poor clinical prognosis remains unknown. An insufficient reversal of cardiac remodeling and decreased LV systolic function may contribute to increased incidences of hospitalization for heart failure and cardiovascular mortality. Because conduction disturbance is more frequently observed after TAVR than after SAVR, efforts must be made to reduce this complication before the TAVR indications are expanded to younger patients, who have a longer expected survival.

Limitations

This study has several limitations. First, this study was a single-center retrospective study, which has inherent limitations. Second, the number of subjects with new LBBB was too small for detailed subgroup analysis. Third, this study included subjects with an advanced age and at variable surgical risk, possibly limiting the generalization of our study results to younger patients, who are at a lower surgical risk. Finally, 1-year follow-up echocardiography data were not available for all patients due to the early occurrence of clinical outcomes and the advanced age of the study population. However, we performed the multiple imputation for missing 1-year echocardiographic data and found similar results with main findings.

CONCLUSION

New-onset persistent LBBB following TAVR is associated with insufficient reverse cardiac remodeling and increased adverse clinical events such as all-cause death, cardiovascular death, and hospitalization for heart failure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Severance Hospital, Yonsei University College of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KK and Y-GK contributed to the conception and design of the work. KK, Y-GK, and CS drafted the manuscript. JR, Y-JL, JS, S-JL, IC, S-JH, C-MA, J-SK, B-KK, and G-RH assisted in data collection and analysis. J-WH, DC, and M-KH contributed to the review and revision of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.893878/full#supplementary-material

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ORIGINAL RESEARCH
published: 02 June 2022
doi: 10.3389/fcvm.2022.859088

Bioprosthetic Valve Fracturing: *In vitro* Testing of Edwards PERIMOUNT Model P 2900

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Background: Bioprosthetic valve fracturing (BVF) results in low gradients following valve-in-valve transcatheter aortic valve replacement (ViV-TAVR). For the commonly used Edwards PERIMOUNT valve data from bench-testing are lacking to provide technical specifications for successful BVF during ViV-TAVR.

Methods: Using four Perimount 19- and 21-mm valves, *in-vitro* high-pressure balloon valvuloplasty with the True Dilatation Balloon Valvuloplasty Catheter and Atlas Gold PTA Dilatation Catheter was performed to analyze balloon-oversizing and pressure-thresholds to successfully achieve BVF.

Results: High-pressure balloons one millimeter larger than the labeled valve size and pressure rates of 20 atm (for Perimount 19-mm) and > 22 atm (for Perimount 21-mm) were required to achieve BVF. Caliper measurements demonstrated 2.5 mm (Perimount 19-mm) and 1.5 mm (Perimount 21-mm) enlarged inner prosthetic diameters after BVF. The Atlas TM Gold PTA Dilatation Catheter achieved BVF with the Perimount 21-mm, whereas the True TM Dilatation Balloon Valvuloplasty Catheter failed in the Perimount 21-mm either for balloon-rupture or pinhole-defect.

Conclusion: Both 19-mm and 21-mm Perimount P 2900 are amendable to BVF, thereby increasing the inner prosthetic diameter. High-pressure balloons 1 mm larger than the labeled valves are essential for this purpose, and the Atlas Gold PTA Dilatation Catheter alone should ensure success in the 21-mm prosthetics.

Keywords: bioprosthetic valve fracturing, valve-in-valve transcatheter aortic valve replacement, *in-vitro*, balloon rupture, transprosthetic gradient

OPEN ACCESS

Edited by:
Giuseppe Tarantini, University of Padua, Italy

Reviewed by:
Cristina Aurigemma, Agostino Gemelli University Polyclinic (IRCCS), Italy
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Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *20 January 2022*
Accepted: *29 April 2022*
Published: *02 June 2022*

Citation:
Ruge H, Alvarez-Covarrubias HA, Deutsch O, Alalawi Z, Vitanova K and Lange R (2022) Bioprosthetic Valve Fracturing: In vitro Testing of Edwards PERIMOUNT Model P 2900. Front. Cardiovasc. Med. 9:859088. doi: 10.3389/fcvm.2022.859088

INTRODUCTION

Valve-in-valve transcatheter aortic valve replacement (ViV-TAVR) is an established therapy for failing surgical bioprostheses in patients with higher operative risks (1, 2). One-year survival after ViV-TAVR is 83%, but mean transprosthetic pressure gradients are determined by the size of bioprosthetics previously implanted (2). In a cohort with small-sized surgical valves (<21 mm inner prosthetic diameter), higher gradients and poor 8-year survival have resulted from ViV-TAVR procedures (1). Bioprosthetic valve fracturing (BVF) is intended to lower transprosthetic

gradients in this setting, especially in patients with small surgical valves (3–5). Although technical specifications (ie, balloon types, sizes, and pressure ratings) needed for successful BVF have been documented for various surgical valves through *in vitro* testing (6–8), there is limited clinical data on BVF utilization frequency or success rates (4, 9). PERIMOUNT surgical valves (Edwards Lifesciences, Irvine, CA, USA), models 2800 and 2900 in particular, have demonstrated inconsistent BVF success (9). Data from *in vitro* studies of Magna and Magna Ease valves (Edwards Lifesciences) have served to guide clinicians in terms of balloon type and sizing, enabling successful BVF during ViV-TAVR procedures (6). However, the PERIMOUNT model 2700 is known for its resistance to BVF.

Between 2012 and 2018, Edwards PERIMOUNT valves (models 2800 and 2900) have been commonly deployed surgical valves, used in 15,000–20,000 implantations annually throughout Europe and the US (personal communication with Edwards Lifesciences). The present *in vitro* study was undertaken to better understand the amenability of a model 2900 PERIMOUNT valve to BVF attempts, determining pressure rates and balloon oversizing metrics required for successful BVF implementation.

METHODS

Materials

The Edwards PERIMOUNT (model P2900) 19- and 21-mm valves used for study came from institutional stock. The P2900 valve has three pericardial leaflets mounted on a cobalt-chromium-nickel alloy stent frame. Its sewing ring has a silicone rubber core and a polytetrafluoroethylene (PTFE) skirt.

For *in vitro* BVF testing, two distinctly different high-pressure balloons were engaged: (1) the True Dilatation Balloon Valvuloplasty Catheter (Bard Peripheral Vascular Inc, Temp, AZ, USA), burst-pressure rating of 6 atm, and (2) the Atlas Gold PTA Dilatation Catheter (Bard Peripheral Vascular Inc), burst-pressure rating of 14 atm. The Edwards Inflation Device (Edwards Lifesciences) allows inflation pressures up to 30 atm.

Bioprosthetic Valve Fracturing

Balloons for BVF were sized 1–3 mm beyond true inner diameters of surgical valves, using the Valve in Valve App (UBQO Ltd. [London, UK] and Dr. Vinayak Bapat [Minneapolis, MN, USA]). True inner diameters were obtained before and after BVF by caliper. In the course of BVF, a high-pressure balloon was connected via high-pressure stopcock (Marquis; Merit Medical Systems Inc., South Jordan, UT, USA) to a 50-ml syringe containing dilute contrast and to a high-pressure indeflator (**Figure 1**). Once the balloon filled with contrast, the stopcock was turned, allowing incremental indeflator pressurization to the point of valve fracture or balloon rupture (**Supplementary Video 1**). The corresponding pressure level was then recorded.

BVF was confirmed under fluoroscopy (**Figure 2**), with visual inspection after removal of the sewing ring (**Figure 3**). The ratio of balloon diameter to inner prosthetic diameter was calculated.

Failure of High-Pressure Balloons

Balloon failures were attributed to either ruptures (**Supplementary Video 2**) or pinhole defects (**Supplementary Video 3**). In the latter events, inflated balloon volumes remained visibly stable, but further pressure increase failed due to inherent microlesions.

RESULTS

In vitro Bioprosthetic Valve Fracturing

Both the 19- and 21-mm PERIMOUNT P2900 valves were amenable to *in vitro* BVF, requiring balloons 1 mm larger than labeled valve sizes for procedural success. Applied pressures of 19–20 atm were sufficient to fracture the 19-mm valve, whereas pressures of 22–25 atm were needed for the 21-mm valve (**Table 1**). Fluoroscopy confirmed frame dehiscence in all valves tested. Caliper measurements also indicated increases in inner diameters after BVF, relative to baseline determinations (19-mm valve: 17.5 mm→ 20 mm; 21-mm valve: 20 mm→ 21.5 mm).

High-Pressure Balloon Performance

In the four 19-mm PERIMOUNT P2900 valves that were tested, BVF was consistently achieved using 20-mm True Dilatation Balloon Valvuloplasty Catheters at pressures of 19–20 atm (**Table 1**). One pinhole defect surfaced within this test series. An 18-mm Atlas Gold PTA Dilatation Catheter inflated to 30 atm remained intact but failed to achieve BVF.

Four 21-mm PERIMOUNT P2900 valves were similarly tested. BVF was consistently achieved using 22-mm Atlas Gold PTA Dilatation Catheters at pressures of 22–25 atm (**Table 1**). True Dilatation Balloon Valvuloplasty Catheters at 20-, 21-, and 22-mm sizes failed to achieve BVF due to ruptures or pinhole defects. A 20-mm Atlas Gold PTA Dilatation Catheter inflated to 30 atm remained intact but failed to achieve BVF.

High-Pressure Balloon Defects

During *in vitro* BVF testing, the high-pressure balloons displayed two modes of failure. There were four ruptures of True Dilatation Balloon Valvuloplasty Catheters at pressures of 18–22 atm (mean, 20 atm), whereas all Atlas Gold PTA Dilatation Catheter remained intact. In the True Dilatation Balloon Valvuloplasty Catheters, pinhole defects undermined balloon pressurization, leading to three failed BVF attempts.

DISCUSSION

During *in vitro* testing of the Edwards PERIMOUNT P2900 valve (both 19- and 21-mm sizes), fracturing of its bioprosthetic ring was fully achievable. However, a balloon 1 mm larger than the labeled valve size (ie, 3 mm beyond inner prosthetic diameter) was required for success. In the 21-mm valve, higher pressure levels were required to achieve BVF. Only the Atlas Gold PTA Dilatation Catheter was capable of doing so, the True Dilatation Balloon Valvuloplasty Catheter failing entirely. Balloon failures resulted from true ruptures or pinhole defects.

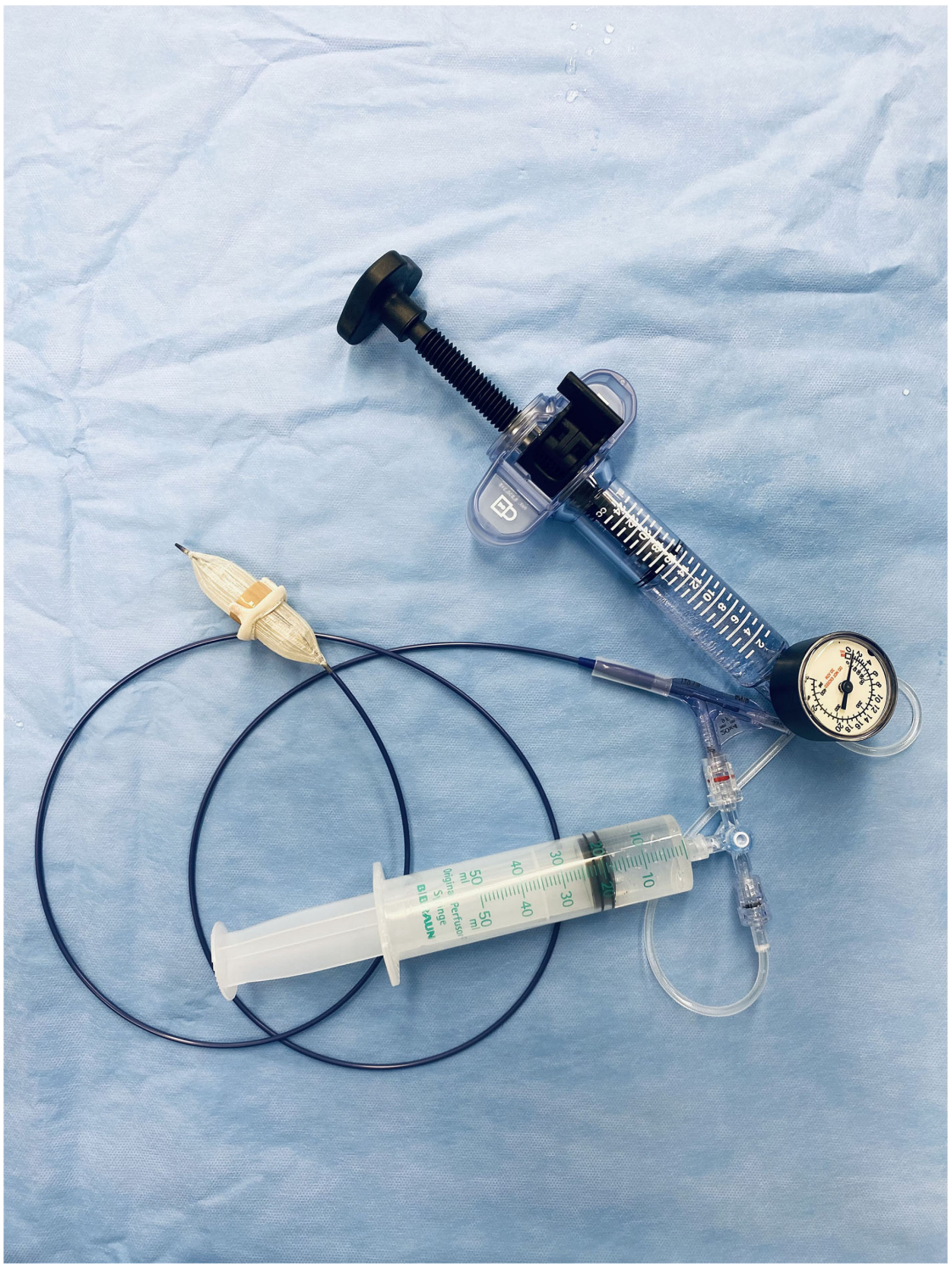

FIGURE 1 | *In-vitro* test setting with a high-pressure balloon connected via high-pressure stopcock to a 50-ml syringe containing dilute contrast and to a high-pressure indeflator.

In vitro BVF Studies

Recent *in vitro* BVF studies have reported technical specifications and feasibility data for various surgical valves other than the PERIMOUNT P2900 (6, 7). Higher pressure levels (ie, 18–24 atm) were required for BVF of surgical bioprostheses with metal rings (e.g., Magna, Magna Ease [Edwards Lifesciences]),

FIGURE 2 | Fluoroscopic confirmation of successful bioprosthetic valve fracturing.

as opposed to those with polymer rings (e.g., Epic [Abbott Laboratories, Chicago, IL, USA], Mosaic [Medtronic, Dublin Ireland], Mitroflow [LivaNova, London, UK]) where 8–12 atm sufficed (5–7). Based on bench testing of analogous devices, balloon oversizing of 1 mm beyond stated valve dimension is recommended (6, 7). For the 19- and 21-mm PERIMOUNT Magna valves, the feasibility of BVF using either an Atlas Gold PTA Dilatation Catheter or a True Dilatation Balloon Valvuloplasty Catheter has been proven at high (24-atm) pressure levels (6). Although the PERIMOUNT P2900 and the Magna have similar fluoroscopic appearances, results of our *in vitro* test series differed. Pressure required (19–20 atm) for the 19-mm PERIMOUNT P2900 was lower than that required (24 atm) for the 19-mm Magna. Also, successful BVF of the 21-mm Magna has been reported at 24 atm, whether by Atlas Gold PTA Dilatation Catheter or True Dilatation Balloon Valvuloplasty Catheter (6). We did not achieve BVF in 21-mm P2900 valves using True Dilatation Balloon Valvuloplasty Catheters. **Table 2** summarizes the currently available data on *in-vitro* BVF studies.

Causes of BVF Failure

Existing clinical data on BVF failure rates are sparse (9). Although balloon ruptures during ViV-TAVR procedures are quite evident by fluoroscopy, pinhole balloon defects are more likely signaled indirectly. For instance, manometer readings may indicate pressure loss or stagnation during full fluoroscopic balloon inflation. In such circumstances, balloons should be deflated, and attempts at BVF terminated. Balloon undersizing also precludes successful BVF.

Clinical Data on BVF

Some clinical case series addressing ViV-TAVR have demonstrated lower transvalvular gradients through BVF, compared with its non-use or with postdilatation, respectively (4, 9). As defined by the Valve Academic Research Consortium (VARC), device success is reportedly higher after ViV-TAVR procedures if BVF is performed (93 vs. 68%; $p < 0.001$) (4); and transvalvular gradients seem to be lower (10). Midterm data

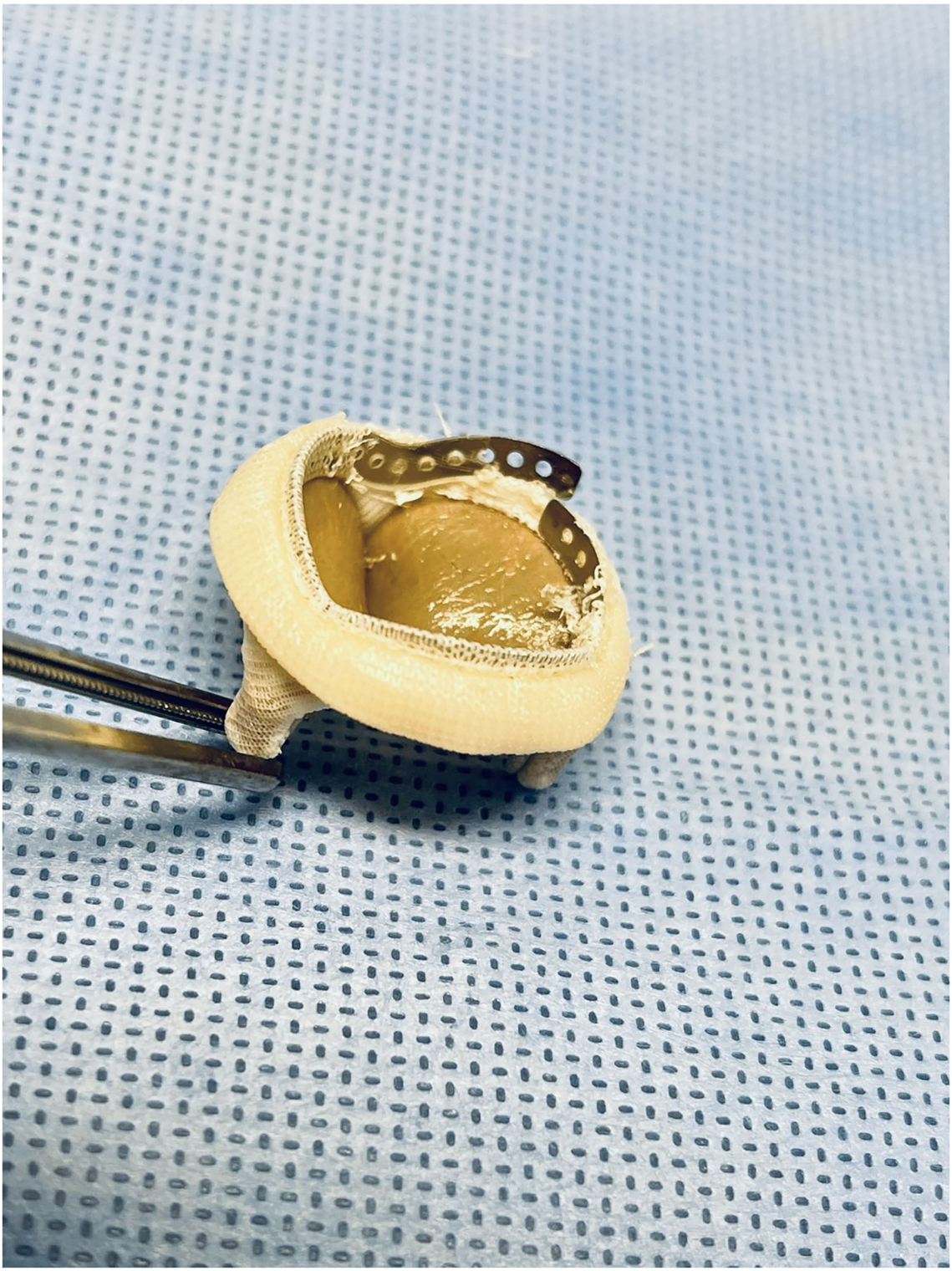

FIGURE 3 | Visual confirmation of bioprosthetic valve fracturing after removal of the sewing ring.

on ViV-TAVR with BVF are scant. Immediate postoperative transvalvular gradients in 139 patients treated thusly were low (9.4 ± 5.8 mmHg) but increased significantly (14.6 ± 7.5 mmHg; $p < 0.001$) at 30 days and remained stable for up to 1-year of follow-up (11). BVF-related complications, such as stroke, annular rupture, and coronary obstruction,

TABLE 1 | *In vitro* fracturing studies of PERIMOUNT model P2900 bioprosthetic valve.

PM 19 - I	TD			
	20 mm			
	19 atm			
PM 19 -II	TD			
	20 mm			
	19 atm			
PM 19 - III	TD	TD		
	20 mm	20 mm		
	19 atm	19 atm		
PM 19 - IV	AG	TD		
	18 mm	20 mm		
	30 atm	19 atm		
PM 21 - I	TD	TD	TD	AG
	21 mm	21 mm	22 mm	22 mm
	20 atm	25 atm	20 atm	25 atm
PM 21 - II	TD	TD	AG	
	21 mm	20 mm	22 mm	
	20 atm	18 atm	22 atm	
PM 21 - III	TD	AG		
	22 mm	22 mm		
	22 atm	25 atm		
PM 21 - IV	AG	AG		
	20 mm	22 mm		
	30 atm	22 atm		

Color-coded outcomes of bioprosthetic valve fracturing attempts:

Successful BVF	Balloon undersizing, no effect	Pinhole defect	Balloon rupture

TD, true dilatation balloon; AG, atlas gold balloon.

have been rare, not exceeding rates cited for ViV-TAVR only (9, 12).

Technical Specifications for BVF Procedure

The present study provides technical specifications for BVF of PERIMOUNT P2900 bioprosthetic valves. Models P2900 and P2800 differ only in their pericardial leaflet treatments. Hence, we presume that the findings herein are applicable to the P2800 model as well.

We do suggest that balloons 1 mm larger than labeled valves be applied in this setting. *In vitro* BVF of the 21-mm PERIMOUNT P2900 also requires use of an Atlas Gold PTA Dilatation Catheter. Because pinhole defects seemed to account for nearly one-half of our balloon failures, we advise continuous monitoring of manometers during any BVF attempts to clearly identify such defects and abort all non-productive efforts.

Randomized clinical studies of ViV-TAVR procedures conducted alone or in conjunction with BVF are needed to verify the hemodynamic benefit of BVF and to establish protocols for its utilization.

TABLE 2 | Overview of perviously reported data and data acquired within the present study on required pressure rates to achieve *in-vitro* BVF using the atlas gold PTA dilatation catheter or true dilatation balloon valvuloplasty catheter (6, 7).

	Labeled valve size	Atlas gold (mm)	Fracture pressure (atm)	True dilatation (mm)	Fracture pressure (atm)	Source data reference
Perimount P 2900	19	20	Not tested	20	19	
Perimount P 2900	21	22	22–25	22	Failed	
Magna ease	19	20	19		Not tested	(7)
Magna ease	19	20	18	20	18	(6)
Magna ease	21	22	21		Not tested	(7)
Magna ease	21	22	18	22	18	(6)
Magna	19	20	24	20	24	(6)
Magna	21	22	24	22	24	(6)
Mosaic	19	20	10		Not tested	(7)
Mosaic	19	20	10	20	10	(6)
Mosaic	21	22	8		Not tested	(7)
Mosaic	21	20	10	20	10	(6)
Mitroflow	19	20	12	20	12	(6)
Mitroflow	21	22	10		Not tested	(7)
Mitroflow	21	22	12	22	12	(6)
St. Jude Epic	21	22	8	22	8	(6)

orange indicated the surgical valves tested in the current study. gray performance of the Atlas Gold balloon in in-vitro BVF studies. blue performance of the True dilatation balloon in in-vitro BVF studies.

CONCLUSION

Both 19- and 21-mm PERIMOUNT P2900 valves are amenable to BVF, thereby increasing inner prosthetic diameters. High-pressure balloons 1 mm larger than labeled valve sizes are essential for this purpose, and the Atlas Gold PTA Dilatation Catheter alone should ensure success in 21-mm prosthetics.

LIMITATIONS

Despite the limited number of valves tested, results were quite consistent. Still, an *in vitro* study may not entirely simulate *in vivo* BVF during transcatheter replacement of a degenerated surgical valve.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

HR is responsible for the study design, data collection, data analysis, data interpretation, and writing the manuscript. HA-C, OD, and ZA contributed in the *in-vitro* testing and manuscript

revision. KV revised the manuscript. RL revised the manuscript and supervised the project. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The manuscript has been copy edited by native English speakers with related biomedical background in BioMed Proofreading® LLC.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.859088/full#supplementary-material

Supplementary Video 1 | Successful bioprosthetic valve fracturing.

Supplementary Video 2 | High-pressure balloon rupture causing failure of bioprosthetic valve fracturing attempt.

Supplementary Video 3 | With pressure increase microlesion with volume loss undermine bioprosthetic valve fracturing attempt.

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BRIEF RESEARCH REPORT
published: 21 June 2022
doi: 10.3389/fcvm.2022.877511

Multi-Slice Computed Tomography Analysis in Patients Undergoing Transcatheter Aortic Valve Replacement – Impact of Workflows on Measurement of Virtual Aortic Annulus and Valve Size

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Exact and reliable measurements of anatomical dimensions in pre-procedural multi-slice computed tomography (MSCT) scans are crucial for optimal valve sizing and clinical results of transcatheter aortic valve replacement (TAVR). This study aimed to investigate interrater reliability between routinely used workflows for pre-procedural analysis. MSCT scans of 329 patients scheduled for TAVR were analyzed using both a 3mensio and SECTRA IDS7 platform. The results were retrospectively compared using the intraclass correlation coefficient, revealing excellent correlation in the analysis of simple diameters and poor correlation in the assessment of more complex structures with impact on calculated valve size.

Keywords: TAVI, TAVR, MSCT, valve sizing, outcome assessment

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Edited by:
Philippe Sucosky, Kennesaw State University, United States

Reviewed by:
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Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *16 February 2022*
Accepted: *18 May 2022*
Published: *21 June 2022*

Citation:
Piayda K, Hellhammer K, Veulemans V, Afzal S, Klein K, Berisha N, Leuders P, Erkens R, Kirchner J, Heidari H, Kelm M, Antoch G, Zeus T and Quast C (2022) Multi-Slice Computed Tomography Analysis in Patients Undergoing Transcatheter Aortic Valve Replacement – Impact of Workflows on Measurement of Virtual Aortic Annulus and Valve Size. Front. Cardiovasc. Med. 9:877511. doi: 10.3389/fcvm.2022.877511

INTRODUCTION

Since its introduction in 2002, transcatheter aortic valve replacement (TAVR) has evolved as an inherent part of cardiovascular care delivery. Over recent years, the implantation technique and pre-procedural assessment advanced tremendously to ensure ideal prosthesis placement and fitting. Especially, multi-slice computed tomography (MSCT) scans have been deeply integrated into daily clinical practice to guarantee optimal valve sizing and clinical results. MSCT scans may be evaluated by different analysis platforms, workflows, and specialties influencing clinical routine and analysis of anatomical dimensions.

We, therefore, investigated the interrater reliability of workflows routinely used by radiologists and cardiologists in the analysis of relevant anatomical dimensions in pre-procedural MSCT scans of patients undergoing TAVR.

METHODS

Three hundred twenty-nine patients with severe, symptomatic aortic stenosis, and scheduled for TAVR underwent non-enhanced, contrast-enhanced, electrocardiogram-gated, and high-resolution MSCT (150 ms, 128 × 0.6 mm, "SOMATOM Definition AS+", Siemens Healthcare) for pre-procedural planning from September 2015 to January 2018. The best systolic phase was used to reconstruct axial images with a slice thickness of 0.6–1 mm, and measurements were performed in accordance with best practice recommendations (1). Each data set of MSCT images was transferred to a dedicated workstation (3mensio Structural Heart^{TM}, Pie Medical Imaging BV, Maastricht, The Netherlands) for evaluation by independent cardiologists (**Table 1**, named "examiner"). In case of complex anatomy or difficult image quality, a dedicated cardiological expert re-evaluated the measurements of the cardiological examiner (**Table 1**, named "Expert"). During this period, this was done in 20% of patients and resulted in high inter-operator reproducibility. Data were directly analyzed with a PACS system workstation (SECTRA IDS7, Sectra AB, Linköping, Sweden) for relevant anatomical structures by a specialized radiologist. Both specialties were extensively trained with internal validation in their routinely used workflow, and workflow users were blinded to the results of the other workflow. All measurements were retrospectively compared using the intraclass correlation coefficient (ICC, Pearson correlation with two-way random/absolute agreement model). TAVR has been carried out based on the 3mensio system, which represents the reference for measurements. During this period, the size of the implanted valves was strictly chosen according to the best practice recommendations of the manufacturers, which are indicated in the respective sizing charts of Edwards (Sapien 3) or Medtronic (Evolut R and Evolut Pro).

The study design and patient selection process are illustrated in **Figure 1**. The study was approved by the local ethics committee, performed in accordance with the Declaration of Helsinki, and registered at Clinical Trials (NCT01805739).

RESULTS

The interrater reliability ranged from excellent in the prediction of simple two-dimensional distance measurements like the sinotubular junction (3mensio: 27.3 mm ± 3.5 vs. Sectra IDS7 26.8 mm ± 3.6, ICC.762 [0.70–0.80]) and the dimensions of the aorta ascendens (3mensio: 31.9 mm ± 4.2 vs. Sectra IDS7: 31.3 mm ± 3.7, ICC 0.756 [0.69–0.80]) to a poor correlation in the assessment of more complex structures like the virtual aortic annulus (3mensio: 22.9 mm ± 2 vs. Sectra IDS7: 24.7 mm ± 3, ICC 0.462 95% CI [0.17–0.63], which is crucial for sizing and the final determination of valve size. Further data is displayed in **Table 1**. Mean difference of the calculated diameter of the virtual aortic annulus averages 2.4 ± 2 mm. Considering 3mensio measurements as a reference, the varying calculated diameter results in different valve sizes in 47.1% of the cases predominantly due to oversizing (**Table 2**).

DISCUSSION

Non-invasive imaging is a very powerful tool and may determine patient eligibility, the access site, and device selection, and helps to identify the best angiographic view for valve delivery (2). Even though, as a strength of this study, we have highly trained experts in both routinely used workflows, the interrater reliability between workflows varied significantly, especially in the assessment of the virtual aortic annulus where MSCT is defined as the gold standard tool for evaluation. Quantitative assessment requires accurate identification of the hinge points of the right and non-coronary cusps to create the virtual annular plane. This can be done manually (in case of Sectra IDS7) or on a software-based facilitated workflow (in case of 3mensio). Although no reference standard for this measurement has been approved, considering which of the two measurements is more correct, a software-based approach may provide a more accurate assessment by minimizing subjectivity. In a cohort of 105 patients, automated 3mensio software showed

TABLE 1 | Computed tomography (CT) evaluation and interclass correlation between 3mensio and Sectra IDS7.

	3mensio		Sectra IDS7	ICC 95% CI
	Examiner	Expert		
Virtual aortic annulus (mm)	22.9 ± 2.0	23.6 ± 2.2	24.7 ± 3.0	0.462 [0.17–0.63]
Sinotubular junction (mm)	27.3 ± 3.5	28.0 ± 3.4	26.8 ± 3.6	0.762 [0.70–0.80]
Sinus of valsalva (mm)	31.3 ± 3.8	32.0 ± 3.9	32.7 ± 3.8	0.627 [0.47–0.72]
Aorta ascendens diameter (mm)	31.9 ± 4.2	31.5 ± 3.8	31.3 ± 3.7	0.756 [0.69–0.80]
Distance to left coronary artery (mm)	13.4 ± 2.6	13.5 ± 2.2	12.3 ± 2.9	0.563 [0.41–0.67]
Distance to right coronary artery (mm)	14.6 ± 3.9	14.1 ± 3.6	13.6 ± 3.5	0.594 [0.46–0.68]
Left ventricular outflow tract angle (degree)	60.2 ± 6.2	58.0 ± 5.9	55.9 ± 15.2	0.025 [0.18–0.28]

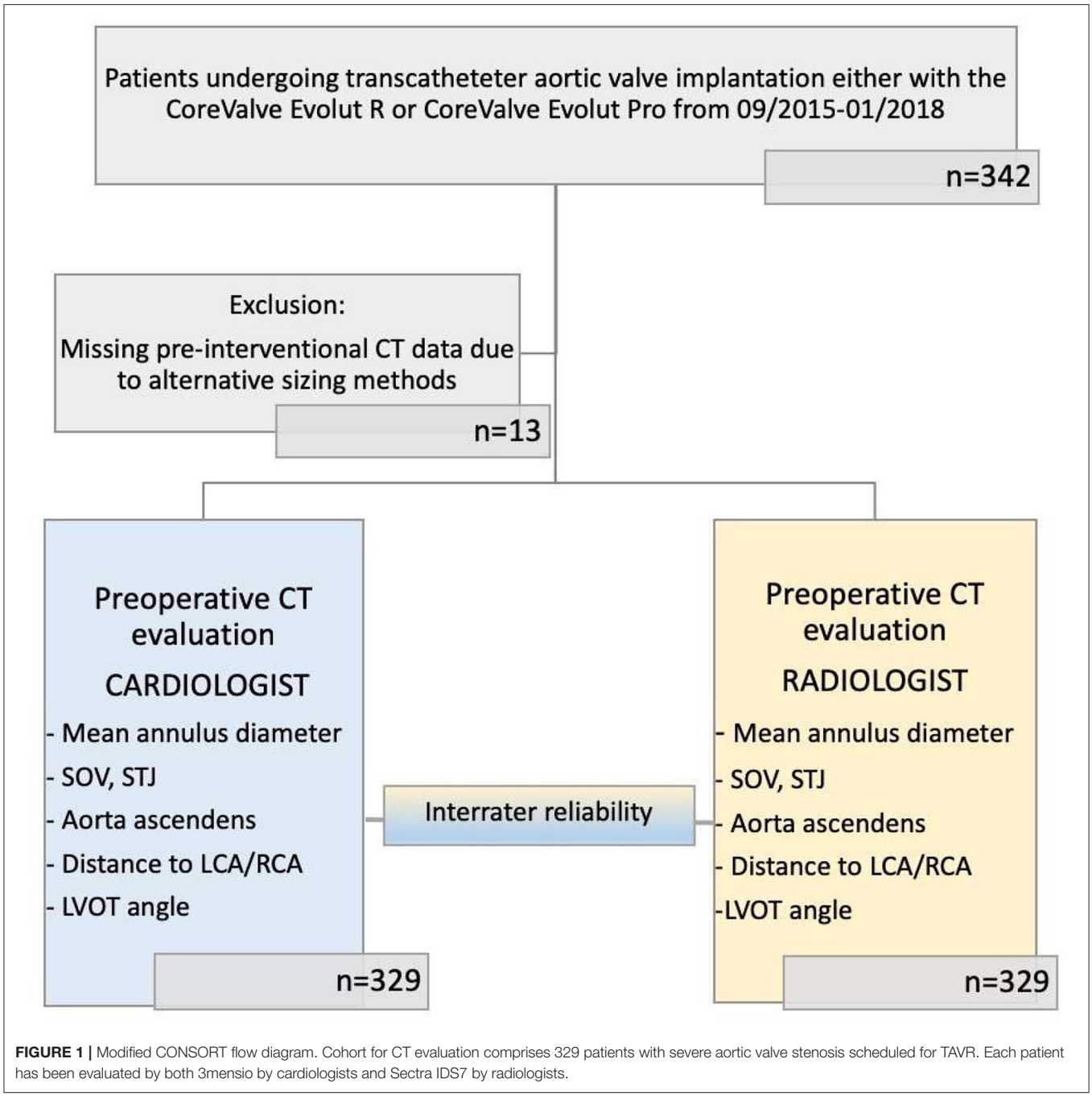

FIGURE 1 | Modified CONSORT flow diagram. Cohort for CT evaluation comprises 329 patients with severe aortic valve stenosis scheduled for TAVR. Each patient has been evaluated by both 3mensio by cardiologists and Sectra IDS7 by radiologists.

TABLE 2 | Practical clinical impact of workflow on valve size selection.

Mean difference of calculated diameter (mm)	2.4 ± 2 (Mean ± SD) 2 [1–3.4] (Median [IQR])
Different valve size based on calculated diameter (%)	155 (47.1)
Oversizing (%)	135 (87.1)
Undersizing (%)	20 (12.9)

Over- and undersizing are estimated considering 3mensio measurements as reference.

equally good reproducibility as manual measurement (3). The same applies to the 3mensio three-dimensional computed tomography (3D-CT) reconstruction tool with regard to accuracy and reproducibility (4). Furthermore, Foldyna et al. observed a significantly faster evaluation with semi-automatic rather than with manual segmentation of pre-interventional MSCT (5) with comparable exactness. In contrast, our results hint at the impact of workflows used in pre-interventional analysis and reveal a poor correlation in the assessment of more complex structures between different workflows despite extensively trained operators. Therefore, workflows have a relevant impact on correct valve sizing and the choice of device highlighting the limited reproducibility between different workflows. We,

therefore, recommend harmonization of the routinely used workflows by interprofessional communication and training. Moreover, studies are evolving, which evaluate the feasibility of AI models and algorithms implemented in analysis software even for small cardiac structures, to detect moderate to high-grade coronary stenosis (6, 7). In the future, it might be promising to validate and standardize AI algorithms to overcome discrepancies in the measurement of complex structures and choose the prothesis with the best hemodynamic and prognostic outcome in patients with aortic valve stenosis scheduled for TAVR.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This study was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Grant No. 397484323.

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Conflict of Interest: VV and TZ have received consulting fees, travel expenses, or study honorariums from Medtronic and Edwards Lifesciences outside of this work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 28 June 2022
doi: 10.3389/fcvm.2022.911234

Mid- to Long-Term Clinical and Echocardiographic Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 02 April 2022
Accepted: 30 May 2022
Published: 28 June 2022

Citation:
Xu S, Zhang E, Qian Z, Sun J, Zou F, Wang Y, Hou X and Zou J (2022) Mid- to Long-Term Clinical and Echocardiographic Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:911234. doi: 10.3389/fcvm.2022.911234

Aims: To date, the prognostic effects of permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR) remain controversial. The purpose of this meta-analysis was to investigate the mid- (1 year) to long-term (> 1 year) clinical and echocardiographic effects of post-procedural PPI in patients after TAVR.

Methods: PubMed, Embase, Web of Science, and Cochrane Library databases were systematically searched from the establishment of databases up to 1 December 2021. Studies comparing clinical and echocardiographic outcomes between patients with and without post-TAVR PPI of ≥ 1-year follow-up were collected for further meta-analysis.

Results: A total of 39 studies comprising of 83,082 patients were included in this meta-analysis. At mid-term follow-up (1 year), the pooled results demonstrated a higher risk of all-cause mortality in patients with post-procedural PPI than those without following TAVR (relative risk (RR), 1.17; 95% CI, 1.10–1.24; $P < 0.00001$). No significant differences were observed in cardiovascular mortality (RR, 0.86; 95% CI, 0.71–1.03; $P = 0.10$) or heart failure rehospitalization (RR, 0.91; 95% CI, 0.58–1.44; $P = 0.69$) at 1-year follow-up. At long-term follow-up (> 1 year), post-TAVR PPI had negative effects on all-cause mortality (RR, 1.18; 95% CI, 1.09–1.28; $P < 0.0001$) and heart failure rehospitalization (RR, 1.42; 95% CI, 1.18–1.71; $P = 0.0002$). There was no difference in long-term cardiovascular mortality between the two groups (RR, 1.15; 95% CI, 0.97–1.36; $P = 0.11$). Left ventricular ejection fraction (LVEF) was not significantly different at baseline (mean difference, 1.40; 95% CI, –0.13–2.93; $P = 0.07$), but was significantly lower in the PPI group at 1-year follow-up (mean difference, –3.57; 95% CI, –4.88 to –2.26; $P < 0.00001$).

Conclusion: Our meta-analysis provides evidence that post-TAVR PPI has negative clinical and echocardiographic effects on patients at mid- to long-term follow-up. Further

studies are urgently needed to explore the cause of these complications and optimize the treatment and management of patients requiring permanent pacing after TAVR.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021289935], identifier [CRD42021289935].

Keywords: transcatheter aortic valve replacement, permanent pacemaker implantation, mortality, heart failure rehospitalization, left ventricular ejection fraction, meta-analysis

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has become a well-established therapy for patients with severe aortic stenosis and high risk for surgical aortic valve replacement (1, 2). Recent randomized controlled trials provided evidence to extend the application of TAVR to low-risk patients (3, 4). Despite technological advances and clinical experience accumulation, atrioventricular node, and infranodal tissues remain easily impaired during the implantation of the valve prosthesis. Conduction abnormalities (e.g., high-degree atrioventricular block and new-onset persistent left bundle branch block) are frequently observed after TAVR, and patients often require permanent pacemaker implantation (PPI) (5). The application of post-TAVR PPI was reported in approximately 2.3–37.7% of patients, and the rates largely vary according to the types and generations of the transcatheter valves (6).

Cardiac pacing is a recommended therapy to reduce the risk of death related to severe bradycardia arrhythmias. However, traditional right ventricular pacing (RVP) can cause electrical and mechanical dyssynchrony (7, 8), thus increasing the risk of mortality and heart failure hospitalization (9–11). Currently, it remains controversial whether the application of PPI could influence the clinical symptoms and survival outcomes after TAVR (12). Previous meta-analyses were limited by a small number of studies or lack of long-term follow-up (13, 14). This meta-analysis aims to investigate the mid- to long-term clinical and echocardiographic outcomes of post-procedural PPI in patients after TAVR.

METHODS

Search Strategy

We performed a systematic literature search in PubMed, Embase, Web of Science, and Cochrane Library from the establishment of databases up to 1 December 2021 by two investigators (Shun Xu and Enrui Zhang) independently. The following strategy was used in PubMed: ((((((“Transcatheter Aortic Valve Replacement” [Mesh]) OR (Transcatheter Aortic Valve Replacement [Title/Abstract])) OR (Transcatheter Aortic Valve Implantation [Title/Abstract])) OR (TAVR [Title/Abstract])) OR (TAVR [Title/Abstract]))) AND (((((“Cardiac Pacing, Artificial” [Mesh]) OR (pacing [Title/Abstract])) OR (pace [Title/Abstract])) OR ((“Pacemaker, Artificial” [Mesh]) OR (pacemaker [Title/Abstract])))). The searching strategies for Embase, Web of Science, and Cochrane Library were provided in **Supplementary Table 1**. We also manually screened reference lists of retrieved reviews, reports, and other relevant publications to identify additional pertinent studies.

Study Design

The protocol of this meta-analysis has been registered in PROSPERO (Registration ID: CRD42021289935). Clinical studies were eligible if they met the following inclusion criteria: (1) studies comparing clinical and echocardiographic outcomes between patients with and without post-procedural PPI after TAVR, including all-cause mortality, cardiovascular mortality, heart failure rehospitalization, and left ventricular ejection fraction (LVEF); (2) studies with a follow-up of $\geq$ 1 year; (3) studies with full texts published in English in peer-reviewed journals. We only included the study containing the most data for multiple publications of the same trial. We excluded review articles, case reports, letters, editorials, articles lacking outcomes of interest, studies without detailed data, and studies with a follow-up of $<$ 1 year. Importantly, we also excluded studies that failed to distinguish patients with PPI before TAVR. Two independent investigators (Shun Xu and Enrui Zhang) assess eligibility by screening and reviewing article titles, abstracts, and full texts. Any disagreement about eligibility was clarified *via* consulting a third investigator (Jinyu Sun).

Data Extraction and Quality Assessment

Two investigators (Shun Xu and Enrui Zhang) independently extracted data for each eligible study. Any disagreement was resolved through discussion with a third investigator (Jinyu Sun) to reach a consensus. The following characteristics were included: first author, year of publication, inclusion period, number and region of centers, sample size, PPI criteria, patient demographic characteristics, and the following mid-term (1 year) to long-term ($>$ 1 year) outcomes, including all-cause mortality, cardiovascular mortality, heart failure rehospitalization, and LVEF.

The quality of studies involved was assessed by two investigators (Shun Xu and Enrui Zhang) independently using the Newcastle-Ottawa Scale (NOS). The NOS tool involved three aspects, and a maximum of 9 stars can be allotted to each study: the selection of cohorts (0–4 stars), the comparability of cohorts (0–2 stars), and the assessment of the outcome (0–3 stars). A NOS score $\geq$ 6 stars indicated moderate-to-high quality, while a NOS score $<$ 6 stars indicated low quality. Discrepancies

Abbreviations: TAVR, transcatheter aortic valve replacement; PPI, permanent pacemaker implantation; RVP, right ventricular pacing; LVEF, left ventricular ejection fraction; NOS, Newcastle-Ottawa Scale; RR, relative risk; CI, confidence intervals; HPSP, His-Purkinje system pacing.

were resolved by consulting a third investigator (Jinyu Sun) to reach a consensus.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as frequencies or percentages. Relative risk (RR) with corresponding 95% confidence intervals (CIs) for each endpoint was calculated and analyzed for categorical variable outcomes. Continuous data were summarized as a mean difference with 95% CI. P-value < 0.05 was considered statistically significant. The heterogeneity between studies was quantified by I-squared (I^2) statistic, with a fixed-effects model adopted when the I^2-value was $< 50\%$ and a random-effects model applied otherwise. Review Manager version 5.3 was used for all the statistical analyses. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15).

RESULTS

Study Selection and Quality Assessment

Figure 1 shows the flow chart of the study selection. A total of 9,852 records were initially identified from the databases according to the searching strategies, including 1,842 from PubMed, 4,782 from Embase, 3,053 from Web of Science, and 175 from Cochrane Library. After title and abstract screening, a total of 4,321 duplicates and 5,461 irrelevant records were excluded, the remaining 70 full-text articles to be reviewed for eligibility. Of those, 22 studies were excluded for having no outcomes of interest or without provided data. Two studies were excluded due to failing to distinguish patients with PPI before TAVR. One study was excluded because the follow-up duration was less than 1 year. Six case reports were also excluded. Finally, 39 studies containing 83,082 patients were included for further analysis (16–54) (**Table 1**).

All included studies had moderate-to-high quality while none had less than 6 points according to NOS: two with 9 points, nineteen with 8 points, six with 7 points, and 12 with 6 points. The details of the quality assessment are shown in **Table 2**.

Mid-Term (1 Year) Clinical Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement

The risk of mid-term all-cause mortality was pooled from 27 studies that included 49,579 patients, and 7,235 patients were implanted with permanent pacemakers after TAVR. There were 1,197 of 7,235 (16.54%) cases of all-cause mortality in the PPI group while 6,285 of 42,344 (14.84%) cases in the no PPI group. The pooled results demonstrated that patients with PPI had a higher risk of death than those without PPI following TAVR (RR, 1.17; 95% CI, 1.10–1.24; $P < 0.00001$; $I^2 = 22\%$; **Figure 2A**). After pooling the results from nine studies, no significant difference in mid-term cardiovascular death was observed (RR, 0.86; 95% CI, 0.71–1.03; $P = 0.10$; $I^2 = 0\%$; **Figure 2B**). The risk of 1-year

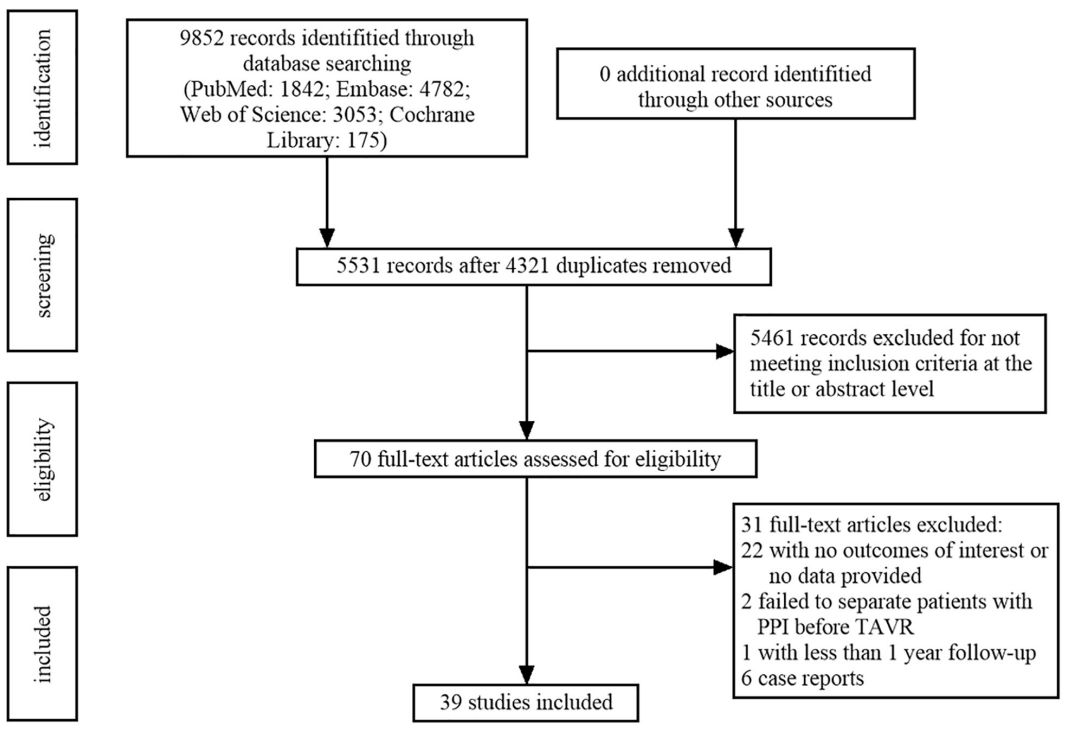

FIGURE 1 | Flowchart of study selection based on the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

TABLE 1 | Summary of studies evaluating mid- to long-term clinical and echocardiographic effects of post-TAVR PPI.

References	Year	Region	Centers	Inclusion period	Sample	PPI criteria	Time of PPI
Rück et al. (16)	2021	Sweden	8	Jan 2008–Dec 2018	3420	NA	≤30 days
Rajah et al. (17)	2021	Arabia	1	Jan 2010–Jan 2019	170	NA	≤30 days
Schoechlin et al. (18)	2021	Germany	1	Jan 2014–Dec 2016	767	Restrictive or liberal strategy	After TAVR
Van Mieghem et al. (19)	2021	International	53	Jan 2016–Dec 2016	886	NA	≤30 days
Clementy et al. (20)	2021	France	NA	Jan 2010–Jun 2019	23060	NA	≤30 days
Weferling et al. (21)	2021	Germany	1	Jan 2010–Apr 2019	1846	ESC 2013 guidelines	Median 3 days
Nicolas et al. (22)	2021	Europe and United States	19	Jan 2013–Dec 2015	922	ESC 2013 guidelines	After TAVR
Alperi et al. (23)	2021	International	>180	Apr 2007–Apr 2020	1987	NA	Before discharge
Ashraf et al. (24)	2020	United States	1	Jan 2012–Jul 2018	243	ACC/AHA/HRS guidelines	≤30 days
Duet al. (25)	2020	China	1	Mar 2013–Oct 2018	256	ACC/AHA/HRS 2012 guidelines	≤30 days
Fujita et al. (26)	2020	Germany	NA	2011–2015	20872	NA	Before discharge
Costa et al. (27)	2019	Italy	1	Jun 2007–Feb 2018	1116	ESC 2013 guidelines	≤30 days
Meduri et al. (28)	2019	International	55	Sep 2014–Dec 2015	688	NA	≤30 days
Maeno et al. (29)	2019	United States	1	Jan 2013–Dec 2015	659	NA	Before discharge
Jørgensen et al. (30)	2019	Denmark	1	Aug 2007–Sep 2017	816	NA	≤30 days
Gonska et al. (31)	2018	Germany	1	Feb 2014–Sep 2016	532	NA	After TAVR
Nadeem et al. (32)	2018	United States	1	2011–2017	672	NA	After TAVR
Alasti et al. (33)	2018	Australia	1	Apr 2012–Oct 2016	152	High-degree AVB, first-degree AVB with LBBB, AF with slow ventricular rate and SSS	≤30 days
Walther et al. (34)	2018	International	12	Dec 2011–Sep 2015	198	NA	≤1 year
Rogers et al. (35)	2018	United States	1	Jan 2013–Dec 2015	614	NA	After TAVR
Aljabbary et al. (36)	2018	Canada	10	Apr 2010–Mar 2015	1257	NA	Before discharge
Chamandi et al. (37)	2018	International	9	May 2007–Feb 2015	1629	ACC/AHA/HRS 2012 guidelines	≤30 days
López-Aguilera et al. (38)	2018	Spain	1	Apr 2008–Dec 2015	217	Third-degree AVB, LBBB or new first-degree AVB with persistent severe bradycardia (< 40 bpm) and developed syncope	After TAVR
Nijenhuis et al. (39)	2017	Netherlands	1	Jun 2007–Jun 2015	155	ESC 2007/2013 guidelines	8 (6–14) days
Engborg et al. (40)	2017	Denmark	1	Mar 2008–Sep 2012	128	High-degree AVB, SSS, LBBB combined with first-degree AVB	≤30 days
Fadahunsi et al. (41)	2016	United States	229	Nov 2011–Sep 2014	9785	NA	≤30 days
Giustino et al. (42)	2016	International	4	Nov 2005–Dec 2011	947	ACC/AHA/HRS 2012 guidelines	After TAVR

(Continued)

TABLE 1 | (Continued)

References	Year	Region	Centers	Inclusion period	Sample	PPI criteria	Time of PPI
Dizon et al. (43)	2015	International	25	May 2007–Aug 2009	1945	NA	≤30 days
Mouillet et al. (44)	2015	France	29	Jan 2010–Oct 2011	833	NA	After TAVR
Kawaguchi et al. (45)	2015	France	1	Feb 2010–Jun 2012	160	NA	After TAVR
Schymik et al. (46)	2015	Germany	1	May 2008–Apr 2012	634	ESC 2013 guidelines	After TAVR
Nazif et al. (47)	2015	International	25	NA	1973	High-degree AVB, SSS, and other bradycardias	≤30 days
Urena et al. (48)	2014	International	8	Jan 2005–Feb 2013	1556	ACC/AHA/HRS 2008 guidelines	≤30 days
Biner et al. (49)	2014	Israel	1	NA	230	Pre-TAVR RBBB, post-TAVR high-degree AVB, alternating BBB, and new LBBB with PR-interval prolongation ≥ 280 ms	After TAVR
Pereira et al. (50)	2013	Portugal	1	Aug 2007–May 2011	58	ESC 2007 guidelines	Range 1–9 days
Houthuizen et al. (51)	2012	Netherlands	8	Nov 2005–Dec 2010	797	NA	After TAVR
De Carlo et al. (52)	2012	Italy	3	Sep 2007–Jul 2010	275	ESC 2007 guidelines	Range 0–12 days
Buellesfeld et al. (53)	2012	Switzerland and Germany	2	Aug 2007–Mar 2010	305	High-degree AVB, new LBBB with PR interval prolongation ≥ 300 ms, and AF with inadequate escape rhythm	≤30 days
D'Ancona et al. (54)	2011	Germany	1	Apr 2008–Mar 2011	322	High-degree AVB and symptomatic bradycardia	≤30 days

TAVR, transcatheter aortic valve replacement; PPI, permanent pacemaker implantation; NA, not available; ESC, European Society of Cardiology; ACC, American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; AVB, atrioventricular block; SSS, sick sinus syndrome; AF, atrial fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; BBB, bundle branch block.

heart failure rehospitalization was assessed in five studies using a random-effects model. As shown in **Figure 2C**, no significant difference was observed in heart failure rehospitalization (RR, 0.91; 95% CI, 0.58–1.44; $P = 0.69$; $I^2 = 83\%$).

Long-Term (> 1 Year) Clinical Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement

Long-term mortality between patients with and without PPI after TAVR was reported in 18 studies enrolling 39,172 patients with a mean follow-up period of 2.59 years. A random-effects model was applied, and patients with PPI after TAVR had a higher risk of all-cause mortality than those without PPI after TAVR (RR, 1.18; 95% CI, 1.09–1.28; $P < 0.0001$; $I^2 = 57\%$; **Figure 3A**). However, there was no statistical difference in long-term risk of cardiovascular mortality between the two groups (RR, 1.15; 95% CI, 0.97–1.36; $P = 0.11$; $I^2 = 59\%$; **Figure 3B**) after a mean follow-up of 2.12 years. Seven studies demonstrated a deleterious effect of PPI on heart failure rehospitalization after a mean follow-up of 2.16 years (RR, 1.42; 95% CI, 1.18–1.71; $P = 0.0002$; $I^2 = 76\%$; **Figure 3C**).

Echocardiographic Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement

Two studies reported LVEF both at baseline and 1-year follow-up. **Figure 4A** shows no significant difference in LVEF between the two groups at baseline (mean difference, 1.40; 95% CI, −0.13 to 2.93; $P = 0.07$; $I^2 = 0\%$). LVEF at 1-year follow-up after TAVR was assessed using a fixed-effect model, and the overall value of LVEF was significantly greater in the no PPI group than in the PPI group (mean difference, −3.57; 95% CI, −4.88 to −2.26; $P < 0.00001$; $I^2 = 0\%$; **Figure 4B**).

DISCUSSION

The results of this meta-analysis can be summarized as follows: (1) patients with post-procedural PPI show a higher risk of all-cause mortality at mid-term follow-up after TAVR; (2) post-TAVR PPI is associated with an increased risk of all-cause mortality and heart failure rehospitalization at long-term follow-up; and (3) post-procedural PPI adversely affect LVEF recovery on patients undergoing TAVR.

TABLE 2 | Quality assessment of the included studies according to the Newcastle-Ottawa Scale (NOS).

References	Selection	Comparability	Outcome	Total stars
Rück et al. (16)	4	2	2	8
Rajah et al. (17)	4	2	2	8
Schoechlin et al. (18)	4	0	2	6
Van Mieghem et al. (19)	4	0	2	6
Clementy et al. (20)	4	0	2	6
Weferling et al. (21)	4	0	3	7
Nicolas et al. (22)	4	2	2	8
Alperi et al. (23)	4	1	2	7
Ashraf et al. (24)	4	0	2	6
Du et al. (25)	4	2	2	8
Fujita et al. (26)	4	0	2	6
Costa et al. (27)	4	2	2	8
Meduri et al. (28)	4	2	2	8
Maeno et al. (29)	4	2	2	8
Jørgensen et al. (30)	4	0	2	6
Gonska et al. (31)	4	2	3	9
Nadeem et al. (32)	4	2	2	8
Alasti et al. (33)	4	2	2	8
Walther et al. (34)	4	1	2	7
Rogers et al. (35)	4	0	2	6
Aljabbary et al. (36)	4	0	2	6
Chamandi et al. (37)	4	1	2	7
López-Aguilera et al. (38)	4	2	2	8
Nijenhuis et al. (39)	4	2	2	8
Engborg et al. (40)	4	2	2	8
Fadahunsi et al. (41)	4	1	2	7
Giustino et al. (42)	4	1	2	7
Dizon et al. (43)	4	0	2	6
Mouillet et al. (44)	4	2	2	8
Kawaguchi et al. (45)	4	2	2	8
Schymik et al. (46)	4	0	2	6
Nazif et al. (47)	4	2	2	8
Urena et al. (48)	4	2	2	8
Biner et al. (49)	4	2	2	8
Pereira et al. (50)	4	0	2	6
Houthuizen et al. (51)	4	0	2	6
De Carlo et al. (52)	4	2	2	8
Buellesfeld et al. (53)	4	2	3	9
D'Ancona et al. (54)	4	2	2	8

Twenty years after the first procedure in 2002 (55), TAVR has become a first-line treatment for patients with symptomatic severe aortic stenosis regardless of the estimated surgical risk (1–4). Although TAVR technology has matured significantly over the years, conduction abnormalities remain one of the major complications to be resolved. Currently, there is insufficient evidence to support that the newer-generation devices could reduce the rate of post-procedural PPI (56, 57). The underlying pathophysiological mechanisms compose of direct trauma, hemorrhage, inflammation, and ischemic injury of the conduction system during the expansion of the valve prosthesis (5). With accumulating TAVR cases, it is important to investigate the mid- to long-term clinical and echocardiographic outcomes of post-procedural PPI after TAVR.

Numerous studies have confirmed that RVP can negatively impact left ventricular function and increase the risk of the occurrence of atrial fibrillation (10, 58–60). The detrimental effects of RVP may elevate the risk of mortality and heart failure rehospitalization. As shown in our study, the pooled results revealed that patients undergoing PPI after TAVR had a higher risk of death at both mid- and long-term follow-up. They were also more likely to be hospitalized for heart failure during long-term follow-up. Similarly, a recent study containing the largest sample size reported that PPI after TAVR was independently associated with higher mortality and heart failure rehospitalization rate during follow-up, which was based on the entire France nationwide-level population (20).

We observed no significant difference in cardiovascular mortality and 1-year risk of heart failure rehospitalization between the two groups in our meta-analysis. The potential protective effects of PPI with respect to lethal bradyarrhythmias may counterbalance the negative effects of ventricular pacing. After the improvement of aortic stenosis, hemodynamic improvement of left ventricular function may compensate for the potential deleterious effects of ventricular pacing in such patients. In addition, implanting biventricular pacemakers in patients after TAVR may partially offset adverse effects linked to RVP.

Inconsistent with our results, few previous meta-analyses showed significant impacts of PPI after TAVR on clinical outcomes (13, 61, 62), except for a study by Faroux et al. (14), which was the first meta-analysis to reveal a significantly higher risk of all-cause death and heart failure rehospitalization in patients with PPI post-TAVR at 1-year follow-up. There are several explanations underlying the conflicting results in different studies. The small number of samples and short follow-up time may account for the distinct results. The occurrence and severity of pacing-induced cardiomyopathy are associated with ventricular pacing burden and duration, especially in patients with long-term pacing percentage $\geq$ 40% (11, 63, 64). Studies on TAVR have shown that new-onset conduction disturbances after TAVR may recover during follow-up, and about half of the patients requiring post-TAVR PPI are not pacing-dependent eventually (65–67). This may also partly explain why there was no significant difference in 1-year heart failure rehospitalization rates between the two groups.

Conduction disturbances occur commonly after TAVR, and an expert consensus algorithm was provided for managing post-TAVR conduction disturbances, but the optimal management of this complication is still unknown (68, 69). Schoechlin et al. (18) compared patients' outcomes between different PPI implantation indications and revealed that the restrictive PPI strategy they adopted reduces the PPI rate significantly and is safe after a follow-up of 3 years. In consideration of the mid- to long-term negative effects demonstrated in our meta-analysis, we recommended adopting a relatively restrictive PPI strategy after TAVR, but the detailed indications and management need to be further explored. Furthermore, His-Purkinje system pacing (HPSP) allows for electrical stimulation signaling through the physiological conduction system, which

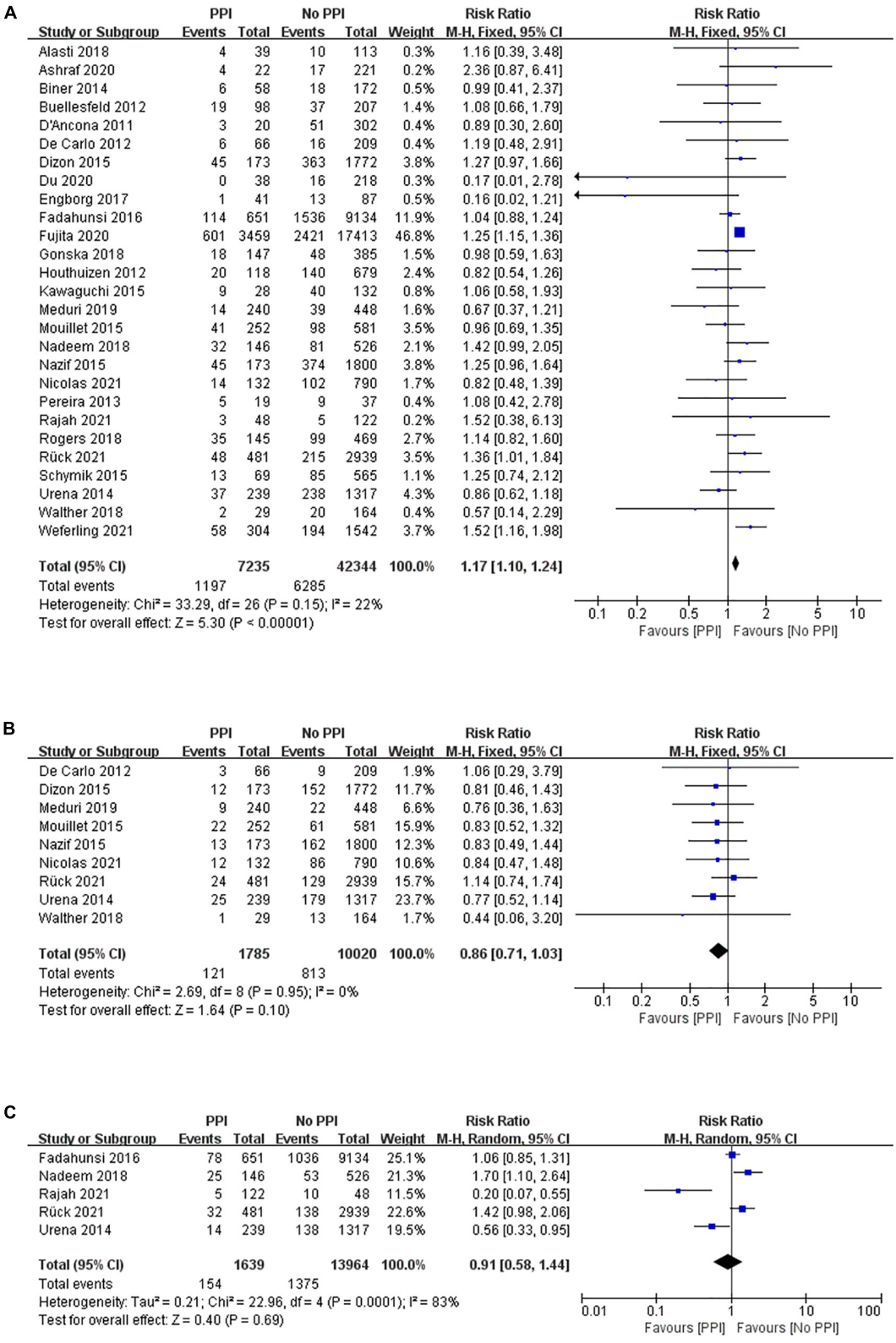

FIGURE 2 | Forest plot of the risk of mid-term (1 year) **(A)** all-cause mortality, **(B)** cardiovascular mortality, and **(C)** heart failure rehospitalization in patients with post-procedural permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR).

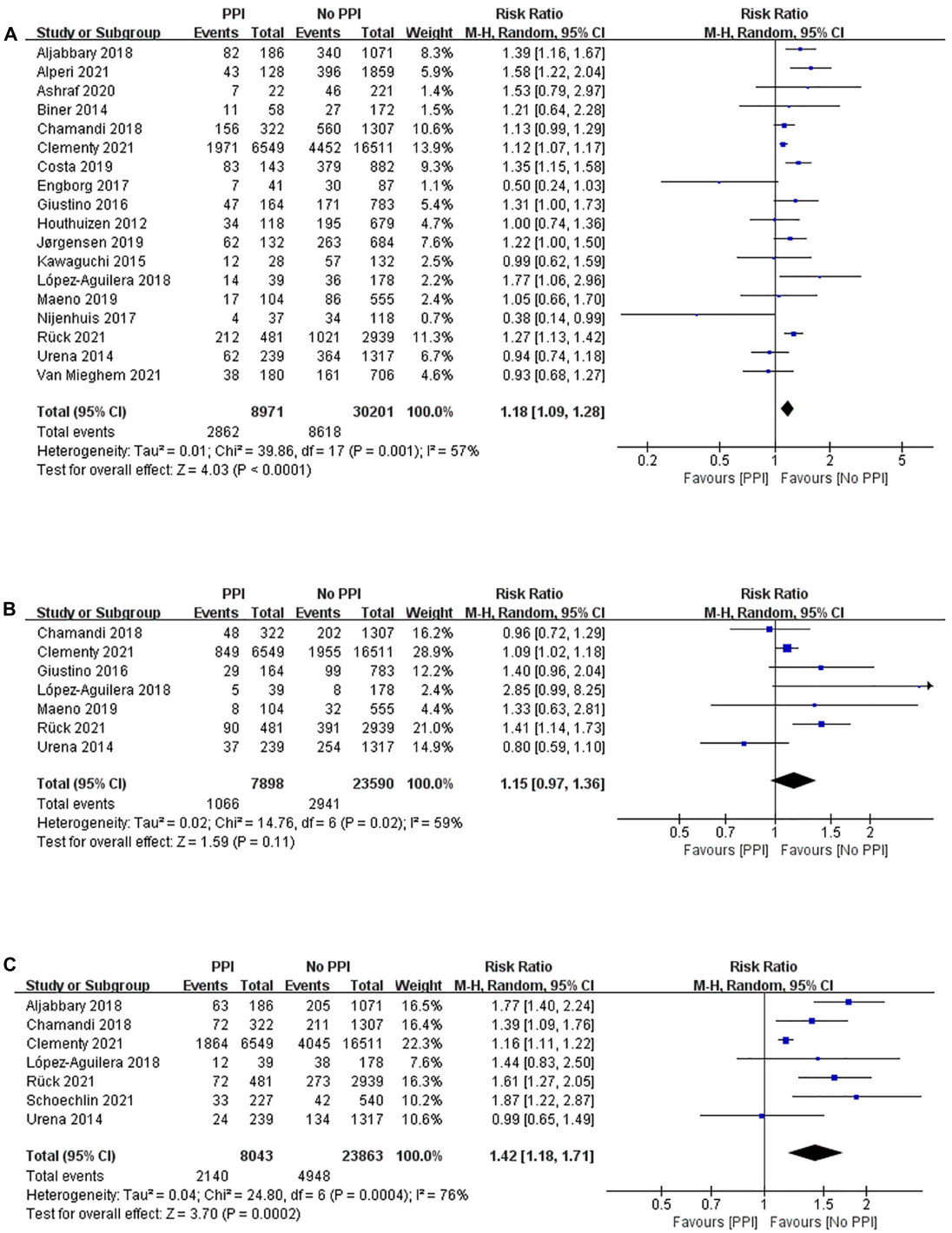

FIGURE 3 | Forest plot of the risk of long-term (> 1 year) **(A)** all-cause mortality, **(B)** cardiovascular mortality, and **(C)** heart failure rehospitalization in patients with post-procedural PPI after TAVR.

has the potential to prevent pacing-induced dyssynchrony, heart failure hospitalization, and mortality (70–73). Previous studies have confirmed the feasibility and safety of HPSP in patients after TAVR. De Pooter et al. (74) found that the valve prosthesis can serve as an anatomical landmark for the implantation of the His-bundle lead. A multicenter study by Vijayaraman et al. (75) revealed that left bundle branch pacing had a higher success rate than His-bundle pacing after TAVR, with more ideal pacing parameters. Eleven patients with reduced left ventricular function who underwent HPSP successfully in this study showed

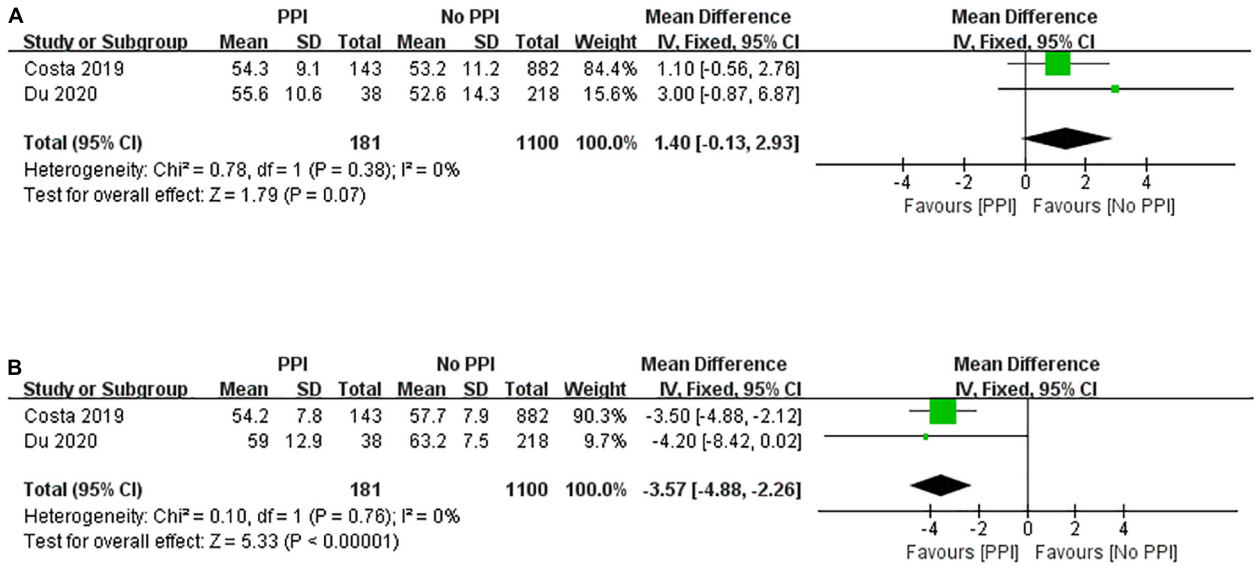

FIGURE 4 | Forest plot of left ventricular ejection fraction at baseline **(A)** and 1-year follow-up **(B)** between patients with and without post-procedural PPI after TAVR.

significant LVEF improvement from 35 to 42% during follow-up. However, there is no systematic large-scale study evaluating the clinical and echocardiographic effects of HPSP in patients undergoing TAVR. Therefore, further studies are needed to focus on this area.

Limitations

Several limitations of our meta-analysis should be acknowledged. First, most studies included in our meta-analysis were retrospective observational studies. Thus, prospective, multi-center, randomized comparative studies are urgently needed. Second, TAVR technology has developed over time, and the types of valve prostheses are different. Patients included in the prior studies might have different PPI inclusion criteria compared with later ones so the heterogeneity among studies was relatively high in our study. Third, we had inadequate numbers of studies reporting ventricular pacing percentage to assess any significance of pacing-induced cardiomyopathy. We also do not have enough information to study other complications of PPI, such as infection, pneumothorax, and pocket hematoma, which may result in significant clinical consequences outside of mortality. Last but not least, our study is a meta-analysis, and we lack access to individual patient data which may provide more information.

CONCLUSION

The present meta-analysis provides evidence that post-TAVR PPI has negative clinical and echocardiographic effects at mid- to long-term follow-up. This study highlights the importance of identifying patients at high risk of developing conduction disturbances and requiring PPI after TAVR. Cardiologists should optimize treatment strategies and management of these patients. TAVR technology should also improve to reduce the incidence of such complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SX, EZ, JS, and JZ contributed to the conception and designed the study. SX, EZ, and JS extracted the data and evaluated the quality. SX and EZ analyzed the data and wrote the manuscript. ZQ, FZ, YW, XH, and JZ critically reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

FUNDING

This study was supported by the National Natural Science Foundation of China (grant no. 82070521, PI: JZ) and the Clinical Competence Improvement Project of Jiangsu Province Hospital (grant no. JSPH-MA-2020-3, PI: JZ).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.911234/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 08 July 2022
doi: 10.3389/fcvm.2022.863968

Arterial Wave Reflection and Aortic Valve Stenosis: Diagnostic Challenges and Prognostic Significance

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Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: 27 January 2022
Accepted: 30 May 2022
Published: 08 July 2022

Citation:
Pagoulatou S, Adamopoulos D, Rovas G, Bikia V, Müller H, Giannakopoulos G, Mauler-Wittwer S, Licker M-J, Stergiopulos N and Noble S (2022) Arterial Wave Reflection and Aortic Valve Stenosis: Diagnostic Challenges and Prognostic Significance. Front. Cardiovasc. Med. 9:863968. doi: 10.3389/fcvm.2022.863968

Introduction: Arterial wave reflection is an important component of the left ventricular afterload, affecting both pressure and flow to the aorta. The aim of the present study was to evaluate the impact of wave reflection on transvalvular pressure gradients (TPG), a key parameter for the evaluation of aortic valve stenosis (AS), as well as its prognostic significance in patients with AS undergoing a transcatheter aortic valve replacement (TAVR).

Materials and Methods: The study population consisted of 351 patients with AS (mean age 84 ± 6 years, 43% males) who underwent a complete hemodynamic evaluation before the TAVR. The baseline assessment included right and left heart catheterization, transthoracic echocardiography, and a thorough evaluation of the left ventricular afterload by means of wave separation analysis. The cohort was divided into quartiles according to the transit time of the backward pressure wave (BWTT). Primary endpoint was all-cause mortality at 1 year.

Results: Early arrival of the backward pressure wave was related to lower cardiac output (Q1: 3.7 ± 0.9 lt/min vs Q4: 4.4 ± 1.0 lt/min, $p < 0.001$) and higher aortic systolic blood pressure (Q1: 132 ± 26 mmHg vs Q4: 117 ± 26 mmHg, $p < 0.001$). TPG was significantly related to the BWTT, patients in the arrival group exhibiting the lowest TPG (mean TPG, Q1: 37.6 ± 12.7 mmHg vs Q4: 44.8 ± 14.7 mmHg, $p = 0.005$) for the same aortic valve area (AVA) (Q1: 0.58 ± 0.35 cm^2 vs 0.61 ± 0.22 cm^2, $p = 0.303$). In multivariate analysis, BWTT remained an independent determinant of mean TPG (beta 0.3, $p = 0.002$). Moreover, the prevalence of low-flow, low-gradient AS with preserved ejection fraction was higher in patients with early arterial reflection arrival (Q1: 33.3% vs Q4: 14.9%, $p = 0.033$). Finally, patients with early arrival of the reflected wave (Q1)

exhibited higher all-cause mortality at 1 year after the TAVR (unadjusted HR: 2.33, 95% CI: 1.17–4.65, $p = 0.016$).

Conclusion: Early reflected wave arrival to the aortic root is associated with poor prognosis and significant aortic hemodynamic alterations in patients undergoing a TAVR for AS. This is related to a significant decrease in TPG for a given AVA, leading to a possible underestimation of the AS severity.

Keywords: arterial wave reflection, aortic valve stenosis, arterial stiffness, transvalvular pressure gradients, arterial hypertension

INTRODUCTION

Afterload is the mechanical load imposed on the left ventricle by both the aortic valve and the systemic circulation and is determined by complex time-varying phenomena. The arterial part has different components and it is best described by the propagative model of the human circulation, which consists of a distensible tube terminating at the peripheral resistance (1). The compliance of the tube permits the generation of a pressure wave, that travels along the arterial tree from the aortic root to the periphery (2).

From a physiological standpoint, the best fitting propagative model also predicts the presence of retrograde pressure waves moving throughout the arterial tree in the opposite direction (from the periphery to the aortic root) (1). This model consist the basis of the arterial reflection theory, which describes arterial reflections occuring at the elastic tube's end, a theoretical area characterized by high levels of resistance (2).

The physiological implications of this phenomenon have been extensively studied, especially as a key mechanism for the development of arterial hypertension with advancing age (3). One of the crucial factors is the timing of the arrival of the reflected wave and specifically how it relates to the ejection period. Many factors have been shown to influence this parameter such as the distance of the reflection sites, the tone of the arterioles as well as the velocity at which the waves travel along the arterial tree, which is determined by the compliance of the system (2). In case of early return (before the closure of the aortic valve), the reflected pressure wave adds to the pressure burden imposed to the left ventricle, becomes a considerable part of the afterload and decelerates blood flow (**Figure 1**). This mechanism provides the pathophysiological background that explains the prognostic impact (cardiovascular events and mortality) of early wave reflections in different populations such as patients with arterial hypertension, end-stage renal and coronary artery disease (4–7).

Aortic valve stenosis (AS) is the most common valvular heart disease in the Western world impacting significantly morbidity and mortality especially in the elderly population (8). In the clinical setting, the evaluation of AS severity relies predominantly on the transvalvular pressure gradients (TPG), defined as the difference in pressure between the left ventricle and the aortic root. A mean TPG of equal or more than 40 mmHg, typically measured by Doppler echocardiography, suggests a severe AS and represents a class I indication for aortic valve replacement in symptomatic patients (9).

Since TPG depends on the transvalvular blood flow (9–12), and based on the arterial wave reflection theory, we hypothesized that TPG may be influenced by the incidence of wave reflection to the aorta. In order to test this hypothesis, we explored the associations between TPG and arterial wave reflection indices in patients with AS, who underwent a thorough hemodynamic assessment before transcatheter aortic valve replacement (TAVR). Finally, in the same population, we explored the prognostic significance of early wave reflection by assessing all-cause mortality at 1 year.

MATERIALS AND METHODS

Study Population

This is a retrospective study based on data collected from the medical records of all patients who underwent a successful TAVR in our department from June 2008 to December 2019 ($n = 480$). The study population comprised patients referred for symptomatic AS of a native valve while presenting a high or intermediate risk for a conventional surgical approach. Sixty-seven patients were excluded due to unavailable, low quality, or missing data from baseline heart catheterization. Twenty-nine patients were excluded due to missing or low-quality baseline echocardiographic Pulsed Wave Doppler measurements and/or invasive aortic pressure measurements during the TAVR. Finally, thirteen patients were excluded because of a delay exceeding 1 year between the baseline heart catheterization and the TAVR. The final cohort consisted of 351 patients, and all data were anonymized prior to analysis. Informed written consent was obtained from each patient for inclusion in the local TAVR database as part of the Swiss prospective registry (NCT1368250) approved by the local Ethics Committee. A detailed study flowchart is depicted in **Figure 2**.

The study population was divided into four groups corresponding to the quartiles (Q) of the transit time of the backward pressure wave (BWTT). For the purpose of the current study, meaningful comparisons in BWTT between subjects can only be performed after taking into account for the relative timing of the arrival of the reflected wave to the systolic period. For this reason, values are expressed as percentage of the ejection duration (ED): Quartile 1 (Q1), $n = 87$, BWTT $\leq$ 11.8% of the ED; Quartile 2 (Q2), $n = 88$, BWTT from 11.9 to 15.5% of the

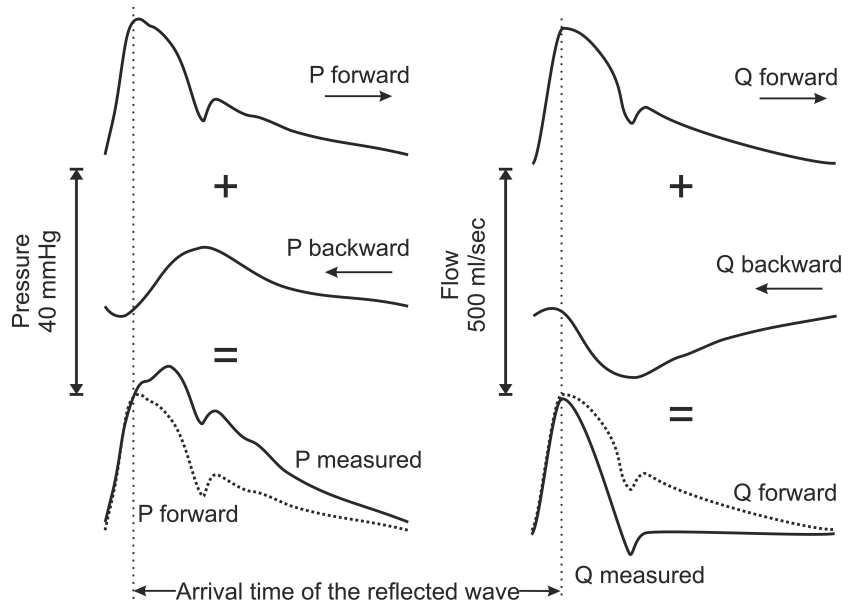

FIGURE 1 | Schematic representation describing the principle of the arterial wave reflection theory and the effects on pressure and flow contour waveform by the reflected waves. P, pressure; Q, blood flow.

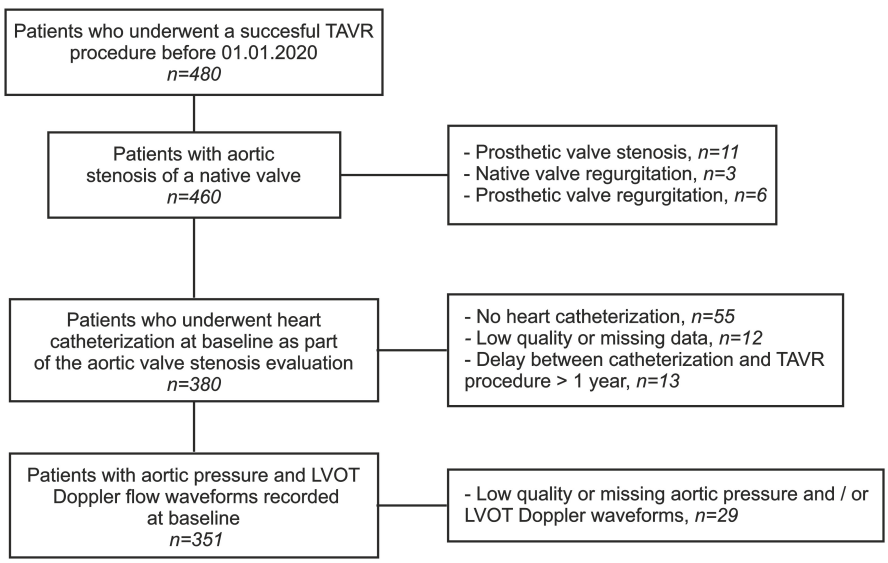

FIGURE 2 | Study flowchart. TAVR, transcatheter aortic valve replacement; LVOT, left ventricular outflow tract.

ED; Quartile 3 (Q3), $n = 88$, BWTT from 15.6 to 22.3% of the ED and; Quartile 4 (Q4), $n = 88$, BWTT $\geq$ 22.4% of the ED.

Right and Left Heart Catheterization

All patients underwent a baseline heart catheterization as part of the standard evaluation of the AS. During this examination, cardiac output (CO) was measured for all patients either by the thermodilution or the modified Fick method with estimated oxygen consumption. CO was also indexed to body surface area (BSA) and cardiac index (CI) was calculated. Stroke volume (SV) was calculated as the ratio of the CO to the heart rate (HR) and was indexed to BSA (SV index [SVi]). Pulmonary artery and wedge pressures were also obtained, while a diagnostic coronary angiography was performed on all patients.

On the day of the TAVR, invasive recordings of the baseline pressure waveform in the aortic root were acquired. For all but five patients, simultaneous left ventricular pressure measurements were available. The heart catheterization protocol included a first 6F "pigtail" catheter (Cordis), which was advanced through the stenotic aortic valve into the left ventricle

from the vascular access for the transcatheter prosthetic valve and a second 6F "pigtail" catheter which was advanced to the aortic root using a second vascular access. Both catheters were connected to a pressure line and a calibrated transducer. In some patients, a double lumen catheter (Langston) was used. The pressure curves were simultaneously recorded over several heartbeats and were subsequently analyzed offline.

Echocardiography

A complete transthoracic echocardiography (TTE) in supine position was performed prior to the TAVR in all study participants. All measurements were conducted by an experienced cardiologist according to standard recommendations for TTE (13). Acquired images were transferred to a dedicated workstation for subsequent offline analysis (IntelliSpace Cardiovascular 5.1, Philips Medical Systems Nederland B.V.). Data on left ventricular geometry were collected, and left ventricular mass was calculated according to the Devereux formula (14). The proximal velocity profile was acquired in the left ventricle outflow tract via Pulsed Wave Doppler in the standard apical 5-chamber view. The aortic flow waveform was subsequently derived after calibration for the invasively measured SV. Aortic valve TPG, ejection fraction (EF), aortic valve area (AVA), AVA indexed to BSA (AVAi), and qualitative evaluation of other valve abnormalities (mitral, tricuspid) were extracted from the standard echocardiographic reports.

Aortic Stenosis Classification

AS classification was performed by the application of the diagnostic criteria proposed by the European Society of Cardiology Guidelines for the management of valvular disease (15); (i) High-gradient AS: AVA < 1 cm^2 or AVAi < 0.6 cm^2/m^2 and mean TPG ≥ 40 mmHg; (ii) Low-gradient AS with reduced EF: AVA < 1 cm^2 or AVAi < 0.6 cm^2/m^2, mean TPG < 40 mmHg and EF $< 50\%$; (iii) Low-flow, low-gradient AS with preserved EF: AVA < 1 cm^2 or AVAi < 0.6 cm^2/m^2, mean TPG < 40 mmHg, EF $\geq 50\%$ and SVi ≤ 35 ml/m^2; (iv) Normal-flow, low-gradient AS with preserved EF: AVA < 1 cm^2 or AVAi < 0.6 cm^2/m^2, mean TPG < 40 mmHg, EF $\geq 50\%$ and SVi > 35 ml/m^2.

Wave Separation Analysis

The left ventricle and aortic root pressure curves recorded before the TAVR were digitized for each patient. A custom, in-house Matlab code was developed to identify the beginning and end of each heartbeat automatically, and the average pressure curves over several (4–8) heartbeats were computed. Subsequently, pressure waveform analysis was performed, and key features were determined, including (i) left ventricle systolic and end-diastolic pressures, (ii) the invasive TPG, calculated as the difference between the left ventricle and aortic pressures (area under the curve, peak to peak and mean), (iii) the aortic systolic, diastolic, mean and pulse pressures and (iv) the valvulo-arterial impedance, defined as the ratio of systolic left ventricular pressure over SVi. According to the Gorlin formula (12), the AVA and AVAi were calculated as the ratio of mean flow and mean TPG:

$$AVA = \frac{Q_{mean}}{44.3\sqrt{TPG_{mean}}} \quad (1)$$

The invasive aortic pressures were subsequently combined with the TTE flow curves for wave separation analysis. The two curves were synchronized for each patient by adopting the second derivative approach, whereby the time lag between the two signals was corrected by calculating the maxima of the second time derivatives (16). Note that any difference in HR between the pressure and flow measurements was accounted for by truncating or extending the diastolic portion of the flow wave. Subsequently, wave separation analysis was performed by applying the standard methodology in the frequency domain. More specifically, the input impedance was derived from the synchronized pressure and flow curves as the ratio of the corresponding harmonics. Aortic characteristic impedance (Zc) was then identified by averaging the input impedance modulus of the 3rd to 9th harmonics (after excluding outlier values greater than three times the median value of input impedance modulus over that range of harmonics). The forward and backward pressure and wave components were subsequently calculated as described by Westerhof et al. (17):

$$P_{forward} = \frac{P+Z_cQ}{2} \; and \; P_{backward} = \frac{P-Z_cQ}{2} \quad (2)$$

$$Q_{forward} = \frac{P_{forward}}{Z_c} \; and \; Q_{backward} = -\frac{P_{backward}}{Z_c} \quad (3)$$

Key features of the forward and backward pressure waves were identified, including the magnitude and timing of the peak pressure, the wave amplitude, and the BWTT, identified by the foot of the curve. Finally, the reflection coefficient was evaluated as the ratio of the backward wave to the forward wave amplitudes. The synchronized pressure and flow signals were additionally used for the calculation of the equivalent total vascular resistance (TVR) and total arterial compliance (TAC) via parameter-fitting on a 2-element Windkessel model as described by Stergiopulos et al. (18).

Procedure Characteristics

Aortic valve replacement was performed by the use of the Medtronic self-expanding CoreValve and Evolut devices (Medtronic Inc., Minneapolis, MN, United States, $n = 341$, 97.1%), the Edwards Sapien S3 (Edwards Lifesciences SA, CA, United-States, $n = 28$, 7.9%) or the Boston neo Accurate (Boston Scientific AG, MA, United States, $n = 5$, 1.5%). Device implantation success was systematically evaluated for all interventions according to the Valve Academic Research Consortium-2 consensus Document criteria (19).

Follow-Up

A post-TAVR follow-up was performed for all patients at 1-, 6-, and 12-months intervals through a clinical visit. All baseline

clinical characteristics and procedural and follow-up data were stored in a dedicated database using a secured online platform[1] (OpenClinica LLC, Waltham, MA, United States). The primary study endpoint was all-cause mortality at 1 year. Events were adjudicated by an external clinical committee.

Statistical Analysis

Categorical variables are reported as counts with percentages. Continuous variables are expressed as mean and standard deviation or as the median and interquartile range for variables with non-normal distribution (normality was assessed by visual inspection of the frequency distributions). Categorical variables are compared among groups by the use of Pearson Chi-Square or the Fischer exact test as appropriate. Continuous variables were compared among the groups using analysis of variance (ANOVA) or the Kruskal-Wallis test for the non-normally distributed data. Levene's test was used to assess the homogeneity of variance among the compared groups, and in case of violation, Welch's ANOVA test was used. In order to assess the independent effect of the BWTT on TPG multiple linear regression model analysis was performed treating BWTT as a continuous variable and after adjusting for the following parameters: Aortic systolic blood pressure, AVA (estimated by the Gorlin formula), Zc, TVR, TAC, gender and height. One-year all-cause mortality rates was calculated from Kaplan-Meier analysis for patients presenting the earliest return of the reflected wave (Q1) as compared to the rest of the population (Q2–Q4). Cox-regression analysis for the same groups was performed to compute hazard ratios and the 95% confidence intervals after verification of the proportional hazard assumption. A multivariate Cox-regression

[1]www.openclinica.com

TABLE 1 | Demographic and clinical characteristics of the study population according to the BWTT quartiles.

	Backward wave transit time				P-value
	Q1 (*n* = 87)	**Q2 (*n* = 88)**	**Q3 (*n* = 88)**	**Q4 (*n* = 88)**	
Demographics					
Age (years)	84 ± 6	85 ± 6	83 ± 6	82 ± 6	0.071
Height (cm)	164 ± 8	162 ± 8	166 ± 10	166 ± 10	0.009
Weight (Kg)	69 ± 14	71 ± 15	70 ± 15	75 ± 15	0.089
BMI (kg/m^2)	25.8 ± 5.4	26.8 ± 5.0	25.4 ± 4.6	27.0 ± 4.9	0.084
BSA (m^2)	1.76 ± 0.19	1.78 ± 0.21	1.8 ± 0.23	1.85 ± 0.21	0.058
Gender (males, *n*, %)	29 (33)	29 (33)	43 (50)	50 (57)	0.002
Pre-intervention risk scores					
Euroscore (%, *n* = 343)	13.6 [8.9–22.1]	15.2 [10.1–23.3]	13.5 [9.4–20.9]	13 [8.9–18.3]	0.336
STS Score (%, *n* = 343)	5.4 [3.4–8.2]	5.3 [3.7–8.3]	4.9 [3.1–7.3]	4.1 [2.8–5.8]	0.013
Comorbidities and risk factors					
Diabetes (%)	27 (31)	30 (34)	22 (25)	24 (27)	0.560
Dyslipidaemia (%)	62 (71)	66 (75)	56 (64)	58 (66)	0.353
Arterial hypertension (%)	69 (79)	73 (83)	70 (80)	72 (82)	0.911
Smokers (%)	8 (9)	3 (3)	7 (8)	8 (9)	0.095
CAD (%)	49 (56)	45 (51)	51 (58)	44 (50)	0.660
Previous MI (%)	10 (12)	13 (15)	9 (10)	12 (14)	0.798
PAD (%)	12 (14)	13 (15)	15 (17)	7 (8)	0.332
COPD (%)	17 (20)	13 (15)	14 (16)	15 (17)	0.854
Renal failure (%)	40 (51)	47 (53)	43 (49)	46 (52)	0.937
Cancer (%)	15 (17)	21 (24)	17 (19)	24 (27)	0.373
Atrial fibrillation/flutter (%)	33 (38)	26 (30)	27 (31)	29 (33)	0.650
Presence of symptoms					
NYHA III or IV (%)	65 (75)	66 (75)	61 (69)	64 (73)	0.822
Syncope (%, *n* = 342)	5 (6)	11 (13)	11 (13)	13 (16)	0.249
Angina (%)	22 (25)	14 (16)	22 (25)	10 (12)	0.080
Baseline medications					
Aspirin (%)	52 (60)	53 (60)	47 (53)	42 (48)	0.291
Oral anticoagulation (%)	27 (31)	26 (30)	25 (28)	25 (28)	0.978
Beta-blockers (%)	35 (40)	38 (43)	33 (38)	34 (39)	0.880
ACE inhibitors (%)	23 (26)	15 (17)	20 (23)	21 (24)	0.499
ARBs (%)	35 (40)	38 (43)	33 (38)	34 (39)	0.880
Statin (%)	52 (60)	50 (57)	44 (50)	49 (56)	0.619

Continuous variables expressed as mean ± standard deviation or median and interquartile range. Categorical variables are expressed in absolute counts and (percentages). P-values obtained by ANOVA or Chi-Square test.

BMI, body mass index; BSA, body surface area; STS, Society of Thoracic Surgeons; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

model was used in order to adjust comparisons between the two groups for potential confounding mortality factors (Model A: STS Score and gender, Model B STS score, gender and tricuspid regurgitation, Model C: Device success). Statistical significance was assumed at a 2-sided *P*-value level of 0.05. Statistical analysis was performed in IBM SPSS statistics (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

RESULTS

Baseline Characteristics

The baseline characteristics of the study population are presented in **Table 1**. Baseline characteristics did not differ among the 4 groups, except for low height and female gender that were associated with early arrival of the reflected wave ($p = 0.009$ and 0.002, respectively).

Invasive Hemodynamics

No significant differences were noted among groups in terms of HR, ED, left ventricular systolic, end-diastolic, mean pulmonary artery, and wedge pressures (**Table 2**). Early arrival of the reflected wave was associated with decreased aortic flow as assessed by CO, CI, SV, SVi, and mean flow rate. Likewise, early arrival of the reflected wave was associated with higher pressure-derived parameters (aortic systolic, mean, and pulse pressures). Finally, early arrival of the reflected wave was associated with lower invasive TPG expressed as area under the curve ($p = 0.027$), peak to peak ($p = 0.012$), and mean ($p = 0.011$) gradients, while

TABLE 2 | Invasive and echocardiographic parameters according to the BWTT quartiles.

	Backward wave transit time				*P-value*
	Q1 (*n = 87*)	**Q2 (*n = 88*)**	**Q3 (*n = 88*)**	**Q4 (*n = 88*)**	
Invasive hemodynamics					
Heart rate (bpm)	76 ± 14	75 ± 12	76 ± 12	75 ± 14	0.916
Ejection duration (ms)	414 ± 55	408 ± 50	417 ± 53	401 ± 51	0.184
Cardiac output (lt/min)	3.7 ± 0.9	4.0 ± 1.0	3.9 ± 1.0	4.4 ± 1.0	<0.001
Cardiac index (lt/min/m^2)	2.1 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.4 ± 0.5	0.003
Cardiac output normalized for height (lt/min/m)	2.3 ± 0.5	2.4 ± 0.6	2.4 ± 0.6	2.6 ± 0.6	<0.001
Stroke volume (ml)	50.4 ± 14.8	54.4 ± 17.3	53.6 ± 17.1	61.1 ± 19.1	0.001
Stroke volume index (ml/m^2)	28.4 ± 7.6	30.4 ± 8.1	29.6 ± 7.8	32.7 ± 8.5	0.004
Stroke volume normalized for height (ml/m^3)	30.7 ± 8.7	33.4 ± 9.9	32.1 ± 9.6	36.6 ± 10.7	0.001
Mean flow rate (ml/s)	123 ± 37	135 ± 45	129 ± 43	153 ± 47	<0.001
LV max pressure (mmHg, *n* = 346)	171 ± 29	168 ± 29	166 ± 32	165 ± 30	0.630
LV end-diastolic pressure (mmHg, *n* = 346)	18 ± 7	16 ± 8	17 ± 7	17 ± 9	0.694
Aortic SBP (mmHg)	132 ± 26	123 ± 25	122 ± 25	117 ± 26	0.001
Aortic MBP (mmHg)	85 ± 15	76 ± 15	80 ± 16	78 ± 16	0.009
Aortic DBP (mmHg)	55 ± 11	51 ± 11	54 ± 12	53 ± 12	0.089
Aortic PP (mmHg)	77 ± 22	72 ± 21	68 ± 23	63 ± 22	<0.001
Ventricular-aortic pressure gradient (AUC, mmHg*s, *n* = 343)	11.8 ± 5.7	13.8 ± 6.4	14.5 ± 6.7	14.3 ± 6.7	0.027
Ventricular-aortic pressure gradient (peak, mmHg, *n* = 346)	38 ± 17	45 ± 22	45 ± 21	48 ± 22	0.012
Ventricular-aortic pressure gradient (mean, mmHg, *n* = 343)	28 ± 13	34 ± 15	35 ± 15	35 ± 15	0.011
Zva (mmHg/ml/m^2, *n* = 345)	6.4 ± 2.1	5.9 ± 2.1	6.0 ± 1.9	5.3 ± 1.6	0.006
AVA (Gorlin, cm^2, *n* = 341)	0.58 ± 0.35	0.56 ± 0.21	0.54 ± 0.21	0.61 ± 0.22	0.303
PAP mean (mmHg)	26 ± 10	25 ± 9	27 ± 11	26 ± 11	0.466
Wedge pressure (mmHg)	15 ± 8	14 ± 7	15 ± 8	15 ± 8	0.296
Echocardiographic parameters					
Transvalvular max pressure gradient (mmHg)	63.9 ± 20.1	68. ± 19.4	71.7 ± 24.2	75.9 ± 22.9	0.003
Transvalvular mean pressure gradient (mmHg)	37.6 ± 12.7	40.2 ± 12.6	42.4 ± 14.7	44.8 ± 14.7	0.005
Transvalvular max velocity (cm/s)	395 ± 64	410 ± 60	418 ± 72	430 ± 65	0.005
Ejection duration (ms)	343 ± 45	337 ± 47	345 ± 47	330 ± 44	0.123
Ejection fraction (%)	62.5 [50–65]	62.5 [50–65]	61.3 [48.8–62.5]	62.5 [53.1–64.4]	0.485
AVA (continuity equation, cm^2)	0.75 ± 0.21	0.75 ± 0.2	0.70 ± 0.21	0.72 ± 0.17	0.255
LV mass (g, *n* = 346)	189 ± 59	200 ± 67	206 ± 71	231 ± 70	<0.001
End diastolic LV diameter (cm)	4.6 ± 0.8	4.4 ± 0.8	4.7 ± 0.7	4.8 ± 0.7	0.041
Aortic regurgitation (≥moderate)	3 (3.4)	2 (2.3)	3 (3.4)	6 (6.8)	0.447
Mitral regurgitation (≥moderate)	7 (8)	3 (3.4)	2 (2.3)	8 (9.1)	0.135
Tricuspid regurgitation (≥moderate)	11 (12.6)	2 (2.3)	4 (4.5)	5 (5.7)	0.031

Continuous variables expressed as mean ± standard deviation or median and interquartile range. Categorical variables are expressed in absolute counts and (percentages). P-values obtained by ANOVA or Chi-Square test.

LV, left ventricle; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; AUC, area under the curve; Zva, valvulo-arterial impedance; AVA, aortic valve area; PAP m, mean pulmonary artery pressure; BSA, body surface area.

AVA remained constant among groups. Two characteristic cases from the Q1 and Q4 groups are depicted in **Figure 3**.

Echocardiographic Parameters

Lower Doppler-derived mean (p = 0.005), maximum TPG (p = 0.003), and maximum transvalvular velocity (p = 0.005) were all associated with shorter BWTT (**Table 2**). AVA calculated according to the continuity equation was comparable among groups. No difference in EF was noted among groups. Tricuspid regurgitation was associated with early arrival of the reflected wave (**Table 2**, p = 0.031), as well as the prevalence of the low-flow, low-gradient AS with preserved EF (Q1: 33.3% vs Q2: 21.3% vs Q3: 20.7% vs Q4: 14.9%, p = 0.033, **Figure 4**).

Arterial Tree and Wave Separation Analysis

Early arrival of the backward wave was associated with higher TVR ($p < 0.001$), lower TAC (p = 0.041) and lower Zc (p = 0.002, **Table 3**). No difference among groups was noted in the forward wave amplitude and timings. Backward wave amplitude and the reflection coefficient were all associated with an early arrival of the reflected wave ($p < 0.001$ for all).

Multiple Linear Regression Analysis

In multivariate analysis, BWTT remained a strong, independent predictor of all TPG measures after adjusting for gender and height, Zc, TVR, and TAC (**Figure 5**, $p < 0.05$ for all).

Transcatheter Aortic Valve Replacement Intervention

Data on the TAVR procedure are presented in **Table 4**. Transfemoral access was the most used approach (n = 341), followed by sub-clavian (n = 4) and trans-apical access (n = 2). 44 patients (12.5%) underwent a concomitant procedure (coronary angioplasty). Device success was achieved in 325 interventions (92.5%), which was comparable among the groups (**Table 4**).

Clinical Outcomes

Clinical follow-up was completed for the totality of the study population. **Figure 6** presents mortality data stratified according to BWTT. Patients with early backward wave return (Q1, ≤25th percentile) exhibited higher all-cause mortality rates at 1 year (unadjusted HR 2.33; 95% CI: 1.17–4.65, p = 0.016), as compared to the rest of the study population. This remained significant even after adjustment for baseline differences including gender and STS score (Model A; adjusted HR 2.38; 95% CI: 1.16–4.89, p = 0.018), for device success rate (Model C: adjusted HR = 2.24 (95% CI: 1.12–4.47, p = 0.022), but not after adjustment for tricuspid regurgitation which was different between the groups (Model B, adjusted HR 2.00, 95% CI: 0.95–4.24, p = 0.064).

DISCUSSION

The main findings of the present study may be summarized as follows: In patients with AS, the early arrival of the wave reflection

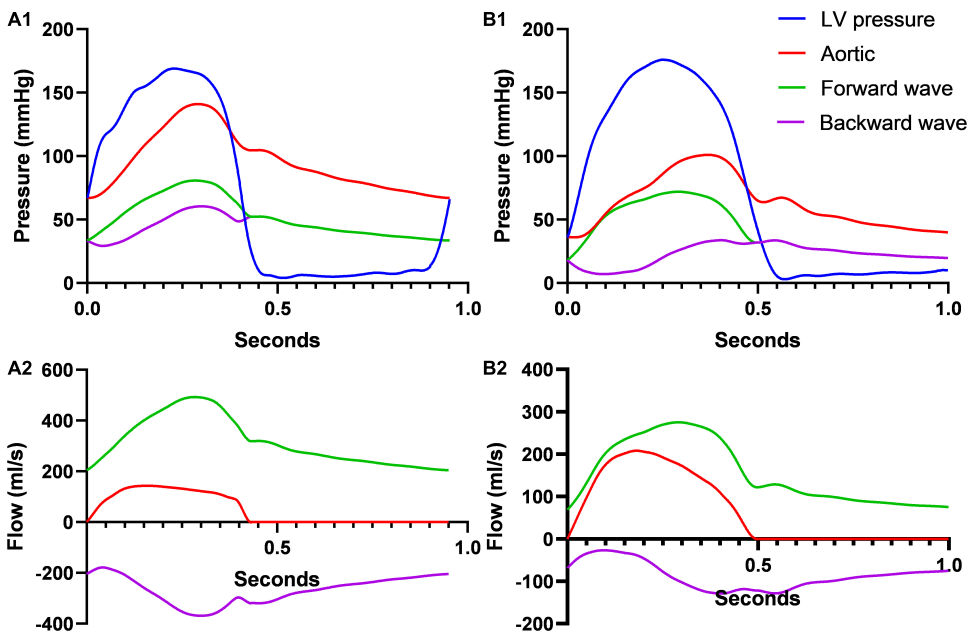

FIGURE 3 | Pressure and flow wave separation analysis for two study participants from the Q1 **(A)** and the Q4 **(B)** groups. Pressure and flow wave separation analysis in a patient with an early (transit time 0.041 s, reflection magnitude 66%, panels **A1,A2**) and a late reflection wave arrival (transit time 0.167 s, reflection magnitude 49%, **B1,B2**) with the same AVA (0.55 cm^2). Early reflection arrival is associated with a much more prominent deceleration of the aortic flow due to the backward wave and a decreased SV (**A2** vs. **B2**, 47 ml vs 68 ml accordingly). In addition, early arrival is associated with increased aortic pressure during systole, with left ventricular pressure being comparable between the two patients (**A1** vs. **B1**).

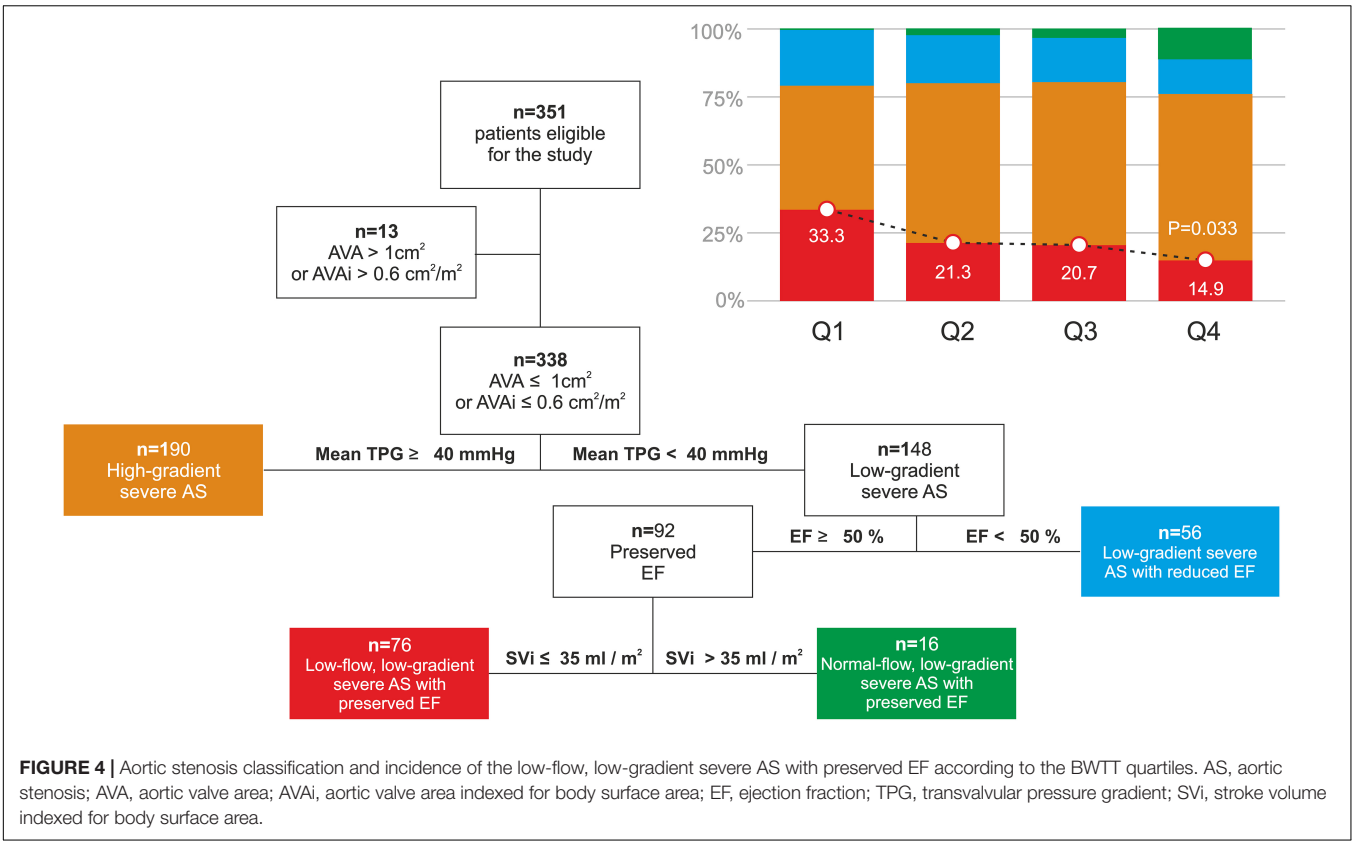

FIGURE 4 | Aortic stenosis classification and incidence of the low-flow, low-gradient severe AS with preserved EF according to the BWTT quartiles. AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed for body surface area; EF, ejection fraction; TPG, transvalvular pressure gradient; SVi, stroke volume indexed for body surface area.

TABLE 3 | Characteristics of the arterial tree and of the forward and backward pressure waveforms as derived from the wave separation analysis according to the BWTT quartiles.

	Backward wave transit time				*P-value*
	Q1 (*n* = 87)	**Q2 (*n* = 88)**	**Q3 (*n* = 88)**	**Q4 (*n* = 88)**	
Arterial tree					
Systemic vascular resistance (mmHg/ml)	1.65 ± 0.64	1.45 ± 0.54	1.50 ± 0.47	1.27 ± 0.46	<0.001
Total arterial compliance (ml· mmHg^{-1})	0.49 ± 0.25	0.58 ± 0.31	0.58 ± 0.28	0.61 ± 0.25	0.041
Characteristic impedance of the aorta (mmHg /ml)	0.14 ± 0.06	0.17 ± 0.08	0.18 ± 0.08	0.18 ± 0.07	0.002
Wave separation analysis					
Forward wave amplitude (mmHg)	49 ± 13	49 ± 15	48 ± 16	48 ± 16	0.841
Time to forward wave peak (ms)	258 ± 43	250 ± 40	258 ± 46	251 ± 44	0.465
Backward wave amplitude (mmHg)	33 ± 11	28 ± 9	27 ± 10	25 ± 9	<0.001
Time to backward wave peak (ms)	294 ± 47	305 ± 51	329 ± 65	354 ± 62	<0.001
Backward wave transit time (ms)	40 ± 9	55 ± 8	77 ± 11	117 ± 23	<0.001
Reflection coefficient (%)	66 ± 13	59 ± 10	58 ± 12	53 ± 10	<0.001

Continuous variables expressed as mean ± standard deviation. P-values obtained by ANOVA.

to the aorta is associated with (a) lower aortic TPG (as assessed either by Doppler echocardiography or heart catheterization) for the same AVA; (b) lower CO, lower SV, and lower mean flow rate during systole, (c) higher aortic systolic and mean pressures and finally (d) poor prognosis as assessed by all-cause 1 year mortality.

Although a causal relationship cannot be established, the present study provides evidence that wave reflections may influence TPG measurements possibly through a flow-dependent mechanism affecting the accuracy of AS evaluation. The shift towards earlier arrival of the reflected waves increases pressure during systole and decelerates substantially the aortic transvalvular flow. According to the Gorlin formula, for a given AVA, TPG depends exclusively on the transvalvular flow, which explains the observed associations (12).

Notably, the present findings suggest a possible physiological explanation for the discrepancies observed in patients with low-flow, low-gradient severe AS and preserved EF. Since its introduction in 2007, this entity has remained a great challenge for the clinical cardiologist both in terms of diagnosis and treatment. It is characterized by a very small AVA (less or equal to

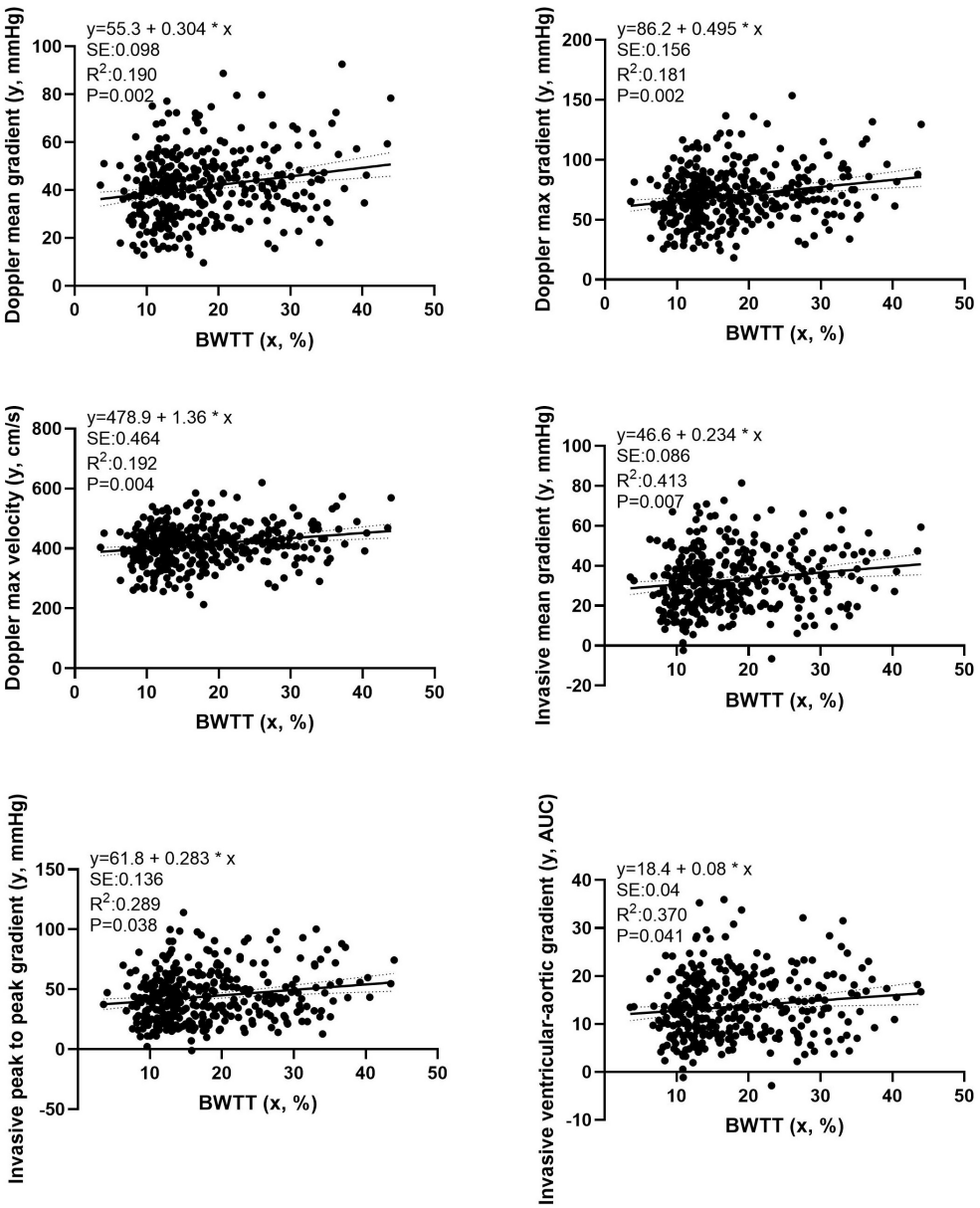

FIGURE 5 | Multiple linear regression analysis examining the independent effect of the BWTT on transvalvular pressure gradients obtained by either echocardiographic or invasive evaluation. Independent variables: Aortic systolic blood pressure; Aortic valve area (estimated by the Gorlin formula); Aortic characteristic impedance; Systemic vascular resistance; Total arterial compliance; gender and height.

1 cm^2) corresponding to a severe AS, but with a mean TPG below 40 mmHg, classifying the stenosis as less severe. The low TPG in these patients is explained by a low-flow state, which is defined by a SVi $\leq$ 35 ml/m^2. The "paradox," though, lies in the fact that the SV is low while at the same time the EF is preserved ($\geq$50%) (20). Different factors have been incriminated for this low-flow state, including atrial fibrillation, small left ventricular cavity size, impaired diastolic filling, left restrictive ventricular physiology, and concomitant valvopathies (21). The findings of the present study suggest that an enhanced arterial wave reflection may also participate in the pathogenesis of the low-flow state in these patients. This is further supported by the fact that reduced TAC (a significant determinant of wave propagation velocity and thus wave reflection) has been consistently observed in patients with low-flow, low-gradient severe AS with preserved EF (20, 22).

In our study, enhanced reflections were associated with stiffer arterial trees (low TAC), which, however, had lower Zc, i.e., lower proximal aortic stiffness. In young adults, the proximal aorta is highly compliant, whereas the peripheral arteries are relatively stiff. In terms of wave propagation, this suggests an important impedance mismatch between the compliant aorta and the branch vessels, which generates reflections

TABLE 4 | Transcatheter aortic valve replacement (TAVR) procedural characteristics.

	Backward wave transit time				P-value
	Q1 (*n* = 87)	Q2 (*n* = 88)	Q3 (*n* = 88)	Q4 (*n* = 88)	
Access site					0.764
Trans-femoral (%)	84 (96.6)	86 (97.7)	85 (96.6)	86 (97.7)	
Trans-apical (%)	0 (0)	1 (1.1)	1 (1.1)	0 (0)	
Sub-clavian (%)	1 (1.1)	1 (1.1)	2 (2.3)	2 (2.3)	
Other (%)	2 (2.3)	0 (0)	0 (0)	0 (0)	
Prosthetic valve type					0.827
Medtronic CoreValve (%)	79 (89.7)	79 (89.8)	79 (89.8)	83 (94.3)	
Edwards Sapien (%)	8 (9.2)	8 (8.0)	7 (8.0)	5 (5.7)	
Boston Acurate (%)	1 (1.1)	2 (2.3)	2 (2.3)	0 (0)	
Procedural specifications					
Concomitant procedure (%)	13 (14.9)	9 (10.2)	13 (14.8)	9 (10.2)	0.642
Device success (%)	79 (90.8)	86 (97.7)	82 (93.2)	78 (86.6)	0.112

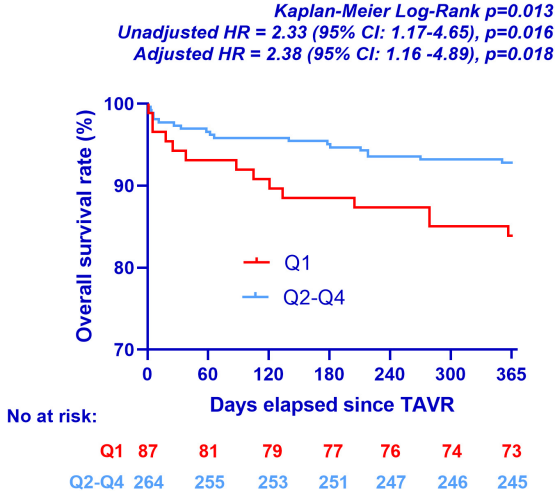

FIGURE 6 | Kaplan-Meier curves for all-cause mortality at 1 year according to BWTT quartiles. Model A: adjusted HR = 2.38 (95% CI: 1.16–4.89, $p = 0.018$), covariates: gender and STS Score. Model B: adjusted HR = 2.00 (95% CI: 0.95–4.24, $p = 0.064$), covariates: gender, STS Score and tricuspid regurgitation. Model C: adjusted HR = 2.24 (95% CI: 1.12–4.47, $p = 0.022$), covariates: Device success. TAVR: transcatheter aortic valve replacement.

(23). Disproportionate stiffening of the proximal aorta and augmentation of the characteristic impedance (typically observed during aging) are therefore associated with a decrease in the impedance mismatch and a decrease in the backward wave amplitude (24). Following this paradigm, we may infer that the enhanced wave reflections in the Q1 group are likely due to a more pronounced impedance mismatch between central and peripheral arteries.

It is interesting to note that the decrease in SV observed with enhanced wave reflection was not associated with a concomitant decrease in EF. This in accordance with previous observations where enhanced arterial wave reflection was associated with preserved EF but reduced left ventricular function as reflected by ventricular longitudinal strain and tissue imaging (25). Another possible explanation is the fact that earlier arrival of the reflected waves is seen in shorter patients (due to the decreased traveling distance of the waves), and short stature is associated with smaller heart size and volumes; thus, the ratio of the SV to the left ventricular end-diastolic volume remains unchanged. Although left ventricular volumes were not measured in our study, left ventricular mass and end-diastolic diameters were lower in patients, with early reflections suggesting smaller left ventricular cavities (**Table 2**). Finally, EF was only visually estimated in our study, a method possibly not sensitive enough to detect changes in EF for subtle changes in SV.

Our study highlights the importance of a detailed analysis of the left ventricular afterload for the accurate evaluation of the severity of the AS. Brachial systolic and diastolic pressures are not sufficient since they do not represent the whole spectrum of the mechanical load imposed on the left ventricle. On the other hand, it would be unrealistic to suggest invasive recordings of the aortic pressure for every patient with AS. The use of the handheld, high fidelity tonometers developed in the last years may be an excellent option since they provide accurate, non-invasive measurements of the pressure waveform of an artery close to the skin (26, 27). The subsequent combination of pressure and flow obtained concomitantly during routine echocardiography provides a detailed description of the left ventricular afterload directly at the patient's bedside.

To attenuate the impact of high after load on TPG, it has been suggested that the assessment of the AS should be repeated after the intravenous or sublingual administration of nitrates (28–34). At conventional dosage, these potent vasodilators act on the wall of the small arteries but have no/little effect on arterioles, large arteries, or the aorta. Since arterioles are unaffected, nitrates do not affect systemic vascular resistance (unless administered in high doses), and their beneficial effect on afterload is considered to be entirely attributable to the reduction in wave reflection amplitude (1). In the absence of a direct effect on large arteries, nitrates do not affect pulse wave velocity, thus have little impact on the delay of the reflected waves (35, 36). Nevertheless, it

should be noted that nitrates also have a significant venodilating effect, which results in pooling of the circulating blood volume in the venous circulation and thus a decrease of the blood return to the heart. Since nitrates decrease both preload and afterload, the cumulative effect on SV and aortic flow is not easily predictable and depends on different factors such as the status of the left ventricular function and the presence or not of reflex sympathetic nervous activity (37). Finally, it should be noted that the hemodynamic responses to nitrates may be attenuated by the development of partial or complete nitrate tolerance.

Another important finding of the present study was the association between early reflection wave arrival (Q1) and all cause 1 year mortality. This is in accordance with observations in other populations such as patients with arterial hypertension, end-stage renal disease and coronary artery disease where arterial reflections present a prognostic significance independently of the traditional risk factors (4–7). This may be explained not only by the increased pressure afterload imposed to the left ventricle but also the concomitant decrease in coronary perfusion pressure because of the shift of wave reflections from the diastolic to the systolic period. The cumulative effect of increased afterload and decreased coronary perfusion alters the myocardial oxygen supply-demand ratio and may predispose to ischemia as shown experimentally by Buckberg et al. (38). Interestingly, the prevalence of tricuspid regurgitation (moderate or severe) was also higher in patients with early reflection (Q1), which blunted the prognostic significance of wave reflection in the multivariate Cox-regression model. Further studies are required in order to elucidate the mechanism of this association.

LIMITATIONS

The study is subjected to the limitations of the retrospective, cohort study design. Wave separation analysis was performed by combining flow and pressure data not simultaneously recorded. In case of difference in HR between the pressure and the flow waveforms, synchronization was achieved by truncating or extending the diastolic portion of the flow wave, which may influence accuracy. However, this can only increase the probability of a type II error (false negative, mistaken acceptance of the null hypothesis). Moreover, CO was acquired invasively by two different techniques (thermodilution or the modified Fick method with estimated oxygen consumption) that may not be used interchangeably. Finally, AS classification was performed by the use of invasive SVi estimation, which is not readily available in clinical routine. Thus, the associations with the incidence of low-flow, low gradient severe AS with preserved EF may not apply when SVi is measured by other techniques with higher variability (e.g., TTE Pulsed Wave Doppler).

CONCLUSION

Early reflected wave arrival at the aortic root, generated by arterial trees with pronounced impedance mismatch between peripheral and central arteries, is associated with poor prognosis and profound hemodynamic changes at the aortic level including a significant decrease in transvalvular aortic flow and concomitant increase in aortic pressures. This is related to a significant decrease in TPG for a given AVA, leading to the underestimation of the AS. Our study highlights the importance of a detailed analysis of the left ventricular afterload for the accurate evaluation of the AS severity for both diagnostic and prognostic purposes.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of institutional restrictions applying to data involving human subjects. Requests to access the datasets should be directed to DA, dionysios.adamopoulos@hcuge.ch and SN, stephane.noble@hcuge.ch.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Geneva Ethics Committee (Commission Cantonale d'Ethique de la Recherche). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SP and DA conceived and designed the research, analyzed the data, prepared the figures, and drafted the manuscript. SN, GG, and HM performed the measurements. SP, NS, and SN interpreted the results. SP, DA, GR, VB, HM, GG, SM-W, M-JL, NS, and SN edited and revised the manuscript and approved the final version of the manuscript.

FUNDING

Open access funding was provided by the University of Geneva.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 22 July 2022
DOI 10.3389/fcvm.2022.928740

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 26 April 2022
ACCEPTED 04 July 2022
PUBLISHED 22 July 2022

CITATION
Frumkin D, Pietron M, Kind A, Brand A, Knebel F, Laule M, Leistner DM, Landmesser U, Krackhardt F, Sherif M, Sündermann SH, Grubitzsch H, Lembcke A, Niehues SM, Stangl K and Dreger H (2022) Valve embolization during transcatheter aortic valve implantation: Incidence, risk factors and follow-up by computed tomography.
Front. Cardiovasc. Med. 9:928740.
doi: 10.3389/fcvm.2022.928740

Valve embolization during transcatheter aortic valve implantation: Incidence, risk factors and follow-up by computed tomography

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Background: In most cases of transcatheter valve embolization and migration (TVEM), the embolized valve remains in the aorta after implantation of a second valve into the aortic root. There is little data on potential late complications such as valve thrombosis or aortic wall alterations by embolized valves.

Aims: The aim of this study was to analyze the incidence of TVEM in a large cohort of patients undergoing transcatheter aortic valve implantation (TAVI) and to examine embolized valves by computed tomography (CT) late after TAVI.

Methods: The patient database of our center was screened for cases of TVEM between July 2009 and July 2021. To identify risk factors, TVEM cases were compared to a cohort of 200 consecutive TAVI cases. Out of 35 surviving TVEM patients, ten patients underwent follow-up by echocardiography and CT.

Results: 54 TVEM occurred in 3757 TAVI procedures, 46 cases were managed percutaneously. Horizontal aorta (odds ratio [OR] 7.51, 95% confidence interval [CI] 3.4–16.6, $p < 0.001$), implantation of a self-expanding valve (OR 4.63, 95% CI 2.2–9.7, $p < 0.01$) and a left ventricular ejection fraction < 40% (OR 2.94, 95% CI 1.1–7.3, $p = 0.016$) were identified as risk factors for TVEM. CT scans were performed on average 26.3 months after TAVI (range 2–84 months) and

detected hypoattenuated leaflet thickening (HALT) in two patients as well as parts of the stent frame protruding into the aortic wall in three patients.

Conclusion: TVEM represents a rare complication of TAVI. Follow up-CT detected no pathological findings requiring intervention.

KEYWORDS

transcatheter aortic valve replacement, complications, valve embolization, valve migration, valve dislocation

Introduction

Transcatheter valve embolization and migration (TVEM) are potential complications of transcatheter aortic valve implantation (TAVI) (1). Recent data from two large retrospective cohorts suggest that TVEM is rare but associated with significantly increased morbidity and mortality (2, 3). Compared to a propensity-matched control cohort of TAVI patients, TVEM resulted in a significant increase of strokes at 30 days and a non-significant trend for a higher stroke rate 1 year after TAVI (2). Subclinical leaflet thrombosis is a frequent finding after TAVI and has been discussed as possible cause of embolic cardiovascular events (4, 5). Accordingly, leaflet thrombosis of embolized valves left in the ascending aorta might be of clinical significance. However, long-term imaging data on the fate of embolized valves is scarce. Therefore, the aim of our study was (i) to analyze the incidence, mechanisms and management of TVEM; (ii) to investigate the risk factors for TVEM and (iii) to examine embolized valves by electrocardiogram (ECG)-gated computed tomography (CT) for late complications such as leaflet and stent thrombosis or aortic wall alterations in a large cohort of TAVI patients.

Materials and methods

Study design

In this retrospective single-center cohort, we screened for cases of TVEM in 3757 consecutive patients undergoing TAVI from July 2009 to July 2021. TVEM was defined according to Valve Academic Research Consortium-2 (VARC-2) criteria (6), with valve embolization or migration during or after implantation taken as inclusion criteria.

Abbreviations: TVEM, trancatheter valve embolization and migration; TAVI, transcatheter aortic valve implantation; ECG, electrocardiogram; CT, computed tomography; VARC 2, Valve Academic Research Consortium – 2; TTE, transthoracic echocardiography; EACVI, European Association of Cardiovascular Imaging; SEV, self-expanding valve; BEV, balloon-expandable valve; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; HALT, hypoattenuated leaflet thickening.

Causes of TVEM were analyzed by review of procedural records and angiographic images. Cases with implantation of a second valve for the treatment of paravalvular leakage (PVL) or after deliberate removal of the first valve due to acute coronary obstruction were excluded from this study.
The prevalence of potential risk factors for TVEM (including comorbidities and aortic root morphology) in our TVEM patients was compared to a control cohort of 200 consecutive patients who underwent TAVI from the period 12/2019 to 05/2020. To ensure that the sample cohort is representative of the total cohort, age and sex were compared. Surviving patients from the TVEM group were asked to participate in the imaging sub-study. Patients who gave consent were examined by transthoracic echocardiography (TTE) and CT to analyze morphologic features of the embolized valve and the surrounding aorta as well as the function of the secondary valve in aortic position.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee and the German Federal Office for Radiation Protection (registration number EA4/177/18).

Angulation of the ascending aorta

Datasets of the planning CT performed prior to TAVI were analyzed using 3mensio Structural Heart 10.2 (Pie Medical

TABLE 1 Distribution of valve types and incidence of transcatheter valve embolization and migration (TVEM).

Valve type	All patients	TVEM	Incidence of TVEM (%)
All	3757	54	1.44
Edwards Sapien XT	302	6	1.99
Edwards Sapien 3	1444	2	0.14
Medtronic Corevalve	625	17	2.72
Medtronic Evolut R/PRO	496	13	2.62
Abbott Portico/Navitor	806	16	1.99
other (Acurate Neo, Allegra, Directflow, Centera, Lotus)	84	0	0

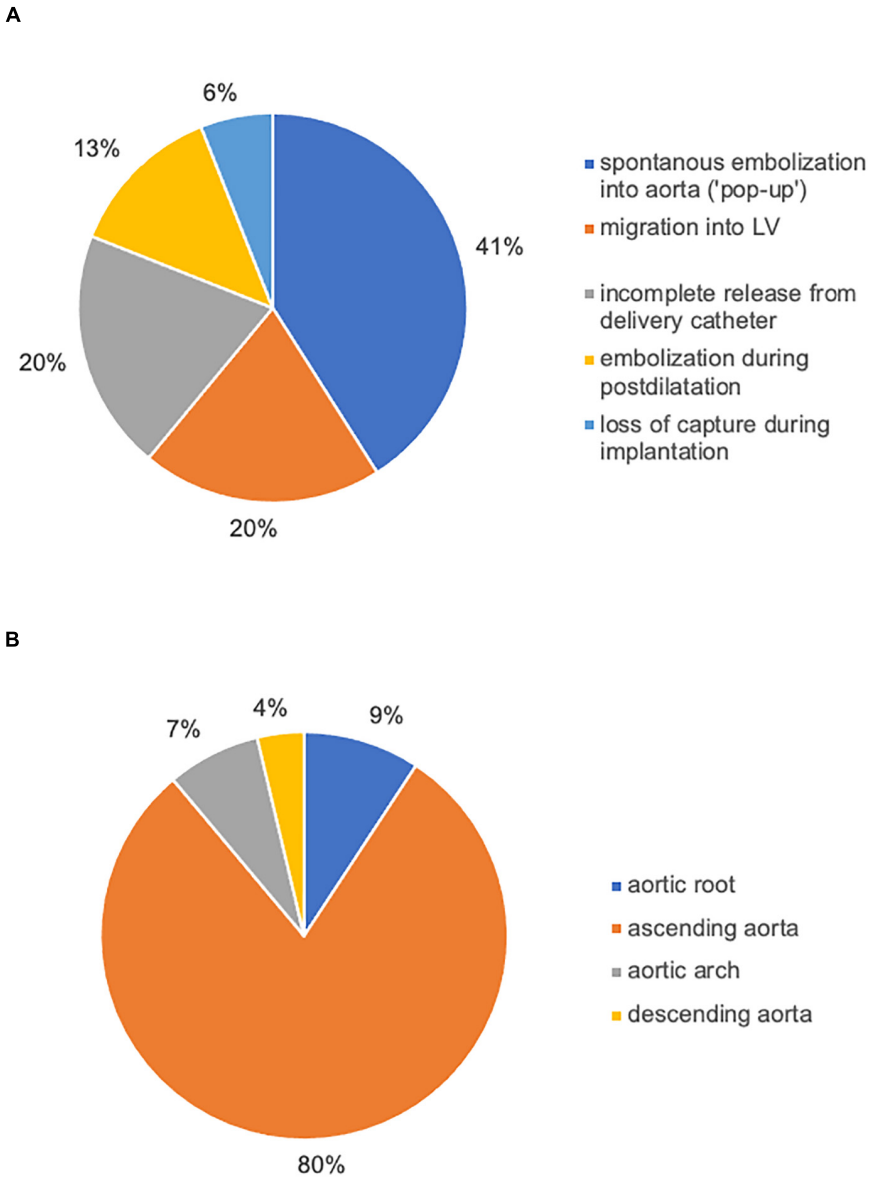

FIGURE 1
Causes of TVEM and the final position of embolized valves left *in situ*. Review of procedural records and angiograms identified five main mechanisms of TVEM during TAVI **(A)**. In the majority of cases, the embolized THV was left in the ascending aorta **(B)**.

Imaging BV, Maastricht, Netherlands). The angle between the ascending aorta and the aortic annulus plane was measured from a coronal projection at the level of the aortic annulus. Horizontal aorta was defined if angulation was > 48° as proposed previously (7).

Echocardiography

A comprehensive transthoracic echocardiographic assessment was performed in accordance with the recommendations of the European Association of Cardiovascular Imaging (EACVI) for echocardiographic assessment of valve stenosis (8) and follow-up management after transcatheter aortic valve implantation (9). All echocardiographic studies were performed by experienced cardiologists on a Vivid E95 (GE Vingmed, Horten, Norway) system with a M5S 1.5–4.5 MHz transducer.

Computed tomography

All follow-up examinations were performed using a 320-row-detector CT system (Aquilion ONE Vision, Canon Medical

Systems, Otawara, Japan) and a two-step imaging protocol: a volume CT scan of the heart ("cardiac CT scan") followed by a spiral CT scan of the thoracoabdominal arteries ("angio CT scan"). The cardiac CT scan was performed as ECG-gated data acquisition covering a full cardiac cycle (i.e., 0–99% of the RR-interval). The detector width was set at 16 cm to cover the entire heart and the ascending aorta in the craniocaudal direction.

All scanning was performed during inspiratory breath-hold at 135 kV tube voltage, 660 mA tube current, and at a gantry rotation time of 275 ms. All images were reconstructed using a standard soft tissue convolution kernel (FC 05) and the implemented iterative reconstruction algorithm (AIDR 3D, strong) at a slice thickness of 0.5 mm, an interval of 0.5 mm and an image matrix of 512 × 512. A total of 80 mL of contrast medium with an iodine content of 370 mg/mL (Ultravist 370; Bayer) was injected intravenously using a dual-head power injector (Dual Shot GX, Nemoto Kyorindo) at a flow rate of 4 ml/s followed by a saline chaser bolus of 40 ml injected with the same flow rate. The CT scans were then initiated using the scanners bolus tracking feature after reaching an attenuation of 200 HU in the descending aorta.

TABLE 2 Baseline characteristics of all transcatheter valve embolization and migration (TVEM) patients and the control cohort.

Baseline characteristics	TVEM ($n = 54$)	Control cohort ($n = 200$)	*P*-value
Age, years	78.8 ± 10.5	80.6 ± 6.3	0.835
Female sex, *n* (%)	30 (55.6%)	92 (46.0%)	0.988
Body mass index, kg/m^2	26.2 ± 4.8	27.6 ± 5.8	0.112
HFrEF (LVEF < 40%), *n* (%)	9 (16.7%)	13 (6.5%)	0.016
Arterial hypertension, *n* (%)	49 (90.7%)	192 (96.0%)	0.975
Prior permanent pacemaker implantation, *n* (%)	8 (14.8%)	26 (13.0%)	0.617
Prior stroke, *n* (%)	4 (7.4%)	17 (8.5%)	0.881
Chronic kidney disease, *n* (%)	22 (40.7%)	79 (39.5%)	0.638

HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; TVEM, transcatheter valve embolization and migration.

TABLE 3 Anatomical characteristics and procedural data in patients with transcatheter valve embolization and migration (TVEM) compared to the control group.

Anatomical and procedural characteristics	TVEM ($n = 54$)	Control group ($n = 200$)	*P*-value
Annular diameter, mm	22.9 ± 1.5	24.3 ± 2.4	0.187
Severe aortic regurgitation, *n* (%)	2 (3.8%)	0 (0%)	0.005
Aortic valve area, cm^2	0.73 ± 0.32	0.79 ± 0.33	0.067
Mean pressure gradient, mmHg	41.4 ± 18.1	41.6 ± 13.2	0.644
V_{max}, m/s	4.00 ± 0.9	4.03 ± 0.65	0.646
Horizontal aorta, *n* (%)	35 (60.5%)	32 (16.0%)	<0.001
Valve type, *n* (%)			
Self-expanding	46 (85.2%)	105 (52.5%)	<0.001
Balloon-expandable	8 (14.8%)	95 (47.5%)	<0.001

V_{max}, maximal velocity; TVEM, transcatheter valve embolization and migration.

Statistical analysis

Statistical Package for Social Studies (SPSS, IBM Corp, Released 2020, IBM SPSS Statistics for Mac OS, Version 27.0. Armonk, NY) was used for statistical analysis. Data were expressed as mean ± standard deviation for continuous variables or as percentage for categorical variables. The significance of differences in clinical data was calculated using the non-parametric Mann-Whitney U test for categorical variables and the Kolmogorov-Smirnov test for continuous variables. Absolute and relative incidence of TVEM in the overall TAVI population was determined. Logistic regression analysis was performed to assess associations of clinical data, type of transcatheter heart valves (THV) and imaging parameters with the occurrence of TVEM. Nagelkerkes R square was obtained to prove validation of the regression model. A *p*-value < 0.05 was considered statistically significant.

TABLE 4 Regression analysis of risk factors for transcatheter valve embolization and migration.

Baseline parameters	Odds ratio	95% CI	*P*-value
Female sex	1.62	0.45–5.73	0.469
Age (per year)	1.04	0.94–1.16	0.44
Body mass index (per kg/m^2)	0.96	0.86–14.3	0.511
Arterial hypertension	1.11	0.82–13.77	0.937
Chronic kidney disease	2.07	0.63–6.80	0.231
Prior permanent pacemaker implantation	1.25	0.23–6.99	0.769
Prior stroke	0.73	0.07–7.33	0.788
HFrEF (LVEF < 40%)	2.94	1.10–7.30	0.016
Severe Aortic regurgitation	1.74	0.74–4.32	0.23
Aortic valve area (per mm^2)	0.421	0.02–12.09	0.614
Mean pressure gradient (per mmHg)	1.01	0.96–1.05	0.77
Aortic annulus size (per mm^2)	0.99	0.99–1.00	0.245
Use of self-expanding valve	4.63	2.21–9.73	<0.001
Horizontal aorta	7.51	3.41–16.55	<0.001

HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; TVEM, transcatheter valve embolization and migration; CI, confidence interval.

Results

Study population and clinical characteristics

Between July 2009 and July 2021, 3757 TAVI procedures were performed in our center. A total of 54 patients met VARC-2 Criteria for TVEM (TVEM group) corresponding to an overall incidence of TVEM of 1.44%. Incidence of TVEM in our registry was clustered in the beginning and then decreased rapidly over the years (up to 3.4% 2009–2013, 0.55% in 2020). 85.2% of TVEM occurred after implantation of a self-expanding valve (SEV), 14.8% after implantation of a balloon-expandable valve (BEV). Overall, the incidence of TVEM was significantly more frequent after implantation of a self-expanding valve compared to implantation of a balloon-expandable valve (2.3 vs. 0.4%, $p < 0.001$). The incidence of TVEM after SEV implantation did not change significantly after introduction of next-generation devices ($p = 0.294$, Corevalve vs. Evolut R/PRO and Portico). The valve types implanted during the study period and their respective incidence of TVEM are given in Table 1. 46 TVEM patients (85.2%) were treated by transcatheter implantation of a second valve while eight patients (14.8%) underwent conversion to surgery. Review of the procedural records and images revealed five major mechanisms for TVEM: (1) spontaneous embolization into the ascending aorta ("pop-up"), (2) migration into the LV, (3) accidental pull-back of the THV into the ascending aorta during removal of the delivery system due to incomplete release of the valve, (4) embolization during postdilatation, and (5) embolization due to loss of capture during implantation. The distribution of the mechanisms of TVEM and the final position of the embolized THV are provided in Figure 1.

To identify risk factors for TVEM, we compared clinical as well as anatomical and procedural characteristics of patients with TVEM with a cohort of 200 consecutive patients from the period 12/2019 to 05/2020 undergoing

TABLE 5 Overview of all patients examined by computed tomography (CT).

Patient	Age at TAVI (years)	Sex	Embolized THV	Mechanism of TVEM	Second THV	Follow-up (months)	Final position of THV	CT finding	Oral anticoagulation
1	73	m	Sapien XT 26 mm	Dislocation into aortic root after loss of capture during postdilation due to severe regurgitation	Sapien XT 29 mm	84	Aortic root	No pathological finding	Yes
2	78	m	CoreValve 29 mm	Valve pulled into ascending aorta due to incomplete release from delivery catheter	CoreValve 29 mm	57	Ascending aorta	No pathological finding	Yes
3	77	f	Portico 29 mm	Valve pulled into ascending aorta due to incomplete release from delivery catheter	Sapien 3 26 mm	43	Ascending aorta	Upper crown protruding into the aortic wall	No
4	79	f	Evolut R 26 mm	"Pop-up" after valve release	Evolut R 26 mm	37	Ascending aorta	Upper crown protruding into the aortic wall	No
5	76	f	Evolut R 26 mm	Valve pulled into ascending aorta due to incomplete release from delivery catheter	Sapien 3 23 mm	19	Ascending aorta	No pathological finding	Yes
6	84	f	Portico 27 mm	"Pop-up" after valve release	Sapien 3 23 mm	9	Ascending aorta	Upper crown protruding into the aortic wall	Yes
7	85	m	Sapien 3 Ultra 26 mm	Loss of capture during implantation	Sapien 3 Ultra 26 mm	6	Aortic arch	No pathological finding	No
8	82	m	29 mm Evolut R PRO	Dislocation into ascending aorta after loss of capture during postdilation due to severe regurgitation	Sapien 3 Ultra 26 mm	4	Descending aorta	No pathological finding	No
9	84	f	Portico 27 mm	"Pop-up" after valve release	Sapien 3 Ultra 23 mm	2	Ascending aorta	Hypoattenuated leaflet thickening at embolized valve	No
10	84	m	29 mm Navitor	"Pop-up" after valve release	Sapien 3 29 mm	2	Ascending aorta	Hypoattenuated leaflet thickening at embolized valve	No

f, female; m, male; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; TVEM, transcatheter valve embolization and migration.

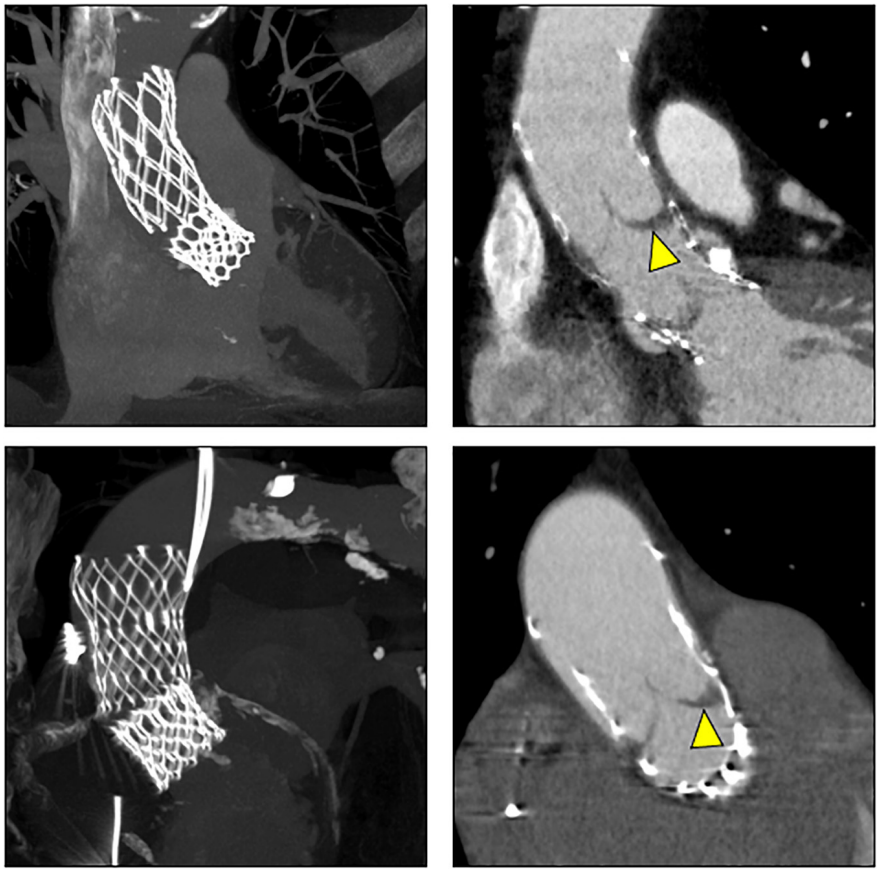

FIGURE 2
Subclinical valve thrombosis in embolized valves. In patients 9 (top) and 10 (bottom; see **Table 5** for details), follow-up CT detected hypoattenuated leaflet thickening (arrow heads) in self-expanding valves embolized into the ascending aorta.

TAVI for native aortic valve disease. Comparison of age and sex between the sample cohort (age 80.4 years ± 6,3; 44.6% female sex) and the total study cohort (age 84.9 years ± 8.3; 51.9% female sex) showed good matching.

Clinical data of both cohorts are outlined in **Table 2**. Compared to the control cohort, significantly more TVEM patients had a history of heart failure with reduced ejection fraction (HFrEF). Age, sex, body mass index (BMI) and other comorbidities which might influence implantation techniques (e.g., renal failure) did not differ significantly between both groups. Anatomical factors like horizontal aorta, severe aortic regurgitation, as well as the use of a self-expanding valve showed significant differences between the groups and were further evaluated by regression analysis (**Table 3**).

Distribution of THV types (SEV vs. BEV) were similar in the overall cohort of 3757 TAVI patients and the control group of 200 patients: 2011 SEV (46.5%) and 1746 BEV (53.5%) in the total cohort vs. 105 SEV (52.5%) and 95 BEV (47.5%) in the control cohort.

Risk factors for transcatheter valve embolization and migration

In a logistic regression analysis, age, sex, BMI, arterial hypertension, prior permanent pacemaker introduction, prior stroke and chronic kidney disease showed no significant relationship for the occurrence of TVEM (**Table 4**). Nagelkerke's R square for the model was 0.497, showing good validation for the model. In contrast, the use of a SEV ($p < 0.001$, OR 4.63, 95% CI 2.2–9.7), the presence of a horizontal aorta ($p < 0.001$, OR 7.51, 95% CI 3.4–16.6) and HFrEF ($p = 0.016$, OR 2.94, 95% CI 1.1–7.3) were significantly associated with a higher risk for TVEM in the regression analysis (**Table 4**).

Follow-up imaging

Out of 54 TVEM patients, none died during the index procedure, in-hospital mortality was 7.4% (4 patients). We tried to contact all patients which were identified as still alive and managed to get in contact with 22 patients. Out of these 22

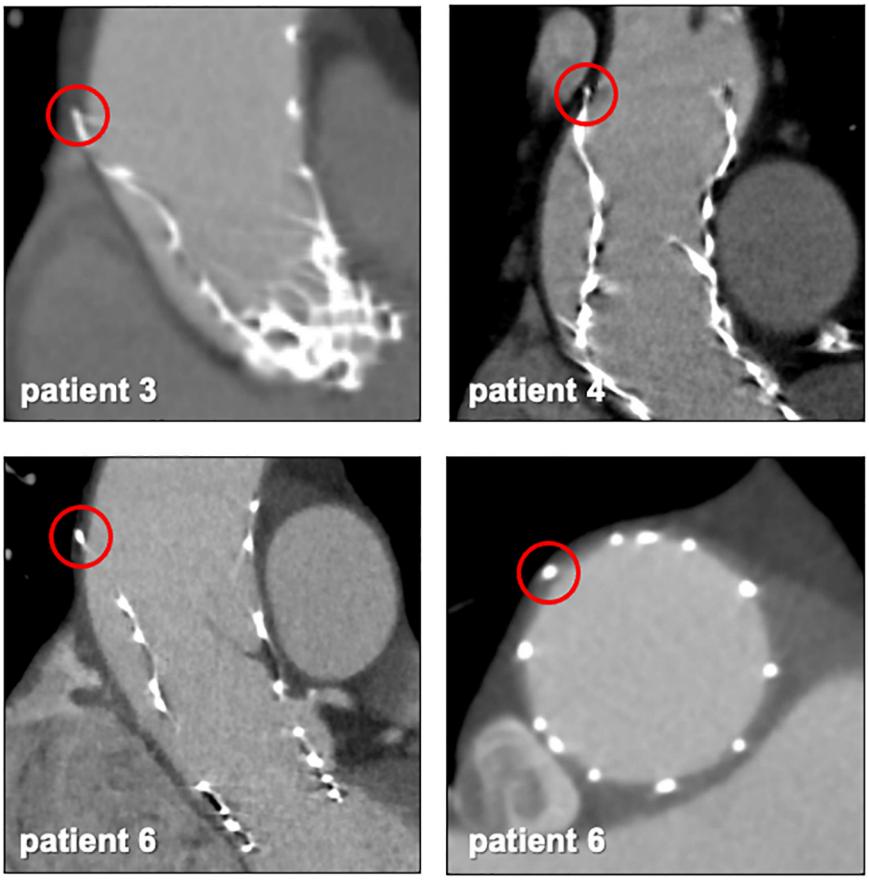

FIGURE 3
Protruding stent frames into the aortic wall. CT follow-up images from patients 3, 4, and 6 (**Table 5**) revealed parts of the upper crown of the stent frame protruding into the aortic wall.

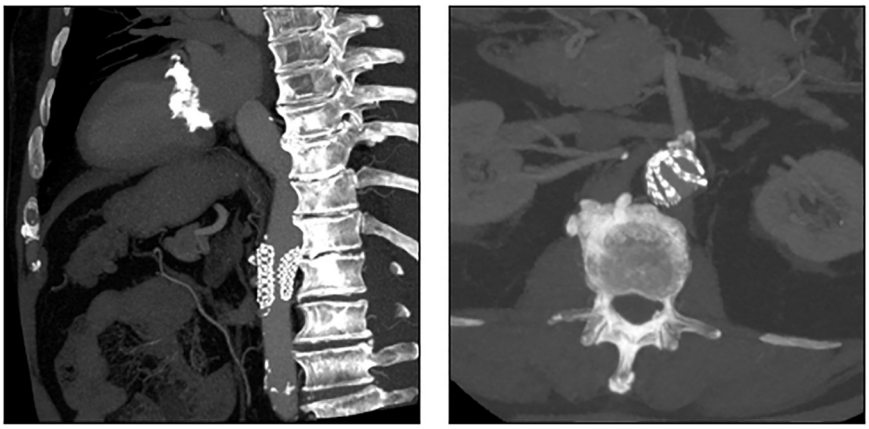

FIGURE 4
CT images of a patient with embolization of an Evolut PRO. In this case (patient number 8 from **Table 5**), the snare used to pull the embolized Evolut PRO further into the ascending aorta was entangled in the valve frame. The bent Evolut PRO was eventually pulled into the descending aorta where the snare could be liberated.

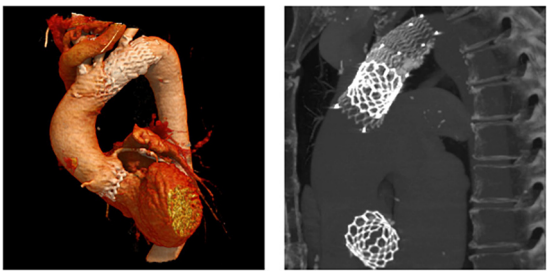

FIGURE 5
CT images of a patient with embolization of a Sapien 3. CT follow-up of patient number 7 (Table 5). After embolization due to loss of capture during implantation, the embolized Edwards Sapien 3 was pulled back into the proximal aortic arch by the semi-inflated delivery balloon and affixed using two self-expanding stents.

patients, ten patients gave consent to undergo follow-up imaging by TTE and CT. Table 5 provides detailed information on the patients included in the imaging sub-study. In most cases, the embolized valves could not be sufficiently visualized by transthoracic echocardiography (TTE). TTE revealed normal function of all secondary THV in the aortic root.

CT exams were performed on average 26.3 months after TAVI (range 2–84 months). Similar to the overall distribution in all TVEM patients (Figure 1B), the embolized valve was left in the aortic root or the ascending aorta in eight of the examined patients. Hypoattenuated leaflet thickening (HALT) was detected in two embolized valves (Figure 2). In these two patients stent frames showed no deformation. In addition, parts of the stent frame protruding into the aortic wall, yet without signs of dissection, were observed in three patients (Figure 3).

In patient 8, the embolized valve remained in the descending aorta. In this particular case, the snare used to pull the embolized Evolut R further into the ascending aorta (to avoid coronary obstruction) was stuck within the valve frame. The bent Evolut PRO was eventually pulled into the descending aorta where the snare could be liberated (Figure 4). Corresponding to the overall lower incidence of TVEM during TAVI using a balloon-expandable valve, only two patients underwent CT follow-up after embolization of an Edwards Sapien 3 caused by loss of capture during implantation. In patient 1, the embolized valve remained in the aortic root and was secured by valve-in-valve-implantation of a second Sapien. In patient 7, management of the TVEM was complicated by a combination of an aneurysm of the ascending aorta and a narrow, calcified arch. Consequently, the embolized valve could neither be implanted into the wide ascending aorta nor withdrawn into the descending aorta. Instead, it was gently pulled back by the semi-inflated delivery balloon as far as possible into the proximal aortic arch and affixed by two self-expanding stents (Figure 5).

Discussion

TAVI is a well-established interventional treatment option for aortic stenosis and a large number of studies have evaluated its safety and efficacy compared to surgical valve replacement. However, data on the incidence and long-term consequences of TVEM in TAVI patients is scarce.

In our single-center cohort of 3757 TAVI patients, 54 TVEM occurred over the course of 12 years. The rate of TVEM in our center (1.44%) falls well within the previously published range of 0.3–1.7% (2, 10, 11). Incidence of TVEM in our registry was higher in the beginning of the study

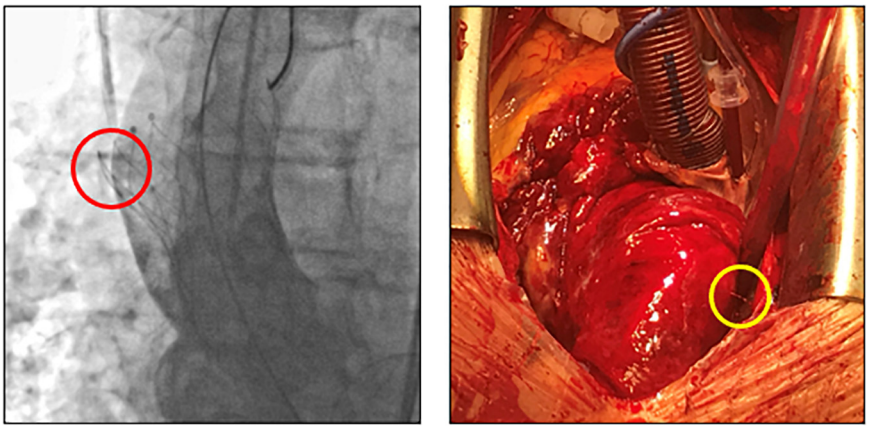

FIGURE 6
Fluoroscopic images and intraoperative situs after perforation of the ascending aorta by an embolized self-expanding valve. Fluoroscopy (left) and intraoperative situs (right) of a patient with hemorrhagic shock due to perforation (circles) of the ascending aorta. After embolization, the self-expanding valve (25 mm Portico) was deliberately pulled further into the ascending aorta to avoid coronary obstruction.

period and then decreased over the years (up to 3.4% 2009–2013, 0.55% in 2020). Many potential causes (e.g., growing experience, technical evolution of the valves, release dates of new generations, decreasing morbidity of patients suitable for TAVI, changes in access evaluation/sizing of valve) were previously described in literature (2) and are excellently summarized by Landes et al. (3). Analysis of procedural reports and images identified spontaneous embolization of self-expanding valves into the ascending aorta ("pop-up"), migration into the LV, incomplete release of the valve from the delivery system, embolization during postdilatation and loss of capture during implantation as the main causes of TVEM over the study period (**Figure 1A**). In accordance with data from a large registry previously published by Kim et al., TVEM could be managed interventionally in the majority of cases but led to conversion to surgery in 14.8% of TVEM patients (2). In 80% of TVEM cases, the embolized valve was left in the ascending aorta (**Figure 1B**).

In agreement with previous data, comparison of TVEM patients to a contemporary cohort of 200 consecutive patients undergoing TAVI for aortic native valve disease identified the use of a self-expanding valve (OR 4.63, CI 2.2–9.7) and the presence of a horizontal aorta (OR 7.51, CI 3.4–16.6) as the main risk factors for TVEM (12, 13). Recently, the impact of a horizontal aorta on procedural success was examined by Abramovitz et al. (7). In patients who underwent TAVI with a SEV, an inverse relationship between horizontal aorta and acute procedural success was shown. In addition to a more difficult THV positioning, TAVI in horizontal aortas is associated with a higher rate for postdilatation – another major mechanism for TVEM identified in our cohort (**Figure 1A**). In addition, reduced left ventricular ejection fraction was associated with a higher risk of TVEM (OR 2.94, 95% CI 1.1–7.3, $p = 0.016$). Rapid valve release to shorten low flow periods as well as avoidance of multiple implantation attempts for the optimization of implantation height might contribute to a higher risk for TVEM in HFrEF patients.

Furthermore, it seemed that smaller annular size (22.9 ± 1.6 mm in TVEM vs 24.3 ± 2.4 mm in the total cohort, $p = 0.187$) are more prone to embolization, yet statistical significance was not reached, therefore the probability of chance cannot be excluded.

Subclinical leaflet thrombosis characterized by hypoattenuated leaflet thickening (HALT) is a frequent finding in transcatheter bioprosthetic aortic valves with a prevalence of up to 28% in short- and long-term CT follow-up (4, 5, 14). To our knowledge, our study is the first to systematically examine embolized valves by CT after mid- to long-term follow-up. HALT was detected in the embolized valves in two TVEM patients (**Figure 2**). Since the number of patients in our imaging sub-study is low it is not possible to draw definite conclusions. Of note, both patients with HALT did not take oral anticoagulants which have been shown to prevent the formation of leaflet thrombosis. In addition, our findings advise some caution as parts of the upper crown of embolized self-expanding valves protruding into the aortic wall were observed in three patients (**Figure 3**). This is reminiscent of another case from our TVEM cohort complicated by valve embolization due to pop-up of a 25 mm Portico self-expanding valve. The embolized valve was snared and pulled into the ascending aorta to avoid coronary obstruction. After successful implantation of a second transcatheter valve (23 mm Edwards Sapien 3) the patient developed hemorrhagic shock. Angiography revealed perforation of the ascending aorta by a part of the upper crown of the THV protruding through the aortic wall. The valve was surgically removed, and the ascending aorta repaired on cardiopulmonary bypass (**Figure 6**). Accordingly, interventionalists should be aware of this potential complication when embolized valves have to be actively pulled up into the ascending aorta using a snare. Patients should be examined by CT in a timely fashion to rule out perforation of the ascending aorta if they develop hemodynamic instability in the postinterventional course.

Limitations

Our results are mainly limited by the retrospective design of our analysis and the low number of patients undergoing follow-up examination by CT. Conclusions in regard of the CT scans should be put in the context of different timing due to the retrospective design. While comparison of age and sex showed that our control sample was representative of our entire TAVI cohort, we cannot exclude the possibility that the prevalence of comorbidities or anatomical features (e.g., aortic angle) changed over time.

Confidence intervals of the odds ratios of our regression model are wide despite the good fit of our model validated by Nagelkerke's R square. Furthermore, our analysis is limited by a potential survivor bias that might miss relevant long-term complications in TVEM patients. However, data from Kim et al. suggest that the major impact on morbidity and mortality of TVEM is limited to the short-term follow-up period after TVEM (2).

Conclusion

In this cohort comprising 3757 patients, TVEM occurred in 1.44%. Most cases can be managed interventionally. Predisposing risk factors for TVEM are horizontal aorta, the use of self-expanding valves and HFrEF. In four out of five cases, the embolized valve remains in the ascending aorta. Importantly, follow-up examinations by CT did not detect relevant pathological findings requiring intervention in patients after TVEM. However, the possibility of subclinical

leaflet thrombosis and of protrusion of parts of the stent frame in the aortic wall should advise caution.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HD and DF designed the study and co-wrote the first draft of the manuscript. DF performed the statistical analysis. MP, AK, and DF recruited patients and acquired and analysed the data. AB and FKn performed and analyzed the echocardiographic examinations. HD, KS, ML, DL, UL, FKr, MS, SS, and HG analyzed procedural reports and angiograms and co-wrote the manuscript. AL and SN performed and analyzed the CT angiograms. All authors contributed to the article and approved the submitted version.

Funding

The authors declare that this study received funding from Abbott. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Conflict of interest

HD, KS, ML, DL, UL, and MS were received financial research support and speakers' fees from Abbott, Edwards LifeSciences and Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 28 July 2022
doi: 10.3389/fcvm.2022.817705

Transcatheter Aortic Valve Implantation for Severe Bicuspid Aortic Stenosis – 2 Years Follow up Experience From India

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Background: Transcatheter aortic valve implantation (TAVI) is challenging in bicuspid aortic valve (BAV) anatomy. The patients are young, morphological phenotypes are many, calcium burden is high and there are technical challenges for best outcomes. Observational studies and registries are available with favorable data and experiences from around the world sharing methodologies and algorithms for sizing and implantation. We, therefore, analysed our data of procedural and in-hospital outcomes of TAVI in Bicuspid Aortic Valve cases performed at two high volume centres in India and their follow up for two years.

Methods and Results: The data were collated and analysed from two centres (Fortis Escorts Heart Institute, New Delhi and Apollo Hospitals, Chennai) in India for patients who underwent TAVI in a BAV anatomy. It included a total of 70 cases from 2 centres. All symptomatic severe AS patients more than and equal to 65 years having bicuspid anatomy were included in the study irrespective of their STS score. Patients under 65 years of age were advised TAVI only if they were at high risk for open heart surgery. These patients were followed for a period of 2 years and the data were analysed. Pre TAVI imaging tools utilised were 2D echo, transthoracic echocardiography (TTE), trans oesophageal echocardiography (TEE), and ECG gated multi slice CT (MSCT) scan imaging. MSCT was utilised for confirmation of the anatomy and classifying the morphological type of valve, measuring, and evaluating all anatomic determinants of aortic root complex for planning the procedure and choice of the valve and its size. Sizing in balloon expanding valve (BEV) and self-expanding valve sizing (SEV) were based primarily on annulus area and perimeter, respectively. The SEV used in our study were the Core Valve and Evolut R (Medtronic, United States) and the BEVs included Sapien3 (Edwards Lifesciences, United States) and Myval (Meril Lifesciences, India). The BAV cohort constituted 24.4% of the total 287 TAVI cases, followed up for 2 years. The mean age of these patients was 72 years. The incidence of male patients was 68.57% and female patients was 31.4%. The Sievers type 1 included 78.5%, type 0 were 21.4% of the cases and there was no case of type 2 in the study. The procedural success was to the tune of 98%. Patients with normal left ventricular ejection fraction (LVEF) improved their symptoms class after TAVI and remained so at 2 years follow up. The poor LVEF

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Edited by:
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Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *18 November 2021*
Accepted: *21 March 2022*
Published: *28 July 2022*

Citation:
Kumar V, Sengottuvelu G, Singh VP, Rastogi V and Seth A (2022) Transcatheter Aortic Valve Implantation for Severe Bicuspid Aortic Stenosis – 2 Years Follow up Experience From India. Front. Cardiovasc. Med. 9:817705. doi: 10.3389/fcvm.2022.817705

subset of patients did not have heart failure admissions and also had improvement in their symptom status. The peak-to-peak aortic valve gradient decreased to 0 mmHg at the end of the procedure in most of the cases. The mean pressure gradient (PG) across the new valve ranged between 0 and 15 mmHg and the aortic valve area (AVA) was close to 2 cm^2. These numbers were consistent at 2 years follow up. Significant paravalvular leak (PVL) 24.28% was seen immediately after deployment of the valve in heavily calcified anatomy but it reduced to mild or trivial PVL after post-dilation and one patient needed a second valve to treat PVL. No patient had more than mild PVL with either type of valve at the end of the procedure. Permanent pacemaker implantation (PPI) was required in 11.4% of the patients within 24 h to 7 days of the procedure. No one needed a PPI in the 2 year follow up. Coronary occlusion did not happen to any patient. No patient had a disabling stroke. Non-disabling stroke was seen in 10% of cases and mostly in the first week or 30 days of the procedure and the incidence was more with BEV (14%) as compared to SEV (8%). There was one case of valve embolisation after 24 h of the procedure, which needed a surgical valve replacement. There was no case of annular injury or injury to other parts of the aortic root complex. Two cases had access vessel (femoral artery) thrombosis at end of the procedure and a third patient had proglide related residual stenosis. Two cases had acute kidney injury and needed dialysis. There was no major bleeding complication in any patient. Peri procedural mortality occurred in two patients. Valve thrombosis was seen in one patient after 3 months, which was treated with oral anticoagulation. Valve degeneration and failure or infective endocarditis were not seen in any patient.

Conclusion: The patients with BAV stenosis who underwent TAVI in this study had good procedural success rates and clinical outcomes. The haemodynamics achieved with both SEV and BEV were good at 2 years. The rates of PVL, PPI, and stroke are similar to that of many other studies and registries. PPI rate and non-disabling stroke incidence appear to be higher similar to many studies done. There was no case of coronary occlusion in the study. Meticulous CT analysis of the aortic root complex, selection of appropriate type and size of the valve, and best implantation practices along with cerebral protection will probably be the key to safer and more successful TAVI in this population.

Keywords: aortic stenosis, bicuspid aortic valve, bicuspid aortic stenosis, Indian population, TAVI – transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become an established treatment for the tricuspid aortic valve in high and intermediate-risk patients with good outcomes and long follow up data. Favourable data for low-risk patients are also in abundance now for the tricuspid valve population (1–5). On the other hand, in bicuspid aortic valve (BAV) disease, the inherent anatomical challenges (6, 7) make TAVI in this subset not easy and straightforward. More data will be required to support the therapy, especially for low-risk patients who are younger and cannot afford to have residual significant gradients, patient prosthesis mismatch, any significant paravalvular leak (PVL), lifelong implantation of a pacemaker, coronary ostia occlusion, and difficult future coronary interventions. This study shares the results of TAVI in India for patients with BAV anatomy.

MATERIALS AND METHODS

Study Design and Patient Population

We collected data for 287 consecutive patients who underwent TAVI at Fortis Escorts Heart Institute, New Delhi and Apollo, Chennai, India between the year 2012 and 2018. The cohort of BAV anatomy who underwent TAVI included a total of 70 patients. TAVI was chosen for symptomatic severe AS patients who were 65 years and above with a low, intermediate, or high STS risk score (8). Those less than 65 years of age were advised of

TAVI if they were high risk cases for SAVR. The BAV could be of any Sievers type (9) of morphology. Exclusion criteria constituted those of age less than 65 years, prohibitive STS risk score (8), patients with other significant valve pathology, severe LV dysfunction left ventricular ejection fraction (LVEF) <20%, the aortic annulus size was out of the range of size of devices available, and if the risk of coronary occlusion was a concern as assessed by the multi slice CT (MSCT) analysis. Patients who had survival of less than a year due to some terminal illnesses were not included in the study. Rheumatic heart disease or multivalvular pathology, pure aortic regurgitation, and valve in valve procedures were also excluded. TAVI was performed under conscious sedation for the majority of cases. The transfemoral route was used for all the cases. The self-expanding valve (SEV) used was Core Valve and Evolut R (Medtronic, United States); and the balloon expanding valve (BEV) used in our study were Myval (Meril Lifesciences, India) and Sapien3 (Edwards Lifesciences, United States). The standard implantation techniques for each type of valve were followed step by step (10–12). The success of the TAVI procedure, complications and clinical outcomes were all defined as per the Valve Academic Research Consortium 2 and 3 (VARC-2 and 3) consensus (13, 14). Patients were put on 75 mg of clopidogrel and aspirin for 3 months and then lifelong aspirin after TAVI. Anticoagulation was on board if there was an indication and or if there was a conformation of thrombus formation by CT scan on the valves in their follow up period. The study was approved by the Internal Review Board and Ethics Committee approval was not required.

Follow up and Data Collection

The patients were followed up at 7 days, 1 month, then annually for 2 years after the TAVI. The majority of patients visited the primary centre, while the others were followed telephonically, and their echo and ECG records performed at another centre were retrieved and added to our database. At each visit, the patient's NYHA functional class was evaluated, and an ECG and standard 2D echo was performed. All clinical events were recorded. Major adverse cardiovascular events were defined as death stroke and myocardial infarction as previously described.

Imaging Methods

Patients underwent a standard screening echocardiogram and contrast enhanced ECG gated multi detector computed tomography (MDCT) before the procedure by the standard of imaging practised for pre and post TAVI work up (15–19). The CT analysis was done by a dedicated 3mensio medical imaging pie medical imaging software. Pre TAVI-CT focussed on confirmation of the bicuspid anatomy, morphological types, calcium score, topography of calcium causing injury to the annulus, LVOT, and coronary ostia occlusion factors. The sizing of the valve was carefully decided mainly based on the size of the annulus, supra-annulus, and LVOT dimensions. Area measurements of annulus and LVOT were considered in the case of BEV. The perimeter of the annulus, LVOT, supra-annular measurements at 4.5 and 8 mm above the annulus were measured for SEV. Intercommissural distance was also an important parameter in choosing the valve size in SEV (16). Contemporary sizing algorithms like CASPER (Calcium Algorithm Sizing for bicusPid Evaluation with Raphe) and **LIRA** (**L**evel of **I**mplantation **RA**phe Annulus method-for Raphe type BAV) were also utilised to decide the size of the valve (20–24). Measurements of STJ, SOV, calcium burden, and distribution, coronary ostia occlusive factors were also considered while sizing the valve (25). BEVs were upsized by 5–10% and SEVs were upsized by 15–25%.

Statistical Methods

The statistical analysis consisted of patient demography, frequency calculation in terms of all baseline characteristics such as age, weight, sex, etc. All continuous variables were analysed using the Student's *t*-test at 95% CI to evaluate the significance for various parameters before, immediately after 7 days later, 1 and 2 years following the TAVI procedure. The non-parametric parameters such as calcification, NYHA functional class, the severity of PVL were estimated using the Chi-square test. Data analysis and interpretation were performed with Stata software ReDEA Institute of Data Science (RIDS). Bartlett's test for equal variance and pairwise tests of difference of means by Games and Howell were applied to evaluate the statistical significance we accounted for the non-homogeneity of variance present in the comparison groups for the pre and post-procedural periods mean pressure gradient (PG) and aortic valve area (AVA) (26).

Study Outcomes

Device implantation was defined as successful vascular access, delivery, and deployment of a single device in the proper anatomic location, the appropriate performance of the THV and retrieval of the delivery system (VARC-2). Valve performance was assessed by measuring mean gradient across the transcatheter heart valve, aortic valve area (AVA) of the THV, and the absence of significant PVL after TAVI at 7 days, annually and 2 years. The need for a permanent pacemaker after the procedure or follow up was also collected into the database at 2 years follow up. THV thrombosis and degeneration was recorded over the two years. Other study outcomes included in-hospital mortality, stroke, VARC-2 major bleeding, acute kidney injury, and vascular complications, which were recorded for analysis. LV systolic function improvement from baseline was also analysed at 2 years. The functional class of the patients was collected from the data for 2 years.

THE RESULTS AND ANALYSIS

The baseline characteristics of bicuspid aortic valve patients in our study have been summarized in **Table 1**. **Table 2** depicts the procedural characteristics and outcomes of TAVI in the study. The total TAVI cases from 2 centres in India included a total of 287 patients with symptomatic severe aortic stenosis followed up for 2 year period. A total of 70 patients (24.4%) constituted the bicuspid aortic population who underwent TAVI. The mean age of patients in our study was 72 years. The majority of patients were in the sixth and seventh decade of life. Male patients constituted 68.57% and female patients were 31.43% of the study population. The PROM STS score consisted of the

TABLE 1 | Base line characteristics of bicuspid aortic valve patients in the study.

Total patients	70
Male: female	48:32
Mean age (years)	72 (±8.49)
Mean weight (in kg)	67.54 (±11.17)
Height (in cm)	161.42 (±8.01)
BMI	25.14 (±6.23)
PROM STS score	
High (0–4)	20%
Intermediate 4–8	47.14%
Low risk ≤	32.86%
Mean STS score	6.00 (±6.54)
Baseline LVEF (%)	50.6 (±13.66)
Pre TAVI-NYHA class	
I	1.4%
II	37%
III	35.7%
IV	25.7%
Sievers type	
Type 1	78.5%
Type 0	21.4%
Number of raphe	
Type 0	No raphe
Type 1	98% had one raphe
Pattern of cuspal fusion	
Type 0	AP 46.6% lateral 53%
Type 1	RCC LCC 96%RCC NCC 3.6%
Severity of calcium in raphe	50% mild12–27% moderate18–37% severe
Right coronary ostia height (mm)	16.9 (±3.3)
Left coronary ostia height (mm)	14.75 (±4.09)
Aortic valve calcification	70%-severe30%-moderate
Aortic root dilation	85.7% ≤40 mm14.3% ≥41 mm

majority of patients in the intermediate (47%) or low risk (32%) group and high-risk patients accounted for 20%. The patients belonged mostly to NYHA II–III (70–80%) and 20–30% belonged to NYHA IV. Dyspnoea was the major presenting symptom for most patients.

Sievers bicuspid valve class of distribution consisted of type 1 (78%), type 0 (21%), and there was no type 2 patient in our study. The number of raphe present in type 0 was zero, one in 98% of type 1 Sievers. There was a very rudimentary raphe rest of 2% for type 1 patients. The commonest cuspal fusion was between the right coronary cusp (RCC) and left coronary cusp (LCC) in type 1. The type 0 had equal types of cusps anterior–posterior and lateral cusps. The distribution of calcium in the raphe was mostly moderate or severe though some patients had a milder degree of calcium in raphe. There was not much difference in male: female and Sievers types of bicuspid valve. The aortic valve calcification was assessed by MSCT and consisted mostly of moderate and severe calcification. A dilated ascending aorta, which is one of the manifestations of aortopathy in BAV patients, was seen in about 14% of patients and the size was between 40 and 51 mm.

The composite end points as given in VARC-2 and 3 consensuses were analysed for all 70 patients (13, 14). **Procedural success rate** was 98.2%. **Mortality** of two patients with numerous comorbidities occurred in our cohort related to chest infection, pneumonia, and sepsis with acute kidney injury in the immediate post procedure period. **The type of valves used** were self expanding in 70% of the cases whereas the balloon expanding platform was used in 30% of cases. The **peak-to-peak gradient** decreased from preprocedural values to less than 15 mmHg in the majority of the patients. There was a need to post dilate in a small percentage of cases where the residual gradients were more than 15 mmHg or more than mild PVL was seen after deployment.

There was a significant **PVL** in close to 20–30% of patients immediately after the procedure who needed post dilation mostly because of the unexpanded frame and the leak reduced to trivial or mild requiring no further action. At the end of the procedure, there was no PVL in 80–85%, mild PVL in 5–7 and 5–20% of patients had trace PVL. There was no statistically significant difference in the degree of PVL between the two groups who had SEV and BEV. The PVL was similar at the end of 2 years whether a BEV or SEV was implanted. Calcium in raphe and valve leads to significant PVL after deployment of the valve. **The mean gradient** of the valve after the procedure also decreased to less than 15–20 mmHg in 100% of the patients as seen at 7 days, 30 days and the mean gradient continued to be mostly less than 15 mmHg–20 mmHg at 2 years after TAVI. **The mean AVA** similarly increased from <1.0 cm^2 to >1.3–2.0 cm^2 in the majority of patients in the same timeline of 2 years after TAVI. Whether this decrease in mean pressure gradient and increase in aortic valve area was statistically significant or not was further analysed by pairwise tests of difference of means by the method described by Games and Howell where adjustment for the unequal variances is done in their formulas to calculate the size of 95% confidence intervals. The average AVA continued to maintain the immediate post procedural values. The PG across the THV remained the same as the post procedure in most of the patients.

The LVEF improved from pre TAVI level to normal or near normal function (LVEF-55–60%). Poor LV systolic function patients improved their function marginally, but the sample size was small in our study and hence analysis was not possible. They had improvement in symptoms and did not have heart failure related admission in the 2 year follow up period. **Improvement in symptoms and functional class** changed and remained the same at 2 years. Most of the patients were in class I at 2 years after TAVI. A valve wise analysis also revealed a similar improvement in the class of patient's symptom status. **Stroke** occurred in 10% of the patients in post procedural period (24 h to 30 days) and was of a non-disabling nature. They all recovered their neurological deficits in 24 h to 4 weeks period. The spectrum of neurological deficit was weakness of hand grip, slurring of speech, aphasia, monoparesis, and or psychiatric manifestation like delirium and confusion. The MRI revealed showers of microemboli in these patients. There was no dense stroke in any case. A valve wise analysis of stroke was performed, which revealed the incidence to be more with BEVs (14.2%) as compared to the 8.1% of patients who had self-expanding valve implantation done. No patient had a stroke beyond 30 days to 2 years of follow up. **High degree conduction system block** did not occur in the majority

TABLE 2 | Procedural characteristics and outcomes.

Anaesthesia used	
Local	85.51% (59)
General	14.49% (10)
Access vessel (transfemoral)	100% (69)
Predilation of native valve	100% (69)
Valve type used	
BEV	30% (21)
SEV	70% (49)
Paravalvular leak immediately at end of implantation	
Mild	68.12% (47)
Moderate	17.39% (12)
Severe	5.8% (4)
Trace	2.9% (2)
Trivial	1.45% (1)
None	4.35% (3)
Post-dilation done to reduce paravalvular leak	
No	76.81% (53)
Yes	23.19% (16)
Paravalvular leak at 7 days	
Mild	11.59% (8)
None	76.81% (53)
Trace	11.59% (8)
Paravalvular leak at 2 years	
Mild	11.76% (8)
None	77.94% (53)
Trace	10.29% (7)
Average of mean pressure gradient at end of procedure (mmHg)	8.5
Average of mean pressure gradient at 2 years after procedure (mmHg)	8.4
Average of aortic valve area pre TAVI (cm^2)	0.54
Average of aortic valve area 2 years after procedure (cm^2)	2.03
Disabling stroke In first 30 days after procedure	
No	100% (70)
Yes	0% (0)
Non-disabling stroke In first 30 days after procedure	
No	90% (63)
Yes	10% (7)
Disabling stroke in 2 years after procedure	
No	100% (70)
Yes	0% (0)
Non-disabling stroke 2 years after procedure	
No	100% (70)
Yes	0% (0)
Average of Echo LVEF % baseline	50.6
Average of Echo LVEF % 2 years after procedure	53.2
Pre-TAVI dyspnoea NYHA class	
I	1.43% (1)
II	37.14% (26)
III	35.71% (25)
IV	25.71% (18)
Post-TAVI dyspnoea NYHA class 2 years after procedure	
I	95.71% (67)
II	4.29% (3)
Non-disabling stroke after 30 days with	
Balloon expanding valve	
No	85.71% (18)
Yes	14.29% (3)
Self expanding valve	
No	91.84% (45)
Yes	8.16 % (4)
Complete heart block needing permanent pacemaker implantation by 30 days	
Balloon expanding valve	
No	95.3% (20)
Yes	4.7% (1)
Self expanding valve	
No	83.67% (41)
Yes	16.32% (8)
Vascular complications	
None	92.86% (65)
Proglide mediated stenosis	1.43% (1)
Thrombotic occlusion	5.72% (4)
PVL immediately at end of implantation	
Balloon expanding valve	
Mild	60% (12)
Moderate	20% (4)
Severe	0% (0)
Trace	5% (1)
Trivial	0% (0)
None	15% (3)
Self expanding valve	
Mild	71.43% (35)
Moderate	16.33% (8)
Severe	8.16% (4)
Trace	2.04% (1)
Trivial	2.04% (1)
None	0% (0)
PVL at 7 days with	
Balloon expanding valve	
Mild	5% (1)
None	80% (16)
Trace	15% (3)
Self expanding valve	
Mild	14.29% (7)
None	75.51% (37)
Trace	10.20% (5)
PVL at 2 years	
Balloon expanding valve	
Mild	5% (1)
None	80% (16)
Trace	15% (3)
Self expanding valve	
Mild	14.58% (7)
None	77.08% (37)
Trace	8.33% (4)
Acute kidney injury	
No	95.71% (67)
Yes	4.29% (3)
THV thrombosis at 2 years	
No	98.57% (69)

(Continued)

TABLE 2 | (Continued)

Yes	1.43% (1)
THV degenration at 2 years	
No	100% (70)
Yes	0% (0)
Procedural mortality	None
Mortality at 7 days after procedure	None
Mortality at 30 days after procedure	2.86% (2)
Mortality at 2 years after procedure	2.86% (2)

of patients. The pacemaker implantation rate was 16% with SEV and 4% with BEVs. There was no **life-threatening** bleeding in any case though some patients received transfusions who had low baseline haemoglobin. **The vascular complications** that occurred in three patients were thrombus formation of the access vessel in two cases: one was managed with ballooning and the other case needed stenting. One patient had proglide related stenosis that was managed by gentle balloon dilation. **All-cause mortality was none at 1 and 2 years** follow up of our patients. **THV valve degeneration and failure at 2 years follow up** was not seen in any case nor the need for balloon valvuloplasty, TAV in TAV or surgical valve replacement was required. Lastly, there were no cases of infective endocarditis in our patients within 2 years follow up. One patient showed increased mean gradient of 40 mmHg across the THV in follow up at 6 months, MSCT showed valvar thrombosis. It was successfully treated by oral anticoagulation.

DISCUSSION

Data regarding the epidemiology of valvular heart disease in India remains scant because of a lack of resources and the maintenance of poor medical records. A single centre study by Manjunath et al. from a high-volume centre in India showed isolated aortic stenosis as the third most common (7.3%) valve lesion in an adult population and degenerative calcific as the most common cause (65%) followed by BAV (33.9%) (27). Rheumatic heart disease contributes to 1.1%. Isolated AS was more common in male patients. In the study again 65.3% had pure AS, 21.9% had pure AR and 12.8% had combined lesion (27).

The first clinical experience of TAVI in India was in 2012 in an octogenarian lady with a previous history of CABG and a porcelain aorta with severe AS that was left unoperated for 12 years and became the cause of her recurrent heart failure admissions (28). TAVI procedure is currently done in 30 centres across India out of which 7 centres cater to the maximum cases (29). Since its introduction, the technology has rapidly expanded and seems on its way to having achieved an all-risk indication and both bicuspid and tricuspid populations are inclusive. Apart from the anatomical factors characteristics of BAV, the important challenges of TAVI in Indian population are cost and reimbursement policy, regulatory body approval, the learning curve and acquiring proficiency by the operators performing the TAVI procedure (29). In a young BAV population, it is a difficult decision for both the physician and the patient to choose TAVI over SAVR as per the present evidence and challenges of this therapy. In a study from India by Sahu et al. (30) a unique observation was made that 60% of TAVI patients are less than 60 years of age and they may not call for TAVI, age is an important determinant for TAVI. It thus has thus important implications for the penetration of TAVI in the Indian subcontinent unless robust evidence is established (30). Our study shows a similar mean age group of patients undergoing TAVI for BAV with severe stenosis as that in the other studies. Male predominance has been found to be there similar to other studies. Type 1 and type 0 are the commonest morphological types and the calcium score of the valves has been moderate to severe in our population.

Outcomes of the early experiences with TAVI in BAV patients were not encouraging in the world data. In the first TAVI series in 2010 (11), the rate of periprocedural complications was high with 13–34% equal to or greater than moderate PVL, 13–43% needed permanent pacemaker implantation (PPI), and 1 year mortality was 4–18% (31). In 2007 Yoon et al. reported a PVL of 10.4%, PPI was 14.7% (32). The STS/ACC TVT registry with all generations of valves showed a PVL of 4.7% at 1 year and the 1 year hazard of stroke (HR, 1.14 (95% CI 0.94–1.39) in the BAV arm (33). Perlman et al. first described a series of 51 patients without any or equal PVL in whom Sapien3 was used (32). The STS/ACC TVT registry also showed better outcomes with the newer generation of valves with a moderate PVL of 3.2%, stroke at 1 year of 3.4%, and 9.1% had PPI. Forrest et al. reported a 15.4% PPI rate with Evolut R/pro and a 3.9% stroke rate at 1 year. Overall, the short-term outcomes improved dramatically with the new generation of valves (34). Waksman has reported no death and no disabling stroke in 61 low risk BAV patients at 30 days, The rate of PPI was 13% and moderate PVL was just 1.6% (35). Similarly the low-risk bicuspid study had 1 death and 1 case of disabling stroke, and PPI was 15% (36). The BIVOLUT X study also showed promising results for TAVI in BAV patients with no PVL and excellent haemodynamic outcomes.

The results of our study are comparable with the aforementioned studies. The patients had a mean STS risk score of 6% and a majority of them had a newer generation of THV implanted. The outcomes of this study are comparable with **other observational studies where low to intermediate risk patients constituted the major percentage of patients**. The calcium burden was mild to moderate in most patients. Type 1 Sievers were the most common variant. SEV were more used than the BEV. Device success, valve performance and clinical outcomes are matched.

The results of our study demonstrate good clinical outcomes among all the patients who underwent TAVI across all risk scores. The AVA and the mean PG achieved at the end of the procedure were well maintained at 2 year follow up and were statistically significant. The **Supplementary Figures 4–12** in the manuscript depict data that has been collated and presented to demonstrate the patient profile, composition, and procedural outcomes.

Limitations of our study include its small sample size; however, we must recognise that TAVI is not a routinely common procedure in India. Therefore, the sample size of 70 provided helpful study results and future applications as the standard of therapy for bicuspid aortic stenosis patients. TAVI being the new procedure in India, the findings of our study can enthuse

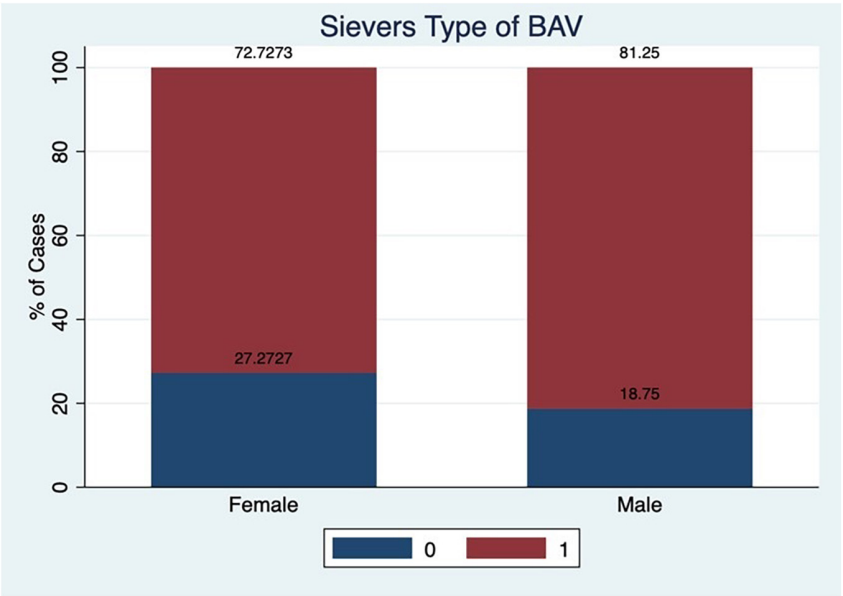

FIGURE 1 | Pair wise comparison of mean pressure gradients over 2 years, statistically significant.

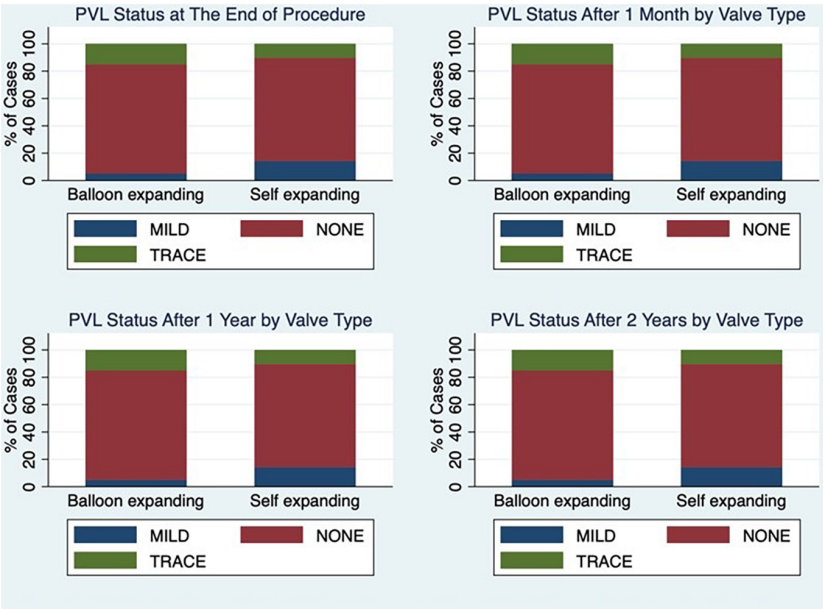

FIGURE 2 | Pair wise comparison of average valve area over 2 years after TAVI.

young interventionalists to pursue research in this area. Our study depicts results that can be expected in real-world clinical practice. All 68 patients at the end of 2 years remained stable, which itself is a testimony to the effectiveness and safety of TAVI in a bicuspid population.

Statistical tests were applied to estimate significant differences between the pre and post procedure AVA and mean PG comparison groups, as depicted in **Figures 1**, **2**. These show good haemodynamics at the end of 2 years, with an average valve area close to the magic number of 2 cm^2 and a mean PG of less than 15 mmHg (**Figure 3**). More haemodynamic data and detailed longer follow up to 5 and 10 years, combined with CT imaging may throw light on early signs of structural degeneration and THVs failure. These aspects would be important for establishing this therapy for a young population who must lead an active life. Those with heavy calcium scores had a greater residual gradient and greater leak immediately after implantation and required post dilation to expand the frame. The peak-to-peak gradient

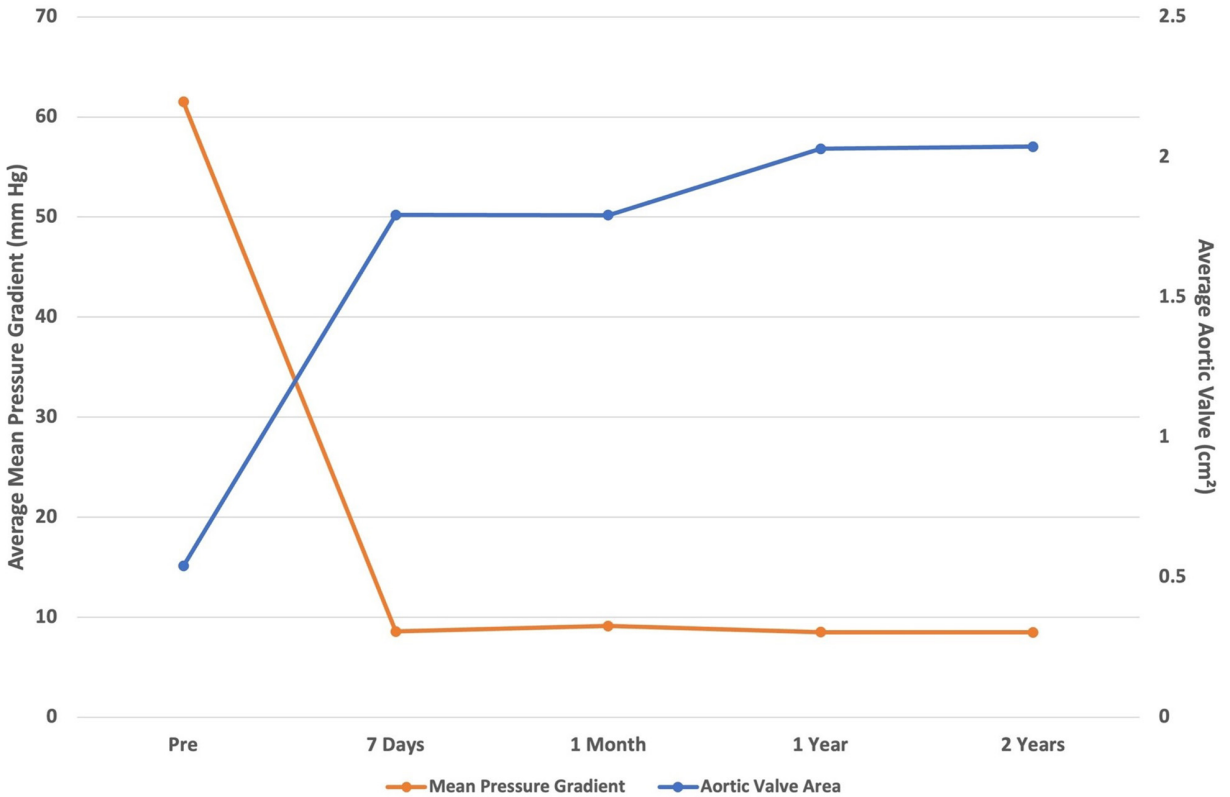

FIGURE 3 | Mean pressure gradient and aortic valve area at 2 years after TAVI.

reduced as did the leak to a mild degree. Sizing of the valve was done by the aforementioned algorithms and consideration of other anatomical factors. Adequate oversizing (5–10%) for BEV and (15–25%) oversizing for SEV were targetted. The risk of patient prosthesis mismatch was from an undersized valve as per the body surface area of the patient, which was also taken into account during valve size selection. If the aortic annulus was smaller in size, we preferred choosing a larger self-expanding valve over a smaller BEV. The size chosen was also not big enough to cause injury to the root.

The selection of the type of valve in our study was performed with some preferences of one over the other, e.g.: a BEV was preferred in the presence of horizontal aortic root and dilated ascending aorta. A BEV was avoided if the aortic annulus calcium extended to the LVOT. BEVs with large open struts were preferred if the coronaries ostia were at risk for occlusion.

Adequate predilation for every case was undertaken in our study. The balloon size for predilation was one size smaller or equal to the size of the minor axis of the aortic annulus diameter. This possibly opened the native valve adequately and prepared a good bed for implantation of the new valve with the least constraint, least gradient, and the least residual leak. This was the key factor in achieving the best haemdynamics, apart from the ideal selection of a particular valve size based on different anatomical measurements and considerations. It also helped provide an estimate of the appropriate size of valve. A shallower positioning and supra-annular implantation were aimed in every SEV case and a 90–10 to 70–30 depth implantation was aimed for in the BEV cases.

Whenever required post dilation was undertaken with an appropriate size of non-compliant balloon (perimeter or area derived diameter) that resulted in eliminating the residual gradient and leak. Post dilation was performed if there was a residual gradient >15 mmHg or a significant PVL was seen due to an under expanded valve. The PVL was moderate to severe in 24.28% of cases immediately after deployment of the valve and was reduced to trace or mild in most of the patients at the end of the procedure, which was maintained at a follow up of 2 years irrespective of the type of valve used. There was no moderate or severe PVL at 2 year follow up. A second valve in valve was implanted for two cases of severe PVL immediately at end of the procedure due to the final deeper implantation of the first valve. Longer years of follow up of the mild PVL would be needed to assess its progression and clinical impact. In our study mal apposition or under expansion of the frame, constraint in the frame due to calcium rocks was the cause of PVL. An under sized valve implantation was not the cause of PVL in the study. Newer generation valves with external skirts also contributed to reducing the PVL to a minimum even in the presence of calcium chunks.

The PPI rate was higher in the SEV group as compared to the BEV group by 30 days. The possible reasons were a final deeper implantation and pre-existing conduction block. PPI was not needed in any patient in either group at 1- or 2-year period follow up. CHB needing PPI is unacceptable for the young population and thus needs more emphasis on shallow but safe depth of implantation, measuring membranous septum length on CT, and positioning it above that level at high pacing rates during deployment to avoid the deep diving of the valve, maintaining the forward push on the wire to prevent diving deep during deployment, recapturing if you have gone deep and very recently cuspal overlap technique has also been used for bicuspid valve implantation.

In our study, disabling stroke happened to none of the patients but 10% of patients had periprocedural non-disabling stroke, which was seen more with BEVs, possibly because of predilation and postdilation in the setting of heavily calcified valves resulting in showers of microemboli. A dedicated cerebral protection device for TAVI is not yet available in the country and so is not used in routine practice. We used one spider filter and an Emboshield device on our patient who had the presence of mobile healed vegetation or atheromatous/calcified mobile mass attached to the leaflet. The patient had no stroke and the debris was trapped. Possible reasons for stroke appear to be the embolising calcium particles from the practice of mandatory predilation. Valve repositioning and repeated recapturing of the self-expanding valves and the post dilation were also factors responsible for the occurrence of stroke. Stroke in the young population is very much an unacceptable complication, as it could be disastrous and ruin their lives. Stroke, even when non-disabling, is unacceptable for a young population and the importance of cerebral protection in the bicuspid population becomes more important. Secondly, the role of routine anticoagulation for 3 months to 1 year also needs to be studied to avoid thrombosis of the microparticles of calcium embolised into cerebral circulation and causing delayed strokes in the first week or by 30 days of the implantation or potentially showers of emboli from a silent thrombosis of the tissue of the new valve.

Symptomatic NYHA class improvement by at least one or more functional classes was seen in 100% of patients. There was an improvement in the class of symptoms for the LV dysfunction subset of patients as well. The LV systolic function was mostly near normal. Those with severe LV dysfunction also had improved ejection fraction by 5–15% but the size of this subset of patients was small and statistical analysis was not possible. A study purely evaluating poor LV systolic function cases is needed to examine why some patients improved only marginally (possibly due to factors like irreversible fibrosis or elements of some kind of cardiomyopathy), which prevented the heart function from improving to near normal. Moreover, we require studies dedicated to looking at readmission rates from heart failure and quality of life indices in the presence of non-improvement of LV systolic function after new valve implantation. Some indices need to be established for suggesting which subset of LV dysfunction patients would improve and who would not improve.

CONCLUSION

The Indian experience of TAVI in the BAV patient population is quite similar to that described in other literature from across the world. The BAV is present in a fairly high percentage of the Indian population of aortic stenosis patients. TAVI is extending fast to this subset of severe AS patients but important aspects of the success of this therapy will be to take into account sizing and implantation, freedom from PVL, pacemaker implantation, and stroke. Coronary safety and ease of access in future are connected to its 10–15 years of durability and freedom from patient prosthesis mismatch. Moreover, our findings indicate that good and sustained haemodynamics with an aortic valve orifice area of around 2 cm^2 should be given to the young population. Once most of these are achieved, the therapy will be used more and large randomised studies will be needed. Meticulous understanding and analysis of CT scan imaging may help to exclude certain sets of these BAV anatomies who are labelled unsuitable for TAVI and should be offered surgery. The suitability of this therapy for very young patients in their 20–50 s is an unanswered question because they may need more than one valve replacement procedure during their life, depending on which therapy is chosen as their index procedure.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

VK, GS, VPS, and VR collated the data from their centres and done the analysis of the entire data. VK wrote the manuscript and referencing. AS reviewed the content of the manuscript and incorporated his needful suggestions and inputs in the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.817705/full#supplementary-material

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Conflict of Interest: AS was Proctor for TAVI and received consulting fee from Meril Lifesciences and Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 29 July 2022
DOI 10.3389/fcvm.2022.931207

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 28 April 2022
ACCEPTED 04 July 2022
PUBLISHED 29 July 2022

CITATION
Testa L, Casenghi M, Criscione E, Van Mieghem NM, Tchétché D, Asgar AW, De Backer O, Latib A, Reimers B, Stefanini G, Trani C, Giannini F, Bartorelli A, Wojakowski W, Dabrowski M, Jagielak D, Banning AP, Kharbanda R, Moreno R, Schofer J, Brinkmann C, van Royen N, Pinto D, Serra A, Segev A, Giordano A, Brambilla N, Agnifili M, Rubbio AP, Squillace M, Oreglia J, Tanja R, McCabe JM, Abizaid A, Voskuil M, Teles R, Zoccai GB, Sondergaard L and Bedogni F (2022) Prosthesis-patient mismatch following transcatheter aortic valve replacement for degenerated transcatheter aortic valves: the TRANSIT-PPM international project.
Front. Cardiovasc. Med. 9:931207.
doi: 10.3389/fcvm.2022.931207

Prosthesis-patient mismatch following transcatheter aortic valve replacement for degenerated transcatheter aortic valves: the TRANSIT-PPM international project

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Background: A severe prosthesis-patient mismatch (PPM) is associated with adverse outcomes following transcatheter aortic valve replacement (TAVR) for

de novo aortic stenosis or a failed surgical bioprosthesis. The impact of severe PPM in patients undergoing TAV-in-TAVR is unknown.

Aim: We sought to investigate the incidence and 1-year outcomes of different grades of PPM in patients undergoing TAV-in-TAVR.

Materials and methods: The TRANSIT-PPM is an international registry, including cases of degenerated TAVR treated with a second TAVR. PPM severity, as well as in-hospital, 30-day, and 1-year outcomes were defined according to the Valve Academic Research Consortium-3 (VARC-3) criteria.

Results: Among 28 centers, 155 patients were included. Severe PPM was found in 6.5% of patients, whereas moderate PPM was found in 14.2% of patients. The rate of severe PPM was higher in patients who underwent TAV-in-TAVR with a second supra-annular self-expanding (S-SE) TAVR (10%, $p = 0.04$). Specifically, the rate of severe PPM was significantly higher among cases of a SE TAVR implanted into a balloon-expandable (BE) device (19%, $p = 0.003$). At 1-year follow-up, the rate of all-cause mortality, and the rate of patients in the New York Heart Association (NYHA) class III/IV were significantly higher in the cohort of patients with severe PPM ($p = 0.016$ and $p = 0.0001$, respectively). Almost all the patients with a severe PPM after the first TAVR had a failed < 23 mm BE transcatheter heart valve (THV): the treatment with an S-SE resolved the severe PPM in the majority of the cases.

Conclusion: After TAV-in-TAVR, in a fifth of the cases, a moderate or severe PPM occurred. A severe PPM is associated with an increased 1-year all-cause mortality.

Clinical trial registration: [https://clinicaltrials.gov], identifier [NCT04500964].

KEYWORDS

TAVR, failed TAVR, TAVR in TAVR, prosthesis-patient mismatch, mortality

Introduction

Prosthesis-patient mismatch (PPM) may occur after surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) when a normally functioning prosthetic valve presents an effective orifice area (EOA) relatively small for the patient's body surface area (BSA), thus not allowing an adequate cardiac output (1). Several studies on patients undergoing SAVR showed that severe PPM was associated with increased mortality and structural valve degeneration, regardless of its severity, in the postoperative period (2, 3). On the other hand, patients treated by means of transcatheter valves, which are characterized by a larger EOA and lower gradient compared to surgical valves, experience a lower incidence of severe PPM: the clinical impact of severe PPM is still controversial (4, 5). Recently, TAVR for a failed surgical bioprosthetic aortic valve [TAVR-valve-in-valve (ViV)] has emerged as an attractive option for patients who are at an increased risk for a surgical redo; although, according to a recent meta-analysis, it may be associated with a higher incidence of severe PPM as compared to redo-SAVR (6, 7). Indeed, over 30% of TAVR-ViV procedures in the Society of Thoracic Surgeons (STS)/the American College of Cardiology, the Transcatheter Valve Therapy (TVT), and the Valve-in-Valve International Database (VIVID) Registries resulted in an elevated postprocedural transvalvular gradient (4, 6). Although, rarely, transcatheter aortic valves can also degenerate (8): the TRANSIT international project collected the largest series of patients with a degenerated TAVR treated by means of a second TAVR (TAV-in-TAVR) and, consistently with a previous smaller registry, showed acceptable procedural and 1-year outcomes (9, 10). In the present TRANSIT-PPM study, we sought to evaluate the incidence and impact of severe PPM on outcomes, in patients undergoing TAV-in-TAVR.

Materials and methods

The TRANSIT-PPM project is an investigator-initiated international multicenter registry, including

consecutive patients undergoing TAVR for a degenerated transcatheter aortic valve (ClinicalTrials.gov Identifier: NCT04500964). We evaluated cases performed with supra-annular self-expanding (S-SE) (CoreValve, Evolut R, and Evolut PRO) and intra-annular balloon-expandable (BE) transcatheter heart valves (THVs) (Edwards SAPIEN, SAPIEN XT, and SAPIEN S3).

Data concerning procedural results and echocardiographic parameters after each TAVR were collected. Data concerning the last available follow-up were also collected. This study was approved by an institutional review committee and the subjects gave informed consent.

Definitions

The registry exclusively collected cases of degenerated TAV treated by means of a second TAVR. Patients undergoing TAV-in-TAVR due to a procedural failure of the indexed TAVR were not included.

Procedural, device success, as well as PPM were defined according to the Valve Academic Research Consortium-3 (VARC-3) definitions (11). In particular, PPM was defined moderate if the predicted EOA was > 0.65 and < 0.85 cm^2/m^2 for patients with body mass index (BMI) < 30 kg/m^2, or > 0.55 and < 0.70 cm^2/m^2 for patients with BMI > 30 kg/m^2, and severe if the predicted EOA was ≤ 0.65 cm^2/m^2 for patients with BMI < 30 kg/m^2 and ≤ 0.55 for patients with BMI > 30 kg/m^2 (8–10).

The left ventricular outflow tract (LVOT) measures have been obtained with the CT scan that all the patients performed before the procedure.

Statistical analysis

Descriptive statistics are reported as mean and SD for normally distributed continuous variables, as median and 25–75th percentile otherwise. Absolute and relative frequencies are reported for categorical variables. For continuous variables, the comparisons were done either with ANOVA or with a non-parametric test (Kruskal–Wallis test). For categorical variables, comparisons among groups were done with the chi-squared tests or Fisher's exact tests. All-cause death was reported using the Kaplan–Meier estimates together with their 95% CI. The Wilcoxon signed rank sum test was used for the comparison of echo parameters in paired analyzes. The cumulative incidences of clinical events at follow-up were assessed with the Kaplan–Meier method and log-rank test. A two-sided P-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 23 (IBM Incorporation, Armonk, NY, United States).

Results

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

The TRANSIT project is an investigator-initiated registry that started collecting data in January 2020 (ClinicalTrials.gov Identifier: NCT04500964). A group of 28 centers took part in the project: 22 in Europe, 4 in North America, 1 in South America, and 1 in the Middle East. Among a total number of about 40,000 procedures performed since 2008, 155 cases of TAV-in-TAVR were eventually included in the TRANSIT-PPM study. Of these, 73 (47%) cases presented a degenerated supra-annular self-expanding valve, while 82 (53%) cases had a degenerated balloon-expandable device.

According to the VARC-3 definitions, 8 (5.2%) and 32 (20.6%) patients, respectively, presented a severe or moderate PPM after the first procedure, while no patients had a mean residual gradient higher than 20 mm Hg or a more than mild aortic regurgitation (AR).

The mean age was 77.9 ± 7.7 years and the male gender was slightly more represented (57.4%). The majority of patients (74%) were in the NYHA class III or IV at admission. The mean left ventricular ejection fraction was 49 ± 13.4. The European System for Cardiac Operative Risk Evaluation I (EuroSCORE I) was 20.3 ± 15.0, the EuroSCORE II was 8.7 ± 7.5, and the STS score was 6.3 ± 5 (**Table 1**). Most patients (57%) had a mainly regurgitant degenerated bioprosthesis, 52 (34%) patients had a stenotic degenerated THV, and 15 (10%) patients had a mixed degeneration of the first implanted valve (**Table 1**).

Patients were grouped and analyzed according to the grade of PPM after the second TAVR: 10 (6.5%) patients had severe PPM, 22 (14.2%) patients had moderate PPM, and 123 (79.3%) patients had no PPM.

There were no differences in BSA and BMI distribution between the groups (**Table 1**). Overall, patients were frequently hypertensive (87%) and dyslipidemic (64%); in particular, the rate of the aforementioned risk factor was higher in patients with moderate or severe PPM ($p = 0.05$ and $p = 0.04$, respectively). No other differences were found among common risk factors such as diabetes, chronic obstructive pulmonary disease (COPD), and severe renal failure (**Table 1**). Risk scores (EuroSCORE I, EuroSCORE II, and STS), as well as mean postprocedural transvalvular gradient, were significantly higher in patients with severe PPM compared to those with moderate or none/mold PPM ($p = 0.03$ and $p = 0.01$, respectively).

Of note, 4 out of 10 patients presenting a severe PPM after TAV-in-TAVR belong to the mixed-degenerated cohort ($p = 0.001$).

TABLE 1 Demographic characteristics of the study population.

	Overall (*N* = 155)	Severe PPM (*N* = 10)	Moderate PPM (*N* = 22)	None (*N* = 123)	*P*-value
Age	77.9 ± 7.7	77.5 ± 7.6	77.9 ± 7.5	79.2 ± 8.7	0.2
Male	89 (57.4%)	2 (20%)	8 (36%)	79 (64%)	0.002
BSA (m2)	1.8 ± 0.2	1.7 ± 0. 07	1.8 ± 0.2	1.8 ± 0.2	0.4
BMI < 21 kg/m2	25 (16%)	1 (10%)	2 (9%)	22 (18%)	0.5
BMI > 30 kg/m2	19 (12%)	0 (0)	2 (9%)	17 (14%)	0.4
Hypertension	135 (87%)	10 (100%)	22 (100%)	103 (84%)	0.05
Dyslipidemia	104 (67%)	6 (60%)	20 (91%)	78 (65%)	0.04
Diabetes	19 (12%)	4 (40%)	6 (27%)	32 (26%)	0.7
Smoker	40 (26%)	2 (20%)	4 (21%)	34 (34%)	0.4
COPD	36 (23%)	3 (30%)	6 (27%)	27 (22%)	0.8
Severe renal failure	28 (18%)	3 (30%)	2 (9%)	23 (19%)	0.3
Dialysis	6 (4%)	1 (10%)	0 (0)	5 (4%)	0.4
Stroke	9 (6%)	1 (10%)	0 (0)	8 (7%)	0.4
Previous pacemaker	50 (32%)	3 (30%)	6 (27%)	41 (34%)	0.8
Previous cardiac surgery	30 (19%)	3 (30%)	4 (18%)	23 (19%)	0.3
HISTORY of MI	42 (27%)	2 (20%)	8 (36%)	32 (26%)	0.5
Previous PCI	65 (42%)	5 (50%)	6 (27%)	54 (45%)	0.3
NYHA III/IV	114 (74%)	7 (70%)	18 (82%)	89 (74%)	0.7
LV ejection Fraction (%)	49 ± 13.4	52.5 ± 10.3	52.6 ± 18.7	48.1 ± 13.1	0.3
Aortic valve area (cm^2)	1.34 ± 0.7	0.75 ± 0.3	1.05 ± 0.5	1.44 ± 0.72	0.03
Euroscore I	20.3 ± 15.0	37.4 ± 17.3	18.4 ± 7.3	18.1 ± 13.0	0.01
Euroscore II	8.7 ± 7.5	15.5 ± 15.0	9.5 ± 1.8	8.2 ± 7.6	0.06
STS Score	6.3 ± 5.9	12.3 ± 14.9	4.7 ± 1.2	6.9 ± 5.7	0.03
Regurgitant degenerated	88 (57%)	3 (30%)	10 (46%)	75 (61%)	0.08
Stenotic degenerated	52 (34%)	3 (20%)	12 (55%)	37 (30%)	0.09
Mixed degenerated	15 (10%)	4 (40%)	0	11 (9%)	0.001

BSA, body surface area; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LV, left ventricle; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

Assessment of the prosthesis-patient mismatch before transcatheter aortic valve-in-transcatheter aortic valve replacement

All the cases of severe PPM after the first TAVR concerned patients with a BE THV (8 patients), with a significantly higher prevalence of ≤ 23 mm THVs (7 out of 8); conversely, no grade of PPM was more frequent among patients with an S-SE THV, in particular in patients with a > 23 mm THV (**Supplementary Tables 1**, **2**).

Procedural results

In this cohort of patients with a degenerated first THV undergoing TAV-in-TAVR, an S-SE THV was implanted in 86 cases (55%), while a BE THV was implanted in the remaining 69 cases (45%) (see **Table 2** for the procedural results). **Supplementary Table 3** shows the iterations of the first and second THV according to the size ≥ 23 mm.

We could not find a specific strategy in the selection of the second TAVR except at the operator's discretion.

The cohort of patients treated by means of an S-SE showed a significantly higher rate of severe PPM compared to those who received a BE (10.4 vs. 1.5%, $p = 0.04$) (**Figure 1**). On the contrary, the rate of moderate PPM was significantly higher in those patients receiving a BE THV (2.3 vs. 29%, $p = 0.0001$).

More in detail, the rate of severe PPM was significantly higher in those patients who received an S-SE device to treat a degenerated BE THV (7/10, $p = 0.003$). The rate of moderate PPM was significantly higher when a BE THV has been used to treat a degenerated BE THV (16/22, $p = 0.0001$) (**Table 3** and **Figure 1**).

Overall, the rates of severe and moderate PPM were significantly higher in patients presenting with a

TABLE 2 Procedural data.

Variables	Overall (*N* = 155)	Severe (*N* = 10)	Moderate (*N* = 22)	None (*N* = 123)	*P*-value
Transfemoral approach	141 (91%)	10 (100%)	18 (81,8%)	113 (91,9%)	0,19
Predilatation	28 (18,1%)	3 (30%)	4 (18,2%)	21 (17,1%)	0,59
Postdilatation	63 (40,6%)	5 (50%)	8 (36,4%)	50	0,77
Contrast (mean ± SD)	93 (18)	93,6 (20)	82,7 (34)	94 (24)	0.3
Aortic dissection	0	0	0	0	–
Annulus rupture	1 (0,6%)	0	0	1 (0,8%)	0,88
Valve embolization	0	0	0	0	–
Myocardial infarction	1 (0,6%)	0	0	1 (0,8%)	0,88
Emergency surgery	1 (0,6%)	0	0	1 (0,8%)	0,88
Coronary obstruction	0	0	0	0	–
Stroke/TIA	0	0	0	0	–
Cardiac tamponade	0	0	0	0	–
Major vascular complication	3 (1,9%)	0	0	3 (2,4%)	0,67
Ventricular arrhythmias	0	0	0	0	–
Device success	126 (81,3%)	2 (20%)	16 (72,7%)	108 (87,8%)	0,12
Mean gradient (mmHg, mean ± SD)	10,3 (4)	11,9 (5)	8,8 (7)	10,4 (4)	0.15

AR, aortic regurgitation; TIA, transient ischemic attack.

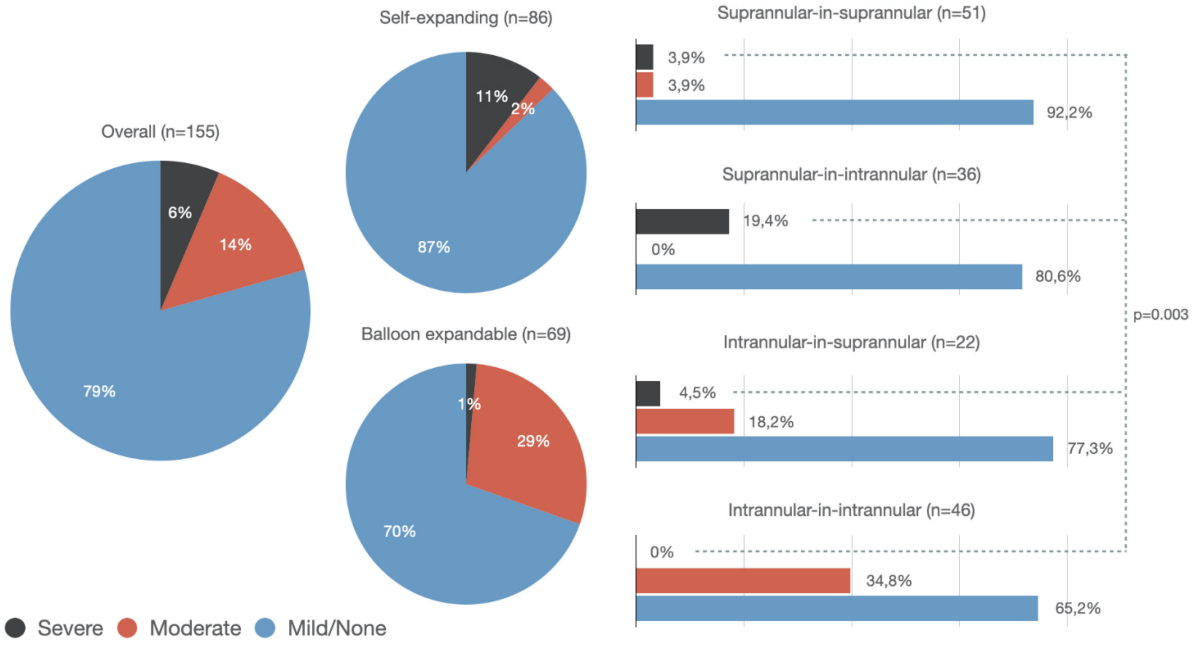

FIGURE 1
Rate of prosthesis-patient mismatch among the overall population (left-sided), patients treated with a second self-expanding transcatheter heart valve (THV) (top center), and patients treated with a second balloon-expandable THV (bottom center). Incidence of severe prosthesis-patient mismatch (PPM) was higher in patients with supra-annular-in-intra-annular THV (p = 0.003). Particularly, a higher rate of severe PPM was observed among the supra-annular-in-intra-annular group compared to the supra-annular-in-supra-annular or intra-annular-in-intra-annular groups (p = 0.02 and p = 0.002, respectively).

degenerated ≤ 23 mm THV (Table 4): in particular, 9 out of 10 cases of severe PPM after the second TAVR occurred in patients with a degenerated first THV of ≤ 23 mm in size.

All the patients with a severe PPM after the first TAVR have been treated with an S-SE: only 1 out of 8 patients had a severe PPM after the second TAVR (Table 5).

TABLE 3 First-second transcatheter aortic valve replacement (TAVR) combinations and subsequent grades of prosthesis-patient mismatch (PPM) (see text for acronyms).

	Overall (N = 155)	Severe PPM (N = 10)	Moderate PPM (N = 22)	None (N = 123)	P-value
2nd S-SE	86 (55%)	9 (90%)	2 (9%)	75 (61%)	0.0001
2nd BE	69 (45%)	1 (10%)	20 (91%)	48 (39%)	0.0001
S-Se in S-SE	51 (33%)	2 (20%)	2 (9%)	47 (38%)	0.02
S-Se in BE	36 (23%)	7 (70%)	0 (0)	29 (24%)	0.0001
BE in S-Se	22 (14%)	1 (10%)	4 (18%)	17 (14%)	0.8
BE in BE	46 (29%)	0 (0)	16 (73%)	30 (24%)	0.0001

TABLE 4 Analysis of the prosthesis-patient mismatch (PPM) occurrence after the second transcatheter aortic valve replacement (TAVR), according to the size of the first transcatheter heart valve (THV).

	Overall (N = 155)	1st TAVR ≤ 23 mm (N = 55)	1st TAVR > 23 mm (N = 100)	P-value
Severe PPM	10 (6.5%)	9 (16.4%)	1 (1%)	0.001
Moderate PPM	22 (20.6%)	14 (25.5%)	8 (8%)	0.004
No PPM	123 (74.2%)	32 (58.2%)	91 (91%)	0.0001

TABLE 5 Different grades of prosthesis-patient mismatch (PPM) after TAV-in- transcatheter aortic valve replacement (TAVR) according to the PPM of the degenerated TAVR.

	Overall (N = 155)	Severe PPM 2nd TAVR (N = 10)	Moderate PPM 2nd TAVR (N = 22)	None (N = 123) 2nd TAVR (N = 123)	P-value
Severe PPM1st TAVR	8 (5.2%)	1 (10%)	2 (9.1%)	5 (4.1%)	0.5
Moderate PPM1st TAVR	32 (20.6%)	6 (60%)	8 (36.4%)	18 (14.6%)	0.0001
No PPM1st TAVR	115 (74.2%)	3 (30%)	12 (54.5%)	100 (81.3%)	0.0001

The VARC-3 defined procedural success rate was 80.6% with 22 (14.2%) patients presenting: a severe PPM (9 patients) and/or residual gradient ≥ 20 mm Hg (13 patients), and 2 (1.3%) patients showing a more than mild AR.

The presence of a no PPM after the first TAVR [hazard ratio (HR) 0.126, 0.31–0.51, p = 0.004], and of a degenerated THV of ≤ 23 mm (HR 19.7, 2.28–157.4, p = 0.006) were independent predictors of severe PPM after the second TAVR.

In-hospital outcomes

Seven patients (4.5%) died during the in-hospital stay, all due to cardiovascular (CV) causes. None presented a severe PPM, while 4 patients had moderate PPM and 3 patients had no significant PPM (p = 0.006). Two patients had a myocardial infarction during the hospital stay. No differences in the incidence of conduction disturbances, pacemaker (PM) implantation, or new-onset atrial fibrillation were observed according to the presence and severity of PPM. Other in-hospital outcomes are shown in Table 6.

30-day and 1-year follow-up

A 30-day cumulative overall mortality rate was 7.1% with no further cardiovascular death and no significant differences reported among groups (p = 0.08). Compared to patients with moderate or no PPM, those patients with a severe PPM showed a higher rate of valve-related hospitalization (p = 0.001) and dyspnea at rest or on mild exertion (the NYHA class III/IV) (p = 0.001) (Table 7). Two cases of valve thrombosis had been detected, both in patients with moderate PPM (p = 0.001).

Cumulative 1-year all-cause mortality was 12.9% (a miscellaneous of pneumonia, sepsis, CV death, and cancer) with a CV-related death occurring in 5.8% of patients. Compared to patients with no and moderate PPM, the rate of all-cause

TABLE 6 In-hospital outcomes.

	Overall (*N* = 155)	Severe PPM (*N* = 10)	Moderate PPM (*N* = 22)	None (*N* = 123)	*P*-value
All cause mortality	7 (4.5%)	0 (0)	4 (18%)	3 (2%)	0.003
Cardiovascular mortality	7 (4.5%)	0 (0)	4 (18%)	3 (2%)	0.006
New onset LBBB	2 (1.3%)	0 (0)	0 (0)	2 (1.6%)	0.8
New onset AF	6 (4%)	1 (10%)	0 (0)	5 (4%)	0.4
New PM	6 (4%)	0 (0)	0 (0)	6 (5%)	0.5
Stroke/TIA	6 (4%)	0 (0)	0 (0)	6 (5%)	0.5
Major vascular complications	4 (2.6%)	0 (0)	2 (9%)	2 (1.6%)	0.1
Major bleeding (≥ BARC-3a)	9 (6%)	1 (10%)	0 (0)	8 (7%)	0.4
MI	2 (1.3%)	1 (10%)	0 (0)	1 (0.8%)	0.04
Valve thrombosis	0 (0)	–	–	–	–
AKI (≥ AKIN-2)	7 (4.5%)	1 (10%)	2 (9%)	4 (3%)	0.3
Sepsis	8 (5%)	1 (10%)	2 (9%)	5 (4%)	0.4

LBBB, left bundle branch block; AF, atrial fibrillation; PM, pacemaker; TIA, transient ischemic attack; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; AKI, acute kidney injury; AKIN, acute kidney injury network classification.

TABLE 7 Cumulative 30-day and 1-year outcomes.

	Overall (*N* = 155)	Severe PPM (*N* = 10)	Moderate PPM (*N* = 22)	None (*N* = 123)	*P*-value
30-day					
CV death	7 (4.5%)	0 (0)	4 (18%)	3 (2.4%)	0.003
All-cause death	11 (7.1%)	1 (10%)	4 (18%)	6 (3.8%)	0.08
Valve related hospitalization	5 (3%)	2 (20%)	0 (0)	3 (2.4%)	0.001
Valve thrombosis	2 (1.3%)	0 (0)	2 (9%)	0 (0)	0.001
NYHA class III-IV	12 (7.7%)	3 (30%)	0 (0)	9 (7.4%)	0.0001
1-year					
All-cause death	20 (12.9%)	4 (40%)	4 (18%)	12 (9.7%)	0.016
CV death	9 (5.8%)	2 (20%)	4 (18%)	3 (2.4%)	0.002
Valve related hospitalization	10 (6.5%)	2 (20%)	2 (9%)	6 (5%)	0.15
Valve thrombosis	2 (1.3%)	0 (0)	2 (9%)	0 (0)	0.002
NYHA class III-IV	9 (5.8%)	2 (20%)	0 (0)	7 (5.7%)	0.0001

CV, cardiovascular.

mortality was significantly higher in patients with a severe mismatch ($p = 0.016$).

With respect to patients with no PPM, both the patients with moderate and severe PPM had a significantly higher rate of cardiac death ($p = 0.002$) (Table 7 and Figure 2).

Valve-related hospitalization occurred in 10 (6.5%) patients, with no significant differences between the groups. The rate of patients in the NYHA class III/IV was significantly higher in the severe PPM cohort ($p = 0.0001$). No cases of valve thrombosis, myocardial infarction (MI), stroke, or valve dysfunction requiring intervention were further recorded.

No differences in the rate of all-cause mortality, CV mortality, and valve-related hospitalization were found among those patients with elevated postprocedural mean gradient (≥ 20 mm Hg), but without severe PPM ($p = 0.2$, $p = 0.5$, and $p = 0.8$, respectively).

Discussion

A second TAVR to treat a degenerated TAVR is a reasonable option with acceptable in-hospital and 1-year outcomes (9). However, likewise, in the field of TAVR in SAVR, a high residual gradient may occur possibly affecting the clinical outcome, especially when associated with a severe PPM.

The TRANSIT-PPM project is the first multicenter, international registry that evaluated the incidence and clinical outcomes of the different grades of PPM after TAV-in-TAVR.

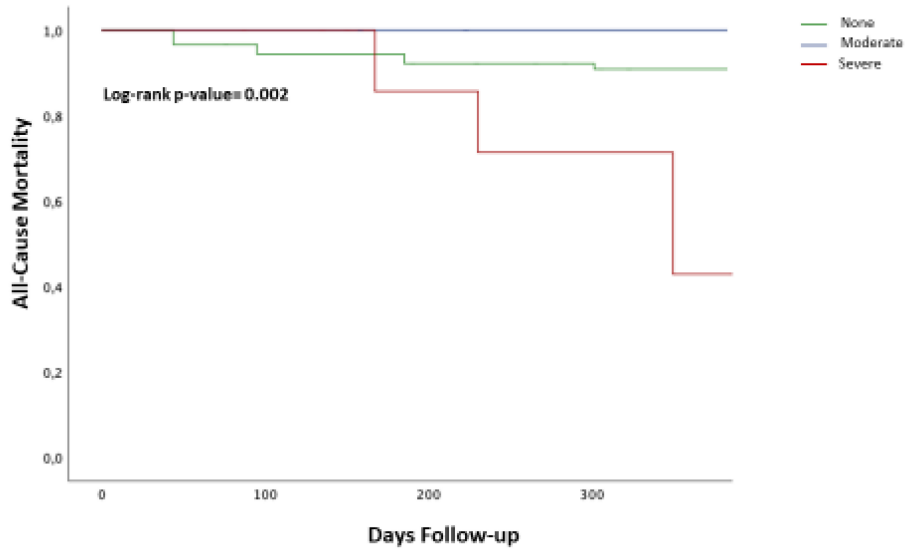

FIGURE 2
The Kaplan–Meier curves of cumulative 1-year all-cause death according to the presence of severe prosthesis-patient mismatch (PPM). The cumulative all-cause mortality rate at 1 year in patients with a severe was higher as compared with patients with moderate PPM or no PPM (log-rank *p*-value = 0.001). Blue line = Moderate/none PPM; Red line = Severe PPM.

The main results of our study may be summarized as follows:

- Severe and moderate PPM was found in 6.5 and 14.2% of patients undergoing TAV-in-TAVR, respectively.
- The rate of severe PPM after TAV-in-TAVR was significantly higher in patients treated with an S-SE THV (10.4%, $p = 0.04$), particularly in those with an S-SE THV implanted into a degenerated BE THV ($p = 0.003$).
- The rate of moderate PPM after TAV-in-TAVR was significantly higher in patients treated with a BE THV (2.3 vs. 29%, $p = 0.0001$), particularly in those with a BE THV implanted into a degenerated BE THV.
- A severe PPM after TAV-in-TAVR is significantly more frequent when treating a degenerated $\leq$ 23 mm THV.
- In the majority of the cases of a degenerated BE THV with a severe PPM, the treatment with an S-SE resulted in a better hemodynamic result.
- A no PPM after the first TAVR (HR 0.126, 0.31–0.51, $p = 0.004$) and a degenerated $\leq$ 23 mm THV (HR 19.7, 2.28–157.4, $p = 0.006$) are independent predictors of severe PPM after TAV-in-TAVR.
- At 1-year follow-up, the rates of all-cause mortality and the NYHA class III/IV were higher in the cohort of patients with severe PPM compared to those patients with moderate or no PPM.

Several studies investigated the incidence and clinical outcomes of PPM after surgical or transcatheter aortic valve replacement conveying conflicting results, mainly due to several methodological differences. Herrmann et al. (3) found that severe PPM was present in 12% of patients treated by means of TAVR and it was associated with a higher 1-year mortality, and heart failure (HF) rehospitalization. Okuno et al. (12) found that the rate of severe PPM was significantly lower in patients undergoing TAVR with a self-expanding device compared to those patients treated with a balloon-expandable device (6.7 vs. 15.6%; $p = 0.003$) with no impact of PPM on cardiovascular mortality or the NYHA class at 1 year. Recently, an analysis of the TVT Registry, including patients undergoing TAVR with self-expanding THVs, showed a rate of severe PPM of 5.3% in patients undergoing *de novo* TAVR and 27% in those patients undergoing TAVR-ViV (13). It is also well established that the results of TAVR-ViV for failed surgical bioprostheses are significantly conditioned by the presence of a preexisting severe PPM, an elevated postprocedural gradient, or a *de novo* mismatch (14). Strategies aiming to reduce the risk of a post-TAVR-ViV severe mismatch include high transcatheter valve implantation (0–2 mm below the prosthesis sewing ring), the use of a supra-annular self-expanding THV, and the use of techniques such as bioprosthetic valve fracture or remodeling (14, 15).

The incidence and clinical impact of the different grades of PPM are unknown in the field of TAV-in-TAVR.

In our study, including 155 patients with a degenerated THV treated by means of a second TAVR, the rates of severe and moderate PPM were 6.5 and 14.2%, respectively, thus slightly higher than that observed in published series on *de novo* TAVR, but lower as compared to TAVR-ViV (12). The latter might be explained by the larger EOA of the TAVR technologies: it is conceivable that, on average, a degenerated TAVR could

have a larger EOA than a degenerated surgical bioprosthesis. This condition obviously allows the implantation of a relatively larger second THV.

Of note, we found a significantly higher rate of severe PPM in patients receiving a second S-SE platform into a degenerated BE THV (10.5%, $p = 0.04$): a possible explanation for this finding might be the fact that almost all the patients presenting with a severe PPM after the second TAVR actually had a degenerated THV $\leq$ 23 mm. In other words, in the presence of quite small anatomy, even the supra-annular position, which is associated with a larger EOA, might not be enough to resolve the PPM (**Figure 1**).

On the other hand, the finding that the use of a BE THV to treat a degenerated BE THV might imply a higher risk of at least a moderate PPM that might be explained by the double intra-annular position, which is surely related to an avoidable reduction of the orifice (**Figure 1**).

After the first TAVR, 8 patients had a severe PPM: all of them with a degenerated BE THV and 7 out of 8 patients with a $\leq$ 23 mm BE THV (see **Supplementary Tables 1**, **2**). These patients have been treated in all the cases with an S-SE and, after the second TAVR, only in 1 case, there was still a severe PPM (**Table 7**). This might be explained by the significantly larger EOA of an S-SE THV, which seems to be a reasonable choice to treat a degenerated BE THV, in the absence of a significant risk of coronary obstruction/sinus sequestration.

A no PPM after the first TAVR is a negative predictor of a severe PPM, while a severe PPM after the first TAVR is a strong positive predictor. Considering the low number of cases with severe PPM, and the relatively small sample size, the multivariate analysis is of a pure hypothesis-generating nature; however, these results seem realistic.

Finally, consistently with the available literature (3, 12, 13), we found a significantly higher rate of 1-year all-cause mortality and the NYHA class III/IV in patients with severe PPM ($p = 0.02$ and $p = 0.0001$, respectively). Whether this can be completely ascribed to the presence of severe PPM or is influenced by increased frailty, presence of significant comorbidity and reduced functional status as reflected by the presence of significantly higher risk scores (**Table 1**) should be further evaluated.

Clinical implications and avenues for future research

The techniques of bioprosthetic valve fracture/remodeling and BASILICA have been successfully applied to the field of ViV to reduce the risk of residual high gradient and coronary obstruction/sinus sequestration in patients with a degenerated surgical bioprosthesis (14, 15). Their role in the field of TAV-in-TAVR is completely unknown. However, the therapeutic strategy in the case of degeneration of the THV should probably be part of the routine evaluation done by the heart team, in particular when dealing with patients with long-life expectancy. In other words, it is quite realistic that the number of patients with a degenerated TAVR will tend to increase in the future.

Clearly, very fragile or old patients will unlikely experience a structural valve deterioration considering their inherent risk of mortality (4): in these cases, the selection of the most appropriate THV should only respect the criteria of feasibility and safety.

Our data also pointed out the importance of the anatomy and, as a consequence, of the choice of the first THV, at the beginning of the "valve journey": small anatomy is obviously the real challenge for the reintervention, as it poses a high risk of coronary obstruction/flow impairment, as well as of severe PPM.

An S-SE might be associated with better durability (14), thus suggesting that it would be the first choice in patients with longer life expectancy; however, it is obvious that an S-SE with high commissure in small anatomy would be at extreme risk for coronary occlusion in case of a reintervention. On the other hand, a BE in small anatomy may be more prone to degenerate because of a higher chance of significant PPM (16); in this case, the treatment with an S-SE, provided suitable anatomy of the aortic root, seems to be promising.

Overall, a tailored approach at the time of the first TAVR is becoming critically important and the implementation of implantation techniques aiming at the commissure-to-commissure alignment should be pursued in every case in order to minimize the subsequent risk of coronary flow impairment and difficult coronary reaccess. Similarly, the evaluation of the risk of significant PPM, which is more likely with BE THVs, should be evaluated with the risk of PVL that, on the contrary, seems to favor the BE THVs, likewise the risk of pacemaker implantation (17–19).

Limitations

Being an investigator-initiated registry, no central adjudication of events has been performed and echo data have been collected by the participating centers. The relatively low sample size does not allow definite conclusions, indeed the latter should be viewed as hypothesis-generating; however, this is the largest series in the field of TAV-in-TAVR and the present analyzes of the PPM may serve to generate and design future studies.

Conclusion

The rate of moderate and severe PPM after TAV-in-TAVR is lower than that observed after TAVR-ViV, but, as expected, higher than TAVR in native aortic annuli. A severe PPM

is associated with increased 1-year mortality and reduced functional capacity. At the time of the first treatment, a modern approach to TAVR should consider the possible future need for a reintervention and its implications, especially when evaluating patients with long-life expectancy in whom a structural valve deterioration is likely to occur.

Impact on daily practice

- Following the degeneration of a THV, the procedure of TAV-in-TAVR will surely be progressively more frequent.

- After a TAV-in-TAVR, the risk of severe PPM is more frequent with specific first-second THVs combinations and it is significantly more frequent when a severe PPM was present yet after the first TAVR.

- A severe PPM implies a higher rate of both the 1-year mortality and the NYHA class III/IV, thus a careful evaluation should be made at the time of the first procedure, at the beginning of the "valve journey."

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ECs of every participating center have been informed. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MC and EC drafted the manuscript. LT and FB provided expert revision. MC performed the statistical analysis. All authors contributed to the collection of the data and provided critical comments to the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.931207/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 09 August 2022
DOI 10.3389/fcvm.2022.938653

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 07 May 2022
ACCEPTED 18 July 2022
PUBLISHED 09 August 2022

CITATION
Khalid AM and O'Sullivan CJ (2022) Commissural alignment in transcatheter aortic valve replacement: A literature review. *Front. Cardiovasc. Med.* 9:938653. doi: 10.3389/fcvm.2022.938653

Commissural alignment in transcatheter aortic valve replacement: A literature review

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Introduction: Transcatheter aortic valve replacement (TAVR) is a minimally invasive procedure to replace a diseased and faulty aortic valve in patients with severe aortic stenosis. As TAVR gains popularity among lower-risk younger patients with a longer life expectancy; there is a need to investigate the long-term shortcomings and limitations of the procedure for this patient group. One such shortcoming is that commissural alignment of transcatheter heart valves (THV) appears to be random; meaning that the THV neo-commissures can misalign with the native commissures of the aortic valve during deployment or self-expansion.

Objectives: Identify techniques and procedures used to obtain commissural alignment in TAVR. Evaluate the effectiveness of these procedures in terms of the degree of commissural alignment. Analyse the impact of commissural alignment on coronary filling and re-access.

Methods: Two electronic online databases were searched to identify existing literature relevant to the aim and objectives of this review: EBSCOhost and PubMed. After search filters were applied and duplicates removed; a total of 64 articles from both databases were screened against the inclusion/exclusion criteria. This resulted in a total of thirteen articles which met the objectives of this review and thus; were included.

Results: All studies focused on a patient centered approach involving pre-TAVR computed tomography to obtain commissural alignment. Other studies modified this approach and combined techniques. All studies that implemented a technique to reduce commissural misalignment were significantly successful in obtaining commissural alignment when compared to a study in which alignment was random when no technique was implemented. Severe coronary overlapping in commissural aligned heart valves was relatively low compared to severe coronary overlapping when no technique was implemented.

Conclusions: An increase in optimal commissural alignment *via* introduction of an alignment technique may seem attractive; however; the categorization of commissural alignment is arbitrary and does not accurately reflect real life clinical implications. Further research is needed to determine whether a routine procedure to achieve commissural alignment is necessary in low-risk younger patients undergoing TAVR.

KEYWORDS

TAVR, *commissures*, transcatheter and surgical aortic valve replacement, SAVR-surgical aortic valve replacement, alignment, THV, transcatheter heart valve

Introduction

Transcatheter aortic valve replacement (TAVR) is a minimally invasive procedure to replace a diseased and faulty aortic valve in patients with severe aortic stenosis (1). Previously; the standard for treatment of aortic stenosis was surgical (open heart) aortic valve replacement (SAVR); and unfortunately patients deemed as high-risk for surgery had limited options for treatment; such as diuretics; which only served as palliative care (2). TAVR was approved by the US Food and Drug Administration for high-risk surgical patients in 2012; allowing such patients an option for long term treatment. More recently; in 2019 it was approved for low-risk patients (2). In a randomized trial; TAVR was concluded to be superior to SAVR at 1 year in terms of deaths related to stroke or rehospitalization at an occurrence of 8.5% for TAVR and 15.1% for SAVR (3, 4). Other randomized trial studies either showed non-inferiority or superiority of TAVR over SAVR (4). The positive response from these trials combined with the fact that as many as 50% of patients with severe aortic stenosis are low risk for surgery has resulted in TAVR becoming the dominant treatment for aortic stenosis (3, 4). As TAVR becomes more popular for lower-risk younger patients with a longer life expectancy; there is a need to investigate the long-term shortcomings and limitations of the procedure for this patient group (3, 5).

One such shortcoming is that commissural alignment of transcatheter heart valves (THV) appears to be random; meaning that the THV neo-commissures can misalign with the native commissures of the aortic valve during deployment or self-expansion (5, 6). In contrast; bioprosthetic valves used in SAVR can be reliably aligned correctly; commissure-to-commissure with the native valve (7). In TAVR; the misalignment may result in the THV neo-commissures partially or fully overlapping the coronary artery ostia (5, 6). As a result; complications can arise if a younger patient needs a percutaneous coronary intervention or redo-TAVR especially since some of them will present with ischemic heart disease later in life (5, 7). With commissural misalignment there is also an increased risk of a leak during diastole because of the unnatural orientation of the THV; this may add undue stress to the THV leaflets (7). Improving commissural alignment in TAVR could possibly make subsequent coronary access and re-do TAVR easier; improve valve durability and enhance coronary blood flow (5, 7). The challenge lies in the fact that aortic anatomy as well as native orientation of the aortic valve differs in every patient; thus a universal approach would not suffice (5). Little attention has been paid to commissural alignment in clinical practice and no official instructions from THV manufacturers exist to achieve commissural alignment (5). Major randomized trials comparing SAVR and TAVR have not considered this limitation either (5).

Abbreviations: TAVR, Transcatheter Aortic Valve Replacement; SAVR, Surgical Aortic Valve Replacement; SAS, Severe Aortic Stenosis; THV, Transcatheter Heart Valve; SHV, Surgical Heart Valve; LCC/RCC, Left Coronary Cusp/Right Coronary Cusp; CT, Computed Tomography; CMA, Commissural Misalignment; RCA/LCA, Right Coronary Artery/Left Coronary Artery; Percutaneous Coronary Intervention, PCI; CAG, Coronary Angiography.

Aim

The aim of this study is to review published literature on procedures used to obtain commissural alignment in TAVR.

Objectives

1. Identify techniques and procedures used to obtain commissural alignment in TAVR.
2. Evaluate the effectiveness of these procedures in terms of the degree of commissural alignment.
3. Analyse the impact of commissural alignment on coronary filling and re-access.

Methods

Two online databases were searched; including PubMed and EBSCOhost (all databases within EBSCOhost were selected); with a publication date range of 2014 to February 2022. The search terms "Transcatheter Aortic Valve Replacement" [Mesh] and "commissural alignment" were utilized in the search strategy. Search filters were applied to reflect the following: articles published in English available in full text with the subjects as adult humans. One reviewer independently identified articles investigating techniques to achieve commissural alignment in TAVR and screened them against the inclusion/exclusion criteria (see appendix A). A summary of the article selection process is given in Figure 1 according to the PRISMA statement. Reference lists of articles were searched to identify any missed studies and relevant articles were included. The quality of individual studies was assessed using the EBL critical appraisal checklist for quantitative studies and the CASP critical appraisal tool for qualitative studies (see appendix B and C). Each study was approved by its local medical ethics committee.

Results

The data extracted from the articles reviewed are detailed in the summary Table 1 below.

Objective 1: Techniques and procedures used to obtain commissural alignment in TAVR

All studies focused on a patient centered approach to obtain commissural alignment. The most common technique to obtain commissural alignment was a patient-centered approach involving pre-TAVR multidetector or multislice CT to create or calculate a projection of the THV on the native aortic valve which may predict the final valve orientation. This was the core methodology used in nine studies (5–11, 14, 15). A subgroup of these studies modified this technique further and combined the CT imaging with fluoroscopic imaging to identify "markers" on the frame of the THV platforms which could be used to align THV and native commissures (5–8). A few studies modified the approach and used computer simulations using a specialized software (3mensio) to create projections onto CT images in order to minimize coronary artery overlap by predicting the optimal orientation for commissural alignment (6, 7, 14, 15). Another technique used was crimping of the THV on to the delivery catheter suited to the aortic anatomy of the patients based on pre-calculated commissural alignment (6, 13).

Objective 2: The effectiveness of these procedures in terms of the degree of commissural alignment

Many studies used a consistent method of assessing the extent of commissural misalignment (CMA) which involved categorizing the alignment into angle deviations (5–9). The categories were: aligned (angle deviation of $<15^{\circ}$); mild CMA (15° to 30°) moderate CMA (30° to 45°) and severe CMA ($>45^{\circ}$). Within the low to high quality studies that assessed this aspect after implementation of alignment techniques; very few patients had severe CMA after TAVR; ranging from 0% to 3.3% of their respective populations (5, 7, 9). However; the occurrence of mild and moderate CMA was more variable between the studies (5, 7, 9). The occurrence of correct alignment was high and occurred in more than half the population in all three studies assessing this aspect; ranging from 60% to 75.5% of their respective populations (5, 7, 9) Comparatively; the study by Fuchs et al. in which techniques to achieve commissural alignment were not implemented; the distributions of occurrences of the alignment categories were found to be random in TAVR (8).

Objective 3: Impact of commissural alignment on coronary filling and re-access

Five studies addressed the impact of commissural alignment on coronary blood flow and subsequent intervention in the form of coronary angiography or PCI. In these studies; severe overlap of either the RCA or LCA with the THV commissures was classified if a THV commissure and coronary ostium were 0° to 20° apart (6, 8, 10, 12, 13). The results were variable as severe overlapping occurred in a range of 9% to 16% of the patients in their respective populations within the various studies (8, 10, 12–14). This was still relatively low compared to severe coronary overlapping when no technique to align commissures was implemented; as in the case of the study by Fuchs et al. in which 50% of cases had severe coronary overlapping. One study found that severe CMA did not result in significant pressure drop within coronary arteries when compared to aligned THVs (8). The success rates for CAG or PCI post-TAVR were significantly lower in patients deemed as unfavorable for coronary access (10). When commissural alignment was achieved successfully; coronary intervention was possible in all cases (14).

Discussion

All studies that implemented a technique to reduce commissural misalignment were significantly successful in obtaining commissural alignment when compared to

TABLE 1 Summary of articles reviewed.

Author(s); (Year); Location; Title	Study population; Sample size; Selection criteria	Study type; Design	Key findings
Bieliauskas et al. (2021), Denmark Patient-Specific Implantation Technique to Obtain Neo-Commissural Alignment with Self-Expanding Transcatheter Aortic Valves (5).	$n = 60$ -Symptomatic SAS -Mean age 79 Exclusion: Non-transfemoral access; bicuspid aortic valve or renal impairment; balloon expandable THVs.	Non-randomized control trial (quasi-experiment) -3 different THV platforms (Evolut R/PRO; ACURATE neo2 and Portico-−20 patients in each group). -Patients underwent CT twice; 3 months before and after TAVR. -Preprocedural CT was used to determine fluoroscopic projection of RCC/LCC cusp overlap view. - Patient-specific implantation technique was based on THV fluoroscopic 'marker' and patient's CT. - Postprocedural CT used to assess commissural alignment (aligned; mild; moderate; severe).	- Mild CMA (<30°) obtained in 53 patients (88%); of which optimal commissural alignment (<15°) was obtained in 36 patients (60%). - Severe CMA (>45°) obtained in 2 patients. -In patients where the fluoroscopic projection was optimally assessed; the success rate of TAVR with optimal alignment or mild CMA was 98%. - The ACURATE neo2 platform produced mild CMA in all 20 cases. - Mild valvular leak was detected in 22 patients.
Fuchs et al. (8); Denmark and USA Commissural Alignment of Bioprosthetic Aortic Valve and Native Aortic Valve Following Surgical and Transcatheter Aortic Valve Replacement and its Impact on Valvular Function and Coronary Filling (8).	$n = 240$ -Symptomatic SAS -Mean age 80 Exclusion: Bicuspid aortic valve or renal impairment.	Non-randomized control trial (quasi-experiment) -28 patients underwent SAVR; and 212 underwent TAVR. - Commissural orientation was assessed pre- and post-AVR within 3 months; CT scans were analyzed separately. - Commissural alignment was calculated using three angles; measured using CT images; into one mean angle deviation. - Commissural alignment was defined as aligned (angle deviation of <15°); mild CMA (15° to 30°) moderate CMA (30° to 45°) and severe CMA (>45°).	- 27 of 28 (96%) SHVs were implanted as aligned. One SHV was implanted with mild CMA. −47 THVs (22%) were implanted as aligned; 53 THVs (25%) were implanted with mild CMA; 46 (22%) had moderate CMA and 66 (31%) had severe CMA. - Commissural alignment in TAVR was shown to be random. - Severe CMA did not result in significant pressure drop within coronary arteries when compared to aligned THVs (0.9 RCA; 1.7 LCA)
Tang et al. (6); Denmark and USA Alignment of Transcatheter Aortic-Valve Neo-Commissures (ALIGN TAVR) (6).	$n = 828$ (483 SAPIEN 3; 245 Evolut; and 100 ACURATE-neo valves) -Symptomatic SAS -Mean age 80.2	Non-randomized control trial (quasi-experiment) -Pre-TAVR CT imaging was overlapped with fluoroscopic views using 3mensio software to map out the neo-commissural alignment of THVs with native commissures. -Coronary artery overlap was characterized as severe if a THV commissure and coronary ostium were 0° to 20° apart.	-Tracking Evolution Hat marker reduced the coronary artery overlap by 36% to 60% ($p < 0.05$). - More than 30% to 50% of cases had CMA where overlap with one or both coronary arteries were present.

(Continued)

10.3389/fcvm.2022.938653

TABLE 1 Continued

Author(s); (Year); Location; Title	Study population; Sample size; Selection criteria	Study type; Design	Key findings
Redondo et al. (7); Spain Accurate Commissural Alignment during ACURATE neo–TAVI Procedure (7).	$n = 11$ -Symptomatic SAS Inclusion: Patients treated with ACURATE-neo THV.	Non-randomized control trial (quasi-experiment) - Computer simulated "in silico" model was developed to predict final THV commissure orientations based on analysis of pre-TAVR CT images. -Patients underwent TAVR guided by computer simulated model. Commissural alignment analyzed using post-TAVR CT.	- None of the 9 accurate commissural alignment cases reported significant coronary artery overlap (0° to 20° apart was deemed sever overlap) - 7 out of 11 cases were aligned (angle deviation of <15°); 1 case had mild CMA (15° to 30°); and the remaining 2 cases had moderate CMA (30° to 45°); as predicted in computer simulation.
De Marco et al. (9); Italy A Patient-Specific Algorithm to Achieve Commissural Alignment with ACURATE-Neo: The Sextant Technique (9).	n = 45 -Symptomatic SAS -Mean age 81.6 Inclusion: Transfemoral TAVR using the ACURATE-neo2 THV.	Non-randomized control trial (quasi-experiment) -Pre- and post-TAVR CT used to calculate an internal bisector of the angle between coronary arteries +/- 15° error range. -THV was rotationally deployed so that one of the THV commissures aligns with the internal bisector. -Commissural alignment was defined as aligned (angle deviation of <15°); mild CMA (15° to 30°) moderate CMA (30° to 45°) and severe CMA (>45°).	-Coronary clearance was achieved in 98% of patients. -No cases of severe coronary artery overlap. - Commissural alignment was achieved in 34 (75.5%) patients; mild CMA in 9 (20%) patients and moderate CMA in 2 (4.5%) patients. - In 42 (93%) patients; final alignment of THV commissures were consistent with the calculated alignment with a mean difference of 10.5° ± 5.2°.
Ochiai et al. (10); USA Coronary Access After TAVR (10).	n = 428 -Symptomatic SAS −66 treated with Evolut R/PRO −345 treated with SAPIEN 3 Exclusion: Poor quality CT images.	Non-randomized control trial (quasi-experiment) -Distance from inflow of the THV to the coronary ostium was measured. -Overlap between THV commissures and the coronary arteries was assessed using post-TAVR CT. -Coronary access deemed as unfavorable if the coronary ostium was in front of the THV commissures above or below the skirt in either artery.	- Unfavorable coronary access was observed in 34.8% for the left coronary artery and 25.8% for the right coronary artery in the Evolut PRO/R group (40 total) -Unfavorable coronary access was observed in 15.7% for the left coronary artery and 8.1% for the right coronary artery in the SAPIEN 3 group (82 in total). -The success rates for CAG or PCI post-TAVR were significantly lower in patients deemed as unfavorable for coronary access in both groups.
Holzamer et al. (11); Germany Multislice Computed Tomography-based Prediction of The	$n = 244$ -Symptomatic SAS Exclusion: Bicuspid aortic valves and valve-in-valve TAVR.	Non-randomized control trial (quasi-experiment) -The line of perpendicularity and implanter views were calculated using multiple plane reconstructions of the patients' pre-TAVR multislice CT scans.	- In 237 patients (97%); the angiogram was able to confirm the predicted line of perpendicularity and predict the optimal orientation of the THV.

(Continued)

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TABLE 1 Continued

Author(s); (Year); Location; Title	Study population; Sample size; Selection criteria	Study type; Design	Key findings
Implantation Plane In Transcatheter Aortic Valve Implantation: Determination of The Line Of Perpendicularity and the Implanter's Views (11).	Bicuspid aortic valve; TAV-in-TAV; or poor quality CTs.	-The line of perpendicularity was confirmed by aortic angiogram and was used to orientate the THV allowing for corrections in commissural alignment.	- 7 patients (3%) needed subsequent corrections to achieve optimal alignment; largest correction was 14°.
Abdelghani M, et al. (12); Germany Coronary Access After TAVR With a Self-Expanding Bioprosthesis: Insights from Computed Tomography (12).	$n = 101$ -Symptomatic SAS -Mean age 81.5 -Evolut PRO/R Exclusion:	Non-randomized control trial (quasi-experiment) - Post-TAVR multislice CT scans (30 days after) were used to assess interference of THV commissures with coronary access. -Included measuring the longitudinal distance from the THV out flow to inflow to the center of the RCA and LCA ostia and the transverse distance between the THV commissures and the coronary ostium.	- The THV commissures vertically aligned with the coronary ostium were 58% and 63% in the RCA and LCA; respectively. - THV commissures were not aligned with the native commissures in 45 patients (47%) - The commissural posts were overlapping a coronary ostium in 15 patients (16%). - Two patients (2%) had a paravalvular leak due to CMA; caused by the sealing skirt.
Rogers et al. (13); USA Feasibility of Coronary Access and Aortic Valve Reintervention in Low-Risk TAVR Patients (13).	$n = 137$ -Symptomatic SAS -Mean age 73.8 Inclusion: Patients treated with the SAPIEN 3 THV.	Non-randomized control trial (quasi-experiment) - Post-TAVR CT scan (30 days after) scans were used to observe the transverse distance between the THV commissures and the coronary ostium. - In a subgroup; intentional crimping of the THV catheter was tested to pre-determine commissural alignment.	- THV commissures overlapping a coronary ostium was observed in 9% to 13% of patients. - Intentional crimping did not significantly impact commissural alignment; orientation of the commissures away from the coronary ostium was achieved in 75% (15/20 patients) who were treated with intentionally crimped alignment compared to 70.3% (45/64 patients) treated with randomly crimped catheters (p=0.69).
Buono et al. (14); Italy Commissural Alignment with New-generation Self-expanding Transcatheter Heart Valves During Aortic Replacement (14).	$n = 4$ - Symptomatic SAS -Mean age 80.75 -One patient treated with	Retrospective case report series - Pre-TAVR multislice CT angiography used to construct angiographic projections in cusp overlap and coplanar views. - Cardiac and vascular structures were analyzed using 3mensio software.	- Commissural alignment was achieved in all circumstances as coronary artery re-cannulation was easily obtained in all cases.

(Continued)

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TABLE 1 Continued

Author(s); (Year); Location; Title	Study population; Sample size; Selection criteria	Study type; Design	Key findings
	ACURATE-neo 2; Evolut R; Portico and NVT Allegra.		
Redondo et al. (15); Spain Commissural vs. Coronary Optimized Alignment During Transcatheter Aortic Valve Replacement (15)	$n = 100$ -Symptomatic SAS Exclusion: Bicuspid aortic valve and poor quality imaging.	Observational (cross-sectional) study -Pre-TAVR CT used to measure distance from native commissures to the RCA and LCA determining eccentricity. -THV virtually placed using simulation with ideal commissural alignment and the degree of coronary overlap was classified. - Three groups defined for coronary overlap: no risk (>35° from neocommissures to coronary ostia); moderate risk (20°-35°); and severe risk (≥20°).	−32 patients had moderate to severe risk of coronary overlap regardless of ideal commissural alignment. - Greater coronary eccentricity was linked with greater risk of moderate to severe coronary overlap regardless of commissural alignment. - When optimal coronary alignment was simulated; it reduced severe coronary overlap in all cases and reduced moderate coronary overlap by 22%.
Tang et al. (16); USA Conventional vs. Modified Delivery System Technique in Commissural Alignment from the Evolut low-risk CT Substudy (16).	$n = 249$ conventional technique patients n =240 modified technique patients - Symptomatic SAS Inclusion: Patients in the Evolut Low Risk LTI substudy.	Non-randomized control trial (quasi-experiment) - Patients underwent high-quality electrocardiographically synchronized CT scans. - Conventional technique patients had the delivery system inserted into femoral artery with flush port at 12 o'clock orientation. Modified technique patients had a 3 o'clock orientation. - Severe coronary artery overlap was defined as 0° to 20°.	- The modified technique had improved commissural alignment and reduced severe coronary artery overlap. - Outer curve hatmaker rate was 89.6% for the modified technique and 67.5% for the conventional. - Out of the conventional technique cohort; 41.6% had severe coronary overlap with the Evolut valve commissure in 1 or both coronary arteries; compared to a reduced 20.8% coronary overlap in 1 or both coronaries using the modified technique.
Tarantini et al. (17); Italy Coronary Access After Transcatheter Aortic Valve Replacement with Commissural Alignment: The ALIGN-ACCESS Study (17).	$n = 206$ - Symptomatic SAS Inclusion: Patients treated with SAPIEN 3; Evolut R/Pro; or Acurate Neo THVs.	Non-randomized control trial (quasi-experiment) - Coronary angiography was performed after TAVR. - 38% of patients received SAPIEN 3; 31.1% Evolut Pro/R and 30.1% Acurate Neo THVs. - Evolut THVs were implanted with an aim of commissural alignment and Acurate Neo THVs were retrospectively assessed to achieve commissural alignment.	- Commissural alignment was achieved in 85.9% of Evolut and 69.4% of Acurate Neo cases. - Coronary access was higher in SAPIEN 3 than both Evolut and Neo THVs regardless of whether they were aligned or misaligned (95% vs. 71% and 46%; respectively). - Cannulation of at least 1 coronary artery was unfeasible in 0% for SAPIEN; 11% in misaligned supr-annular and 3% aligned supra-annular THVs.

10.3389/fcvm.2022.938653

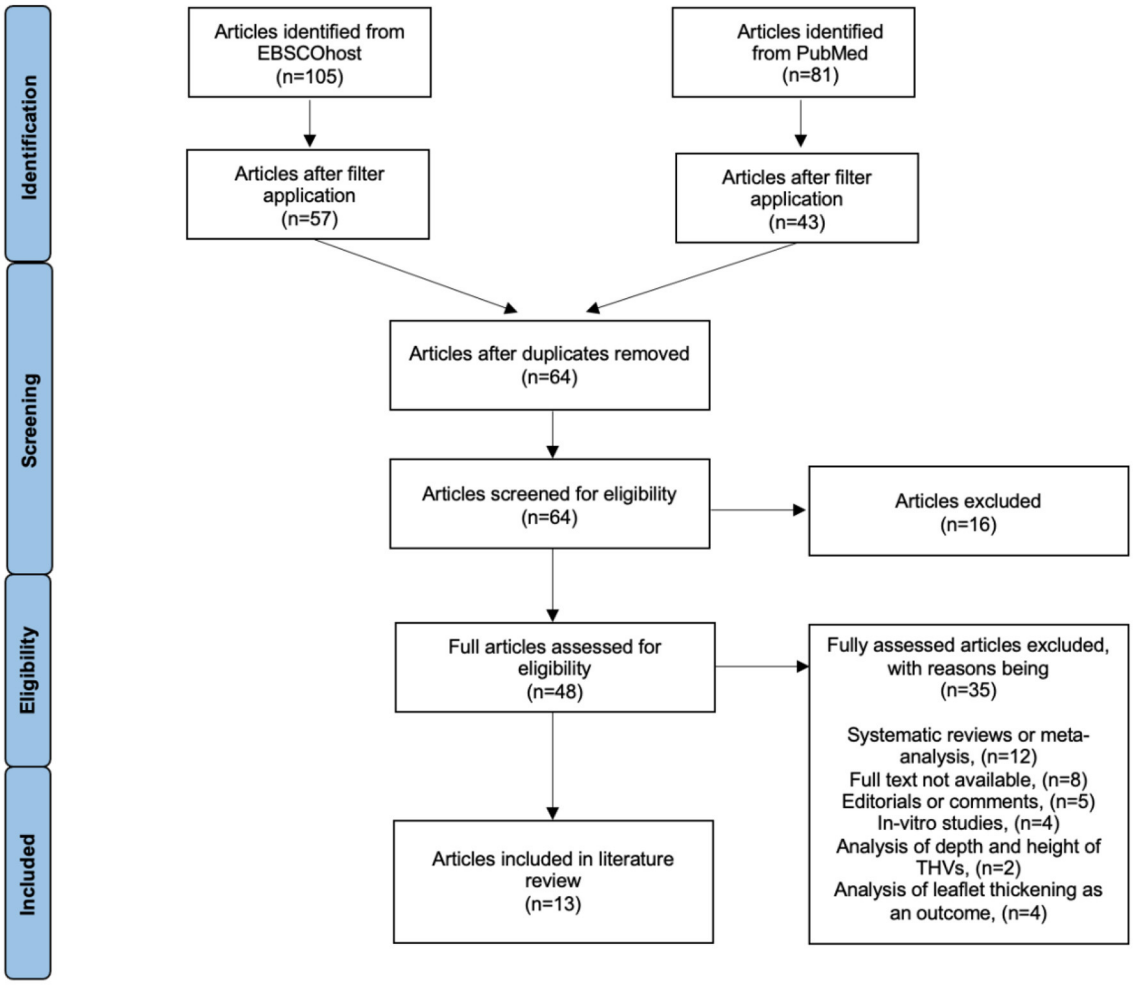

FIGURE 1
PRISMA flow diagram for selection process of relevant articles.

the study by Fuchs et al. in which alignment was random when no technique was implemented. An increase in optimal commissural alignment of 22% (8) to 75.5% (10) via introduction of an alignment technique may seem attractive; however; one major shortcoming of these results was that classification of commissural alignment was artificial and did not reflect the clinical implications of even mild CMA. There was no method to measure differences in clinical implications of CMA in slight adjustments of THV orientation by 1° angle deviation in either direction. Thus; the categorization of commissural alignment was arbitrary and does not accurately reflect real life clinical implications.

Another major shortcoming of the results was that an angle deviation of <15° was considered as commissural alignment; whereas severe coronary artery overlap was defined if a THV commissure and coronary ostium were 0° to 20° apart. This means that if the THV was aligned with the native commissures of the aortic valve at 15°; a slight overlap of even one of the commissures with either coronary artery could be deemed as severe coronary overlap and thus coronary intervention unfeasible. These contradictory classifications between studies open the question for validity and the clinical implications of these studies. Post-TAVR intervention feasibility was hypothetical in most studies and was only carried out in a clinical scenario within a subset of the sample population treated. Thus; the validity and application to real world scenarios on a larger scale is questionable.

Comparisons between commissural alignment achieved in the different THV platforms were drawn in a few studies and the results from Ochiai et al. (10) and Tarantini et al. (17) may indicate that the SAPIEN 3 platform is favorable to commissural alignment and subsequent coronary access as patients receiving this platform had considerably lower percentages of unfavorable coronary access. For example; when compared to the Evolut and

Acurate Neo platforms; coronary access was higher in SAPIEN 3 than both Evolut and Neo THVs regardless of whether they were aligned or misaligned (95% vs. 71% and 46%; respectively). This is however contradictory to the findings of the study by Bieliauskas et al. (5) in which the Acurate Neo platform had the highest rate of achieving mild CMA compared to others. It is too early to determine which platform is best suited for commissural alignment as they require different techniques to achieve commissural alignment and each patient is individual in the selection of the THV platform based on their clinical situation; comorbidities; anatomy of the aortic root and the potential access route (18).

Due to the recency of commissural alignment in TAVR; a clear gap can be identified in the research area; which is that the long-term implications of commissural alignment have not been studied. From the lack of long-term studies; cardiologists around the world are not sure if commissural alignment is if even worth adopting as a routine procedure for low-risk younger patients with aortic stenosis as the long-term benefits or complications are not known. A cohort study design where low risk patients who have undergone TAVR using a commissural alignment technique are observed for a minimum of 10 years is needed to justify the adoption of commissural alignment as a routine procedure.

The limitations of this review include the relative recency of commissural alignment in TAVR as a topic; thus the articles reviewed had very similar study designs and lacked control groups to compare outcomes such as coronary filling and intervention. This also means that the data extracted from the articles was very similar and could easily be interpreted as a continuous study. On the other hand; the relative recency of this topic also creates the strengths of this literature view as since the studies available are limited; a comprehensive review was able to be carried out covering most of the literature available for the topic at hand.

Author contributions

AK is the primary author and CO'S is the project supervisor. Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.938653/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 24 August 2022
DOI 10.3389/fcvm.2022.965440

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 09 June 2022
ACCEPTED 01 August 2022
PUBLISHED 24 August 2022

CITATION
Xiao Y, Bi W, Qiao W, Wang X, Li Y and Ren W (2022) Prognostic value of ventricular longitudinal strain in patients undergoing transcatheter aortic valve replacement: A systematic review and meta-analysis.
Front. Cardiovasc. Med. 9:965440.
doi: 10.3389/fcvm.2022.965440

Prognostic value of ventricular longitudinal strain in patients undergoing transcatheter aortic valve replacement: A systematic review and meta-analysis

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Introduction: Strain obtained by speckle tracking echocardiography (STE) can detect subclinical myocardial impairment due to myocardial fibrosis (MF) and is considered a prognostic marker. Aortic stenosis (AS) is not only a valve disease, but also a cardiomyopathy characterized by MF. The purpose of this study was to systematically review and analyze ventricular strain as a predictor of adverse outcomes in patients with AS undergoing transcatheter aortic valve replacement (TAVR).

Methods: PubMed, Embase, and the Cochrane library were searched for studies that investigated the prognostic value of impaired ventricular strain on patients with AS undergoing TAVR with all-cause mortality (ACM) and major adverse cardiovascular events (MACE). Pooled odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated to assess the role of left (LVLS) and right (RVLS) ventricular longitudinal strain in the prognostic prediction of patients with AS undergoing TAVR. Sensitivity and subgroup analysis was performed to assess heterogeneity.

Results: Twelve studies were retrieved from 571 citations for analysis. In total, 1,489 patients with a mean age of 82 years and follow-up periods varying between 1 year and 8.5 years were included. Meta-analysis showed the impaired LVLS from eight studies was associated with an increased risk for combined ACM and MACE (OR: 1.08, 95% CI: 1–1.16; $p = 0.037$), and ACM alone (HR: 1.08, 95% CI: 1.01–1.16; $p = 0.032$). Impaired RVLS from four studies was associated with an increased risk of combined ACM and MACE (OR: 1.08, 95% CI: 1.02–1.14; $p < 0.01$), and ACM alone (HR: 1.07, 95% CI: 1.02–1.12; $p < 0.01$).

Conclusions: This meta-analysis demonstrated that ventricular strain, including LVLS and RVLS, had a substantial prognostic value in ACM or combined ACM and MACE, which could be used as a valid marker for risk stratification in patients with AS undergoing TAVR.

KEYWORDS

strain, echocardiography, aortic stenosis, transcatheter aortic valve replacement, meta-analysis

Introduction

Aortic stenosis (AS) is the most common valvular heart disease and is characterized by progressive calcification of the aortic valve, obstructing the left ventricular outflow tract, leading to heart failure and even death (1). Heart failure develops from myocardial cell hypertrophy leading to atrophy, myocardial fibrosis (MF), and death (2). Therefore, AS is also considered cardiomyopathy characterized by MF resulting from chronic pressure overload of the left ventricle (3, 4). Aortic valve (AV) replacement to treat AS can be accomplished using surgical and transcatheter approaches. Transcatheter aortic valve replacement (TAVR) has developed as a breakthrough therapeutic advance in the treatment of symptomatic patients with severe AS, especially elderly and vulnerable patients. Recent evidence suggests that TAVR is also a safe option for patients of low to intermediate risk (5, 6). Therapeutic decisions are based on the pre-procedural evaluation, but pre-procedural risk assessment is challenging and data regarding parameters predicting clinical outcomes are limited.

Echocardiography is the primary modality for diagnosis of AS, allowing for evaluation of AV status, including morphology, area, and transvalvular velocities or gradients, which can also be used for assessment of ventricular morphology and function. Measurement of left ventricular (LV) systolic function with LV ejection fraction (EF) has been linked to worse outcomes in patients undergoing TAVR. Speckle-tracking echocardiography (STE) has emerged as a sensitive technique to detect subclinical myocardial impairment due to MF (7, 8). Strain derived from STE is a novel parameter to assess segmental myocardial deformation, which is more sensitive than LVEF in evaluating ventricular dysfunction caused by MF (9) and provides incremental prognostic information in severe patients with AS (10). The LV longitudinal strain (LVLS) assessment provides independent prognostic value and is recommended for inclusion in TAVR risk stratification models (11). The right ventricular longitudinal strain (RVLS) has also been considered a feasible parameter for assessing right ventricular (RV) systolic function and is associated with all-cause mortality (12). However, there is only limited data on the prognostic value of LVLS and RVLS in patients with AS undergoing TAVR and some of the results are conflicting. The purpose of this study was to systematically review and analyze LVLS and RVLS as a predictor of adverse outcomes in patients with AS undergoing TAVR.

Methods

Screening of publications

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and protocols. Using the electronic databases of PubMed, Embase, and the Cochrane library, publications on patients with AS having taken STE examination undergoing TAVR were searched from the earliest available date of indexing up to March 31, 2022. A search strategy was used based on combined terms: (1) "transcatheter aortic valve replacement" or "TAVR" or "transcatheter aortic valve implantation" or "TAVI" and (2) "speckle tracking" or "strain" or "STE" and (3) "echocardiography", or "echocardiogram" and (4) "ventricular" or "ventricle." Ethics committee approval was not necessary because all data was extracted from existing literature.

Data extraction and quality assessment

According to the above protocol, duplicate records and studies that did not provide information of interest were excluded. The parameter LVLS or RVLS was evaluated by STE in patients with AS undergoing TAVI, with sufficient data to retrieve odds ratio (OR), hazard ratio (HR), and corresponding 95% confidence intervals (CIs). The primary endpoint was all-cause mortality (ACM). The secondary endpoint was major adverse cardiovascular events (MACE) comprising cardiovascular death and any cardiovascular events, including hospital admission for heart failure, acute myocardial infarction, or stroke. Data on demographic variables and echocardiographic parameters were also extracted from each study. Demographic variables included sample size, mean age, gender, body weight index (BMI), history of hypertension, diabetes mellitus (DM), dyslipidemia, coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD), mean STS score, NYHA functional class, risk profile, the mean or median time of follow-up, and hospitalization rate and event rate. Echocardiographic parameters included mean AV area, mean AV pressure gradient, AV velocities, LVEF, and LVLS or RVLS. Two researchers independently reviewed selected articles and when there was disagreement between authors, consensus on final inclusion was reached through a third researcher.

The quality of included studies was assessed using the Newcastle–Ottawa quality assessment scale (NOS) in three broad categories. The scores were displayed on a nine-point scale with poor quality (0–2 points), medium quality (3–5 points), and high quality (6–9 points).

Data synthesis and statistical analysis

The OR and HR with 95% CIs were extracted for meta-analysis. If the studies did not report HRs directly, Kaplan–Meier curves were read using Engauge Digitizer version 4.1.

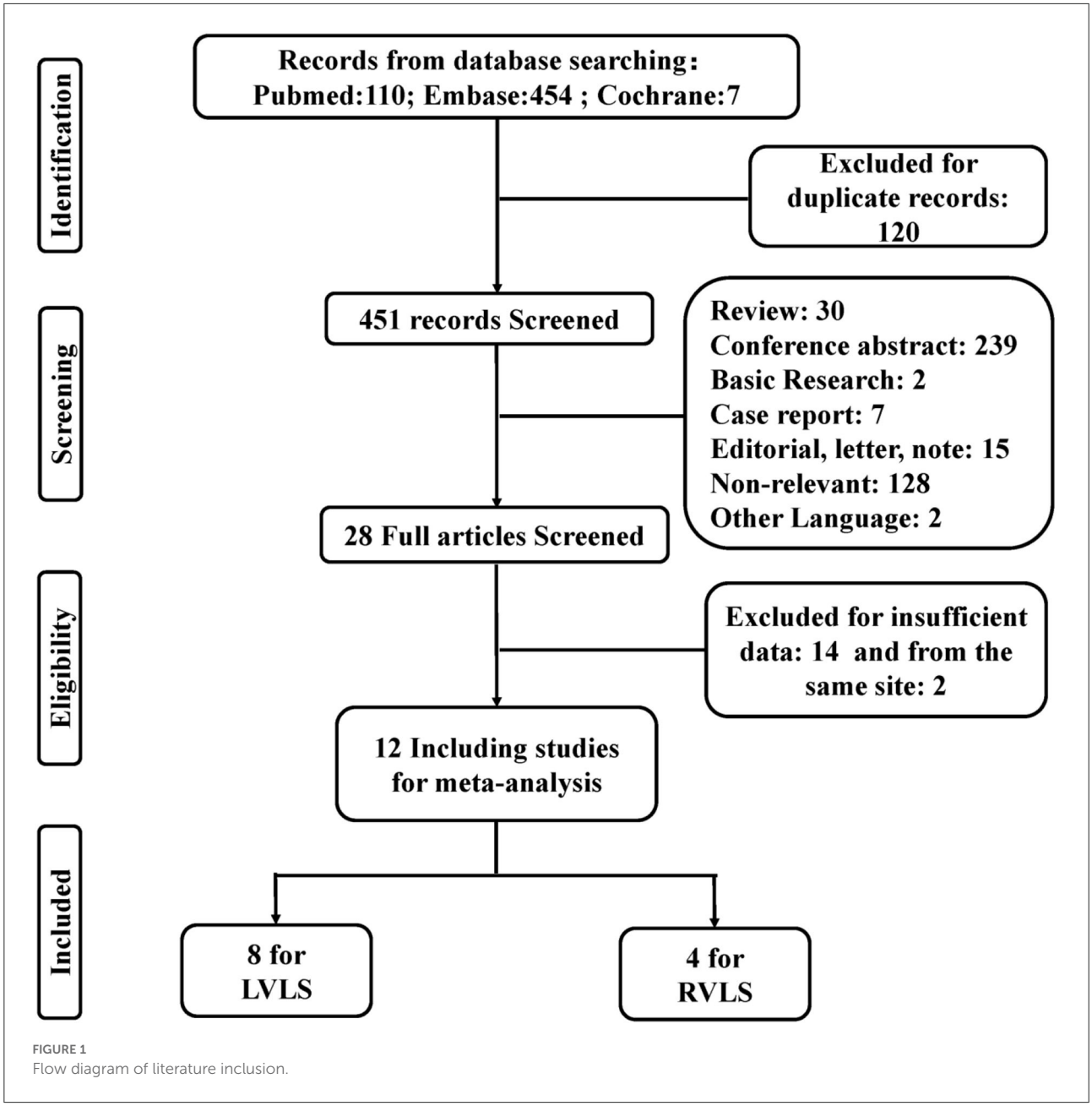

FIGURE 1
Flow diagram of literature inclusion.

The pooled effect was evaluated using Z scores. Heterogeneity among studies was assessed using Chi-square Cochran's Q test to measure the inconsistency. The I^2 statistic was used to describe the proportion of total variation in studies due to heterogeneity. An I^2 statistic of <25% indicated low heterogeneity, while over 50% indicated a high heterogeneity. Statistical analyses were performed using STATA V.15.1 (Stata Corp LP), with $p < 0.05$ considered statistically significant. Publication bias was assessed by the Egger's test for included studies. Sensitivity analyses were performed by one-to-one exclusion studies to estimate the stability of pooled results.

Results

Literature search and study selection

A total of 571 records were found from the electronic databases using the search strategy, with 120 duplicate records excluded. Articles without data of interest providing useful data were excluded, including 239 conference abstracts, 30 reviews, two basic research studies, seven case reports, 15 editorials, notes and surveys, 128 non-relevant records, and two non-English language studies. The remaining 28 studies

were further evaluated based on full-text articles. Another 14 articles were excluded due to insufficient data and two articles were eliminated because of overlapping data from the same site (13, 14). The remaining 12 studies were included in the meta-analysis to calculate pooled OR or HR, two of which were read using Engauge Digitizer (11, 15). Of these, eight were used for LVLS analysis and four for RVLS analysis. The study selection procedure is shown in Figure 1.

Study characteristics and quality assessment

A total of 12 studies involving 1,489 patients were included for final analysis, of which two were prospective and 10 were retrospective. The size of the patient population varied significantly between 88 and 499 individuals, of which 44.4% were male and the mean age was 82 years old. Eighty-two percent of patients had hypertension, 31% had diabetes mellitus, 76% had dyslipidemia, 56% had CAD, 18% with COPD, 69% NYHA functional class III/IV, and the mean STS score was seven. Most patients were at high-risk for operation. These studies were published between 2017 and 2022. The characteristics of the studies and the participants are summarized in Table 1. All the included studies were high quality using NOS, with six studies receiving eight points and six studies receiving seven points, as presented in Table 1.

Echocardiographic parameters of the included studies presented with a mean AV area of.64 cm^2 and a mean pressure gradient ranging from 41 to 57 mm Hg. The average LVEF was 57%. The mean pre-TAVR LVLS was −14% and RVLS was −21%. Nine studies reported the ACM and three studies reported MACE on LVLS, as well as three studies reported the ACM, and one study reported MACE on RVLS. The follow-up duration was reported to varying between 1 year and 8.5 years, and the event rate ranged from 10 to 82%. The echocardiographic parameters and prognostic information of the participants are summarized in Table 2.

Overall analysis

Eight studies were eligible for the analysis of the combined endpoint of ACM and MACE. The pooled estimates showed an increased risk of combined ACM and MACE in all included patients with impaired LVLS (OR: 1.08, 95% CI: 1–1.16) with statistically significant heterogeneity ($I^2 = 67.\%$, $p = 0.037$) as seen in Figure 2.

Four studies were included for RVLS analysis. The pooled estimates also showed an increased risk of combined ACM and MACE in patients with impaired RVLS (OR: 1.08, 95% CI: 1.02–1.14) with statistical heterogeneity ($I^2 = 71.0\%$, $p < 0.01$) as seen in Figure 3.

TABLE 1 Characteristics of included studies.

Study	Country	Year	Design	Size	Male	Mean age (years)	Mean BMI (kg/m^2)	Hypertension	Diabetes mellitus	Dyslipidemia	CAD	COPD	NYHA functional class III/IV	Mean STS score	Risk profile	NOS*
Wani et al. (16)	USA	2022	Retrospective	204	46.0%	85	NR	71.6%	32.8%	NR	69.1%	36.3%	80.0%	6.9	High	7
Shimoni et al. (17)	Israel	2021	Prospectively	88	44.3%	81	28.6	94.0%	43.0%	91.0%	60.0%	NR	15.0%	NR	NR	8
Ferreira et al. (18)	Portugal	2021	Retrospective	89	43.8%	82.1	27.1	86.5%	28.1%	64.0%	51.7%	NR	71.9%	5.5	NR	7
Omran et al. (19)	Germany	2021	Retrospective	229	38.0%	83.8	NR	78.6%	21.0%	NR	54.1%	15.7%	84.3%	5.6	High	8
Koschutnik et al. (20)	Austria	2021	Prospectively	204	49.0%	80.9	26.9	90.0%	28.0%	69.0%	53.0%	11.0%	65.0%	3.8	NR	7
Vizzardi et al. (21)	Italy	2020	Retrospective	56	42.9%	81.6	26.6	69.6%	28.6%	NR	50.0%	21.4%	75.0%	NR	High	8
Medvedofsky et al. (12)	USA	2020	Retrospective	334	41.0%	83	27	94.0%	33.0%	79.0%	58.0%	11.0%	88.0%	9.2	High	7
Dahl Pedersen et al. (22)	Denmark	2020	Retrospective	499	47.0%	79.8	NR	75.0%	21.0%	NR	29.0%	14.0%	65.0%	NR	NR	8
Fukui et al. (11)	USA	2020	Retrospective	331	49.0%	83	NR	NR	NR	NR	NR	NR	NR	8.4	High	8
Suzuki-Eguchi et al. (23)	Japan	2018	Retrospective	128	16.0%	83.7	NR	72.7%	27.3%	NR	34.4%	NR	NR	NR	NR	7
Sato et al. (28)	USA	2017	Retrospective	209	58.0%	81	NR	84.0%	41.0%	78.0%	84.0%	NR	94.0%	9.6	High (69%)	8
Kobayashi et al. (15)	USA	2017	Prospectively	128	58.0%	83.4	27.1	84.0%	32.0%	72.0%	75.0%	NR	56.0%	7.8	High	7

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; NYHA, New York Heart Association; NOS, Newcastle-Ottawa Scale; NR, Not reported.
*The median/mean follow-up time ≥24 months were scored.

TABLE 2 Echocardiographic parameters and prognostic information of included studies.

Study	Mean AV area (cm^2)	Mean AV pressure gradient (mmHg)	AVmax (m/s)	$LVEF_{pre}$	$LVEF_{pos}$	LV/RV LS_{pre}	LV/RV LS_{pos}	Cut-off of LS	HR/OR (95%CI)	Index	Ventricular	Outcome	Event rate	Hospitalization rate (%)	Mean or median of follow-up	Equipment or platform
Wani et al. (16)	0.77	41.8	NR	55	57	13.9±4.3	14.8±4.3	NA	0.97 (0.91–1.03)	OR	LV	MACE	35%	30	1 year	GE Vivid E9, E95
Shimoni et al. (17)	0.71	45.9	NR	53.7	53.7	17±5	18.4±4.9	NA	1.130 (1.008–1.127)	HR	LV	ACM	20%	42	1,150 days	GE Echo PAC 202
Ferreira et al. (18)	0.6	57	NR	56.7	NR	13.0±3.8	NR	NA	1.00 (0.88–1.14)	HR	LV	ACM	18%	NR	13.4 months	GE Vivid 9, Vivid E95
								14.8	2.08 (0.59–7.31)							
Omran et al. (19)	0.72	47	NR	51.4	NR	20.0±7.6	19.8±7.8	NA	1.05 (1.01–1.10)	HR	RV	ACM	17%	NR	929 days	NR
Koschutnik et al. (20)	NR	NR	NR	57	NR	22.8±6.9	NR	NA	1.44 (1.03–2.01)	OR	RV	MACE	28%	5	13.7 months	GE Vivid E9,Vivid 7
								20	1.74 (0.91–3.32)							
Vizzardi et al. (21)	NR	51	NR	51	NR	17.6±4.8	NR	NA	1.14 (1.072–1.213)	HR	RV	ACM	82%	NR	8.5 years	GE, Philips, Siemens
Medvedofsky et al. (12)	0.44	49	NR	53	NR	24.6±6.3	26.9±5.8	NA	1.04 (1.01–1.07)	HR	RV	ACM	24%	NR	1 year	Philips iE33; EPIQ 7C
Dahl Pedersen et al. (22)	0.68	41	NR	50.9	NR	12.9±4	NR	12.9	1.52 (0.96–2.40)	HR	LV	ACM	15%	NR	743 days	GE Vivid E 90
Fukui et al. (11)	NR	NR	NR	62.2	NR	18.2±4.1	NR	16	1.36 (0.93–1.99)	HR	LV	ACM	37%	NR	31 months	GE Vivid E95,
Suzuki- et al. (23)	0.65	50	4.5	62	64	15±4.4	16±4.3	NA	1.23 (1.05–1.45)	OR	LV	MACE	10%	NR	591 days	NR
Sato et al. (28)	NR	47	4.37	50	53	12.0±3.7	13.0±3.6	NA	1.05 (1.002–1.11)	HR	LV	ACM	56%	NR	1,345 days	Xcelera, Philips
Kobayashi et al. (15)	0.63	49.6	NR	54	NR	13.0 ± 3.3	NR	15	1.35 (0.24–7.49)	HR	LV	ACM	19%	NR	376 days	GE Vivid E9, E95

AV, aortic valve; LVEF, left ventricular ejection fraction; LS, longitudinal strain; HR, hazard ratio; OR, odds ratio; LV, left ventricular; RV, right ventricular; ACM, all-cause mortality; MACE, major adverse cardiovascular events; NR, Not reported; NA, not applicable.

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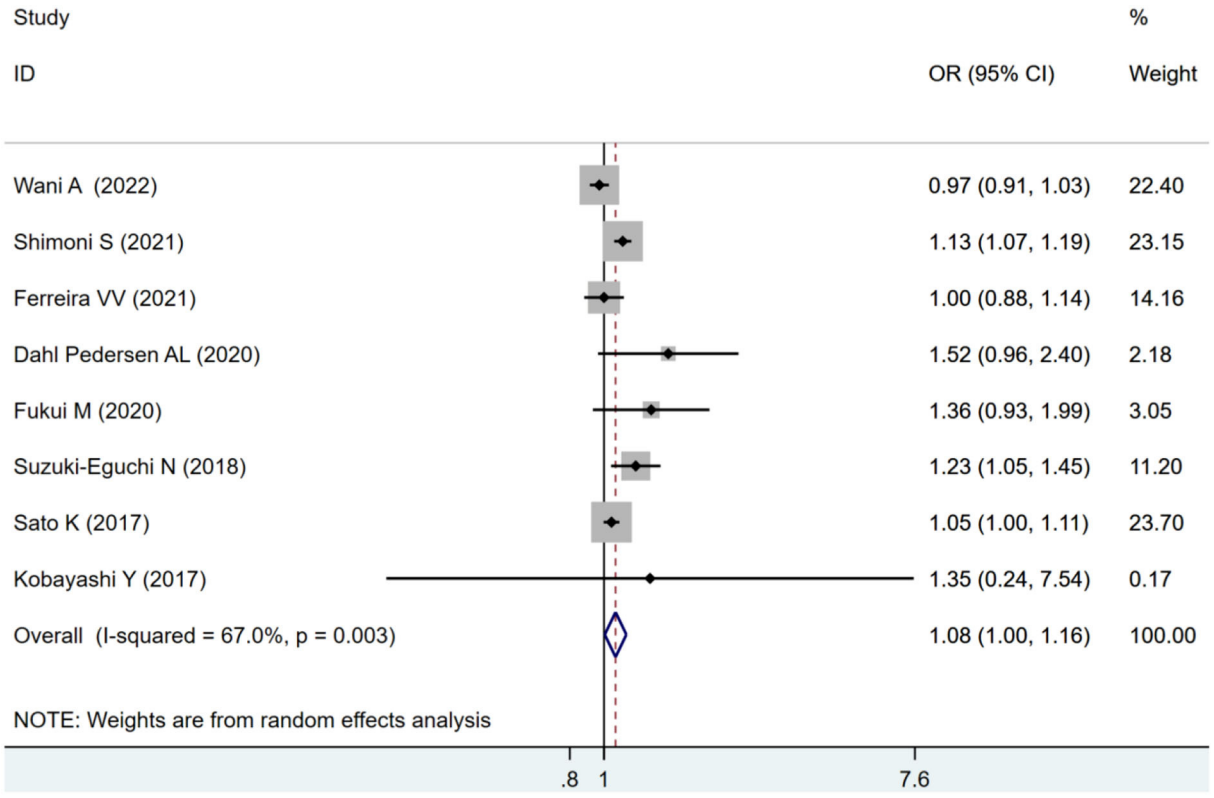

FIGURE 2
Forest plot demonstrating the association between LVLS and combined ACM and MACE in Patients with AS undergoing TAVR.

Subgroup analysis

To assess the possible effect of factors on heterogeneity across studies, a subgroup analysis was performed. According to the adverse outcome of ACM or MACE, the included studies were divided into subgroups and analyzed separately. For ACM subgroup analysis, four studies using LVLS as a continuous variable showed that impaired pooled LVLS significantly increased the risk of ACM (HR: 1.08, 95% CI: 1.01–1.16; $I^2 = 58.2\%$, $p = 0.032$) without evident heterogeneity in Figure 4A. Three studies using LVLS as a binary variable with previously reported cut-offs found that LVLS did not significantly increase the risk of ACM (HR: 1.41, 95% CI: 0.99–2.01; $I^2 = 0.0\%$, $p = 0.06$), with no statistical heterogeneity as seen in Figure 4B.

Two studies were eligible for analyzing the secondary endpoint of MACE, showing no significant increase in MACE risk (OR: 1.08, 95% CI: 0.86–1.36; $I^2 = 86.2\%$, $p = 0.52$) with statistically significant heterogeneity in Figure 4C.

As suggested by Fukui et al. (11), 55% was used as the cut-off value for LVEF analysis, impaired LVLS significantly increased the risk of combined ACM and MACE (OR: 1.10, 95% CI: 1.02–1.18; $I^2 = 47.6\%$, $p = 0.011$) without statistically significant heterogeneity in the LVEF of <55% group as in Figure 5A, but there was no significant increase in the risk of combined ACM and MACE (OR: 1.07, 95% CI:0.94–1.22; $I^2 = 69.1\%$, $p = 0.303$) with statistical heterogeneity in the group with LVEF exceeding 55% in Figure 5B.

Three studies were included for ACM-alone analysis, where impaired RVLS significantly increased the risk of ACM (HR: 1.07, 95% CI: 1.02–1.12; $I^2 = 71.6\%$, $p < 0.01$) with significant heterogeneity as seen in Figure 6.

Publication bias and sensitivity analyses

There was a non-significant publication bias for LVLS (p for Egger's test = 0.335) and RVLS (p for Egger's test = 0.135) in association with combined ACM and MACE in Supplementary Figure S1. A sensitivity analysis was performed to explore the stability of the results. Nonindividual exclusion of studies altered the pooled strain, which supported the robustness of these results in Supplementary Figure S2.

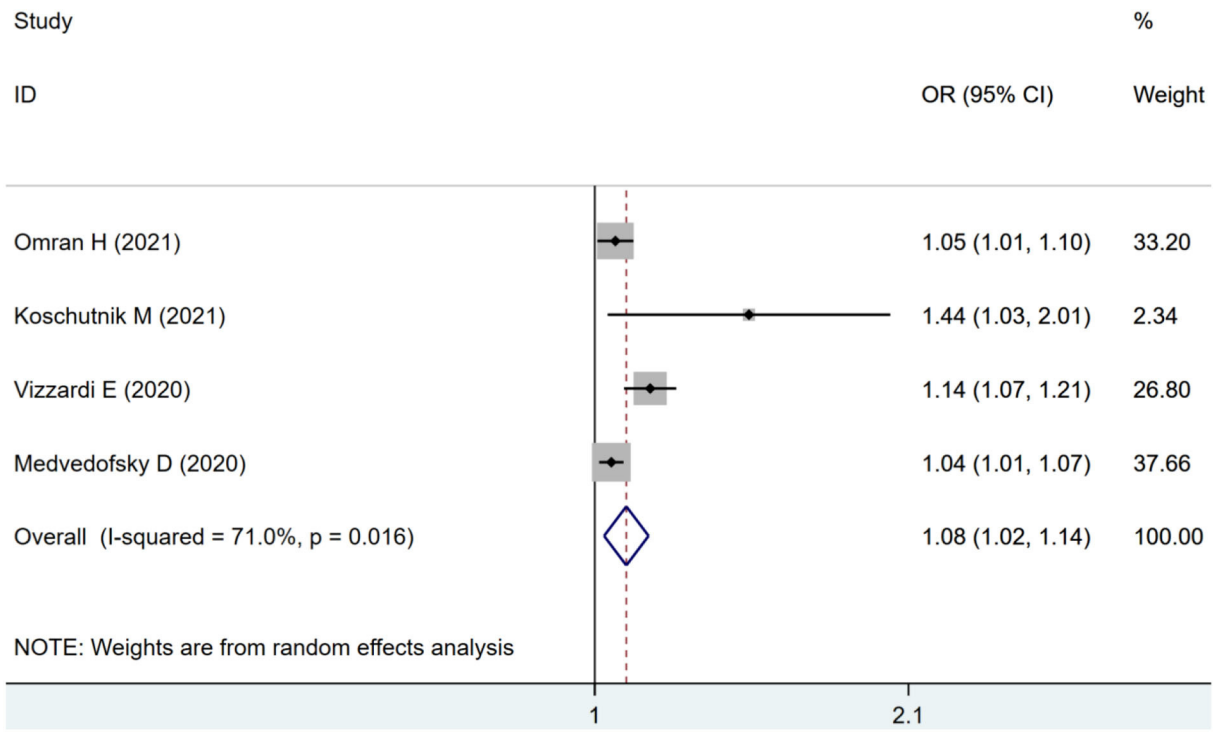

FIGURE 3
Forest plot demonstrating the association between RVLS and combined ACM and MACE in patients with AS undergoing TAVR.

Discussion

The procedure of TAVR has gained popularity with severe symptomatic AS and has been further developed and trialed in intermediate and low-risk patients (24). As the use of TAVR is extended to younger, lower-risk patients, various overriding issues arise and comprehensively precise assessment becomes the basis for determining successful outcomes for intervention (25). Echocardiography is a simple but useful tool for managing the entire TAVR process, including perioperative assessment of annulus measurements, cardiac function and concomitant valve disease, intraoperative guidance, postoperative assessment of prosthesis function, location, hemodynamic change, and cardiac function recovery (26). The LVEF measured by echocardiography has been considered a main prognostic marker, but it has limitations as it represents the global change in LV volume and cannot reflect subtle myocardial changes.

The LV systolic dysfunction in patients with AS may be due to reversibly increased afterload from the stenotic valve and irreversible intrinsic myopathy. The LV dysfunction detected by strain in patients with AS has been associated with fibrosis, suggesting myocardial impairment from increased afterload. Impaired LVLS has been reported to exacerbate adverse cardiovascular outcomes in patients with asymptomatic AS (27). After TAVR, LVLS improvement was dependent on the degree of fibrosis, LVLS in patients with severe AS might independently predict mortality or an adverse event. But the current results were controversial. Some studies revealed a significant prognostic value of LVLS (17, 28) and concluded baseline LVLS was associated with poor survival (11, 23), but others also found it not associated with a survival benefit (15, 16, 18, 22). This meta-analysis found that the impaired pooled LVLS was associated with an increased risk for combined ACM and MACE. Subgroup analysis found ACM alone was the major factor, but only for LVLS used as the continuous variable, while the pooled result was not significant when different cut-off values, including −14.81% (18), 16% (11), 12.9% (22), and 15% (15), were used. When subgroup analyses were performed based on LVEF using 55% as the cut-off value, the pooled result showed that the impaired LVLS was associated with combined ACM and MACE in the LVEF below 55% group, but not when LVEF exceeds 55%. The pooled results suggested that baseline LVLS provided an independent prognostic value for adverse outcomes, especially for ACM and patients with reduced LVEF, which could be incorporated in TAVR risk stratification models.

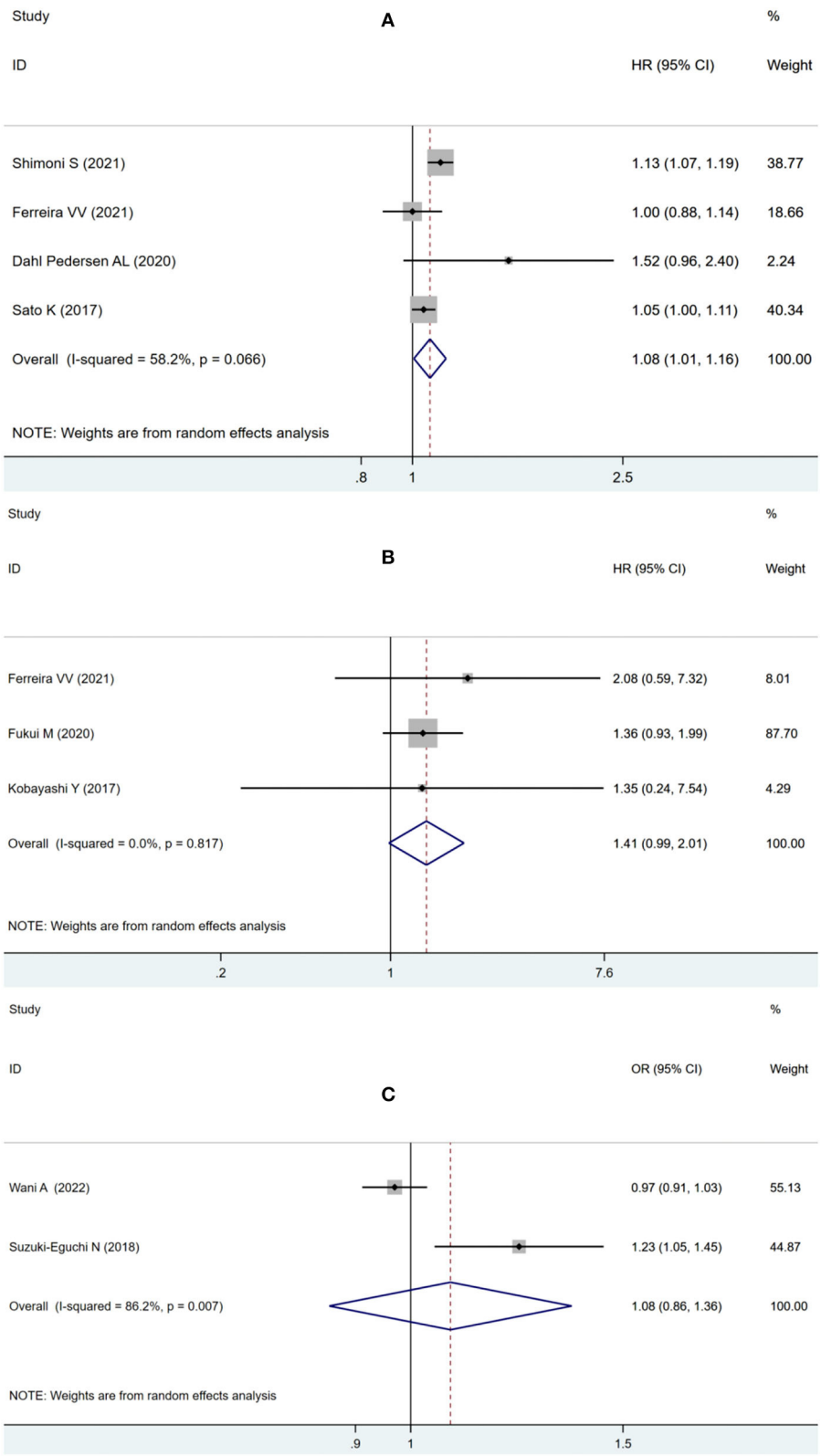

FIGURE 4
Forest plot demonstrating the association between LVLS as continuous variable **(A)** or binary variable with previously reported cut-offs **(B)** and ACM in patients with AS undergoing TAVR; Forest plot demonstrating the association between LVLS and MACE in patients with AS undergoing TAVR **(C)**.

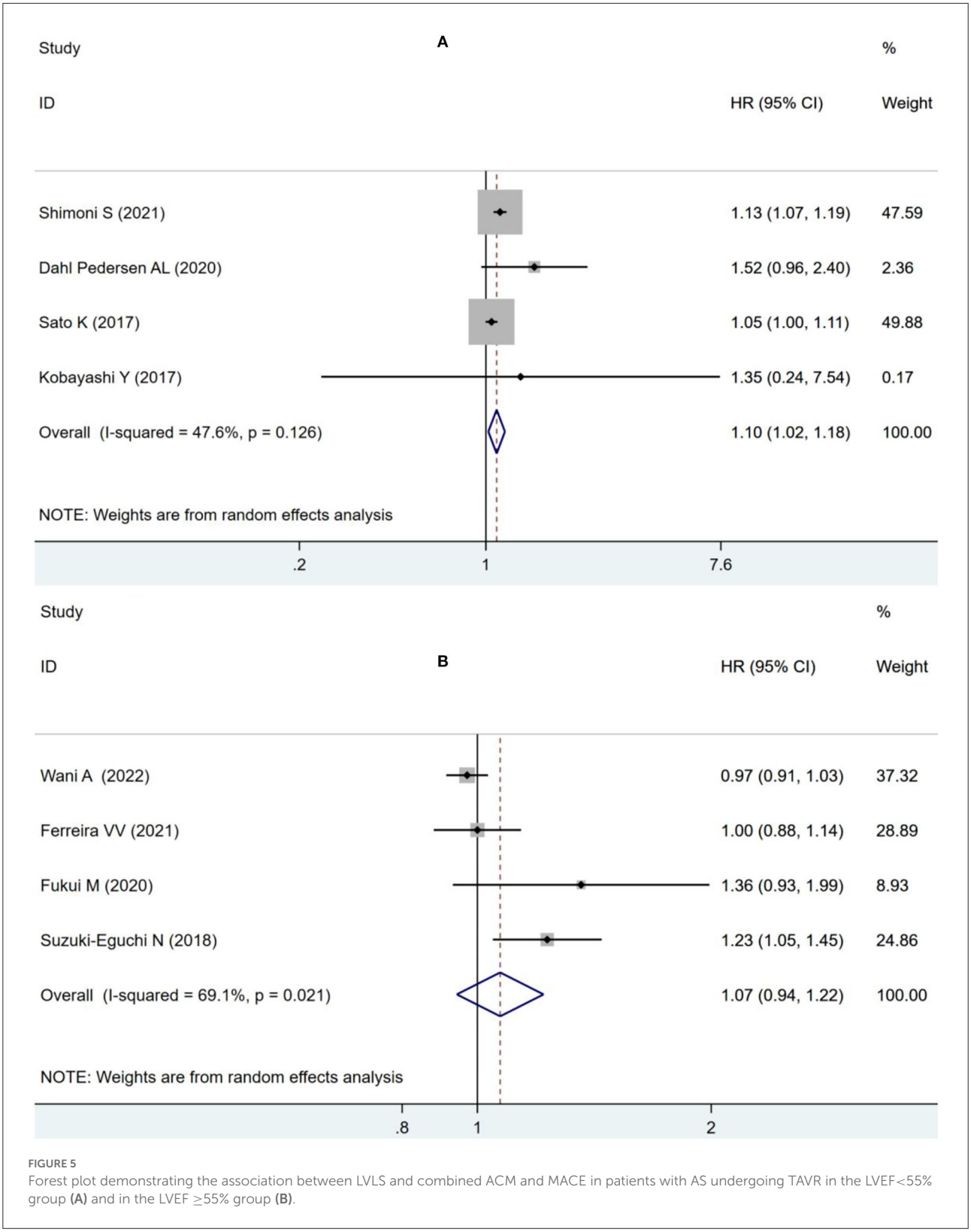

FIGURE 5
Forest plot demonstrating the association between LVLS and combined ACM and MACE in patients with AS undergoing TAVR in the LVEF<55% group **(A)** and in the LVEF ≥55% group **(B)**.

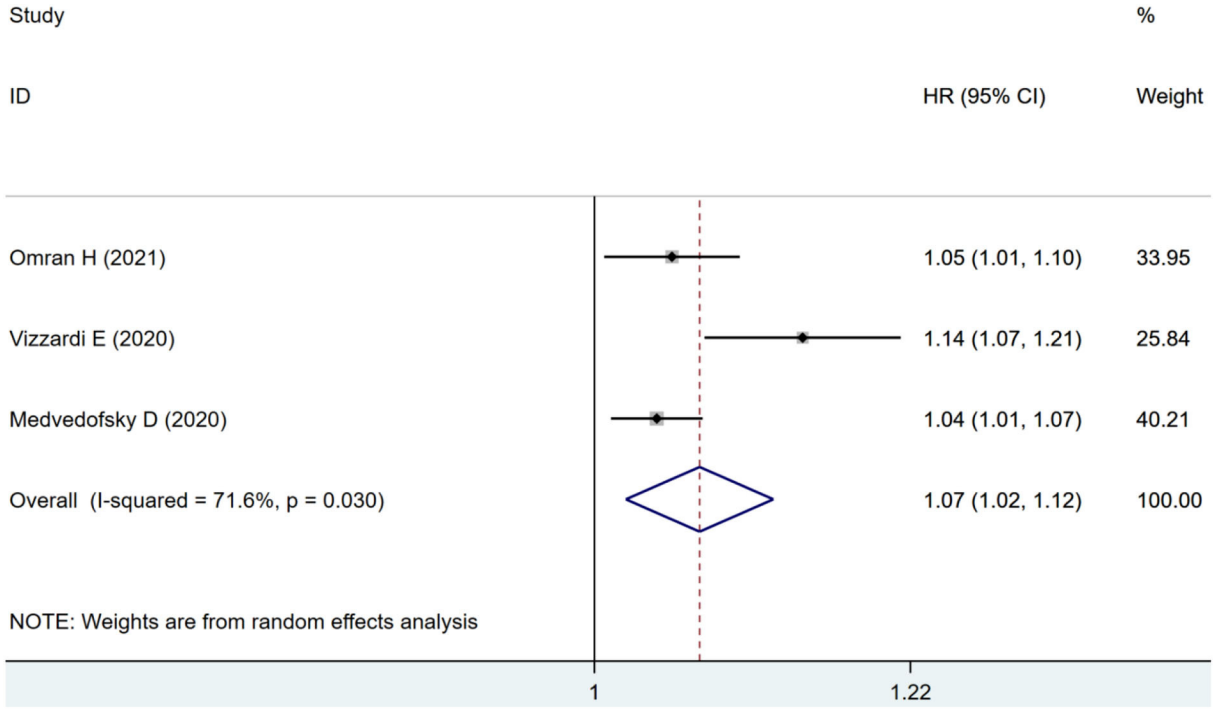

FIGURE 6
Forest plot demonstrating the association between RVLS and ACM alone in patients with AS undergoing TAVR.

There is increasing evidence for the impact of RV dysfunction on mortality after TAVR. The RVLS is also a sensitive marker for detecting subclinical RV dysfunction. Conflicting results have been reported with respect to RVLS association with mortality after TAVR. Omran et al. (19) reported that pre-procedural RVLS significantly predicted long-term all-cause mortality in patients undergoing TAVR; Medvedofsky et al. (12) and Vizzardi et al. (21) also reported a significant association with mortality after TAVR. However, Koschutnik et al. (20) reported no echocardiographic measure, including RVLS was significantly associated with outcome. The results of this meta-analysis were consistent with most results, confirming the better performance of STE in RVLS analysis and its prognostic value in patients undergoing TAVR.

The current study does have some limitations. First, heterogeneity among the studies was observed. The origin of heterogeneity may be due to population characteristics, especially for follow-up time. Given the limited data, meta-regression was not performed. Second, some studies did not provide data directly, but it was obtained from Kaplan-Meier curves, which may increase heterogeneity. Finally, for LVLS analysis, some studies provide the parameter as a continuous variable, and some studies provide binary variables with diverse cutoff values. Well-designed and larger-scale prospective studies are needed to identify LVLS for early recognition of risk stratification in patients with AS undergoing TAVR.

Conclusion

This meta-analysis demonstrated that ventricular strain including LVLS and RVLS exhibited a substantial prognostic value in ACM or combined ACM and MACE, which could be used as a valid marker for risk stratification in patients with AS undergoing TAVR.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YX and WR came up with the idea and supported the work. YX and WB wrote the manuscript. YX and WQ independently screened eligible studies and evaluated the quality of studies. YX and XW independently extracted the baseline and outcome data. The disagreement was resolved by YL and WR. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.965440/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 06 September 2022
DOI 10.3389/fcvm.2022.910693

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 01 April 2022
ACCEPTED 08 August 2022
PUBLISHED 06 September 2022

CITATION
Pagnoni M, Meier D, Luca A, Fournier S, Aminfar F, Gentil P, Haddad C, Domenichini G, Le Bloa M, Herrera-Siklody C, Cook S, Goy J-J, Roguelov C, Girod G, Rubimbura V, Dupré M, Eeckhout E, Pruvot E, Muller O and Pascale P (2022) Yield of the electrophysiological study in patients with new-onset left bundle branch block after transcathether aortic valve replacement: The PR interval matters.
Front. Cardiovasc. Med. 9:910693.
doi: 10.3389/fcvm.2022.910693

Yield of the electrophysiological study in patients with new-onset left bundle branch block after transcathether aortic valve replacement: The PR interval matters

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Background: Studies suggest that performing an electrophysiological study (EPS) may be useful to identify patients with new-onset left bundle branch block (LBBB) post-TAVR at risk of atrioventricular block. However, tools to optimize the yield of such strategy are needed. We therefore aimed to investigate whether 12-lead ECG changes post-TAVR may help identify patients with abnormal EPS findings.

Materials and methods: Consecutive patients with new-onset LBBB post-TAVR who underwent EPS were included. PR and QRS intervals were measured on 12-lead ECG pre-TAVR and during EPS. Abnormal EPS was defined as an HV interval > 55 ms.

Results: Among 61 patients, 28 (46%) had an HV interval > 55 ms after TAVR. Post-TAVR PR interval and ΔPR (PR-post−pre-TAVR) were significantly longer in patients with prolonged HV (PR: 188 ± 38 vs. 228 ± 34 ms, $p < 0.001$, ΔPR: 10 ± 30 vs. 34 ± 23 ms, $p = 0.001$), while no difference was found in QRS duration. PR and ΔPR intervals both effectively discriminated patients with HV > 55 ms (AUC = 0.804 and 0.769, respectively; $p < 0.001$).

A PR > 200 ms identified patients with abnormal EPS results with a sensitivity of 89% and a negative predictive value (NPV) of 88%. ΔPR ≥ 20 ms alone provided a somewhat lower sensitivity (64%) but combining both criteria (i.e.,

10.3389/fcvm.2022.910693

PR > 200 ms *or* ΔPR ≥ 20 ms) identified almost every patients with abnormal HV (sensitivity = 96%, NPV = 95%). Selecting EPS candidate based on both criteria would avoid 1/3 of exams.

Conclusion: PR interval assessment may be useful to select patients with new-onset LBBB after TAVR who may benefit most from an EPS. In patients with PR ≤ 200 ms *and* ΔPR < 20 ms the likelihood of abnormal EPS is very low independently of QRS changes.

KEYWORDS

electrophysiological study (EPS), trans-catheter aortic valve replacement (TAVR), atrioventricular block (AV block), HV interval, PR interval

Introduction

Trans-catheter aortic valve replacement (TAVR) has initially been developed for the treatment of severe aortic stenosis in patients deemed at high-risk for conventional surgical approach (1). Technical and procedural improvements in the last years have now expanded its use to lower-risk patients (2).

Even if the incidence of major complications has decreased over the years, conduction disturbances such as high degree atrioventricular block (AVB) or new-onset left bundle branch block (LBBB) remain relatively common (3). Despite an incidence of about one-fourth, the management of new-onset LBBB remains a matter of debate. Its association with increased all-cause and cardiovascular mortality, progression to high degree AVB and need for PM implantation has been shown (3, 4), but the lack of consensus and guidelines has led to substantial heterogeneities in practice. One of the unresolved issues pertains to the exact role of electrophysiological study (EPS) in patients with conduction disturbances post-TAVR. Despite some conflicting results, studies have suggested that performing an EPS after TAVR may be a useful strategy to identify patients who truly need PM implantation in case of new-onset LBBB (5–8). Based on these evidences, a recent scientific expert panel document (3) stated that *an EPS may be a reasonable option in patients with new-onset LBBB, or ECG changes with pre-existing conduction disturbances, when either the QRS or the PR interval exceeds 150 and 240 ms, respectively.*

In order to better define the role of EPS and to optimize its yield, the aim of the present study is to investigate the correlation between post-procedural PR and QRS changes and abnormal HV interval findings during EPS in patients with new-onset LBBB after TAVR. The study is based on the simple assumption that, in case of QRS prolongation, the HV interval should remain normal as long as one fascicle conducts normally, while an abnormal HV interval should imply a PR interval modification (perceptible or not). Accordingly, the hypothesis is that in new-onset LBBB, the analysis of the PR interval may identify more specifically patients with prolonged HV conduction compared to the analysis of the QRS complex.

Abbreviations: AUC, area under the curve; AVB, atrioventricular block; ECG, electrocardiogram; EPS, electrophysiological study; IQR, interquartile range; LBBB, left bundle branch block; NPV, negative predictive value; OR, odd ratio; PPV, positive predictive value; PM, pacemaker; RBBB, right bundle branch block; ROC, receiver-operating characteristic; SD, standard deviation; TAVR, trans-catheter aortic valve replacement.

Materials and methods

Design and study population

This is an observational study conducted in two Swiss hospitals including patients with new-onset LBBB post-TAVR. All consecutive patients who underwent an EPS after TAVR between April 2015 and December 2020 were included. Exclusion criteria for analysis were atrial fibrillation/flutter during EPS, previously implanted PM and any type of persistent AVB post-TAVR requiring pacemaker implantation.

Intraventricular conduction disturbances were defined according to the criteria approved by the American Heart Association (9). TAVR procedure were performed using the self-expandable Evolut R and Evolut R Pro (Medtronic, Minneapolis, MN), and the balloon-expandable Sapien 3, (Edwards Life Science, Irvine, CA).

Written informed consent was obtained from all patients and the study was approved by the local ethics committee (Cantonal Ethics Committee Vaud, CER-VD).

Electrophysiological study and electrocardiogram analysis

EPS was systematically performed in patients with persistent new-onset LBBB post-TAVR as part of our standard tailored management strategy.

The EPS assessment was performed either during the TAVR procedure or within the following days after the procedure in patients with persisting conduction abnormalities. For patients who underwent an HV interval assessment both during and after the TAVR procedure, the second EPS was considered for the analysis.

One or two quadripolar diagnostic catheters were percutaneously inserted through the femoral vein (electrode spacing 5-5-5 mm, 4 mm electrode tip size, Supreme SJN, St. Jude Medical®, St Paul, MN). Surface ECG and bipolar intracardiac electrograms were monitored continuously and stored on a computer-based digital amplifier/recorder system (Axiom Sensis XP®, Siemens, Berlin, Germany and EPTracer®, Cardiotek, Maastricht, Netherlands). Bipolar electrograms were sampled at 2 kHz and band-pass filtered from 30 to 400 Hz. The 12-lead ECG recorded during the EPS was analysed at 100 mm/s sweep speed, with a standard gain of 1 mV/cm and a filter setting of 0.05 Hz (high pass)-100 Hz (low pass). The quadripolar diagnostic catheter was positioned at the most proximal His potential to measure the AH and HV intervals. The mean value of 3 measurements was used. Care was taken to rule out abnormal His potentials suggestive of intra-His conduction delay.

To reproduce real life conditions, the baseline ECG used for analysis the day before the TAVR procedure was recorded on a standard electrocardiograph (Schiller AG, Baar, Switzerland). The ECG was analysed at 50 mm/s sweep speed. Two investigators blinded to the EPS results independently analysed the ECG. In case of disagreement, a consensus was obtained with a third senior investigator.

The analysis was performed using two different cut-offs to define a pathologic HV interval: > 55 and > 60 ms.

Statistical analysis

Categorical variables are expressed as frequencies (%) and continuous variables as mean ± standard deviation (SD) or median [interquartile range (IQR)] where indicated. Continuous variables were compared by two-tailed paired *t*-test or Mann–Whitney *U*-test in case of abnormal distribution. Categorical variables were tested using Chi-squared tests.

A logistic regression model was used to assess the interdependence of HV interval impairment and ECG prognostic factors. Univariate analyses were performed to reveal unadjusted significant associations between ECG variables and prolonged HV. These variables were entered in the multivariate model to assess adjusted associations between outcomes and covariates.

Receiver-operating characteristic (ROC) curves were generated using the presence of a prolonged HV interval as endpoint: area under the curve (AUC) comparisons were made and the optimal cutoff value was chosen using the Youden Index.

TABLE 1 General characteristics and medical history.

	All patients (*n* = 61)
Age median [IQR]	81 [76–86]
Sex: male	25 (41%)
BMI; Mean ± SD	26 ± 4
Hypertension; *n* (%)	44 (72.1%)
Dyslipidaemia; *n* (%)	32 (52.5%)
Diabetes; *n* (%)	16 (26.2%)
History of atrial fibrillation; *n* (%)	13 (21.3%)
Previous stroke; *n* (%)	8 (13.1%)
CAD; *n* (%)	20 (32.8%)
Chronic renal failure; *n* (%)	15 (24.6%)
Smoking history; *n* (%)	10 (16.4%)
LVEF; Mean ± SD	62 ± 9
Type of valve	
Balloon-Expandable; *n* (%)	43 (70.5%)
Self-Expandable; *n* (%)	18 (29.5%)

Statistical analysis was carried out using SPSS 24.0 software (SPSS Inc., Chicago, IL), or Matlab (Mathworks, Natick, MA, United States) and 2-sided *p*-values < 0.05 were considered statistically significant.

Results

Patients' characteristics

A total of 78 consecutive patients who developed new-onset LBBB post-TAVR between April 2015 and December 2020 were considered for inclusion. Of those, 17 (21.8%) were excluded due to atrial fibrillation or atrial flutter. Thus, the analysis was performed on a final set of 61 patients. The median age of the population was 81 [76–86] years and 25 patients (41%) were males. Balloon- and self-expandable valves were used in 43 (70.5%) and 18 (29.5%) patients, respectively. The EPS was performed during the TAVR procedure in 26 patients, and 2–10 days following the procedure in 35 patients (median time 3 [2–6] days). Patients' characteristics are summarized in **Table 1**.

Surface electrocardiogram and HV-interval assessment

The PR and QRS interval pre-TAVR were 185 ± 35 and 96 ± 11 ms, respectively. The PR interval increased to 206 ± 41 ms and the QRS widened to 146 ± 13 ms post-TAVR. A PR interval > 200 ms was observed in 35 patients (57.4%). The ΔPR, defined as the difference between PR interval pre- and post-TAVR was ≥ 20 ms in 27 (44.3%) patients. QRS duration was > 150ms in 26 (42.6%) patients. Regarding the QRS axis, a deviation to the left was observed post-TAVR. A total

of 23 patients (37.7%) presented a new left-axis deviation post-TAVR – moderate (between −30° and −45°) in 20 (32.8%) patients, and extreme (beyond −45°) in 3 (4.9%) patients. The pre- and post-TAVR ECG findings are summarized in Table 2.

The median HV interval duration post-TAVR in new-onset LBBB was 54 [50–65] ms. An abnormal HV interval exceeding the 55 ms or 60 ms cut-off values was found in 28 (45.9%) and 17 (27.9%) patients, respectively. An HV interval > 70 ms was found in 9 (14.8%) patients.

HV interval assessment according to the *PR interval*

The post-TAVR PR and ΔPR interval durations were significantly longer in patients with an HV interval > 55 ms post-TAVR (228 ± 34 vs. 188 ± 38 ms, $p < 0.001$ for the PR interval; and 34 ± 23 vs. 10 ± 30 ms, $p = 0.001$ for the ΔPR interval). Similar findings were observed when considering an HV interval cut-off of 60 ms (229 ± 34 vs. 197 ± 40 ms, $p = 0.006$ for the PR interval, 34 ± 21 vs. 16 ± 31 ms, $p = 0.024$ for the ΔPR interval). The pre-implantation baseline PR interval did not show a statistically significant difference between patients with normal and prolonged HV interval independently from the considered cut-off. The HV interval assessment according to the PR interval are summarized in Table 2.

HV interval assessment according to *QRS duration and axis*

The QRS and ΔQRS duration post-TAVR did not differ significantly between patients with normal and abnormal HV interval using both a 55 or 60 ms cut-off values. Regarding the QRS axis, ΔAxis and the occurrence of a new left axis deviation did not differ significantly between both groups for both HV interval cut-off values. The HV interval assessment according to the post-TAVR QRS duration and axis are summarized in Table 2.

Proposed electrocardiogram cut-off values to predict abnormal electrophysiological findings

The ROC curve analysis to discriminate patients with an HV interval exceeding 55 ms yielded an optimal cut-off for the PR interval post-TAVR of 199.5 ms (Sensitivity = 92.9%, Specificity = 66.7%, Youden Index = 0.595; AUC = 0.804, $p < 0.001$). The optimal ΔPR interval for the same cut-off was > 13 ms (Sensitivity = 85.7%, Specificity = 63.6%, Youden Index = 0.494; AUC = 0.769, $p < 0.001$; Figure 1A).

TABLE 2 ECG findings before and after TAVR according to the HV interval assessment.

	All patients ($n = 61$)	Cut-Off HV interval: 55 ms			Cut-Off HV interval: 60 ms		
		HV ≤ 55 ($n = 33$)	HV > 55 ($n = 28$)	*P-value*	HV ≤ 60 ($n = 44$)	HV > 60 ($n = 17$)	*P-value*
PR interval							
PR Pre; Mean (IQR)	185 ± 35	178 ± 35	194 ± 33	0.059	182 ± 34	195 ± 36	0.187
PR Post; Mean ± SD	206 ± 41	188 ± 38	228 ± 34	<0.001	197 ± 40	229 ± 34	0.006
PR interval > 200 ms; *n* (%)	35	10	25	<0.001	19	16	<0.001
ΔPR; Mean ± SD	21 ± 29	10 ± 30	34 ± 23	0.001	16 ± 31	34 ± 21	0.024
QRS interval							
QRS Pre; Mean ± SD	96 ± 11	95 ± 11	97 ± 11	0.413	95 ± 12	98 ± 10	0.333
QRS Post; Mean ± SD	146 ± 13	145 ± 14	148 ± 13	0.355	145 ± 14	149 ± 10	0.235
QRS interval > 150 ms; *n* (%)	26	14	12	0.973	19	7	0.887
ΔQRS; Median (IQR)	53 [43–59]	52 [42–60]	53 [44–57]	0.546	52 [42–59]	53 [42–59]	0.778
QRS Axis							
QRS Axis Pre; Median (IQR)	0° [−15° to 30°]	15° [−15° to 30°]	−8° [−15° to 16°]	0.144	8° [−15° to 30°]	0° [−23° to 23°]	0.435
QRS Axis Post; Median (IQR)	−15° [−45° to 15°]	−15 [−45° to 38°]	-45 [−45° to -4°]	0.037	−15° [−45° to 26°]	−45° [−45° to −8°]	0.052
New Left Axis Deviation post-TAVR; *n* (%)	23	10	13	0.195	14	9	0.127
ΔAxis; Mean ± SD	−20° ± 41	−14° ± 41°	−27° ± 42°	0.222	−15° ± 42°	−34° ± 38°	0.097

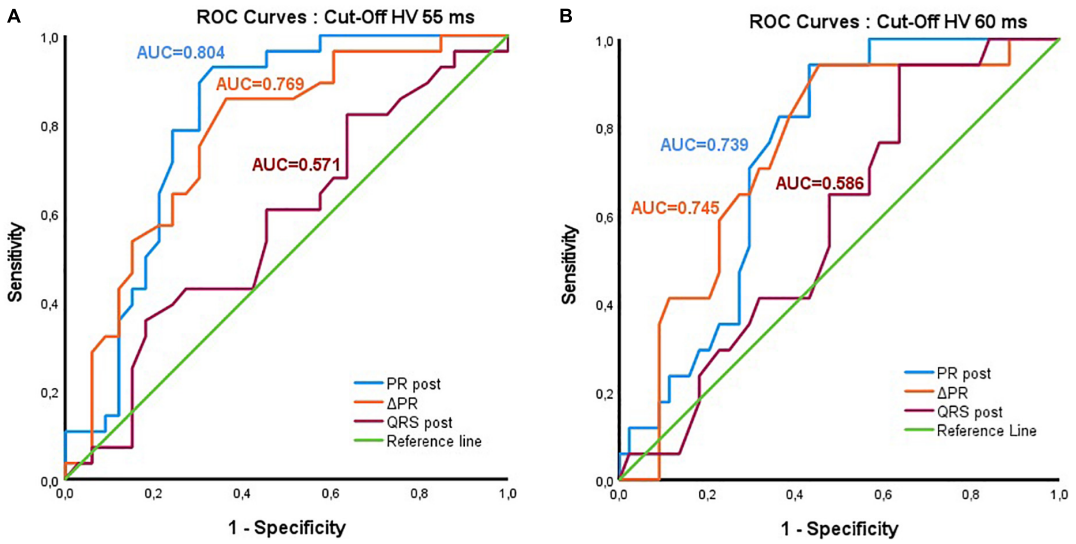

FIGURE 1
ROC curves for PR, ΔPR and QRS intervals to discriminate patients with abnormal HV after transcatheter aortic valve replacement: **(A)** HV interval cut-off 55 ms; **(B)** HV interval cut-off 60 ms.

For the 60 ms HV cut-off value, the analysis yielded an optimal cut-off of > 202 ms for the PR interval (Sensitivity = 94.1%, Specificity = 56.8%, Youden Index = 0.509; AUC = 0.739, p = 0.004), and > 13 ms for ΔPR (Sensitivity = 94.1%, Specificity = 54.5%, Youden Index = 0.487; AUC = 0.745, p = 0.003) (**Figure 1B**).

In order to provide ECG cut-off values that can be used readily in clinical practice, considering the difficulty to measure lower than 20 ms intervals on standard ECG recordings, a PR interval > 200 ms and a ΔPR interval ≥ 20 ms were used for further analysis.

Prediction of abnormal HV interval based on the electrocardiogram findings

On univariate analysis, the presence of PR interval > 200 ms post-TAVR was predictive of a prolonged HV interval, both for the 55 and 60 ms cut-offs (OR: 19.2, 95% CI: 4.7–78.4, p < 0.001 and OR: 21.1, 95% CI: 2.6–173.0, p = 0.005, respectively). Regarding the PR interval change post-TAVR, a ΔPR interval ≥ 20 ms predicted both an HV interval > 55 and 60 ms (OR: 4.8, 95% CI: 1.6–14.3, p = 0.005, and OR: 4.6, 95% CI: 1.4–15.6, p = 0.013, respectively).

Importantly, neither a QRS interval > 150 ms nor a new left axis deviation post-TAVR predicted abnormal EP results using both cut-offs.

On multivariate analysis, a PR interval > 200 ms was the only factor independently associated with a prolonged HV interval for both a 55 and 60 ms cut-offs (OR: 18.0, 95% CI 3.9–83.4, p < 0.001 and OR: 16.7, 95% CI: 1.9–146.2, p = 0.011, respectively). Univariate and multivariate analyses are presented in **Table 3**.

Predictive value of PR interval assessment to predict abnormal HV interval

A PR interval exceeding 200 ms provided an 89% sensitivity and an 88% negative predictive value (NPV) (specificity = 70%, positive predictive value (PPV) = 71%) to identify patients with an HV interval exceeding 55 ms. When using a 60 ms cut-off value, the sensitivity and NPV increased to 94 and 96%, respectively (specificity = 57%, PPV = 46%).

A ΔPR ≥ 20 ms provided a somewhat lower sensitivity (64%) and NPV (71%) for the HV cut-off of 55 ms (specificity = 73%, PPV = 67%). For the 60 ms cut-off value, sensitivity was 71%, while the NPV was 85% (specificity = 66%, PPV = 44%).

Combined use of PR and ΔPR interval to predict a prolonged HV interval

The combined use of *either* an abnormal PR *or* ΔPR interval, allowed a notable increase in sensitivity to discriminate patients with abnormal HV interval. The finding of a PR interval > 200 ms *or* a ΔPR interval ≥ 20 ms, yielded a 96% sensitivity and 95% NPV (specificity = 55%, PPV = 64%)

TABLE 3 Prediction of abnormal HV post-implantation based on the electrocardiogram.

Cut-Off HV interval: 55 ms

				Univariate analysis		Multivariate analysis	
	Total	**HV ≤ 55**	**HV > 55**	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***
Patients	61	33	28				
PR interval > 200 ms	35	10	25	19.2 (4.7–78.4)	<0.001	18.0 (3.9–83.4)	<0.001
ΔPR ≥ 20 ms	27	9	18	4.8 (1.6–14.3)	0.005	3.6 (0.9–13.5)	0.059
QRS interval > 150 ms	26	14	12	1.0 (0.4–2.8)	0.973	1.8 (0.4–7.3)	0.413
New left axis deviation	23	10	13	2.0 (0.7–5.7)	0.198	1.6 (0.4–6.6)	0.482

Cut-Off HV interval: 60 ms

				Univariate analysis		Multivariate analysis	
	Total	**HV ≤ 60**	**HV > 60**	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***
Patients	61	44	17				
PR interval > 200 ms	35	19	16	21.1 (2.6–173.0)	0.005	16.7 (1.9–146.2)	0.011
ΔPR ≥ 20 ms	27	15	12	4.6 (1.4–15.6)	0.013	3.1 (0.8–12.3)	0.108
QRS interval > 150 ms	26	19	7	0.9 (0.3–2.9)	0.887	1.4 (0.3–5.6)	0.661
New left axis deviation	23	14	9	2.4 (0.8–7.6)	0.132	1.9 (0.5–7.4)	0.349

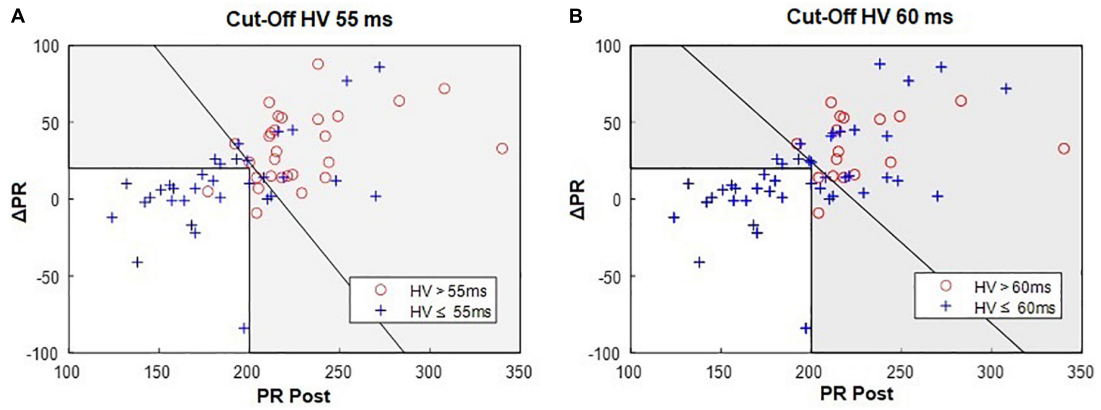

FIGURE 2
Bivariate analysis of the PR and ΔPR intervals: 96% (27/28) of patients with an HV > 55 ms **(A)** have PR > 200 ms OR ΔPR ≥ 20 ms; **(B)** 100% (17/17) of patients with an HV > 60 ms have PR > 200 ms OR ΔPR ≥ 20 ms. In each graph, the oblique line indicates the optimal separation between normal and abnormal HV intervals. Gray area represents the acceptance zone for the parallel testing, i.e., PR post > 200 ms OR ΔPR ≥ 20 ms.

to identify patients with an HV interval exceeding 55 ms (Figure 2A). The only missed case was a patient with a borderline HV interval (58 ms). Accordingly, using this combined assessment with an HV interval cut-off of 60 ms identified all patients with abnormal EP results (sensitivity and NPV of 100%, specificity = 43%, PPV = 40%; Figure 2B). A selective strategy which would consist in performing EPS only in case of an abnormal PR *or* ΔPR interval, would avoid 19 (31%) exams in our study population with a PPV of 64%.

On the other hand, considering the combined use of both an abnormal PR *and* ΔPR interval increased the specificity at the cost of a lower sensitivity. Thus, the finding of both a PR interval > 200 ms *and* a ΔPR interval ≥ 20 ms yielded a specificity of 88% and a PPV of 80% (Sensitivity = 57%, NPV = 71%) for the 55 ms HV cut-off value. Similar results were found for the HV cut-off of 60 ms.

The performance of the combined use of PR and ΔPR interval to predict a prolonged HV interval is summarized in Table 3.

Discussion

Main findings

The major finding of the present study is the identification of ECG parameters which allow selecting patients with new-onset LBBB after TAVR who may benefit most from performing an EPS in order to rationalize its use. In patients with a post-TAVR PR interval $\leq$ 200 ms *and* a ΔPR $<$ 20 ms, an EPS will have an extremely low yield and may therefore be avoided. Importantly, these findings hold true independently of the QRS changes in duration or axis.

In this study population, the use of the proposed PR interval assessment to selectively perform an EPS would avoid about one third of exams in patients with new-onset LBBB without missing any patients with significantly prolonged HV interval (i.e., $\geq$ 60 ms). The PPV of such strategy would be 64%.

Role of the electrophysiological study in new-onset left bundle branch block

The lack of guidelines in the management of patients with new-onset LBBB after TAVR has led to substantial heterogeneities in practices. Indications for PM implantation are currently tailored individually based on either the 12-lead ECG alone (e.g., based on PR interval and/or QRS duration) (10, 11), or the results of EP testing (6–8, 12). More recently, Knecht et al. showed that a management strategy based on a simple HV interval measurement performed with the temporary pacemaker wire could safely identify patients with LBBB who will not develop high degree AVB with a NPV of 90% (6). A recent scientific expert panel state that an EPS was a reasonable option in patients with new-onset LBBB when either the QRS or the PR interval exceeds 150 and 240 ms, respectively (3). The present study adds on accumulated evidences showing that a management strategy based on EP testing should rely on the absolute PR value and its changes, but not on the QRS duration, in order to select the best candidates for EP testing.

In new-onset LBBB, a tailored strategy based on the PR interval assessment may help rationalize resource utilization and hospitalization length without compromising safety.

HV interval cut-off

In the present study, we analysed two different cut-off values to define a pathologic HV interval, namely $>$ 55 and $>$ 60 ms. These two cut-off values are the most stringent that have been used by some groups to justify prophylactic PM implantation (6, 7, 13). Nevertheless, in most previous studies as well as in the above-mentioned expert panel and the latest ECG Guidelines on cardiac pacing, higher cut-offs have generally been used to justify PM implantation, ranging from 70 to 100 ms (3, 5, 8, 12, 14–16). Accordingly, a strategy relying on a selective use of EPS that is able to identify the vast majority of patients with an HV interval above these more stringent cut-offs should likely be safe. The recent data by Knecht et al. (6) support this hypothesis; they showed that an HV interval $\leq$ 55 ms assessed within 24h of the TAVR procedure identified patients with LBBB who did not develop high-grade AVB with a NPV of 90%. Our proposed strategy combining the PR and ΔPR interval assessment, identified patients above this 55 ms cut-off with a 95% NPV. The NPV was 100% for an HV cut-off of 60 ms. This cut-off may be more relevant for clinical decision making, at least in terms of prophylactic PM implantation, since it is more in the range of the values generally used by most groups to justify prophylactic PM implantation. Rivard et al. (7) showed that in patients with new-onset LBBB, a postprocedural HV interval $\geq$ 65 ms predicted AVB with 83% sensitivity and 82% specificity. Similarly, a recent review of the literature on EPS after TAVR suggested that EPS-guided PM implantation should be based on HV interval values in the range of 65–75 ms or more (17). Finally, from an electrophysiological standpoint, it is worth noting that in the setting of LBBB, some authors (18) believe that 60 ms is a more appropriate upper limit of normal HV interval. Indeed, considering that the left side of the septum is normally activated earlier by the left bundle branch, differences of 5–15 ms in the HV interval are sometimes observed with the development of LBBB despite intact right bundle branch conduction (19).

Analysis of the PR interval to predict the risk of atrioventricular block and abnormal electrophysiological study findings

The relevance of the PR interval assessment to stratify the risk of advanced AVB and abnormal EPS findings has been reported by other groups (10–12, 14, 20, 21). Akin et al. showed that new-onset LBBB with PR interval $>$ 200 ms post-TAVR was predictive of high-grade AVB, and 18 of the 22 patients suffering from first-degree AVB demonstrated prolonged HV interval. Toggweiler et al. (11) and Jorgensen et al. (10) both evaluated predictors of delayed high-degree AVB occurring within 30 days of the TAVR procedure in a total population of about 1500 patients. They both demonstrated a similar association with first-degree AVB post-TAVR and the risk of subsequent high-degree AVB. In the study by Toggweiler et al., the proportion of high-grade AVB was 6.8 and 15.7% in patients with LBBB with and without first degree AVB, respectively ($p < 0.001$).

Regarding the relevance of assessing the pre- and postprocedural PR interval changes, Tovia et al. found that, out of 24 patients with LBBB, none of the patients without post procedural PR prolongation, using a ΔPR interval cut-off $>$ 20 ms as proposed in our study, had

significant infranodal disease (12). Mangieri et al. showed that among 611 patients after TAVR, the two independent predictors of late PM implantation (≥48 h) were baseline RBBB, and the amount of PR prolongation post-TAVR (OR for each 10 ms increments: 1.31; 95% CI: 1.18–1.45; $p < 0.001$) (21). Of note, the reported mean ΔPR interval in patients requiring PM implantation was consistently of about 40 ms among studies that reported this variable (20, 21).

Considering the aim of our proposed strategy to limit the number of EPS without missing patients with abnormal HV interval, the above-mentioned evidences tend to support an EPS selection process incorporating both the PR (10, 11, 14), and the ΔPR interval (12, 20, 21).

QRS duration to predict the risk of atrioventricular block and abnormal electrophysiological study findings

Among patients with new-onset LBBB, we did not find any correlation between the QRS interval and abnormal HV interval at EPS. To our knowledge, there are no data available addressing the correlation between the QRS interval (beyond 120 ms) and the HV interval in new-onset LBBB after TAVR. Furthermore, only limited data showed that, in new-onset LBBB, a longer QRS duration (i.e., >150–160 ms) may be associated with an increased risk of delayed high-degree AVB compared to a relatively narrower QRS *irrespective of the PR interval*. Urena et al. found that in patients with new-onset LBBB and a QRS interval > 160 ms at discharge, the risk of sudden cardiac death was significantly increased (9.9 vs. 3% in patients with new-onset LBBB and QRS-interval ≤ 160 ms), suggesting a higher rate of advanced heart block in these patients as an etiology. This assumption was based on the fact that no increased risk of SCD was observed in patients with new-onset LBBB and PM implantation before discharge (4). On the other hand, Jorgensen et al. provided some more direct evidence showing that high-degree AVB with insufficient escape rhythm only occurred with longer QRS duration (≥150 ms) in patients in sinus rhythm with LBBB (7.1%; 95% CI 2.6–14.7%) (10).

Study limitations

The proposed strategy to select EPS candidate should be validated in a separate and larger patient population. Moreover, the aim of the study was to provide a key to rationalize the use of EPS in patients with new-onset LBBB post-TAVR but it did not evaluate the ability of the EPS to identify patients at risk of AVB. Further studies are needed for this purpose.

The yield of the EPS was considered exclusively on the basis of the basal HV interval assessment but other maneuvers may further stratify the risk of AVB. The use of incremental atrial pacing or pharmacological challenge (such as ajmaline or procainamide) to stress the His-Purkinje system would have possibly revealed additional patients at risk of AVB despite normal basal HV interval. The proportion of such patients is, however, expected to be limited. It was indeed observed in one out of the 35 patients who underwent a comprehensive EP evaluation.

In our study, the assessment of the HV interval was performed early post-TAVR in a significant subset of patients, while it has been suggested that EPS is best performed 3 days or more after TAVR and after conduction abnormalities have stabilized (16, 22). Nevertheless, since the aim was to correlate the surface ECG to the HV assessment at a given moment, we think that this limitation does not significantly affect the applicability of our findings.

Finally, since our strategy is based on the PR interval assessment, it cannot be implemented in patients with AF which represent about one fifth of patients, both in our study and in previous studies (6, 10, 11).

Conclusion

The PR interval assessment in patients with new-onset LBBB after TAVR may be a useful simple tool to select patients who may benefit most from an EPS and rationalize its use. Namely, for patients with a post-TAVR PR interval ≤ 200 ms, and a ΔPR < 20 ms, an EPS will have an extremely low yield independently of QRS changes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee Vaud,

CER-VD. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MP, DM, PP, OM, and SF were involved in both the conception of the study and analysis of the data. SC, J-JG, MD, VR, CR, AL, FA, PG, CH, GD, ML, CH-S, GG, EP, and EE contributed to the analysis and interpretation of data. All authors contributed substantially to the realization of this study and participated in drafting and revising the manuscript and gave their approval to the submitted version.

Funding

The present study was funded by a grant from the Fondation Vaudoise de Cardiologie Interventionnelle. DM was supported by the Swiss National Science Foundation (grant P2LAP3_199561).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 14 September 2022
DOI 10.3389/fcvm.2022.902564

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 23 March 2022
ACCEPTED 29 August 2022
PUBLISHED 14 September 2022

CITATION
Khokhar AA, Ponticelli F, Zlahoda-Huzior A, Chandra K, Ruggiero R, Toselli M, Gallo F, Cereda A, Sticchi A, Laricchia A, Regazzoli D, Mangieri A, Reimers B, Biscaglia S, Tumscitz C, Campo G, Mikhail GW, Kim W-K, Colombo A, Dudek D and Giannini F (2022) Coronary access following ACURATE neo implantation for transcatheter aortic valve-in-valve implantation: *Ex vivo* analysis in patient-specific anatomies. *Front. Cardiovasc. Med.* 9:902564. doi: 10.3389/fcvm.2022.902564

Coronary access following ACURATE neo implantation for transcatheter aortic valve-in-valve implantation: *Ex vivo* analysis in patient-specific anatomies

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Background: Coronary access after transcatheter aortic valve implantation (TAVI) with supra-annular self-expandable valves may be challenging or un-feasible. There is little data concerning coronary access following transcatheter aortic valve-in-valve implantation (ViV-TAVI) for degenerated surgical bioprosthesis.

Aims: To evaluate the feasibility and challenge of coronary access after ViV-TAVI with the supra-annular self-expandable ACURATE neo valve.

Materials and methods: Sixteen patients underwent ViV-TAVI with the ACURATE neo valve. Post-procedural computed tomography (CT) was used to create 3D-printed life-sized patient-specific models for bench-testing of coronary cannulation. Primary endpoint was feasibility of diagnostic angiography and PCI. Secondary endpoints included incidence of challenging cannulation for both diagnostic catheters (DC) and guiding catheters (GC). The association between challenging cannulations with aortic and transcatheter/surgical valve geometry was evaluated using pre and post-procedural CT scans.

Results: Diagnostic angiography and PCI were feasible for 97 and 95% of models respectively. All non-feasible procedures occurred in ostia that underwent prophylactic "chimney" stenting. DC cannulation was challenging in 17% of models and was associated with a narrower SoV width (30 vs. 35 mm, $p < 0.01$), STJ width (28 vs. 32 mm, $p < 0.05$) and shorter STJ height (15 vs. 17 mm, $p < 0.05$). GC cannulation was challenging in 23% of models and was associated with narrower STJ width (28 vs. 32 mm, $p < 0.05$), smaller transcatheter-to-coronary distance (5 vs. 9.2 mm, $p < 0.05$) and a worse coronary-commissural overlap angle (14.3° vs. 25.6°, $p < 0.01$). Advanced techniques to achieve GC cannulation were required in 22/64 (34%) of cases.

Conclusion: In this exploratory bench analysis, diagnostic angiography and PCI was feasible in almost all cases following ViV-TAVI with the ACURATE neo valve. Prophylactic coronary stenting, higher implantation, narrower aortic sinus dimensions and commissural misalignment were associated with an increased challenge of coronary cannulation.

KEYWORDS

transcatheter aortic valve implantation (TAVI), valve-in-valve transcatheter aortic valve implantation, coronary access, ACURATE neo^{TM}, aortic stenosis

Introduction

Transcatheter aortic valve-in-valve implantation (ViV-TAVI) is a recommended treatment for degenerated surgical bioprosthetic valves (SBV) in patients deemed high-risk for re-do surgical aortic valve replacement (SAVR) (1). SBV have limited durability and when they fail, ViV-TAVI has shown favourable procedural and clinical outcomes compared to re-do SAVR (2–4). The number of ViV-TAVI procedures is further expected to increase given the expansion of TAVI toward low surgical-risk patients, in whom ViV-TAVI represents a potential treatment strategy for the lifelong management of severe aortic stenosis (5–8). As a consequence, an increased cumulative risk for repeat invasive angiography or percutaneous coronary intervention (PCI) procedures is expected in the next years (9–11). Therefore, the evaluation of coronary access following ViV-TAVI is increasingly relevant when considering the optimal sequential valve treatment for younger patients (7).

Coronary access following TAVI can be challenging and if un-feasible is associated with adverse outcomes (11–13). Prior studies have identified various anatomical, procedural and device-related factors, which can influence the challenge of coronary access following TAVI and TAVI-in-TAVI procedures (14–21). However, comparatively little data exists on coronary access following ViV-TAVI, where the additional presence of the surgical valve frame and leaflets might make coronary re-engagement more challenging (22, 23).

Therefore, we simulated diagnostic angiography and PCI procedures to determine the feasibility and challenge of coronary access in 3D printed patient-specific models derived from a cohort of patients who underwent ViV-TAVI.

Abbreviations: ViV-TAVI, valve-in-valve transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; PCI, percutaneous coronary intervention; LCA, left coronary artery; RCA, right coronary artery; DC, diagnostic catheter; GC, guiding catheter; CT, computed tomography; VTC, virtual transcatheter-to-coronary distance; MTC, measured transcatheter-to-coronary distance.

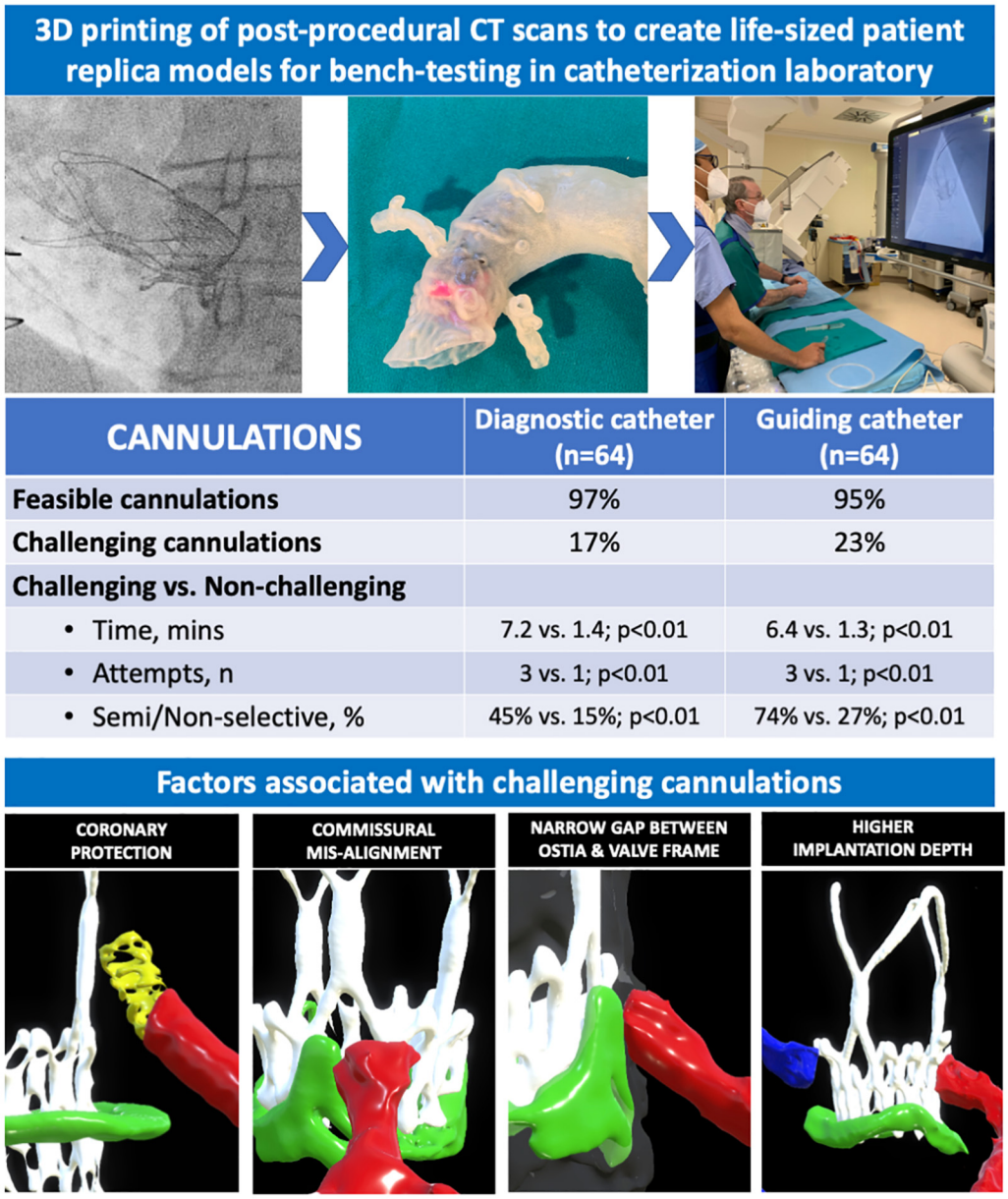
Materials and methods

Patient cohort

The bench-models were derived from a real cohort of consecutive patients who underwent ACURATE neo (Boston Scientific, Marlborough, MA, USA) valve implantation to treat degenerated SBV across three high-volume European centres between February 2018 and February 2020. All patients were deemed high-surgical risk for re-do SAVR following local heart team discussion. All procedures were performed from transfemoral access and choice of valve sizing and implantation technique was left to the operator's discretion. Ethical approval for this study was obtained in accordance to the local policy of each institution.

Imaging analysis

All patients underwent pre and post-procedural contrast-enhanced CT scans using a 128-slice or greater multidetector-row scanner with ECG gating of both systolic and diastolic



GRAPHICAL ABSTRACT
Central illustration: Evaluating feasibility and challenge of coronary cannulation after ViV-TAVI with ACURATE neo valve.

phases with varying temporal windows to optimise image quality. All images were analysed by three independent cardiologists using a dedicated CT analysis software (Horos, version 3.3.6, OsiriX, Switzerland).

On the pre-procedural scan, baseline measurements of the aortic root, coronaries and surgical bioprosthesis were performed in accordance with current recommendations (24). On the post-procedural scan, the geometrical relationships between the transcatheter valve with the SBV and native aortic/coronary anatomy were evaluated by measuring the vertical and horizontal distances between the coronary ostia and transcatheter valve frame, the implantation depth and the extent of overlap between the coronary ostia and commissural posts (**Supplementary Figure 1**).

Creation of 3D printed models

Raw data from each scan was exported in the Digital Imaging and Communication in Medicine (DICOM) format and the aorta, left ventricular blood pool, surgical/transcatheter valves and coronary arteries were

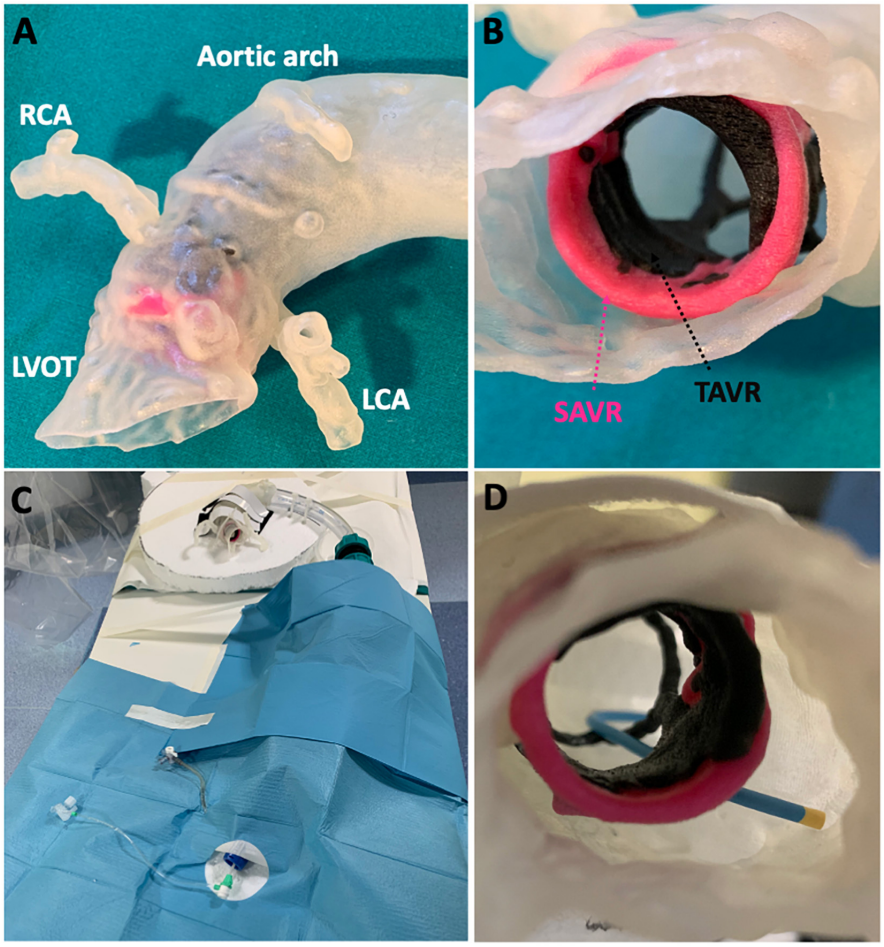


FIGURE 1
Patient-specific 3D printed models. Post-procedural CT was used to **(A)** 3D print a patient-specific anatomical model complete with **(B)** surgical and transcatheter valves. Each patient model was **(C)** assembled in the catheterization laboratory to simulate **(D)** coronary cannulation procedures.

segmented using semi-automatic segmentation algorithms (region growing/thresholding/level-tracing) with added manual corrections.

The segmented models were converted into 3D digital models, which were exported as.*stl* files into a computer assisted design (CAD) software (GrabCAD, Stratasys, USA) for 3D printing. Polyjet technology was used to print the patient-specific 3D models (J720 3D printer, Stratasys) (**Supplementary Figure 2**). The entire aortic arch, ascending aorta and aortic root along with the coronary arteries was printed together using the same material, whilst the surgical and transcatheter heart valves were printed during the same process but using a different more rigid material.

Each 3D printed model was an exact 1:1 sized replica of the patient's true anatomy and surgical/transcatheter valve geometry (**Figures 1A,B**). The materials were selected following preliminary bench-testing to ensure that catheter, wire and device movements closely matched *in vivo* conditions. Each patient model was attached to a prosthetic descending aorta with a femoral access sheath inserted for bench-testing (**Figures 1C,D**). The authenticity of the final assembled bench-model in terms of performing angiography and PCI procedures was independently confirmed by expert interventional operators (CT, AC, FG, DD).

Bench-testing

To evaluate the feasibility and challenge of coronary access, each patient-specific bench-model was assembled under cardiac catheterization laboratory conditions, using real equipment to simulate diagnostic angiography and PCI procedures under fluoroscopy (**Supplementary Figure 2**). Two expert (defined as > 2,000 PCI, 400 TAVI and > 50 ViV-TAVI procedures) interventional cardiologists were instructed to perform a diagnostic angiogram and PCI to both the right and left

TABLE 1 Summary of clinical, procedural, and imaging data for each patient in study cohort.

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Clinical data																
Age	79	84	80	81	49	66	82	72	81	71	74	72	75	83	85	63
Sex	M	F	F	M	M	M	M	M	M	M	F	M	M	M	F	M
STS	3.36	3.66	2.6	2.39	0.7	1.27	2.56	1.78	1.71	1.12	2.78	1.32	1.71	2.84	2.91	1.6
Surgical bioprosthesis																
Type	MF	MF	P	CE	CE	MF	MF	MF	CE	H	H	P	MF	P	MF	MF
Size	27	23	19	25	27	25	23	25	23	23	25	23	25	23	21	25
Age, years	7	10	17	14	13	9	10	10	17	7	10	2	10	14	10	11
Mechanism of failure	R	S	S	R & S	R	R	S	S	R	R	R & S	R & S	S	R	S	R & S
Aortic Root	Bentall	Normal	Normal	Normal	Hemashield	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Bentall	Bentall
TAVR																
ACURATE size	M	S	S	M	L	S	S	S	S	S	S	S	S	S	S	S
Coronary protection	Stent	Stent	No	No	No	No	Wire only	Wire only	No	No	No	No	No	No	Wire only	Wire only
Pre-procedural CT																
SoV width	36	28	31	35	47	52	35	33	38	32	38	25	40	30	36	31
STJ width	32	25	28	32	46	39	34	30	31	28	36	25	35	28	30	34
STJ height	28	15	11	21	26	32	17	17	21	17	17	9	22	14	31	17
LCA height	5	3.5	3	11	2.5	11	5.5	5.5	16.5	3.2	7.5	5.2	12.5	8	1	6.5
RCA height	5	4	6	14.5	17	21	12	12	17	10	7.6	3	12	11.5	14	8.2
LCA VTC	3.8	3.9	4	10	11	20	10	10	11	9.4	9.6	3	11	5.5	6.17	6
RCA VTC	4.6	7.5	4.5	5	12.3	19.2	8	8	8.1	4	8.8	5	10.5	4.5	7.2	6
Post-procedural CT																
Implant depth	9.9	3.8	3.6	4.3	5.52	8.4	6.6	0.55	4.2	4.8	4.9	3.2	5.6	-0.5	1	5.9
LCA MTC	6.2	5	4	14	12.9	20	9.9	5.4	10.7	9.2	12.1	4.9	10.7	6.2	9.7	6.1
RCA MTC	3	4.7	6.9	8.2	15.5	22.5	7	6.2	3.4	1.6	13	5.6	14.6	4.4	9.3	8.1
LCA CCA	19.22	19.5	26.41	17.5	24.16	14.27	2.47	25.46	35.44	11.13	61.14	19.15	63.18	36.45	25.57	67.43
RCA CCA	34	4.17	12.3	41.1	51.6	2.2	5.23	49.34	16.17	5.3	31.16	18.41	30.42	11.46	41.55	36.58

M, male; F, female; STS, society of thoracic surgeons predicted risk of mortality; MF, mitroflow; P, perimount; CE, Carpentier Edwards; H, hancock; R, regurgitation; S, stenosis; TAVR, transcatheter aortic valve replacement; SoV, Sinus of Valsalva; STJ, sinotubular junction; LCA, left coronary artery; RCA, right coronary artery; VTC, virtual transcatheter-to-coronary distance; MTC, measured transcatheter-to-coronary distance; CCA, coronary-commissural angle.

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TABLE 2 Data on diagnostic catheter cannulations.

	Both ostia ($n = 64$)	LCA ($n = 32$)	RCA ($n = 32$)	*P*-value
Angiography feasibility	62 (97%)	32 (100%)	30 (94%)	$p = 0.49$
Cannulation selectivity				
Selective	51 (82%)	25 (78%)	26 (87%)	$p = 0.94$
Semi-selective	9 (15%)	5 (16%)	4 (13%)	
Non-selective	4 (6%)	2 (6%)	2 (7%)	
Cannulation attempts				
1	49 (79%)	23 (72%)	26 (87%)	$p = 0.55$
2	9 (15%)	7 (22%)	2 (7%)	
3+	6 (10%)	2 (6%)	4 (13%)	
Cannulation time				
<2 min	32 (52%)	14 (44%)	18 (60%)	$p = 0.44$
2–5 min	20 (32%)	12 (38%)	8 (27%)	
>5 min	12 (19%)	6 (19%)	6 (20%)	
Cannulation advanced techniques				
Wire-assisted	7 (11%)	5 (16%)	2 (7%)	*p = 0.46*
Guide-extension	1 (2%)	1 (3%)	0 (0%)	
Balloon-assisted	1 (2%)	1 (3%)	0 (0%)	

Data presented as *n* (%). LCA, left coronary artery; RCA, right coronary artery.

coronary arteries of each bench-model. Both operators were blinded to the pre and post-procedural CT scan data and each operator was blinded to the cannulation strategies and techniques used by the other operator.

All procedures were performed from the femoral access route using 6Fr catheters. For the diagnostic angiography, the operators were instructed to start with the Judkins right (JR4) and Judkins left (JL4) catheters to reflect conventional practice. If initial cannulation was unsuccessful, the subsequent choice of catheter or cannulation strategy was left to the discretion of the operator. Following diagnostic angiography, the operators were instructed to perform PCI of the proximal right coronary artery (RCA) and left anterior descending artery (LAD). The operators were free to select their preferred guiding catheters, wires and any additional equipment to complete the procedure.

For each procedure, the following data were recorded: cannulation selectivity (selective, semi-selective, non-selective), number of cannulation attempts, fluoroscopy time, catheters used, cannulation techniques and additional equipment used (e.g., guide-extension catheters). The topography of cannulation in relation to the transcatheter heart valve was noted and recorded as either above or below the upper crown and catheter passage inside or outside valve frame.

Study outcomes

The primary outcome of the study was the feasibility of diagnostic angiography and PCI. A diagnostic angiogram was considered feasible if complete opacification of the coronary vessels was obtained following contrast media injection. A PCI was considered feasible if the vessel was successfully wired distally, a 2.5 mm × 20 mm semi-compliant balloon (Euphora, Boston Scientific, USA) was inflated, followed by successful advancement and retraction of a 3.5 mm × 20 mm drug-eluting stent (Resolute Onyx, Medtronic) in the proximal segment of the vessel.

The secondary outcome was to determine the incidence of challenging diagnostic catheter (DC) and guiding catheter (GC) cannulation, defined as, if for at least one operator either of the two criteria were met:

1. Cannulation was not feasible or non-selective;
2. Cannulation was selective/semi-selective but required greater than 5 min of fluoroscopy time and at least two attempts.

In addition, the association between challenging cannulations with the imaging variables derived from the pre and post-procedural CT scans was evaluated.

Statistical analysis

Categorical variables are expressed as numbers and percentages and continuous variables as median and interquartile range (IQR) or mean and standard deviation (SD). Categorical data were compared using the chi-squared test or Fisher exact test as appropriate. For comparison of continuous variables, the Student's *t*-test or Mann-Whitney U test was applied depending on the normality of distribution (assessed by

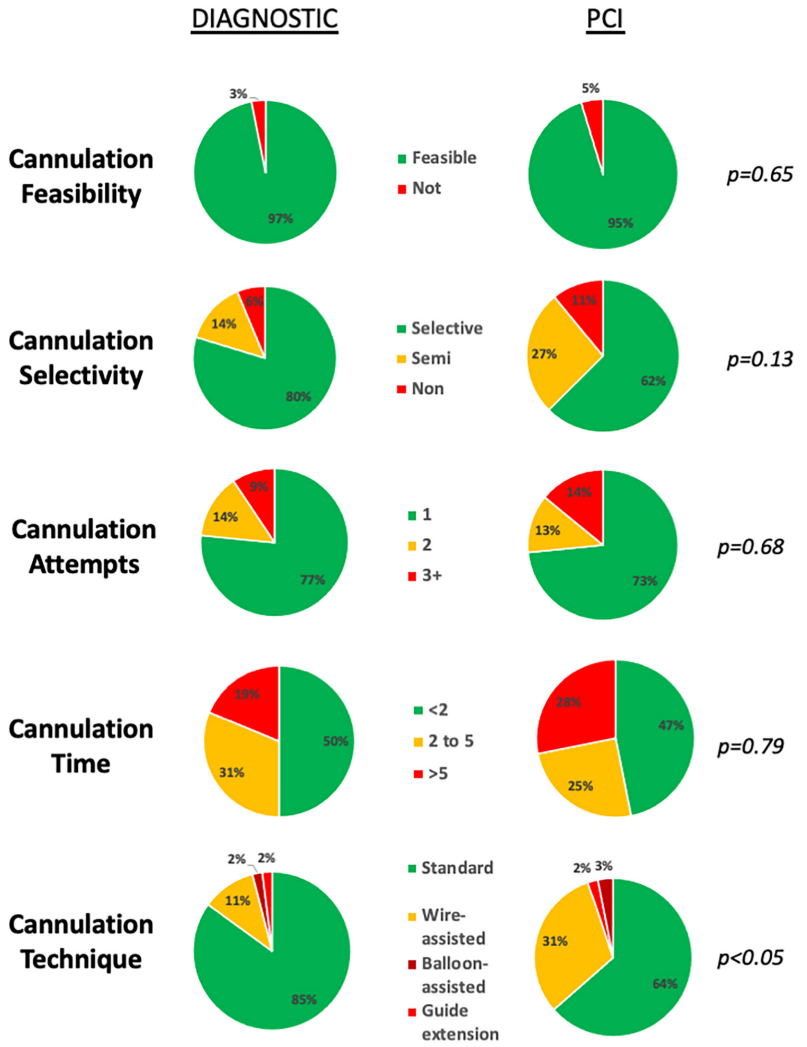

FIGURE 2
Feasibility and challenge of diagnostic and guiding catheter cannulations. Cannulation feasibility, selectivity, number of attempts and time was equivalent for both diagnostic and guide catheter cannulations. Use of advanced techniques, was more frequently required for guiding catheter cannulations.

the Kolmogorov-Smirnov test). A 2-sided p-value < 0.05 was considered as statistically significant. All statistical analysis were performed using StataIC version 17.0 (StataCorp, IBM).

Results

Sixteen consecutive patients underwent transfemoral ViV-TAVI with the ACURATE neo valve. Baseline characteristics, procedural and CT imaging data of the study population are presented in Table 1. The mean age was 77 years, 75% were male and mean STS score was 2.09. Mechanism of SBV failure was stenosis, regurgitation or mixed in 6 (38%), 6 (38%) and 4 (25%) cases, respectively. A size S of the ACURATE neo valve was implanted in 13 (81%) cases with prophylactic "chimney" stenting performed for both ostia in 2 (13%) patients. Two operators independently attempted both diagnostic angiography and PCI of each coronary ostium, resulting in a total of 64 diagnostic cannulations and 64 PCI procedures.

Diagnostic angiography

The primary outcome of diagnostic angiography feasibility was observed for 62/64 (97%) cannulations. Cannulation was not feasible for both operators in one RCA ostium, which underwent prophylactic stenting during the ViV-TAVI procedure. Data on DC cannulations are presented in Table 2. Median number of cannulation attempts was 1 (IQR: 1-1) and

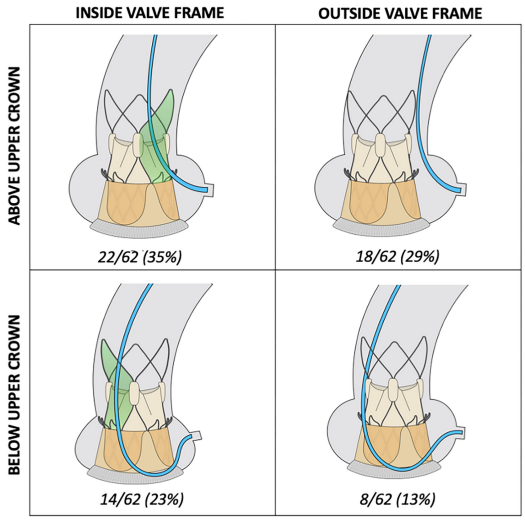

FIGURE 3
Topography of diagnostic cannulation in relation to valve frame. Access to the coronary ostium was pre-dominantly achieved from above the upper crown of the ACURATE neo valve (64%). In 42% of cannulations, coronary cannulation was successfully performed by completely bypassing the valve frame.

median cannulation time was 1 min 48 s (IQR: 1 min 5 s–3 min 11 s). The majority of cannulations required no more than a single cannulation attempt (49/62, 79%). Selective cannulation was achieved in 51/62 (82%) and most of the cannulations required less than 2 min of fluoroscopy time (32/62, 52%). Advanced cannulation techniques were required for 9/62 (15%) cannulations, with 0.014" coronary wire-assisted cannulation being the main technique of choice (**Figure 2**). There was no significant difference observed in cannulation feasibility, selectivity, attempts, time or technique used between the LCA and RCA (**Table 2**).

Choice of catheters selected and topography of cannulation in relation to the valve frame is shown in **Supplementary Figure 3** and **Figure 3**, respectively. Differences in procedural outcomes between the operators as well as the individual operator's perceived level of difficulty for performing diagnostic angiography are reported in **Supplementary Table 1** and **Supplementary Figure 4**, respectively.

Percutaneous coronary intervention

Performing a complete PCI procedure was feasible in 61/64 (95%) of cases. PCI could not be performed for ostia that underwent prophylactic coronary stenting (1 LCA cannulation, 2 RCA cannulations) (**Table 3**).

Compared to DC, a greater percentage of GC cannulations were either semi- (14 vs. 27%) or non-selective (6 vs. 11%) (**Figure 2**). Median cannulation time was 2 min 5 s (IQR: 48 s-5 min 12 s). Advanced techniques to achieve guide catheter cannulation were required in 22/64 (34%) of cannulations, with the use of a 0.014" coronary wire only or in addition to a guide-extension catheter or balloon-assisted technique required for 19/64 (30%), 2/64 (3%) and 1/64 (2%) of cannulations, respectively (**Table 3**). A wider selection of guiding catheters were selected particularly for cannulation of the LCA (**Figure 3**).

Differences in procedural outcomes between the operators as well as the individual operator's perceived level of difficulty for performing PCI are reported in **Supplementary Table 1** and **Supplementary Figure 4**, respectively.

Challenging cannulation

The secondary outcome criteria for challenging cannulation were met for 11/64 (17%) of DC and 15/64 (23%) of GC cannulations. Data regarding the cannulation procedures, transcatheter and surgical valve types and pre- and post-CT imaging analysis for challenging DC and GC cannulations is presented in **Supplementary Tables 2, 3**.

Challenging cannulations were associated with a longer cannulation time (DC: 7 min 16 s vs. 1 min 25 s, $p < 0.01$; GC: 6 min 9 s vs. 1 min 15 s, $p < 0.01$), required a greater number of attempts [DC: 3 (IQR: 2–4) vs. 1 (IQR: 1–1), $p < 0.01$; GC: 3 (IQR: 2–3) vs. 1 (IQR: 1–1), $p < 0.01$] and were associated with more semi- and non-selective cannulations (DC: 45 vs. 15%, $p < 0.01$; GC: 74 vs. 27%, $p < 0.01$) (**Table 4**).

Use of non-standard cannulation techniques (0.014" coronary guide wire-assisted, guide-extension catheter or balloon-assisted cannulation) were more frequently required for challenging versus non-challenging DC (wire: 27 vs. 6%, guide-extension: 9 vs. 0%, balloon: 9 vs. 0%; $p < 0.01$) and GC cannulations (wire: 53 vs. 20%, guide-extension: 13 vs. 2%, balloon: 7 vs. 0%; $p < 0.01$) (**Table 4**).

Factors associated with challenging cannulations

Challenging DC and GC occurred when coronary ostia arose below the upper crown of the THV, there was a narrow sinus gap between the transcatheter/surgical valve frames and aortic wall, commissural mis-alignment and when prophylactic "chimney" stenting was performed. In the most challenging cases, the combination of these factors resulted in prolonged cannulation times, requiring multiple attempts with the use of advanced techniques (**Figure 4**).

Differences in pre- and post-procedural CT imaging data were evaluated between challenging and non-challenging cannulations (**Table 4**). Aortic sinus dimensions, as evaluated

TABLE 3 Data on guiding catheter cannulations.

	Both ostia (n = 64)	LCA (n = 32)	RCA (n = 32)	P-value
Procedural feasibility	61 (95%)	31 (97%)	30 (94%)	$p = 0.50$
Guiding catheter cannulation	61 (95%)	31 (97%)	30 (94%)	$p = 0.50$
Vessel wiring	61 (95%)	31 (97%)	30 (94%)	$p = 0.50$
Vessel POBA	61 (95%)	31 (97%)	30 (94%)	$p = 0.50$
Vessel stenting	61 (95%)	31 (97%)	30 (94%)	$p = 0.50$
Cannulation selectivity				
• Selective	40 (66%)	19 (59%)	21 (66%)	$p = 0.87$
• Semi-selective	17 (28%)	9 (28%)	8 (25%)	
• Non-selective	7 (11%)	4 (13%)	3 (9%)	
Cannulation attempts				
• 1	47 (77%)	24 (75%)	23 (72%)	$p = 0.58$
• 2	8 (13%)	6 (19%)	2 (6%)	
• 3+	9 (15%)	2 (6%)	7 (22%)	
Cannulation time				
• <2 min	30 (49%)	16 (50%)	14 (44%)	$p = 0.52$
• 2–5 min	16 (26%)	9 (28%)	7 (22%)	
• >5 min	18 (30%)	7 (22%)	11 (34%)	
Cannulation techniques				
• Standard	39 (64%)	19 (59%)	2 (63%)	$p = 0.63$
• Wire-assisted	19 (31%)	10 (31%)	20 (63%)	
• Guide-extension	2 (3%)	2 (6%)	0 (0%)	
• Balloon-assisted	1 (2%)	0 (0%)	1 (2%)	

by SoV and STJ width, were smaller for both challenging DC ($p < 0.05$) and GC ($p = 0.05$) cannulations. Challenging cannulations were associated with lower left (3.6 vs. 4.8 mm) and right (3.8 vs. 4.8 mm) coronary heights but this difference was not statistically significant.

On post-procedural CT, the measured transcatheter-to-coronary (MTC) distance (5 vs. 9.2 mm; $p < 0.05$) and commissure-coronary angle (14.3° vs. 25.6°; $p < 0.01$) were both significantly lower for challenging GC cannulations. Implantation depth was numerically lower (DC: 3.8 vs. 4.8 mm, $p = 0.23$; GC: 3.8 vs. 4.8 mm; $p = 0.57$) for challenging cannulations.

The impact of each pre- and post-CT imaging parameter on diagnostic and guiding catheter cannulation time, numbers of attempts and selectivity are presented in **Supplementary Tables 4, 5**. In summary, cannulation time with both DC and GC was prolonged when either the implantation depth was < 4 mm, coronary ostia were located below the upper crown or the virtual-transcatheter distance (VTC) was < 6 mm (p-values for all < 0.05) (**Figure 5**). For DC cannulation, an implantation depth < 4 mm, was associated with increased cannulation attempts and worsening cannulation selectivity. For GC cannulations increased attempts and worsening cannulation selectivity was observed when the MTC < 6 mm and the coronary-commissural angle was < 40° (p-values for all < 0.05).

Discussion

This exploratory study is the first study to systematically evaluate diagnostic and guide catheter cannulation following ViV-TAVI with the ACURATE neo valve. Bench-testing of patient-specific 3D printed models demonstrated (**Graphical Abstract**):

1) Feasibility to perform diagnostic angiography and PCI was 97 and 95%, respectively.
2) Seventeen percentage of diagnostic and 23% of guiding catheter cannulations were challenging requiring greater fluoroscopy time, number of attempts, semi- or non-selective cannulation and use of advanced techniques.
3) The main reasons for challenging cannulation were prophylactic stenting performed during the ViV-TAVI procedure, smaller aortic sinus dimensions, severe commissural mis-alignment and when ostia arose below the upper crown of the valve, which could be due to higher implantation depths or lower coronary heights.
4) Implantation depth < 4 mm, virtual transcatheter-to-coronary (VTC) distance < 6 mm, measured transcatheter-to-coronary (MTC) distance < 6 mm and coronary-commissural angle < 40° were more frequently observed in challenging cannulations.

TABLE 4 Differences in procedural and CT imaging data between challenging and non-challenging diagnostic and guiding catheter cannulations.

	Diagnostic catheter cannulation			Guiding catheter cannulation		
	Challenging $n = 11$	Non-challenging $n = 53$	*P*-value	Challenging $n = 15$	Non-challenging $n = 49$	*P*-value
Cannulation data						
Cannulation feasibility	9 (82%)	53 (100%)	0.05	12 (80%)	49 (100%)	<0.05
Cannulation time, min	7.16 (5.2–10.23)	1.42 (1.04–2.39)	<0.01	6.35 (5.2—14.1)	1.25 (0.46—2.45)	<0.01
Cannulation attempts	3 (2-4)	1 (1-1)	<0.01	3 (2-3)	1 (1-1)	<0.01
Cannulation selectivity						
• Selective	6 (55%)	45 (85%)	<0.01	4 (27%)	36 (73%)	<0.01
• Semi-selective	1 (9%)	8 (15%)		4 (27%)	13 (27%)	
• Non-selective	4 (36%)	0 (0%)		7 (47%)	0 (0%)	
Cannulation techniques						
• Standard	4 (36%)	50 (94%)	<0.01	1 (7%)	38 (78%)	<0.01
• Wire-assisted	3 (27%)	3 (6%)		8 (53%)	10 (20%)	
• Balloon-assisted	1 (9%)	0 (0%)		1 (7%)	0 (0%)	
• Guide-extension catheter	1 (9%)	0 (0%)		2 (13%)	1 (2%)	
Pre-procedural CT						
Coronary height, mm	6 (4–8)	8.2 (5–12)	0.21	6 (4–10)	8.2 (5–12.5)	0.29
Sinus of Valsalva width, mm	30 (28–31)	35 (32–38)	<0.01	31 (28–36)	35 (32–38)	0.05
Sinotubular junction width, mm	28 (25–34)	32 (30–35)	<0.05	28 (25–32)	32 (30–35)	<0.05
Sinotubular junction height, mm	15 (11–17)	17 (17–26)	<0.05	15 (11–28)	17 (17–22)	0.09
Virtual transcatheter-to-coronary distance, mm	5.5 (4.5–7.5)	7.2 (5–10)	0.32	4.6 (4–7.5)	8 (6–10)	0.07
Post-procedural CT						
Implantation depth, mm	3.8 (3.2–5.9)	4.8 (3.6–5.6)	0.23	3.8 (3.6–6.6)	4.8 (3.2–5.6)	0.57
Relationship to risk plane						
• Above	2 (18%)	22 (42%)	0.13	3 (20%)	21 (43%)	0.14
• Below	9 (82%)	31 (58%)		12 (80%)	28 (57%)	
Measured transcatheter-to-coronary distance, mm	6.1 (4.9–6.9)	8.2 (5.4–12.1)	0.30	5 (4–6.9)	9.2 (6.1–12.1)	<0.05
Coronary-commissural angle, degrees	18.4 (4.2–36.5)	25.6 (16.2–36.6)	0.19	14.3 (5.3–26.4)	25.6 (17.5–41.1)	<0.01

Values are *n* (%), mean ± SD or median (IQR).

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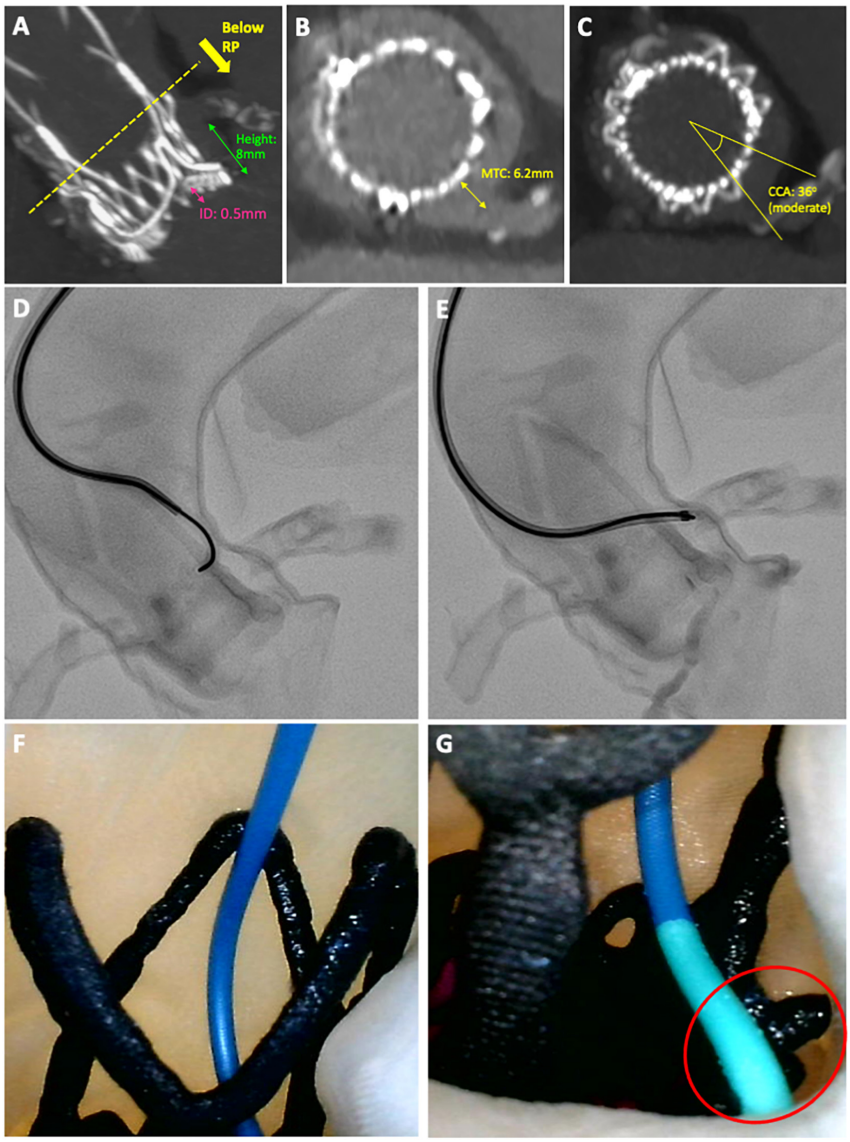

FIGURE 4
Case example of a challenging diagnostic cannulation. An 83-year old male underwent ACURATE neo implantation to treat a 14-year old degenerated Perimount23 surgical bioprosthesis. Post-procedural CT showed **(A)** a high implantation with low-lying coronary arteries, **(B)** a narrow gap between valve frame and aortic wall and **(C)** moderate overlap between the commissural posts and coronary arteries, all implying challenging cannulation. **(D,E)** Semi-selective cannulation of the LCA was achieved using an Amplatz Left 2 guiding catheter with 0.014 wire-assistance, after 17 min of fluoroscopy time and four attempts. **(F,G)** Camera placed internally demonstrating cannulation technique of approaching the ostium from above and resting the distal tip of the guiding catheter on the upper crown of the ACURATE neo adjacent to the LCA.

Assessing the feasibility of coronary access and PCI is increasingly relevant as TAVI expands toward younger and lower-risk patients who have an increased life-time risk for repeat invasive angiography due to progression of CAD (9–12). Studies using pre or post-procedural CT to virtually assess coronary access have suggested that challenging or un-feasible cannulation may occur following 9–35% TAVR (16–18), 27–78% of TAVI-in-TAVI (19, 20, 25) and 58% of ViV-TAVI (22) procedures. However, data from real studies of post TAVI cannulation are more re-assuring with success rates for diagnostic cannulation and PCI success ranging between 90–100 and 92–97%, respectively, even in the acute setting (11–14, 26–28).

In our study the feasibility for diagnostic angiography and PCI was 97 and 95%, respectively. These findings are encouraging in the setting of ViV-TAVI, where the presence of the SBV frame and leaflets should further hamper coronary cannulation. Several explanations for these favourable results could be considered. All cannulations were performed by senior interventionists experienced in catheter selection and

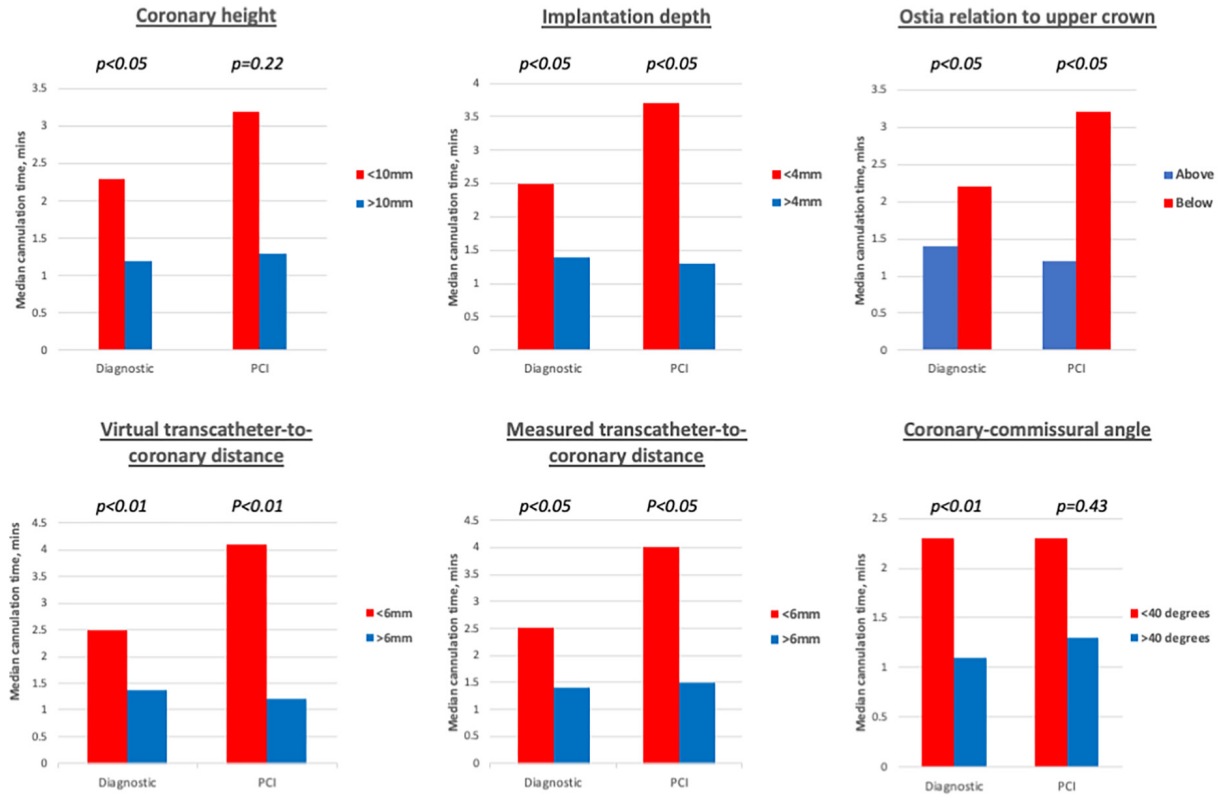

FIGURE 5
Diagnostic cannulations times associated with different imaging cut-offs. Prolonged diagnostic cannulation times were observed when coronary height < 10 mm, implantation < 4 mm, ostia arose below the upper crown, virtual and measured transcatheter-to-coronary distances < 6 mm and coronary-commissural angle < 40 degrees. For guiding catheter cannulations, significantly prolonged cannulation times were only observed for implantation depth < 4 mm, ostia arising below the upper crown, virtual, and measured transcatheter-to-coronary distances < 6 mm.

cannulation techniques required for post-TAVI coronary access (27). Moreover, the transcatheter valve design may have a significant impact upon the feasibility of coronary access (14, 16). All the patients underwent ViV-TAVI with the ACURATE neo valve, which has a split-level design consisting of a short lower stent frame and large open-celled upper stabilisation arches. This unique design is potentially advantageous for coronary access, as it provides operators with different possible cannulation routes to the coronary ostium (**Figure 3**). In contrast, valves with larger stent-frames such as the Corevalve/Evolut platform are associated with more challenging or un-feasible coronary cannulation although data is conflicting (11–14).

Factors associated with challenging cannulation

A combination of multiple anatomical, procedural and device-related factors contribute to the challenge of coronary access (14, 27). Proposed classification schemes for coronary access have highlighted three key factors: (1) implantation depth, (2) gap between valve frame and aortic wall and the (3) extent of commissural alignment (15, 29). Previously we showed that an implantation depth > 4 mm suggested more favourable coronary access without impacting upon post-procedural gradients (22). Similarly, our bench study demonstrates that an implantation depth > 4 mm was associated with a shorter cannulation time, more selective cannulations and fewer cannulation attempts when using a DC. Moreover, GC cannulation times were also shorter with advanced techniques required less frequently. The reason for favourable coronary access at lower valve implantations is that more ostia are likely to be located above the covered stent frame, which cannot be traversed by a catheter.

Ostia deemed challenging to cannulate had smaller aortic dimensions as assessed by SoV and STJ width. A narrow aortic sinus translates into a smaller gap available between the THV frame and aortic wall for subsequent catheter entry. Previous studies have used different methodologies to measure and evaluate this gap (14, 16–19, 22, 30), with current classification schemes suggesting that a 2 mm cut-off distance identifies

challenging or un-feasible coronary access (15, 29). However, in our cohort the median MTC distance was 7.55 mm and only one coronary ostium had a MTC gap < 2 mm. In contrast, we found that a cut-off of 6 mm was a more useful discriminator for challenging cannulation, with prolonged diagnostic cannulation times, increased attempts for guide catheter cannulation and fewer selective cannulations achieved when the MTC was < 6 mm compared to > 6 mm. Although a 2 mm gap allows for a 6Fr (∼1.8 mm) catheter to enter the aortic sinus, it may not account for the additional space required to manoeuvre the catheter in order to achieve stable, supportive and selective cannulation, particularly for guiding catheters. Greater insights into the necessary space required for successful cannulation might be obtained by analyzing the volume and three-dimensional morphology of the aortic sinuses (30).

Overlap between a THV commissural post and coronary ostia is common following TAVR and may pose a significant challenge to coronary cannulation (16, 18, 29, 31). However, to date no study has evaluated how the extent of commissural-coronary overlap can directly influence cannulation challenge and feasibility. In our cohort, severe overlap or mis-alignment, defined as a coronary-commissural angle (CCA) < 20° was present in 15/32 (47%) coronary ostia. The average CCA for challenging DC and GC cannulation was 14.3° and 18.4°, respectively. However, the impact of severe overlap was greater for GC cannulations, which required more attempts and advanced techniques and resulted in fewer selective cannulations. This finding could be explained by the fact that guiding catheters are stiffer, and the reduced flexibility makes it more challenging to navigate around the obstacle of the THV commissural post. Therefore, a 0.014" coronary wire or guide-extension catheter is often required to achieve selective cannulation with adequate support to complete the PCI. The incidence of severe coronary overlap is expected to be lower as procedural techniques designed to achieve commissural alignment with the ACURATE neo valve are adopted (32). Of note, in our cohort systematic techniques to achieve commissural alignment with the ACURATE neo valve were not adopted. However, the impact of these techniques in reducing the challenge of coronary access, particularly in the setting of ViV-TAVI remains to be determined.

Coronary protection with the chimney technique resulted in 2/64 (3%) DC and 3/64 (5%) GC cannulations being unfeasible. In one patient, PCI to both coronary arteries was not feasible due to an inability to cannulate the neo-ostia, which were located in an un-favourable position for cannulation (**Supplementary Figure 5**). This highlights the importance selecting an appropriate coronary protection strategy, which will also maintain long-term coronary access. Consideration should be given to the stent positioning, extent of stent protrusion and for certain cases alternative coronary protection strategies such as Bioprosthetic Aortic Scallop Intentional Laceration Coronary Artery (BASILICA) may be considered (33).

Limitations

Our study is limited to a small sample of ViV-TAVI patients in whom only the ACURATE neo valve was utilised, therefore these findings cannot be applied to other transcatheter heart valves. Cannulations were performed by two experienced interventional operators and variations in their preferred techniques could have accounted for some of the observed differences. Furthermore, cannulation challenge and feasibility may vary amongst operators particularly due to different levels of expertise in post-TAVI coronary access. However, in this context, the fact that certain cannulations were challenging or even un-feasible for experienced operators is highly relevant. Due to the design and assembly of the bench-models, all cannulations were performed from the femoral access route and catheters and techniques selected could be different if the cannulations were performed from the trans-radial access. The prosthetic descending aorta and femoral access may not have replicated real-life ilio-femoral tortuosity which can contribute to the challenge of coronary cannulation. Finally, the nature of bench-testing means that these results were obtained following cannulation of static ostia in *ex vivo* models, which may not fully reflect the dynamic *in vivo* conditions. However, given that these models were 3D printed based on post-procedural CT scans, ensured that the complex anatomical relationships between the transcatheter/surgical valves with surrounding aorta and coronary ostia was preserved.

Conclusion

In this exploratory bench-analysis, diagnostic angiography and PCI was found to be highly feasible following ViV-TAVI with the ACURATE neo valve. Important factors associated with non-feasible or challenging cannulation included prophylactic "chimney" stenting, higher implantation, narrower aortic sinus dimensions and severe commissural misalignment.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Maria Cecilia Hospital, Cotignola, Italy. The patients/participants provided their written informed consent to participate in this study. Written Informed Consent was

obtained for the publication of any potentially identifiable images or data included in this article.

Author contributions

AK, FP, AZ-H, CT, ACo, DD, and FGa contributed to conception and design of the study. AK, ACo, MT, AL, RR, and KC collected the data and maintained the database for the duration of the study. AK, FGi, AL, and FGa performed the computed tomography analysis and maintained the imaging database for the study. AK, AS, SB, and GC performed statistical analysis. AK wrote the first draft of the manuscript. AZ-H, AS, W-KK, GM, and FGi wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This study was supported by a research grant from Boston Scientific. The submission fees were covered by Imperial College London.

Conflict of interest

AK has received speaker fees from Boston Scientific. AM received an institutional grant from Boston Scientific. W-KK has received personal fees from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, and Meril Sciences. DD was scientific advisor to Boston Scientific.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.902564/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Post-procedural CT analysis. For each coronary ostium in the cohort, post-procedural CT analysis of implantation depth, relationship to upper crown, gap between valve frame and ostium and coronary-commissural angle was performed.

SUPPLEMENTARY FIGURE 2
Creation of 3D-printed model. Study flowchart demonstrating how post-procedural CT was segmented and processed to print the 3D models, which were then assembled for bench-testing under real catheterization laboratory conditions.

SUPPLEMENTARY FIGURE 3
Diagnostic and guiding catheters selected for cannulation. The Judkins Right 4 catheter was the most frequently selected catheter for the RCA whilst a greater range of catheters diagnostic and particularly guiding catheters were selected for cannulating the LCA.

SUPPLEMENTARY FIGURE 4
Operator reported difficulty in diagnostic and PCI cannulation for each patient model. The two operators were asked to report their difficulty in completing the diagnostic and PCI cannulations for each ostium. Responses were recorded on a scale of 1-10 (1 = extremely easy).

SUPPLEMENTARY FIGURE 5
Location of neo-ostium following chimney stenting. Case example of an 84-year old female who underwent ACURATE neo implantation to treat a degenerated Mitroflow prosthesis. Due to high-risk for coronary obstruction, coronary protection of the LCA **(A,C)** and RCA **(B,D)** using the "chimney" technique was performed. The yellow start denotes the location of the neo-stent which was un-feasible to cannulate.

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 16 September 2022
DOI 10.3389/fcvm.2022.988840

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 07 July 2022
ACCEPTED 30 August 2022
PUBLISHED 16 September 2022

CITATION
Schenk J, Kho E, Rellum S, Kromhout J, Vlaar APJ, Baan J, van Mourik MS, Jorstad HT, van der Ster BJP, Westerhof BE, Bruns S, Immink RV, Vis MM and Veelo DP (2022) Immediate reduction in left ventricular ejection time following TAVI is associated with improved quality of life.
Front. Cardiovasc. Med. 9:988840.
doi: 10.3389/fcvm.2022.988840

Immediate reduction in left ventricular ejection time following TAVI is associated with improved quality of life

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Background: TAVI has shown to result in immediate and sustained hemodynamic alterations and improvement in health-related quality of life (HRQoL), but previous studies have been suboptimal to predict who might benefit from TAVI. The relationship between immediate hemodynamic changes and outcome has not been studied before. This study sought to assess whether an immediate hemodynamic change, reflecting myocardial contractile reserve, following TAVI is associated with improved HRQoL. Furthermore, it assessed whether pre-procedural cardiac power index (CPI) and left ventricular ejection fraction (LVEF) could predict these changes.

Methods: During the TAVI procedure, blood pressure and systemic hemodynamics were prospectively collected with a Nexfin® non-invasive monitor. HRQoL was evaluated pre-procedurally and 12 weeks after the procedure, using the EQ-5D-5L classification tool.

Results: Overall, 97/114 (85%) of the included patients were eligible for analyses. Systolic, diastolic and mean arterial pressure, heart rate, and stroke volume increased immediately after TAVI (all $p < 0.005$), and left ventricular ejection time (LVET) immediately decreased with 10 ms (95%CI = −4 to −16, $p < 0.001$). Overall $HRQoL_{index}$ increased from 0.810 [0.662–0.914] before to 0.887 [0.718–0.953] after TAVI ($p = 0.016$). An immediate decrease in LVET was associated with an increase in $HRQoL_{index}$ (0.02 index points per 10 ms LVET decrease, $p = 0.041$). Pre-procedural CPI and LVEF did not predict hemodynamic changes or change in HRQoL.

Conclusion: TAVI resulted in an immediate hemodynamic response and increase in HRQoL. Immediate reduction in LVET, suggesting unloading of the ventricle, was associated with an increase in HRQoL, but neither pre-procedural CPI nor LVEF predicted these changes.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT03088787

KEYWORDS

TAVI, quality of life, ejection fraction, cardiac power index, hemodynamics

Introduction

The prevalence of severe aortic stenosis (AoS) in elderly (>75 years) is 3.4%, with a yearly mortality rate of 25% (1, 2). Transcatheter aortic valve implantation (TAVI) has been shown to reduce mortality and AoS related symptoms and to improve quality of life in the majority of patients (3). However, the risk of poor outcome 1 year after the procedure varies between 11 and 26% (3). Risk stratifying models, based on patient characteristics such as AoS severity, multi-morbidity, frailty and cognition, have been shown suboptimal in predicting clinical benefit from TAVI (3–5).

Repairing an aortic valve outflow obstruction results in significant hemodynamic alterations. Both immediate and sustained changes following TAVI have been studied, showing an overall increase in systolic blood pressure (6–11) and some (6, 7), but not all (8, 11), found an increase in stroke volume and cardiac output. An increase in blood pressure in the days or even weeks following TAVI has been associated with improved clinical outcome (11–13). However, the relationship between immediate hemodynamic changes and outcome has not been studied.

It has been hypothesized that a baseline difference in myocardial contractile reserve could affect hypertension onset and, consequently, the prognosis following TAVI (11). In addition, a meta-analysis showed an increased risk of mortality in patients with low (<30%) left ventricular ejection fraction (LVEF) compared to patients with normal LVEF (14). A recent study, using the LVEF (<50%) to classify left ventricular dysfunction, did not confirm the previously mentioned hypothesis (15).

Since myocardial contractility and the severity of the AoS can independently vary within and between patients, the averaged fraction of volume ejected by the heart might not be an ideal variable to classify left ventricular dysfunction in this particular population. The cardiac power index (CPI) is the product of simultaneously measured cardiac output and mean arterial pressure, indexed to the body surface area, representing the hydraulic function of the heart (16). CPI has been shown to correlate with varying outcomes in differing populations of patients with cardiovascular disease (17–21). Furthermore, baseline CPI was recently shown to be a strong predictor of 1 year mortality following TAVI (22).

In this study we hypothesize that an immediate hemodynamic response, reflecting a change in myocardial contractility (i.e., contractile reserve) following TAVI is associated with a post-procedural change in health-related quality of life (HRQoL). Furthermore, we aim to assess whether baseline LVEF and CPI, can be used to predict both the immediate hemodynamic response and a change in HRQoL.

Abbreviations: AoS, aortic stenosis; CPI, cardiac power index; HRQoL, health related quality of life; LVEF, left ventricular ejection fraction; LVET, left ventricular ejection time; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiogram.

Methods

Study design and ethical considerations

This was a single center, prospective cohort study conducted at the Amsterdam University Medical Centre, location AMC, in Amsterdam, the Netherlands. Prior to the study, the local medical ethical committee approved the study protocol and the trial was registered with the NIH, U.S. National Library of Medicine at ClinicalTrials.gov (NCT03088787). The trial was conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice, and written informed consent was obtained from each patient prior to inclusion. Patients were recruited on the day prior to their intervention, from the 30th of March 2017 until the 28th of February 2019.

Study participants

Patients ≥18 years old with severe degenerative aortic valve stenosis, scheduled for TAVI via femoral approach were eligible for inclusion. Patients with a congenital unicuspid or bicuspid valve; being treated with an intra-aortic balloon pump; with an

inability to perform a Nexfin measurement at the left-hand side, or a bodyweight below 40 kg were excluded.

Study outcomes and definitions

The primary outcome of this study was the association of immediate hemodynamic alterations with a change in HRQoL following TAVI. Secondary outcomes were the association of baseline LVEF and CPI with hemodynamic alterations and change in HRQoL.

The studied hemodynamic variables were computed from the continuous blood pressure waveform that was collected using a Nexfin® non-invasive blood pressure monitor at all time-points. Studied variables, at baseline, pre-procedure and post-procedure were: systolic, diastolic, and mean arterial pressure (MAP, mmHg); heart rate (beats·min^{-1}); stroke volume (SV, ml); cardiac output (CO, L·min^{-1}); systemic vascular resistance (SVR, dynes·s·cm^{-5}); left ventricular ejection time (LVET, ms), and the maximal rate of rise of systolic pressure (dP/dt, mmHg·s^{-1}). SV was calculated with the ^{cc}Nexfin CO-Trek algorithm, dividing the time-integral area under the systolic part of the arterial pressure curve by the aortic input impedance (23–25). CO was then calculated by multiplying SV with heart rate. Stroke work (SW) was calculated as SV multiplied by MAP (ml·mmHg^{-1}).

The hydraulic function of the heart was defined as the CPI (W·m^2) and was calculated as [(MAP * CO/451)] / body surface area (BSA, m^2) (19). CPI was additionally classified as low ($<$0.44 W·m^{-2}) or normal ($\geqq$0.44 W·m^{-2}) according to results by Grodin et al. (21). The EQ-5D-5L health state classification (26) was used to evaluate HRQoL.

Study procedures

Patients were treated according to the TAVI-procedure standard of practice, were kept awake and received local anesthesia. All patients received an Edwards SAPIEN 3 Transcatheter Valve, with some patients requiring aortic valvuloplasty prior to valve implementation.

Data collection and analyses

Baseline characteristics, including medical history, and transthoracic echocardiogram (TTE) findings were collected from electronic patient records. Pre-procedural left ventricular function (LVF) grade was collected from TTE findings. Pre-procedural LVEF was determined using automatic whole-heart segmentation in 4D Coronary Computed Tomography Angiography (CCTA). This deep learning-based method segments the cardiac chambers and myocardium, allowing automatic identification of end-systolic and end-diastolic phases and subsequent calculation of the ejection fraction (27). HRQoL status was evaluated pre-procedurally in the hospital, and repeated 12 weeks after the procedure by phone. $HRQoL_{index}$ scores were calculated using the Dutch tariff value set (28), ranging from −0.446 to 1, with a negative score indicating a health state worse than death.

Before starting the procedure, a finger cuff with a light-emitting and light sensitive diode for plethysmography (Nexfin, Edwards Lifesciences, Irvine, CA, USA) was strapped around the middle phalanx of the middle or index finger at the left hand to obtain a non-invasive continuous blood pressure registration (sampled at 200 Hz). Measurements were stopped at the end of the procedure, at discharge to a nursing ward.

Offline analysis of the blood pressure waveform data was performed with MATLAB (MathWorks, Inc, Natick, MA). Two researchers (JS and EK) manually selected three pre-defined artifact-free time frames. The baseline time frame consisted of 10 min of blood pressure data, collected in the treatment room in a supine position before the start of the procedure. The direct pre-TAVI time frame consisted of 20 s of artifact-free waveform data and was selected in the 3 min of data measured directly before valve implantation, or before initial aortic valvuloplasty, when performed. The direct post-TAVI time frame was selected in the 3 min of data measured directly after valve implantation (Figure 1).

Patients in whom no artifact-free waveform data could be selected, and patients who either needed pacemaker support or showed newly onset arrhythmia in the previously defined time windows, were excluded from further analysis.

Sample size

The sample size calculation technique for multiple regression, as defined by Green (29), was used to calculate the sample size. The effect size (f^2) of TAVI on the average $HRQoL_{index}$ score was estimated at 0.2. Given the a-priori interest in the association of ten predictors, 91 patients would provide 80% power to detect a statistically significant association for each predictor, with a 0.05 two sided significance level.

Statistical analyses

Continuous data are presented as median with interquartile range (IQR), or as a mean with standard deviation (SD) when normally distributed. Normality of distribution was assessed visually using histograms and Q-Q plots. Differences between continuous data were analyzed using the Student's *t*-test when normally distributed, or using the Wilcoxon rank-sum test when non-normally distributed. Categorical data are presented as frequencies with percentages. Differences between categorical

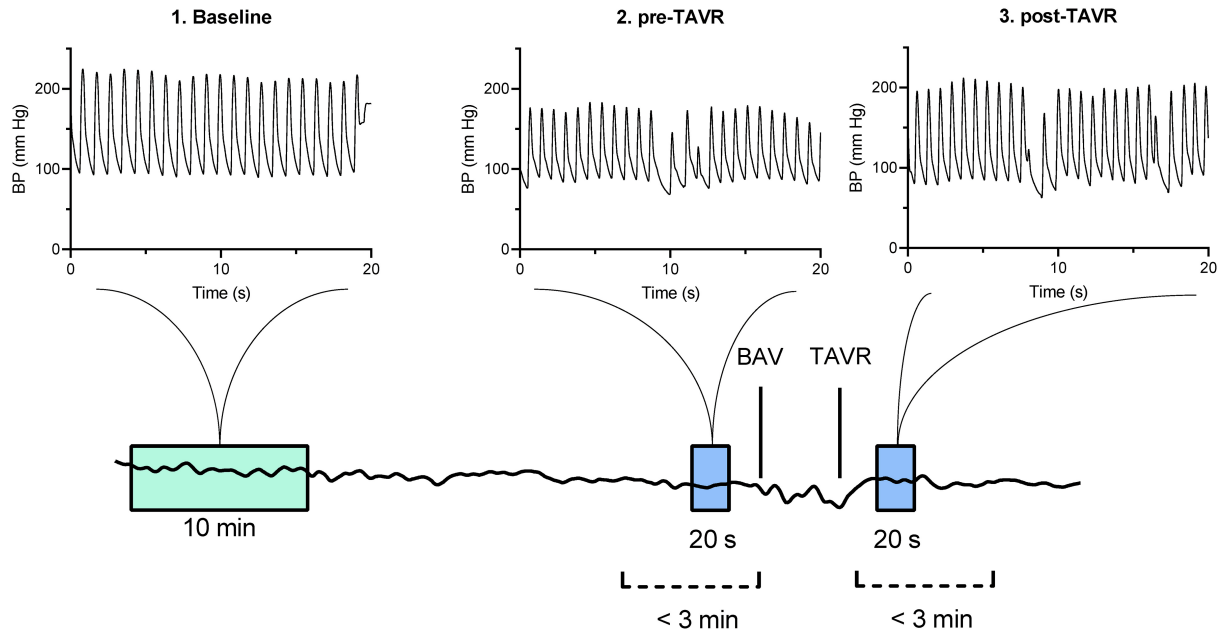

FIGURE 1
Timeframe and measurement selection, visualized within a random patients' total procedure waveform data. BAV, balloon aortic valvuloplasty; TAVI, Transcatheter Aortic Valve Implantation.

data were analyzed using the Fisher's exact test. Differences in the repeated measurements of hemodynamic variables (pre-TAVI vs. post-TAVI) were analyzed using the paired Student's *t*-test. During the planning stage of this study, valvuloplasty was identified as a possible confounding variable. It likely results in an increase in elapsed time between the pre- and post-TAVI measurement and has shown to induce ventricular stunning, potentially affecting pressure measurements (30). Potential group differences in immediate hemodynamic changes between patients with and without valvuloplasty prior to valve implementation were analyzed using generalized linear mixed-effect models.

Furthermore, generalized linear mixed-effect models were used to analyze: the association of immediate hemodynamic changes with change in HRQoL; the association of pre-procedural LVEF and CPI with immediate hemodynamic changes; and the association of pre-procedural CPI with change in HRQoL. Multiple imputation was used to impute missing data, assuming the data to be missing at random, validated by Little's MCAR test (31). When data was deemed missing at random, the multivariate imputation by chained equations (MICE) (32) method was used to impute data. For each of the analyses, $p < 0.05$ was considered statistically significant. Statistics were done using R v4.0.3 (R Core Team, Vienna, Austria), employing the nlme (v3.1-152) and the mice (v3.13.0) packages. JS had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

Measurements were performed in 114 patients, of whom 97 were eligible for analysis. No artifact-free waveform data could be selected in seven patients, seven other patients showed newly onset arrhythmia, and three patients were depending on pacemaker support directly following valve implantation (Figure 2). Table 1 shows the baseline characteristics of patients included for analysis. Mean age was 81 ± 6 years, median NT-pro-BNP level was 1,173 pg·ml^{-1} [581–3,121], and most patients suffered from pre-existing hypertension (60%). Table 2 shows the averages of pre-procedural TTE measurements. Aortic stenosis was graded as severe in most patients (92%), with a mean aortic valve area of 0.78 ± 0.18 cm^2. The average aortic valve mean,- and maximum gradient were 38.8 ± 15.4 mmHg and 65.5 ± 24.3 mmHg, respectively. The average pre-procedural LVEF was calculated at 54 ± 17%, and showed agreement with the TTE graded left ventricular function (Supplementary Figure 1).

Immediate hemodynamic changes after TAVI

The immediate change in hemodynamic variables was calculated for each patient and then averaged (Table 3, Figure 3).

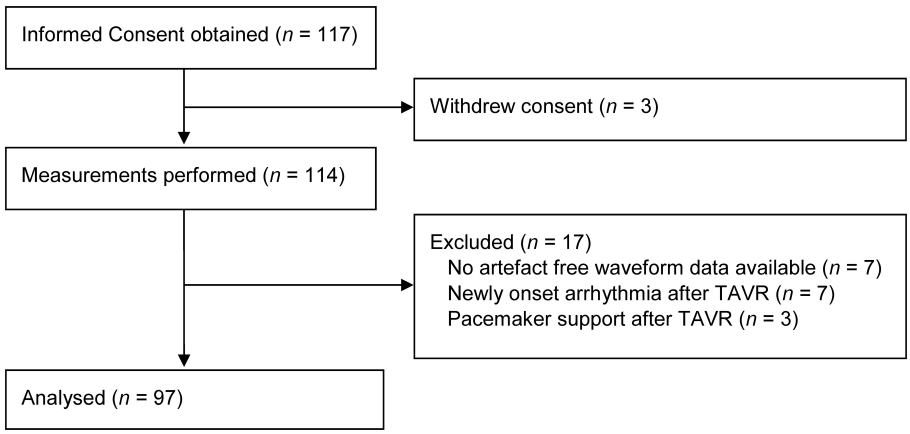

FIGURE 2
Study flow diagram.

On average, systolic, diastolic and mean arterial pressure increased significantly, as did the average heart rate and stroke volume. Left ventricular ejection time was reduced with 10 ms (95%CI = −4 ms to −16 ms, $p < 0.001$) and the maximal rate of rise of systolic pressure (dP/dt) was increased by 67% (414 mmHg·s^{-1}, 95%CI = 335 mmHg·s^{-1}-494 mmHg·s^{-1}, $p < 0.001$). There was no statistically significant immediate change in systemic vascular resistance.

There was a 336 s difference (95%CI = 269 s−402 s, $p < 0.001$) in elapsed time between pre-, and post-TAVI measurements when comparing patients with and without aortic valvuloplasty. When comparing these groups, no significant differences in immediate hemodynamic response were found.

Primary outcome: The association of immediate hemodynamic changes with changes in health-related quality of life

Median baseline $HRQoL_{index}$ score was 0.810 [0.662–0.914], and increased to 0.887 [0.718–0.953] after the procedure (Wilcoxon rank sum, $p = 0.016$). Baseline characteristics of patients with stable or improved HRQoL ($n = 64$) were comparable with those of patients with decreased HRQoL ($n = 33$; Supplementary Tables 1, 2). The post-procedure index score of one patient and baseline index scores of nine patients were imputed.

Employing generalized linear mixed models, and corrected for within-subject correlation in repeated measures, an immediate decrease in LVET was associated with a post-procedural increase in $HRQoL_{index}$ (0.02 index points increase per 10 ms LVET decrease, $p = 0.041$; Figure 4). Immediate changes in pressure (systolic, diastolic and mean arterial) and changes in other hemodynamic variables were not associated with a change in HRQoL.

Secondary outcomes

Median baseline CPI was 0.50 [0.38–0.64], with CPI classified as low in 36 patients and normal in 60 patients. Normal baseline CPI predicted a higher immediate change in SV (3.97 ml difference, $p = 0.049$) and a larger immediate change in SVR (240 dynes·sec·cm^{-5} difference, $p = 0.015$). Baseline CPI classifications did not predict a change in HRQoL. There was no association of pre-procedural LVEF with any of the hemodynamic changes or change in HRQoL.

Discussion

In this study we hypothesized that an immediate hemodynamic response, reflecting a change in myocardial contractility (i.e., contractile reserve), following TAVI would be associated with a post-procedural change in HRQoL. We confirm that TAVI resulted in an overall significant increase in HRQoL and found that an immediate decrease in LVET was associated with an increase in HRQoL. We confirmed the immediate hemodynamic response found in previous research (6–9), showing an increase in blood pressure, stroke volume, cardiac output and maximal rate of rise of systolic pressure (dP/dt) accompanied by a decrease in LVET, without a significant change in systemic vascular resistance. The secondary aim of this study was to investigate whether the hemodynamic and HRQoL changes could pre-procedurally be predicted using either the LVEF or CPI. We found that pre-procedural LVEF was not associated with any of the changes,

10.3389/fcvm.2022.988840

TABLE 1 Baseline characteristics.

	Overall ($n = 97$)
Male (%)	43 (44.3)
Age (y)	81 (5.6)
Weight (kg)	79.2 (18.3)
Height (cm)	167 (9)
BMI ($kg \cdot m^{-2}$)	28.1 (5.7)
ASA classification (%)	
I	1 (1.0)
II	6 (6.2)
III	73 (75.3)
IV	17 (17.5)
MET score (median [IQR])	6 [5, 6]
Medical history (%)	
Hypertension	58 (59.8)
Dyslipidemia	29 (29.9)
DM type II	29 (29.9)
Congestive heart failure	18 (18.6)
CVA	16 (16.5)
Myocardial Infarction	14 (14.4)
COPD	14 (14.4)
None	15 (15.5)
Pre-procedural hearth rhythm (%)	
Sinus rhythm	69 (71.1)
Atrial fibrillation	19 (19.6)
Other	9 (9.3)
NT-proBNP (median [IQR])	1173 [510, 3121]
LVEF	54 (17)

BMI, body mass index; ASA, American Society of Anaesthesiologists; MET, metabolic equivalent task; DM, diabetes mellitus; CVA, cerebral vascular accident; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVEF, left ventricular ejection fraction.

TABLE 2 Pre-procedural transthoracic echocardiogram results.

	Overall ($n = 97$)
Left ventricular function grade (%)	
Good	46 (47.9)
Mildly impaired	31 (32.3)
Moderately impaired	10 (10.4)
Poor	7 (7.3)
Very poor	2 (2.1)
Left Ventricular Hypertrophy (%)	58 (65.2)
Right ventricular function grade (%)	
Good	75 (83.3)
Mildly impaired	9 (10.0)
Moderately impaired	5 (5.6)
Poor	1 (1.1)
Very poor	0
Aortic insufficiency grade (%)	
None	16 (18.4)
Trace	9 (10.3)
Grade 1: Mild	44 (50.6)
Grade 2: Moderate	13 (14.9)
Grade 3: Moderate to severe	2 (2.3)
Grade 4: Severe	3 (3.4)
Aortic stenosis grade (%)	
Mild	2 (2.1)
Moderate	6 (6.4)
Severe	86 (91.5)
Aortic valve area (cm^2)	0.78 (0.18)
Aortic valve area index (cm^2/m^2)	0.38 (0.13)
Aortic valce max gradient (mmHg)	65.48 (24.26)
Aortic valve mean gradient (mmHg)	38.84 (15.38)

Pre-procedural transthoracic echocardiogram results were collected from patient records. Measurements and grading were performed and documented by an echocardiography specialist.

and that the CPI could predict the amount of immediate change in stroke volume and vascular resistance, but was not prognostic for change in HRQoL.

TAVI resulted in a significant and clinically relevant improvement in HRQoL, which is in line with various other studies (33–38). Patients requiring TAVI are mostly elderly with a high surgical risk, reduced exercise capacity, fatigue, and as a result, reduced HRQoL. Rather than mortality, improvement in quality of life is the most important patient-related outcome following TAVI (33). While association does not imply causation, the reduction in LVET found in this study might reflect the adaptive capacity of the left ventricle, following the sudden repair of the aortic outflow obstruction. We hypothesize that, when left ventricular volume loading remains equal and the afterload is greatly and suddenly reduced, an immediate reduction in time and contractile effort needed to eject the volume can be expected in patients with normal left ventricular function. Consequently, a reduction in LVET might reflect a myocardial contractile adaptive capacity, rather than a myocardial contractile reserve, previously hypothesized as the underlying mechanism for a difference in improved outcome following TAVI (11). Thus, we hypothesize that the immediate increase in maximal rate of rise of systolic pressure (dP/dt) simply reflects the sudden afterload reduction, rather than an increase in left ventricular contractility. When the left ventricle has the capacity to immediately adapt to the TAVI induced afterload reduction, pre-procedural symptoms that are primarily caused by the outflow obstruction might reduce, which could explain a potential increase in HRQoL. Patients with reduced adaptive capacity might show less immediate changes in hemodynamic variables reflecting this capacity,

TABLE 3 Immediate hemodynamic changes following TAVI.

	Pre-TAVI (SD)	Post-TAVI (SD)	Immediate change (95% CI)	% change	*p*-value
Systolic pressure (mmHg)	137.5 (27)	151.8 (31.9)	14.2 (9.4 to 19.0)	11%	**<0.001**
Diastolic pressure (mmHg)	65.6 (11.2)	68.9 (12.3)	3.2 (1.3 to 5.2)	6%	**0.001**
MAP (mmHg)	91.4 (15.8)	98 (18)	6.6 (3.7 to 9.5)	8%	**<0.001**
HR (beats·min^{-1})	72.7 (15.5)	76.2 (15.1)	3.6 (1.3 to 5.8)	7%	**0.002**
SV (ml)	69.2 (21.2)	72.6 (20.4)	3.4 (1.4 to 5.4)	7%	**0.001**
CO (L·min^{-1})	4.9 (1.7)	5.4 (1.8)	0.5 (0.3 to 0.7)	14%	**<0.001**
SVR (dynes·sec·cm^{-5})	1675 (722)	1604 (661)	−71 (−165 to 24)	0%	0.142
LVET (ms)	332 (33)	322 (33)	−10 (−16 to −4)	−3%	**<0.001**
dP/dt (mmHg·sec^{-1})	724 (368)	1138 (575)	414 (335 to 494)	67%	**<0.001**
SW (ml·mmHg^{-1})	6349 (2210)	7071 (2358)	722 (517 to 927)	14%	**<0.001**

Pre-TAVI and Post-TAVI values are given as mean with standard deviation. MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; LVET, left ventricular ejection time; dP/dt, maximal rate of rise of systolic pressure; SW, stroke work. Bold values indicate a statistically significant difference between the Pre-TAVI and Post-TAVI value.

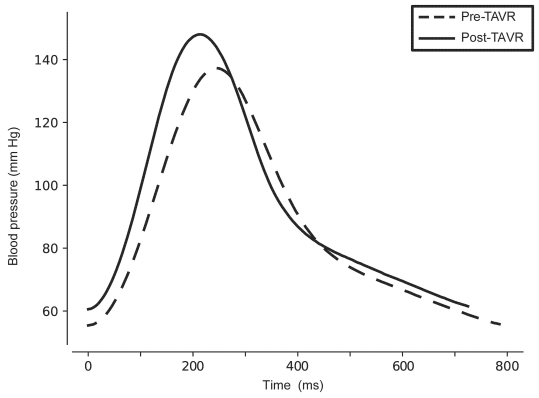

FIGURE 3
Visualization of the immediate blood pressure waveform change following TAVI. To compose this figure, waveform data of a representative patient was used, whose changes were in line with the average change of the studied population. Pre- (dashed) and Post-TAVI (solid) waveforms were composed by selecting the first 15 beats of each respective time window, trimmed to have the same duration and finally averaged.

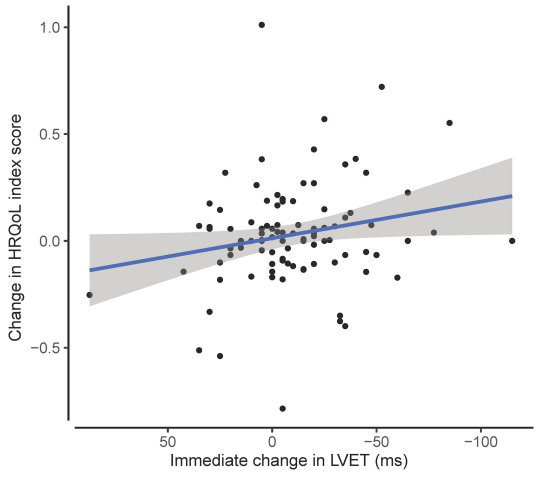

FIGURE 4
The association of the immediate change in LVET with the change in HRQoL index score following TAVI. Post TAVI HRQoL index score increases with 0.02 index points per 10ms immediate decrease in LVET ($p = 0.042$). HRQoL, health related quality of life; LVET, left ventricular ejection time.

despite reduction of the outflow obstruction. Consequently, these patients might show less reduction of pre-procedural symptoms and, with it, less change in the quality of life following the procedure.

Various studies have shown that an increase in heart rate can affect the LVET in a sample of patients without alterations to their cardiac structure. However, studies showing the linear relationship of heart rate with ejection time were conducted in a steady-state of circulating volume. We believe that, in this very specific sample, adjusting for the increase in heart rate would result in overcorrection and might induce a type II error. This is underlined by the fact that, besides an average 7% increase in HR, there also was an average 7% increase in stroke volume while LVET still decreased. The removal of the aortic stenosis thus allows the left ventricle to eject more volume, in a smaller amount of time. Moreover, when we analyzed the relationship between LVET and quality of life index in a multivariable regression and the change in heartrate (corrected for the change in stroke volume) is added as an effect modifying factor, the regression coefficient is altered by <10%, indicating that there is no significant effect modification (Supplementary Table 3).

The immediate reduction in LVET might already be present after initial valvuloplasty, which we did not assess in this study. It would be interesting for future studies to measure whether the subsequent valve implementation would have any additional

hemodynamic effect in patients that did not immediately show LVET reduction after valvuloplasty. When this is not the case, the immediate hemodynamic response after initial valvuloplasty might be indicative of the additional therapeutic effect of a subsequent valve implementation. This question was beyond the scope of this study. Furthermore, future studies might be able to provide insight in the correlation of immediate LVET reduction following TAVI with sustained increased blood pressure and mortality.

We found no relevant differences in baseline characteristics between patients with reduced HRQoL and patients with stable or improved HRQoL. Even though severely reduced pre-procedural LVEF has shown to predict mortality after TAVI (14), LVEF was not associated with differences in immediate hemodynamic alterations or change in HRQoL in our study. The CPI has previously shown to be the strongest hemodynamic correlate of mortality in varying cardiac patient groups (20), including the TAVI population (22). We hypothesized that the pre-procedural CPI would allow prediction of immediate hemodynamic alterations and improvement in HRQoL. Our results show that CPI, in line with LVEF, was unable to pre-procedurally identify patients that show an increase in HRQoL following TAVI. Furthermore, CPI was unable to predict the immediate alterations in variables reflecting a change in myocardial contractility.

Limitations

It has previously been shown that rapid ventricular pacing used for aortic valvuloplasty and valve deployment can result in ventricular stunning, which could have affected pressure measurements (30). However, when the immediate hemodynamic responses between patients with and without aortic valvuloplasty were compared, no significant differences were found, indicating that the potential additional impact of ventricular stunning in patients requiring valvuloplasty did not alter the results.

The cohort consisted of mainly elderly patients with severe AS. Therefore, the results might not be generalizable to other patient groups. Furthermore, the sample size of this prospectively collected cohort was not large, but the hemodynamic changes and the associations found were highly significant, indicating validity of the results. Additionally, since no flow data was collected, stroke volume and consequently the cardiac output were calculated with the ^{cc}Nexfin CO-Trek algorithm. Employing this algorithm to calculate stroke volume has shown to be less precise in specific subgroups of critically ill patients (39, 40). Non-invasive continuous blood pressure measurement has shown to be accurate in patients with severe aortic stenosis (41, 42). It is unclear whether severe aortic stenosis could affect stroke volume estimations. Since our calculations were based on repeated measurement within each patient, the percentile change in stroke volume is likely to accurately reflect the alterations following TAVI. The accuracy of non-invasively measuring change in stroke volume is underlined by comparable findings, where invasively acquired pressure waveforms in the ascending aorta were used to assess the acute hemodynamic effects following TAVI, using an identical methodology in time frame selection (8).

The increase in $HRQoL_{index}$ score was considered a clinically relevant change. The increase was larger than the estimation of minimally important difference when using the EQ-5D-5L health state classification tool, ranging from 0.037 to 0.069 (43). However, even though the EQ-5D-5L tool is easy to use and understand, it might pose a limitation due to its potential ceiling effect (26). Comparable future studies could provide additional insight using a more extensive survey, such as the Medical Outcomes Study 36-Item Short Form (44).

Conclusions

TAVI resulted in an immediate hemodynamic response and an increase in HRQoL. Immediate reduction in LVET, suggesting unloading of the ventricle, was associated with an increase in HRQoL, but neither the pre-procedural CPI nor LVEF was able to predict these changes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to j.schenk@amsterdamumc.nl.

Ethics statement

The studies involving human participants were reviewed and approved by Medisch Ethische Toetsingscommissie (METC): Amsterdam University Medical Centre, location AMC, Amsterdam, the Netherlands. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JS: conception, design, analysis and interpretation of data, and drafting of the manuscript. EK: analysis and interpretation of data and final approval of the manuscript submitted. SR and MV: conception and design and final approval of the manuscript submitted. JK, AV, JB, BW, and SB: final approval of the manuscript submitted. MM and HJ: conception and final approval of the manuscript submitted. BS: interpretation of data and final approval of the

manuscript submitted. RI: design and final approval of the manuscript submitted. DV: conception, design, interpretation of data, and final approval of the manuscript submitted. All authors contributed to the article and approved the submitted version.

Conflict of interest

Author AV has received personal fees and other from Edwards Lifesciences and Philips outside the submitted work. Author RI has received a grant from Edwards Lifesciences outside the submitted work. Author JB has received a grant from Edwards Lifesciences outside the submitted work. Author DV has received personal fees and other from Edwards Lifesciences, Philips and Hemologic outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.988840/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 21 September 2022
DOI 10.3389/fcvm.2022.973889

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 20 June 2022
ACCEPTED 30 August 2022
PUBLISHED 21 September 2022

CITATION
Tan CH, Lee Y-T, Kuo YC, Tsao T-P, Lee K-C, Hsiung M-C, Wei J, Lin K-C and Yin W-H (2022) Clinical outcomes and cumulative healthcare costs of TAVR vs. SAVR in Asia. *Front. Cardiovasc. Med.* 9:973889. doi: 10.3389/fcvm.2022.973889

Clinical outcomes and cumulative healthcare costs of TAVR vs. SAVR in Asia

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Objectives: This study compared transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) in terms of short- and long-term effectiveness.

Methods: This retrospective cohort study based on nationwide National Health Insurance claims data and Cause of Death data focused on adult patients (n = 3,643) who received SAVR (79%) or TAVR (21%) between 2015 and 2019. Propensity score overlap weighting was applied to account for selection bias. Primary outcomes included all-cause mortality (ACM), hospitalization for heart failure, and a composite endpoint of major adverse cardiac events (MACE). Secondary outcomes included medical utilization, hospital stay, and total medical costs at index admission for the procedure and in various post-procedure periods. The Cox proportional-hazard model with competing risk was used to investigate survival and incidental health outcomes. Generalized estimation equation (GEE) models were used to estimate differences in the utilization of medical resources and overall costs.

Results: After weighting, the mean age of the patients was 77.98 ± 5.86 years in the TAVR group and 77.98 ± 2.55 years in the SAVR group. More than half of the patients were female (53.94%). The incidence of negative outcomes was lower in the TAVR group than in the SAVR group, including 1-year ACM (11.39 vs. 17.98%) and 3-year ACM (15.77 vs. 23.85%). The risk of ACM was lower in the TAVR group (HR [95% CI]: 0.61 [0.44–0.84]; $P = 0.002$) as was the risk of CV death (HR [95% CI]: 0.47 [0.30–0.74]; $P = 0.001$) or MACE (HR [95% CI]: 0.66 [0.46–0.96]; $P = 0.0274$). Total medical costs were significantly higher in the TAVR group than in the SAVR in the first year after the procedure ($1,271.89 ± 4,048.36 vs. $887.20 ± 978.51; $P = 0.0266$); however, costs were similar in the second and third years after the procedure. The cumulative total medical costs after the procedure were significantly higher in the TAVR group than in the SAVR group (adjusted difference: $420.49 ± 176.48; $P = 0.0172$).

Conclusion: In this real-world cohort of patients with aortic stenosis, TAVR proved superior to SAVR in terms of clinical outcomes and survival with comparable medical utilization after the procedure.

KEYWORDS

aortic stenosis (AS), transcatheter aortic valve replacement (TAVR), surgical aortic valve replacement (SAVR), real-world effectiveness, health outcomes, healthcare utilization and associated direct cost

Introduction

Aortic stenosis (AS) is associated with a high risk of death; however, many patients cannot undergo surgical aortic valve replacement (SAVR) due to time constraints and surgery-related risks. Transcatheter aortic valve replacement (TAVR) is an alternative to SAVR for patients with severe AS. Since its introduction in 2002, more than 300,000 TAVR procedures have been performed worldwide.

Some previous randomized controlled trials comparing TAVR with SAVR reported that TAVR provides significant survival benefits for high-risk patients with severe AS (1–5). Other trials in intermediate-risk patients with severe AS reported that SAVR and TAVR are similar in terms of the risk of death or disabling stroke (6–8). Recent trials in low-risk patients reported that TAVR is superior to SAVR with respect to the composite rate of all-cause mortality (ACM), stroke or rehospitalization in the first year after the procedure (9), and non-inferior in the second year (10). Similar non-inferior findings have been reported in other clinical trials of low-risk patients (11, 12). Previous studies have also reported that pacemaker use and the incidence of left bundle branch block (LBBB) were higher among patients who received TAVR (11, 13). Nonetheless, TAVR tends to outperform SAVR in terms of infective endocarditis (14). Retrospective observational studies based on medical registries or hospital data have reported comparable clinical outcomes for the two procedures in terms of mortality and major adverse cardiac and cerebrovascular events (15–19); however, the availability of short or mid-term follow-up data has been limited.

Randomized controlled trials and observational studies have demonstrated the efficacy of TAVR within a selected cohort of patients and hospital centers; however, there has been limited research on the long-term dissemination and utilization of TAVR vs. SAVR in routine clinical practice. Previous studies pertaining to the cost of AS care have yielded inconsistent results. In general, the initial costs of TAVR are higher than those of SAVR; however, the utilization of post-procedure resources tends to be lower, with follow-up costs proportional to risk at the patient level. Essentially, researchers have yet to elucidate the actual costs associated with TAVR and SAVR over various post-procedure periods.

This study compared TAVR and SAVR in terms of effectiveness, medical utilization, and medical costs during the procedure and in various post-procedure phases.

Materials and methods

Study design and data source

This non-interventional, retrospective cohort study compared TAVR and SAVR in terms of clinical outcomes and medical utilization in a real-world setting. The single-payer mandatory National Health Insurance (NHI) program currently covers more than 99% of the 23 million residents of Taiwan. The NHI claims database comprises all longitudinal medical claims data from insured individuals, including ambulatory visits, hospital admissions, procedures, medication, rehabilitation, and home care since 1995. This study linked national NHI claims data and Cause of Death data from the Health and Welfare Data Science Center for the period 2015–2019.

This study was approved by the Institutional Review Board of National Yang Ming Chiao Tung University (IRB no. YM110048E).

Study cohort

Patients were diagnosed with AS based on the International Classification of Diseases, Ninth Revision, Clinical Modification, and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) (Supplementary Table 1). We recruited a total of 4,157 patients with AS who had undergone TAVR ($n = 505$) or SAVR ($n = 4,157$) during the study period (Figure 1). We excluded patients <20 years ($n = 13$), those who were missing gender data ($n = 8$), those who received both TAVR and SAVR during index hospitalization ($n = 1$), those who presented a malignant tumor before treatment ($n = 439$), those who received valve-related surgery during the index hospitalization, and those with a history of HIV ($n = 1$). A final study cohort of 3,643 patients was included in our analysis.

The first TAVR procedure in Taiwan was performed as a clinical trial in 2010 and the first TAVR device was approved by the Taiwan FDA in 2012. Early valve technologies included

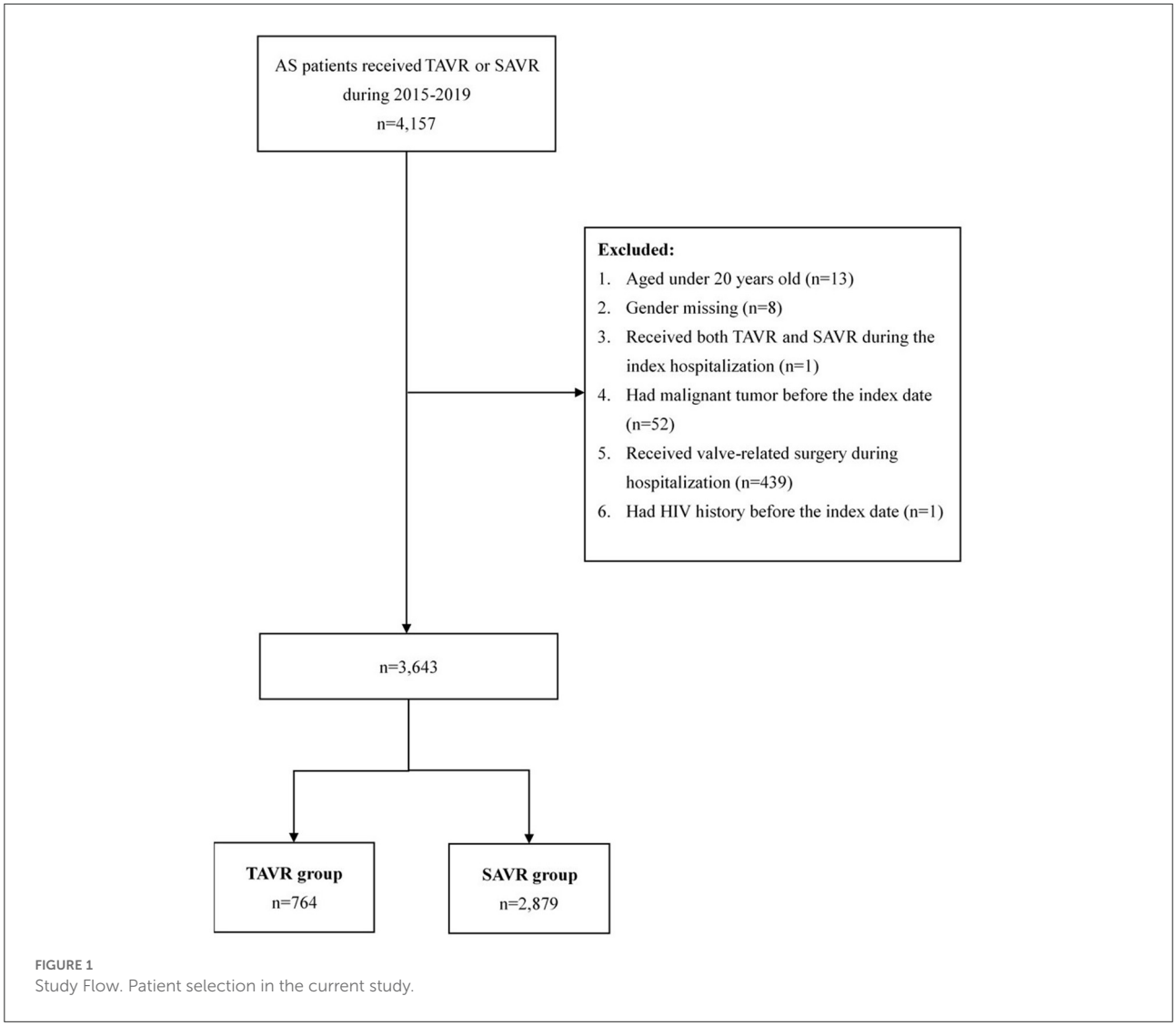

FIGURE 1
Study Flow. Patient selection in the current study.

CoreValve (Medtronic Inc., Minneapolis, MN), Lotus (Boston Scientific, Natick, MA), and Sapien XT (Edwards Lifesciences, Irvine, CA), which were launched, respectively, in 2012, 2015, and 2016. New-generation TAVR devices, including Evolut R (Medtronic Inc., Minneapolis, MN), Sapien 3 (Edwards Lifesciences, Irvine, CA) and Portico (Abbott Vascular Inc., Santa Clara, CA), all of which were introduced in 2017 (20). Most of the TAVR operations during the study period (2015–2019) involved new-generation devices.

Variable definitions

Primary outcomes included all-cause mortality (ACM), hospitalization for heart failure (HHF), and a composite major adverse cardiovascular event (MACE), including myocardial infarction (MI), stroke, and cardiovascular (CV) death. We also evaluated individual outcomes of MI, stroke, and CV death. The follow-up time was defined as the interval between TAVR or SAVR (index hospitalization) and the date of death, as recorded in the Cause of Death data or the date of observed outcomes.

Secondary outcomes in this study included the medical utilization and costs associated with TAVR or SAVR in the index admission patient receiving the procedure and in various periods after the procedure. The length of stay and hospitalization cost at index admission were estimated for cost analysis. Medical utilization related to AS, including the number of outpatient visits, length of stay, cost of outpatient visit, admission cost, and total medical cost, were aggregated for various post-procedure periods. We also evaluated cumulative medical costs, number of outpatient visits, and length of stay after the procedure.

The primary independent variable was the treatment strategy (TAVR or SAVR). Covariates included patient

age, gender, treatment year, marital status, education level, Elixhauser comorbidity index, hospital frailty risk score (21), dialysis, hypertension, received percutaneous coronary dilation during the 365 days prior to index hospitalization, concomitant medications (lipid-lowering therapies, antiplatelet, anticoagulants, non-steroidal anti-inflammatory drug (NSAID), angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, antihypertensive medications, and anti-diabetes medications), and ownership and accreditation level of hospital at which the patient received treatment. The definitions of comorbidities and concomitant medications are listed in the Supplementary Tables 1, 2.

Statistical analysis

Categorical and ordinal variables are presented as frequency and continuous variables are presented as mean and standard division (SD). Propensity scores based on the above variables were used to account for confounding by intervention. Overlap weighting was also used to minimize the influence of extreme propensity scores in individuals (22–24). Standardized differences (StD) between tcovariates of these two groups were compared before and after propensity score (PS) overlap weighting (25).

The cumulative incidence of adverse health outcomes was estimated using Kaplan-Meier survival curves based on propensity score overlap weighting. The Cox proportional hazard model with a robust estimator was used to evaluate the association of TAVR vs. SAVR treatment with ACM using propensity score overlap weighting. In evaluating health outcomes other than ACM (i.e., HHF, MI, stroke, and CV death), the Fine and Gray proportional sub-distribution hazard model with PS overlap weighting was used to account for competing risk of death. Adjusted hazard ratios for health outcomes are presented. Prespecified subgroup analysis was conducted according to age group (<70 years and ≧70 years), gender, comorbidities, prevalent dialysis, hypertension, and hospital frailty risk score. The proportional hazard assumptions were assessed using a graphic plot of $\ln\{-ln[S(t)]\}$ curves of the two treatment groups, wherein the appearance of reasonably parallel lines indicated no violation. In sensitivity analysis, we applied landmark estimates obtained using the Kaplan-Meier method with an 18-month grace period after the procedure to avoid immortal-time bias and reverse causation.

Generalized estimation equation (GEE) models were used to estimate the effects of the treatment strategy on the number of outpatient visits, length of stay, and costs. All costs are presented in US dollars ($) based on an exchange rate from TWD of 1:28. All p-values were two-sided and $P < 0.05$ was considered statistically significant. The syntax "PROC PHREG" was used to analyze health outcomes with time to event, while "PROC GENMOD" was used to analyze medical utilization and costs. All analyses were performed using SAS version 9.4 (SAS, Gray, North Carolina).

Results

Participant characteristics

A total of 3,643 patients were involved in the analytic dataset, including 764 who underwent TAVR and 2,879 who underwent SAVR. The mean age was 77.98 years (SD = 5.86), a small majority (53.94%) were women, and 22.07% of the patients had previously received percutaneous coronary dilatation. The mean Elixhauser comorbidity index was 1.46 (SD = 0.96). As for hospital level, 38.79% of the patients received treatment in a public hospital and 66.42% received treatment in a medical center. Table 1 presents the demographics of patients at baseline before and after propensity score overlap weighting.

Clinical outcomes

Within a median follow-up of 2.02 years (Q1–Q3: 0.81–3.49; mean ± SD: 2.20 ± 1.51), a total of 162 deaths occurred, including 88 deaths due to CV incidents. In-hospital mortality was higher among patients who underwent SAVR than among those who underwent TAVR (10.92% vs. 3.83%), and 30-day mortality after discharge was also higher among patients who underwent SAVR (8.08% vs. 2.26%) (Supplementary Table 3). Prior to adjustment, the TAVR group had a lower percentage of patients free from hospitalization due to heart failure (HHF) ($P = 0.0049$), major adverse cardiovascular event (MACE) ($P = 0.0002$), cardiovascular death ($P < 0.0001$), and all-cause mortality ($P < 0.0001$; Figure 2). The landmark estimates of all-cause mortality at 18 months were consistent (Supplementary Figure 1).

The total number of deaths per 1,000 person-years were 82.40 and 130.51 in the TAVR and SAVR groups, respectively. The number of cardiovascular deaths per 1,000 person-years were 36.54 and 79.27 in the TAVR and SAVR groups, respectively. The weighted rates of MACE per 1000 person-years were 65.91 and 101.65 in the TAVR and SAVR groups, respectively. After propensity score overlap weighting, TAVR was significantly associated with a lower risk of all-cause mortality (HR, 0.61 [95% CI, 0.44–0.84]), major adverse cardiovascular event (HR, 0.66 [95%, 0.46–0.96], and cardiovascular death (HR, 0.47 [95% CI, 0.30–0.74]) (Table 2). We observed no significant differences between the TAVR and SAVR groups in terms of the risk of hospitalization due to heart failure, myocardial infarction, or stroke.

In subgroup analysis (Figure 3), the risks of all-cause mortality, CV death, and MACE were significantly lower in the TAVR group than in the SAVR group for patients

TABLE 1 Baseline characteristics of patients before and after propensity score overlap weighting.

	Unweighted			After propensity score weighting		
	TAVR ($n = 764$)	SAVR ($n = 2,879$)	StD	TAVR	SAVR	StD
Year of treatment, %						
2015	15.84	25.04	0.143	18.52	18.52	0.000
2016	20.55	18.27		22.03	22.03	
2017	21.47	17.75		20.20	20.20	
2018	21.73	19.45		20.41	20.41	
2019	20.42	19.49		18.84	18.84	
Age, mean (SD)	81.32(7.76)	66.97(11.76)	1.440	77.98(5.86)	77.98(2.55)	0.000
Gender, %						
Male	46.07	56.58	−0.211	46.06	46.06	0.000
Female	53.93	43.42		53.94	53.94	
Marital status, %						
Unmarried	1.18	5.52	0.335	1.63	1.63	0.000
Married	57.85	67.14		61.12	61.12	
Divorced, widowed, or others	40.97	27.34		37.25	37.25	
Educational level, %						
Bachelor's, master's, and doctoral degree	70.94	68.08	−0.035	76.19	76.19	0.000
High school graduate	17.15	22.96		15.41	15.41	
Others	11.91	8.96		8.40	8.40	
Comorbidity in 365 days before the index hospitalization, %						
Elixhauser comorbidity index, mean (SD)	1.58(1.41)	1.02(1.27)	0.420	1.46(0.96)	1.46(0.53)	0.000
Hospital frailty risk score, mean (SD)	0.79(1.50)	1.26(1.90)	0.279	1.15(1.24)	1.18(0.66)	−0.032
Median (Q1–Q3)	0(0–1.4)	0(0–2.05)		0(0–1.8)	0(0–1.8)	
Dialysis	22.12	18.51	0.090	23.94	23.94	0.000
Hypertension	27.88	19.31	0.203	27.38	27.38	0.000
Received PCI/CABG	31.54	10.80	0.525	22.07	22.07	0.000
Concomitant medication in 365d before the index hospitalization, %						
Statins	54.06	46.82	0.145	54.26	54.26	0.000
Other lipid-lowering drugs, excluding statins	4.71	5.18	−0.021	5.85	5.85	0.000
Antiplatelet	76.05	62.52	0.296	73.67	73.67	0.000
Anticoagulant	18.59	9.62	0.260	15.43	15.43	0.000
NSAID	66.88	71.38	−0.097	68.88	68.88	0.000
ACEI	15.45	15.46	0.000	15.43	15.43	0.000
ARB	62.70	53.00	0.197	61.16	61.16	0.000
Beta blocker	65.97	59.92	0.126	65.16	65.16	0.000
Calcium channel blocker	64.92	51.34	0.278	62.29	62.29	0.000
Thiazide	14.4	6.88	0.246	11.58	11.58	0.000
Loop diuretic	61.26	43.49	0.362	55.42	55.42	0.000
Metformin	15.58	14.90	0.019	15.98	15.98	0.000
Oral hypoglycemic agent	31.15	24.66	0.145	30.66	30.66	0.000
Insulin	3.53	3.02	0.029	3.37	3.37	0.000
Hospital ownership, %						
Public hospital	42.02	38.35	−0.046	38.78	38.78	0.000
Private hospital	8.38	11.11		9.15	9.15	
Non-profit hospital	49.61	50.54		52.07	52.07	
Hospital accreditation level, %						
Medical center	67.67	69.95	0.045	66.42	66.42	0.000
Regional hospital	32.33	29.45		33.58	33.58	
Local hospital	0	0.59		0.00	0.00	

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; StD, standardized difference; NSAID, non-steroidal anti-inflammatory drug; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

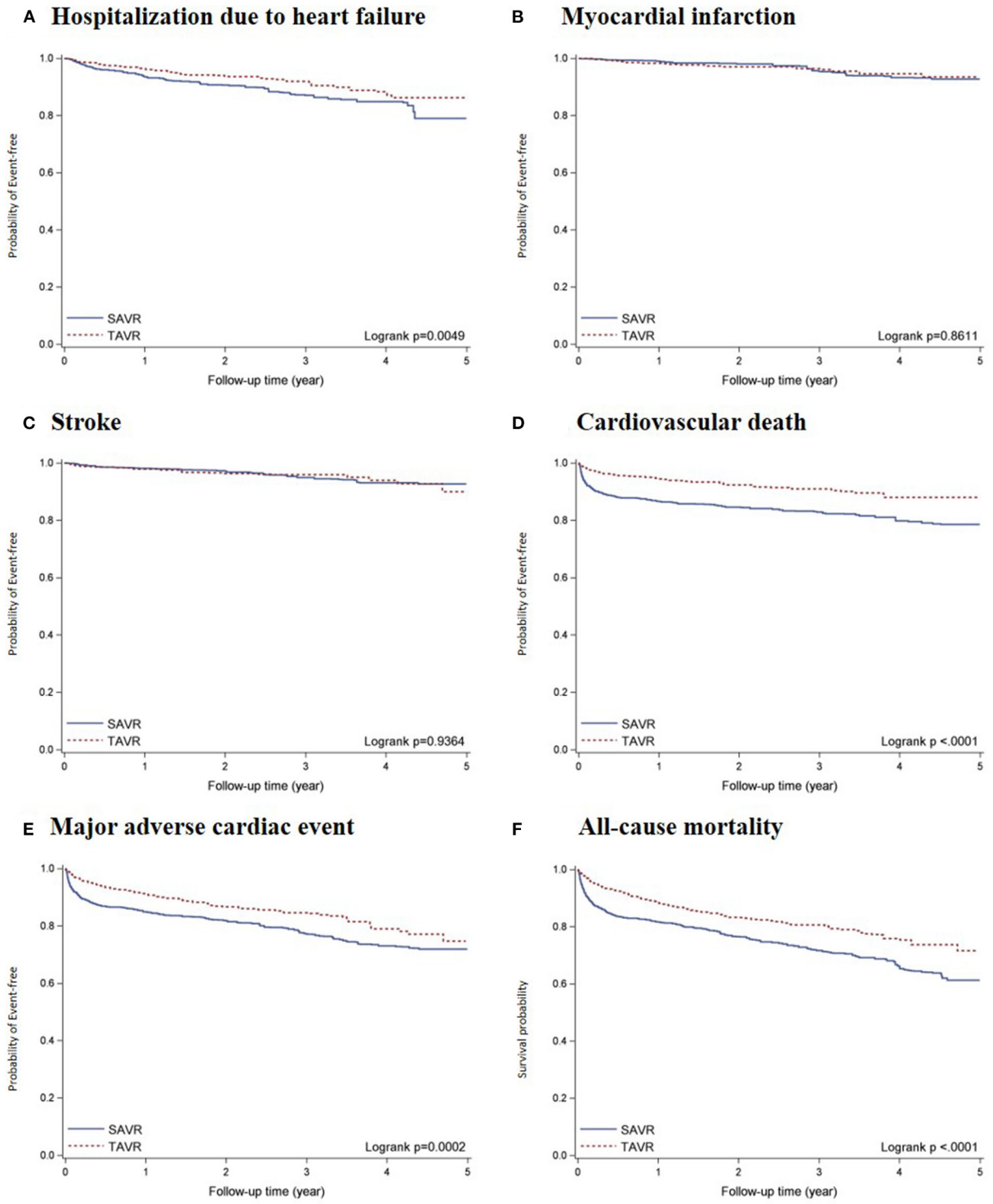

FIGURE 2
Kaplan-Meier survival curves of all-cause mortality and incident CV-related outcomes comparing TAVR vs. SAVR after propensity score overlap weighting: **(A)** HHF; **(B)** MI; **(C)** Stroke; **(D)** CV death; **(E)** MACE; and **(F)** ACM. Results of Kaplan-Meier survival analysis of primary and secondary outcomes after propensity score overlap weighting.

TABLE 2 Comparison of TAVR and SAVR in terms of health outcomes in 3,643 AS patients after propensity score overlap weighting.

	No. of events (%)		Follow-up period (PYs)		Weighted rate/ 1,000 PYs	adj-HR (95% CI)	*P*
			mean (SD)	median (Q1–Q3)			
HHF							
SAVR	34	9.06	1.84 (0.52)	1.66 (0.46–2.98)	49.26	1.00 [Reference]	
TAVR	25	6.66	2.04 (1.01)	1.79 (0.73–3.16)	32.65	0.78 (0.46–1.33)	0.3654
MI							
SAVR	10	2.62	1.94 (0.53)	1.77 (0.59–3.04)	13.53	1.00 [Reference]	
TAVR	11	2.96	2.08 (1.01)	1.95 (0.78–3.24)	14.24	1.33 (0.54–3.25)	0.5340
Stroke							
SAVR	12	3.23	1.93 (0.53)	1.77 (0.56–3.05)	16.75	1.00 [Reference]	
TAVR	13	3.53	2.07 (1.01)	1.90 (0.78–3.24)	17.06	1.28 (0.56–2.93)	0.5649
CV death							
SAVR	59	15.62	1.97 (0.53)	1.80 (0.60–3.10)	79.27	1.00 [Reference]	
TAVR	29	7.71	2.11 (1.01)	1.99 (0.82–3.28)	36.54	0.47 (0.30–0.74)	0.0011
MACE							
SAVR	73	19.42	1.91 (0.52)	1.76 (0.56–3.01)	101.65	1.00 [Reference]	
TAVR	51	13.51	2.05 (1.01)	1.80 (0.75–3.18)	65.91	0.66 (0.46–0.96)	0.0274
ACM							
SAVR	97	25.71	1.97 (0.53)	1.80 (0.60–3.10)	130.51	1.00 [Reference]	
TAVR	65	17.39	2.11 (1.01)	1.99 (0.82–3.28)	82.40	0.61 (0.44–0.84)	0.0022

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; HHF, hospitalization due to heart failure; MI, myocardial infarction; CV, cardiovascular; MACE, major adverse cardiac event; ACM, all-cause mortality.

aged >70 years, females, and those with a low Elixhauser comorbidity index, regardless of the hospital frailty risk score. TAVR was also associated with a lower risk of all-cause mortality among patients with a history of dialysis (HR, 0.59 [95% CI, 0.37–0.95]) as well as among those without a history of dialysis (HR, 0.62 [95% CI, 0.39–0.97]).

Medical utilization and costs

The medical utilization and costs at admission and in post-procedure periods are reported in Table 3. The mean length of stay during the index hospitalization was shorter in the TAVR group than in the SAVR group (19.20 ± 14.37 days vs. 29.50 ± 9.61 days, $P < 0.0001$). Hospitalization costs were significantly lower in the TAVR group ($14,016.81 ± 8,460.95) than in the SAVR group ($22,752.06 ± 5,835.91) ($P < 0.0001$). The mean aggregated total medical costs, including all ambulatory visits and all admissions in the first year after treatment, were $1,271.89 (SD = 4,048.36) in the TAVR group and $887.20 (SD = 978.51) in the SAVR group ($P = 0.0138$). However, note that we did not observe a significant difference between the TAVR and SAVR groups in terms of total medical costs in the second ($P = 0.1256$) or third year ($P = 0.5997$) after treatment. Cost associated with outpatient visits in the second year was higher in the TAVR group than in the SAVR group ($393.60 ± 812.47 vs. $299.68 ± 218.77; $P = 0.0425$).

In the multivariate analysis (Table 3), the length of stay (adjusted difference: $-10.24 ± 0.73, $P < 0.0001$) and the corresponding hospitalization costs (adjusted difference: $-8,711.25 ± 423.46, $P < 0.0001$) of index admission were lower for patients who underwent TAVR than for those who underwent SAVR. The cost of outpatient visits in the first, second, and third years after treatment was significantly higher for patients who underwent TAVR than for those who underwent SAVR. Furthermore, total medical costs in the first year after treatment were higher for the TAVR group than for the SAVR group (adjusted difference: $339.47 ± 153.11, $P = 0.0266$), due to higher costs for outpatient visits in the TAVR group. No significant differences were observed between the TAVR and SAVR groups in terms of total medical cost in the second and third years after the procedure.

During the 5-year follow-up period, the cumulative total medical costs associated with TAVR ($2,078.12 ± 4,480.30) were slightly higher than those of SAVR ($1,558.62 ± 1,368.77; $P = 0.0480$). After adjustment for other covariates, cumulative medical costs were significantly higher in the TAVR group than in the SAVR group (adjusted difference: $420.49 ± 176.48, $P = 0.0172$), whereas the cumulative length of stay was shorter in the TAVR group (adjusted difference: $-1.06 ± 0.47$, $P = 0.0245$).

	adj-HR (95% CI)	p-value	Interaction p-value
All-cause mortality			
Age			0.9675
<70 yrs	0.83 (0.23 - 3.04)	0.7806	
>=70 yrs	0.59 (0.42 - 0.82)	0.0020	
Gender			0.6083
Male	0.72 (0.46 - 1.14)	0.1603	
Female	0.51 (0.32 - 0.83)	0.0062	
Elixhause comorbidity index			0.9461
<2	0.53 (0.33 - 0.87)	0.0118	
>=2	0.68 (0.43 - 1.06)	0.0850	
Hopsital frailty risk score			0.8024
<2	0.51 (0.33 - 0.78)	0.0018	
>=2	0.71 (0.42 - 1.22)	0.2146	
Dialysis history			0.6548
No	0.59 (0.37 - 0.95)	0.0289	
Yes	0.62 (0.39 - 0.97)	0.0382	
CV death			
Age			0.6774
<70 yrs	0.39 (0.04 - 3.55)	0.4033	
>=70 yrs	0.47 (0.29 - 0.75)	0.0017	
Gender			0.5350
Male	0.69 (0.35 - 1.36)	0.2801	
Female	0.32 (0.16 - 0.65)	0.0015	
Elixhause comorbidity index			0.4523
<2	0.38 (0.20 - 0.72)	0.0029	
>=2	0.59 (0.29 - 1.23)	0.1611	
Hopsital frailty risk score			0.3004
<2	0.34 (0.18 - 0.63)	0.0006	
>=2	0.69 (0.29 - 1.66)	0.4089	
Dialysis history			0.1771
No	0.35 (0.17 - 0.71)	0.0038	
Yes	0.63 (0.34 - 1.19)	0.1568	
MACE			
Age			0.6616
<70 yrs	0.53 (0.13 - 2.26)	0.3937	
>=70 yrs	0.66 (0.44 - 0.98)	0.0382	
Gender			0.4974
Male	0.84 (0.48 - 1.49)	0.5591	
Female	0.52 (0.31 - 0.88)	0.0150	
Elixhause comorbidity index			0.5731
<2	0.51 (0.29 - 0.88)	0.0162	
>=2	0.82 (0.49 - 1.39)	0.4696	
Hopsital frailty risk score			0.4048
<2	0.54 (0.33 - 0.87)	0.0107	
>=2	0.90 (0.45 - 1.80)	0.7676	
Dialysis history			0.3808
No	0.64 (0.38 - 1.09)	0.0982	
Yes	0.71 (0.41 - 1.23)	0.2232	

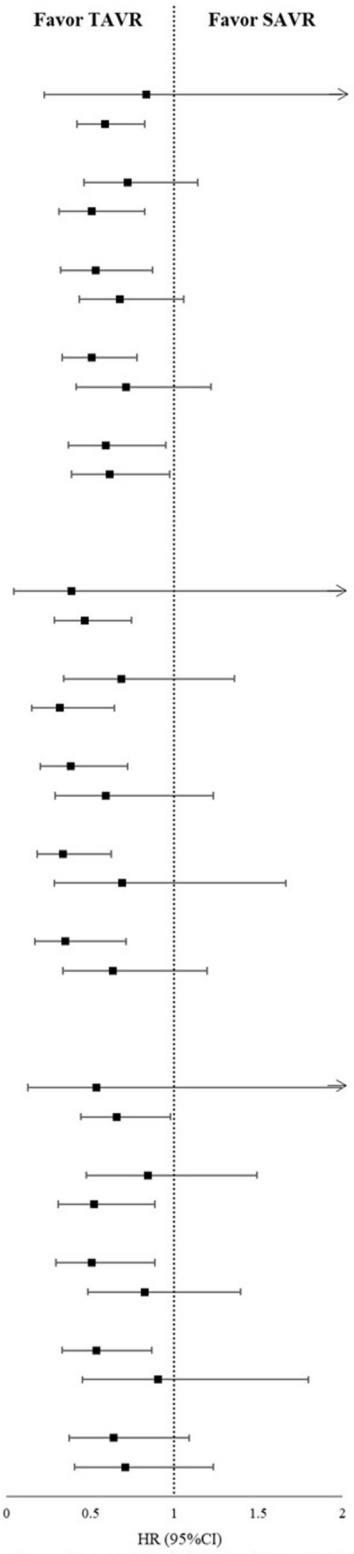

FIGURE 3
The impact of the interaction between selected categories and TAVR vs. SAVR on the risk of all-cause mortality, CV death, and MACE, after propensity score overlap weighting. Comparison of TAVR and SAVR in terms of MACE, CV death, and ACM among selected baseline characteristics after propensity score overlap weighting. Subgroup analysis comparing TAVR and SAVR as a function of age group, gender, comorbidity score, hospital frailty risk score, and history of dialysis. Outcomes included in the subgroup analysis were all-cause mortality, cardiovascular death, and major adverse cardiovascular event.

TABLE 3 Medical utilization during surgery and in different post-procedure periods after propensity score overlap weighting.

	TAVR	SAVR	difference (TAVR-SAVR)	*P*	adj-difference (TAVR-SAVR)	*P*
	Mean (SD)	Mean (SD)	Estimate (SE)		Estimate (SE)	
Medical utilization of index hospitalization						
Length of stay (day)	19.20 (14.37)	29.50 (9.61)	−10.30 (0.89)	<.0001	−10.24 (0.73)	<.0001
Median (Q1–Q3)	13 (8–12)	21 (14–35)				
Hospitalization cost (US$)	14,016.81 (8,460.95)	22,752.06 (5,835.91)	−8,735.25 (530.07)	<.0001	−8,711.25 (423.46)	<.0001
Medical utilization in 1st year after index hospitalization						
No. of outpatient visits	7.88 (5.71)	7.55 (2.82)	0.33 (0.28)	0.2262	0.33 (0.27)	0.2164
Length of stay (day)	1.01 (5.98)	1.48 (3.61)	−0.47 (0.32)	0.1428	−0.55 (0.31)	0.0755
Outpatient visit cost (US$)	747.41 (678.07)	495.61 (235.24)	251.80 (28.51)	<.0001	252.34 (27.76)	<.0001
Hospitalization cost (US$)	524.48 (3,977.36)	391.59 (948.42)	132.89 (153.05)	0.3853	87.12 (150.24)	0.5620
Total medical cost (US$)	1,271.89 (4,048.36)	887.20 (978.51)	384.69 (156.16)	0.0138	339.47 (153.11)	0.0266
Medical utilization in 2nd year after index hospitalization						
No. of outpatient visit	8.18 (5.81)	8.09 (2.79)	0.09 (0.36)	0.8012	0.13 (0.28)	0.6454
Length of stay (day)	0.12 (1.00)	0.30 (1.08)	−0.18 (0.08)	0.0270	−0.18 (0.08)	0.0322
Outpatient visit cost (US$)	393.60 (812.47)	299.68 (218.77)	93.92 (46.22)	0.0425	88.94 (31.83)	0.0052
Hospitalization cost (US$)	43.20 (349.78)	76.25 (280.50)	−33.05 (24.95)	0.1854	−29.64 (23.22)	0.2017
Total medical cost (US$)	436.80 (877.04)	375.93 (352.32)	60.87 (52.07)	0.2427	59.29 (38.71)	0.1256
Medical utilization in 3rd year after index hospitalization						
No. of outpatient visit	2.48 (3.41)	2.50 (2.00)	−0.02 (0.22)	0.9361	−0.07 (0.17)	0.6653
Length of stay (day)	0.08 (1.00)	0.34 (2.27)	−0.26 (0.14)	0.0681	−0.26 (0.17)	0.1127
Outpatient visit cost (US$)	265.10 (787.76)	188.39 (191.54)	76.71 (45.31)	0.0909	70.08 (30.52)	0.0217
Hospitalization cost (US$)	24.30 (293.34)	70.89 (346.97)	−46.59 (25.99)	0.0732	−48.74 (26.98)	0.0708
Total medical cost (US$)	289.40 (846.25)	259.28 (399.06)	30.12 (52.59)	0.5669	21.34 (40.66)	0.5997
Cumulative medical utilization after index hospitalization						
Total medical cost (US$)	2,078.12 (4,480.30)	1,558.62 (1,368.77)	489.50 (247.20)	0.0480	420.49 (176.48)	0.0172
Total outpatient visits	14.96 (12.96)	14.85 (7.27)	0.11 (0.79)	0.8906	−0.09 (0.62)	0.8857
Total length of stay	1.26 (6.21)	2.22 (6.41)	−0.97 (0.48)	0.0438	−1.06 (0.47)	0.0245

Discussion

This study compared TAVR and SAVR for the treatment of AS based on a large nationwide claim database. To date, this is the most extensive and comprehensive report on patient demographics, clinical outcomes, and medical utilization during and after treatment. The principal findings of this study can be summarized as follows: (1) TAVR is superior to SAVR in terms of overall survival, CV-related survival, and MACE; and (2) TAVR shortens the length of stay which reduced hospitalization costs during the procedure but had slightly higher cumulative medical cost after the procedure.

Observational data suggest that TAVR is superior to SAVR in terms of mortality. Based on the National Readmission Database, Lemor et al. reported that TAVR was superior to SAVR in terms of in-hospital mortality rate, 30-day mortality, and 30-day readmission rate (17). Based on a nationwide registry in Finland, Virtanen et al. reported that TAVR and SAVR were similar in terms of 30-day mortality and 3-year survival (18). In our 5-year follow-up of the current study, the risk of patients experiencing MACE was 34% lower in the TAVR group compared to the SAVR group, the risk of CV death was 53% lower, and the risk of ACM was 39% lower. Our landmark analysis on outcomes for the period 18 months to 5 years after the procedure revealed that TAVR was associated with a lower likelihood of all-cause death. The low incidence of mortality in the TAVR group during this time period may be attributed to a lower incidence of bleeding, transfusion, and post-operative complications (3, 14, 18, 26).

Advanced kidney disease was identified as a risk factor for patients in both groups and a significant predictor of mortality for patients in the TAVR group (27). Previous studies reported that the short-term survival benefits of TAVR therapy are also applicable to patients with chronic kidney disease or end-stage renal disease (28–30). We also found that within a 5-year follow-up period, the risk of all-cause mortality in the TAVR group was 38% lower among patients with a history of dialysis and 41% lower among those without a history of dialysis. As in

previous studies, we determined that the benefits of TAVR could extend to patients with or without advanced kidney disease who did not undergo surgery. In the current study, TAVR was associated with a lower risk of all-cause mortality, CV death, and major adverse cardiovascular events among patients with a relatively low hospital frailty score. This result was consistent with previous studies showing that frail patients inevitably face an elevated risk of mortality after receiving TAVR (31–33). All-cause mortality at 1 year after TAVR in this study (11.39%) was lower than that of the high-risk patient in the PARTNER I trial (24.2%) (3). Although the inclusion criteria for the PARTNER I trial and Taiwan's NHI reimbursement criteria for TAVR were similar, the patients in our study were younger (77.98 vs. 83.6 years) and had less comorbidity than those included in the PARTNER I trial, which may be the possible reason for the lower mortality at 1 year in the current study. However, the all-cause mortality of the TAVR group at 1 year and 2 years in our study was similar to the PARTNER II trial (11.39 vs. 12.3% at 1 year; 16.74 vs. 16.7% at 2 years) (6, 8). In Taiwan, the NHI reimbursed TAVR to high-risk patients; however, partial intermediate-risk patients could receive TAVR if they are over 80 years.

In the current study, we found that the length of stay at the index admission patient received treatment was significantly shorter in the TAVR group than in the SAVR group, which was consistent with previous studies (34–36). We also found that the hospitalization cost was 1.6 times higher for SAVR patients than for TAVR patients, and the difference remained significant after adjusting for baseline characteristics. Based on electronic health records in Germany, Kaier et al. (37) reported that the cost of hospitalization for TAVR (mean ± SD, 33,936 ± 6,601) was higher than the costs for SAVR (mean±SD, 19,055 ± 11,976). In 2012, Medicare payments for 4,083 TAVR patients [median, $50,200; interquartile range (IQR), $39,800–64,300)] was slightly higher than that for SAVR patients (median, $45,500; IQR, $34,500–63,300; $P < 0.01$) in a propensity-matched population. These findings can be attributed to differences in patient populations, analytic perspectives, and other factors. First, the cost of TAVR was higher than that of SAVR; however, payments for the implanted valve prosthesis was partially covered by the NHI in Taiwan. In addition, non-procedure costs were lower due largely to significantly shorter in-hospital stays (35).

Few studies have compared costs over the long term. Based on the Nationwide Readmissions Database in the US, Glodsweig et al. estimated the inpatient costs for 6 months (36). They found that the total admission costs associated with TAVR ($10,996) were slightly higher than those of SAVR ($7,285). Analysis related to the cost-effectiveness of the PARTNER II trial revealed that 1-year follow-up costs of TAVR were significantly lower than those for SAVR (risk-adjusted difference: $11,377; $P < 0.001$) (35). In the current study, the outpatient visits cost and total medical costs at first year after treatment were higher for TAVR than for SAVR; however, we did not observe a significant difference in total medical costs in the second or third year after the procedure. This balancing of costs can possibly be attributed to a shorter length of stay and a lower hospitalization cost in the TAVR group. The higher cumulative medical costs in the TAVR cohort during the post-procedure period can be attributed to higher medical costs in the first year and higher costs for outpatient visits in the second and third years after the procedure. In current study, more than 90% of the total medical cost of TAVR group in the second and third years after treatment was contributed by the cost of the outpatient visit. Patients generally require frequent checkups and imaging tests to verify that the device is operating properly after TAVR, which may be the potential reason for the higher outpatient visit cost of TAVR than SAVR.

Our findings contribute to an understanding of short- and long-term clinical outcomes of these procedures as well as cumulative medical utilization and costs. Claims data are widely used to define a cohort of patients, and procedural and diagnostic codes are used to accurately determine the corresponding health outcomes (38). One of the benefits of using data from routine clinical practice is the availability of large amounts of patient-level information by which to capture relevant characteristics. This is particularly important for patients with complex medical conditions, many of whom are excluded from trials due to comorbidities (e.g., end-stage renal disease, previous peripheral intervention, or dementia) and concomitant medications (e.g., anticoagulant regimens) (6), which puts them at increased risk of cardiovascular events and death. We gained a number of insights through our use of propensity score overlap weighting to minimize variance in the correlations between TAVR and SAVR. Propensity score matching has been widely used in previous observational studies to adjust for differences in measured characteristics; however, the effectiveness of these methods is limited in situations where initial differences between groups are large and do not achieve good balance or have worse precision (39). In the current study, we also evaluated follow-up costs based on NHI claims data and the corresponding payments. There is a high probability that this approach is able to capture follow-up costs that might otherwise be overlooked (particularly costs associated with rehabilitation, home care, and outpatient services). Accordingly, we were able to determine that long-term follow-up costs for TAVR were comparable to those for SAVR, which has not previously been reported (40, 41).

The current study has several limitations. First, observational studies are unable to provide conclusions as strong as those obtained using randomized controlled trials, due to residual confounding factors and the fact that treatments are not randomly assigned. In the current study, we used propensity score overlap weighting to minimize selection bias between groups; however, the risk of confounding variables cannot be excluded. We also employed an administrative follow-up scheme to minimize loss to follow-up. Second, our use of claim

data also introduced inevitable coding errors. Nonetheless, we sought to reduce misclassification bias by linking NHI claims data with Cause of Death data based on scrambled identification to identify instances of death. We also used procedural billing codes to facilitate endpoint identification (38). Third, the dataset used in the current study lacked relevant clinical information related to STS, EureSCORE, and echocardiographic findings, all of which could have an impact on the severity of the disease. It is important to note that TAVR is reimbursed by the NHI; however, AS patients who receive TAVR must meet the following requirements: (a) New York Heart Association Function Class II-IV; (b) Aortic area (AVA) of 0.8 cm^2 or an AVA index of $\leqq$0.6 cm^2/m^2, and either a mean gradient $\geqq$40 mm Hg or peak aortic jet velocity > 4 m/s; (c) Excessive risk for open-heart surgery, as designated by at least two cardiac surgery doctors; (d) STS Score >10% or Logistic EuroSCORE I >20%, or 80 years and older, or previous history of cardiac surgery (CABG or valve-related surgery), serious porcelain aorta, liver cirrhosis (Child A or B), or lung insufficiency (FEV < 1 ml). Patients with AS who received SAVR in Taiwan were mostly intermediate to low risk. Therefore, we used the Elixhauser comorbidity index, hospital frailty risk scores, comorbidities (including dialysis, previous percutaneous coronary dilation, or arterial endarterectomy), and concomitant medication (including insulin) as an indirect adjustment for severity. The Elixhauser comorbidity index includes 31 comorbidities, including congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, chronic pulmonary disease, complicated diabetes, renal failure, and coagulopathy (42, 43). The hospital frailty score is a significant predictor of all-cause mortality and rehospitalization among patients receiving TAVR (33, 44). Through these means, we may adjust the severity indirectly and our results reported survival benefit of TAVR with comparable post-procedure costs. Finally, reimbursements pertaining to TAVR and SAVR differ among different healthcare systems, so that our results are not necessarily generalizable to other countries.

To summarize, our 5-year data comparing TAVR or SAVR for AS in terms of outcomes and medical costs revealed that TAVR is superior to SAVR in terms of survival benefits and comparable follow-up costs. Our findings suggest that TAVR may be a better treatment strategy for AS based on clinical and economic considerations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data used in this study was obtained from the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare. Researchers and doctors in Taiwan could apply to the data and analyze it on-site. Requests to access these datasets should be directed to https://dep.mohw.gov.tw/dos/cp-5119-59201-113.html.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of National Yang Ming Chiao Tung University (IRB no: YM110048E). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ET, Y-TL, YK, T-PT, K-CLe, M-CH, JW, K-CLi, and W-HY: conception and design. ET, Y-TL, YK, K-CLi, and W-HY: analysis and interpretation of data. ET, Y-TL, YK, and W-HY: drafting the manuscript. ET, K-CLi, and W-HY: final approval of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Yang Ming Chiao University and Cheng Hsin General Hospital (Grant No. CY11001).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.973889/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 05 October 2022
DOI 10.3389/fcvm.2022.951943

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Imaging, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 24 May 2022
ACCEPTED 09 September 2022
PUBLISHED 05 October 2022

CITATION
Suhai FI, Varga A, Szilveszter B, Nagy-Vecsey M, Apor A, Nagy AI, Kolossváry M, Karády J, Bartykowszki A, Molnár L, Jermendy ÁL, Panajotu A, Maurovich-Horvat P and Merkely B (2022) Predictors and neurological consequences of periprocedural cerebrovascular events following transcatheter aortic valve implantation with self-expanding valves.
Front. Cardiovasc. Med. 9:951943.
doi: 10.3389/fcvm.2022.951943

Predictors and neurological consequences of periprocedural cerebrovascular events following transcatheter aortic valve implantation with self-expanding valves

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Aims: To evaluate the patient- and procedure-related predictors of transcatheter aortic-valve implantation (TAVI)-associated ischemic brain lesions and to assess the effect of silent cerebral ischemic lesions (SCIL) on neurocognitive function.

Methods and results: We investigated 113 consecutive patients with severe aortic stenosis who underwent brain magnetic resonance imaging (MRI) within a week following TAVI. To assess periprocedural cerebral ischemic lesions, diffusion-weighted MRI was utilized. We used multivariate linear regression to identify the independent predictors of TAVI-related ischemic lesion volume (ILV) and periprocedural stroke. Neurocognitive evaluation was performed before and following TAVI at 6-month and one-year follow-up. Following TAVI, a total of 944 new cerebral ischemic lesions were detected in 104 patients (92%). The median ILV was 257 μl (interquartile range [IQR]:97.1–718.8μl) with a median lesion number of 6/patient [IQR:2–10]. The majority of ischemic lesions were clinically silent (95%), while 5% of the lesions induced a stroke, which was confirmed by MRI. Predilatation (β = 1.13[95%CI:0.32–1.93], $p = 0.01$) and the number of valve positioning attempts during implantation (β = 0.28[95%CI:0.06–0.50], $p = 0.02$) increased the log-transformed total ILV. Predilatation (OR = 12.04[95%CI:1.46–99.07], $p = 0.02$) and alternative access routes (OR = 7.84[95%CI:1.01–61.07], $p = 0.02$) were associated with stroke after adjustments for comorbidities and periprocedural factors. The presence of SCILs were not associated with a change in neurocognitive function that remained stable during the one-year follow-up.

Conclusion: While periprocedural ischemic lesions are frequent, most of them are clinically silent and might not impact the patients' neurocognitive function. The number of valve positioning attempts, predilatation, and alternative access routes should be taken into consideration during TAVI to reduce the ILV and risk for stroke.

KEYWORDS

cerebral embolism, transcatheter aortic valve implantation, cardiac CT angiography (CTA), stroke, magnetic resonance imaging

Introduction

Aortic stenosis (AS) is the most common valvular disease in developed countries (1, 2). The prevalence is increasing with age, and it has substantial impact on the mortality and morbidity in the elderly population (3). Surgical aortic valve replacement (SAVR) has been the standard treatment for patients with severe AS. Transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective alternative to SAVR in symptomatic patients with high or prohibitive risk and as a valid alternative to AVR in patients with intermediate risk (4–9). TAVI has been expanded to lower risk patient population, according to the 2020 US guideline, and it can be considered for symptomatic patients between the ages of 65 and 80 years and for asymptomatic patients <80 years with an ejection fraction of <50% (10, 11). It has been shown that TAVI is superior to medical therapy and balloon valvuloplasty in patients who are not suitable for open-heart surgery (12, 13) and could potentiate reverse remodeling of the left ventricle (14).

Cerebrovascular events (CVE) after TAVI are among the most worrisome complications, increasing the risk of morbidity and mortality at short- and long-term (15–17). The incidence of CVE after TAVI ranges from 1–11% according to different studies and meta-analyses, and it varies according to the definition, albeit the incidence of periprocedural stroke is slightly lower in patients with new generation devices as compared to patients with first generation valves (17–20). In addition to the clinically apparent ischemic brain lesions, several cerebral magnetic resonance imaging (MRI) studies showed a very high (58–91%) incidence of clinically silent new ischemic lesions after TAVI, regardless of the transcatheter valve type and approach (21–24). Although periprocedural stroke presents only in a small proportion of patients, silent cerebral embolism is a common finding associated with this procedure. Furthermore, the real impact of these silent cerebral ischemic lesions (SCIL) on cognitive function and development of future cerebral complications are still under debate (25). It has been suggested that SCILs after TAVI are associated with an increased risk of dementia, cognitive decline, and depression (26–28).

Our primary aim was to identify patient- and procedure-related predictors of ischemic brain lesions and stroke following TAVI, as well as their occurrence and distribution using diffusion MRI. Our secondary aim was to assess the effect of SCILs on the patients' neurocognitive function.

Abbreviations: ACE, Addenbrooke's cognitive assessment; AS, aortic stenosis; AVCS, aortic valve calcium scor; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; ILV, ischemic lesion volume; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; MMSE, mini-mental state examination; SAVR, surgical aortic valve replacement, SCIL, silent cerebral ischemic lesion, TAVI, transcatheter aortic valve implantation; 6M, 6-month follow-up; 1Y, one-year follow-up.

Materials and methods

Study population and design

In a single-center, prospective cohort study, we analyzed consecutive patients who underwent CT angiography (CTA) for pre-TAVI planning and brain MRI following TAVI as part of the RETORIC study (Rule out Transcatheter Aortic Valve Thrombosis with Post Implantation Computed Tomography trial, NCT02826200) (29). The valve implantations were performed between November 2016 and June 2018, and patients were followed up until 1 year.

This study was approved by the local and national ethical committees and was performed in accordance with the Helsinki declaration. Written informed consent was obtained from all patients.

Image acquisition for TAVI planning

We used the following CTA protocol for every pre-TAVI planning CT: first, we acquired a prospectively ECG triggered non-contrast scan from the entire heart (120 kV, slice thickness of 3 mm, increment 1.5 mm). This

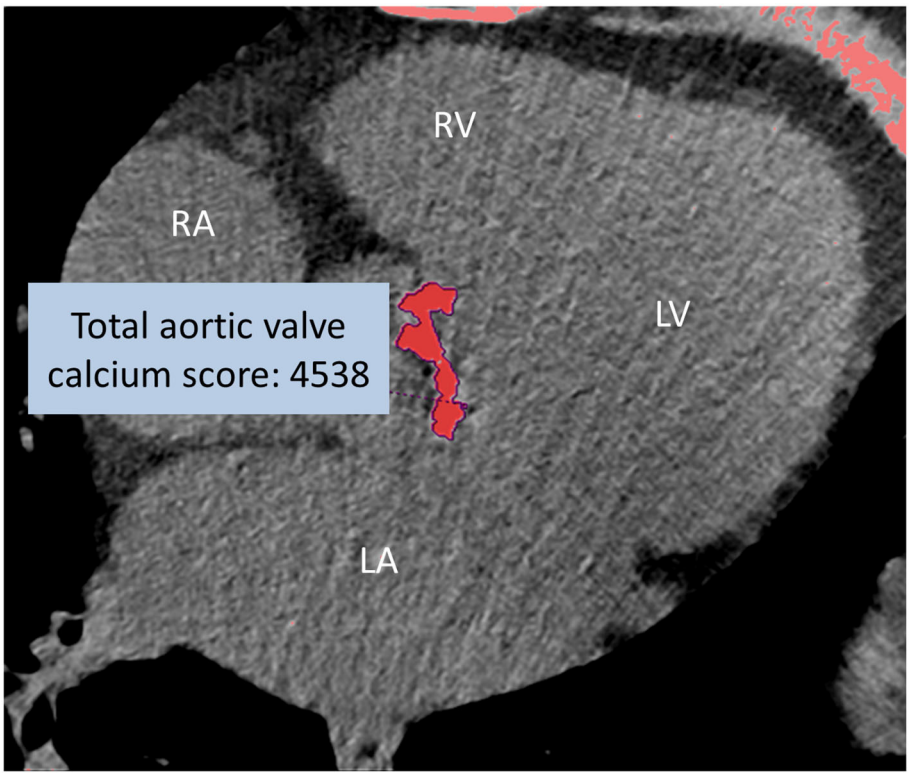

FIGURE 1
Non-enhanced CT of severe aortic valve calcification (total AVCS: 4538). Calcium scoring of the aortic valve using post-processing software by the Agatston method. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

TABLE 1 Procedural characteristics.

Patient data ($N = 113$)	
Aortic valve calcium score	3,321.6 ± 1,944.7
Bicuspid aortic valve, *n* (%)	15 (13.3)
Access route (TF vs. TS/TC), *n* (%)	105 (92.9) vs. 6 (5.3) vs. 2 (1.8)
Predilatation, *n* (%)	15 (13.3)
CoreValve vs. evolutr vs. portico, *n* (%)	9 (8.0) vs. 75 (66.3) vs. 29 (25.7)
Number of attempts to position	1.7 ± 0.9
Malposition/Migration, *n* (%)	5 (4.4)
Postdilatation, *n* (%)	89 (78.8)
New-onset atrial fibrillation *n* (%)	8 (7.1)
Vascular and acces-related complications, *n* (%)	26 (23.0)
Minor (according to VARC-3 criteria)	17 (15.0)
Major (according to VARC-3 criteria)	9 (8.0)

VARC-3, Valve Academic Research Consortium, TF, Transfemoral, TS, Trans-subclavian, TC, Transcarotid.
Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as numbers and percentages.

was followed by a retrospectively ECG gated CTA of the aorta (from the level of thoracic inlet to the level of the femoral head) and the heart, during a single breath-hold, using a 256-slice CT scanner (Philips Healthcare, 270 ms rotation time, tube voltage of 100–120 kV based on body mass index) for TAVI planning. We administered 75 ml contrast agent with 4.5 ml/s flow, and images were acquired with 1 mm slice thickness and 1 mm increment using iterative reconstruction (iDose^4 and IMR, Philips Healthcare).

Cardiac CTA image analysis

Two radiologists assessed the calcification of the aortic valve, the annulus, the left ventricular outflow tract, the ascending aorta, and the aortic arch. The severity of calcification was qualitatively graded as mild, moderate, and severe. The aortic valve calcium score (AVCS) was measured on the non-contrast cardiac CT by the Agatston method (Figure 1), with care taken to exclude calcium originating from the extravalvular structures (30), using a semi-automated software tool (Heartbeat-CS, Philips Intellispace v6.0.4). The measurements were performed in a random order, and investigators were blinded to the scan date and patient data.

TAVI procedure

Prosthetic valves were implanted with the standard technique, by using local anesthesia with conscious sedation during the procedure. Transfemoral route was the preferred access, and the trans-subclavian or transcarotid route was considered an alternative route. Embolic protection devices were not used in this cohort. Only self-expandable valves were used in our study. Adverse events were defined according to the Valve Academic Research Consortium-3 definitions (VARC-3) (31, 32). Procedural factors such as balloon predilation and postdilatation, the number of attempts to position, and events of valve dislocation were evaluated and collected in a dedicated database (Table 1).

Brain MRI examination

We performed brain MRI in the first week (4 days after TAVI on average) to detect cerebral ischemic lesions. Patients were excluded, if there was a contraindication to MRI or if they had poor image quality. After applying the abovementioned exclusion criteria, 113 patients were analyzed (Figure 2).

The MRI examinations were performed on a 1.5T MR scanner (Achieva, Philips Medical Systems) using an eight-channel head coil in the first week (mean 4 days) after TAVI (referred to as discharge MRI). Fluid-Attenuated Inversion Recovery (FLAIR), T2-weighted, T2*-gradient echo, high resolution 3D T1-weighted gradient echo sequences were obtained with diffusion MRI. MRI was repeated at 6-month

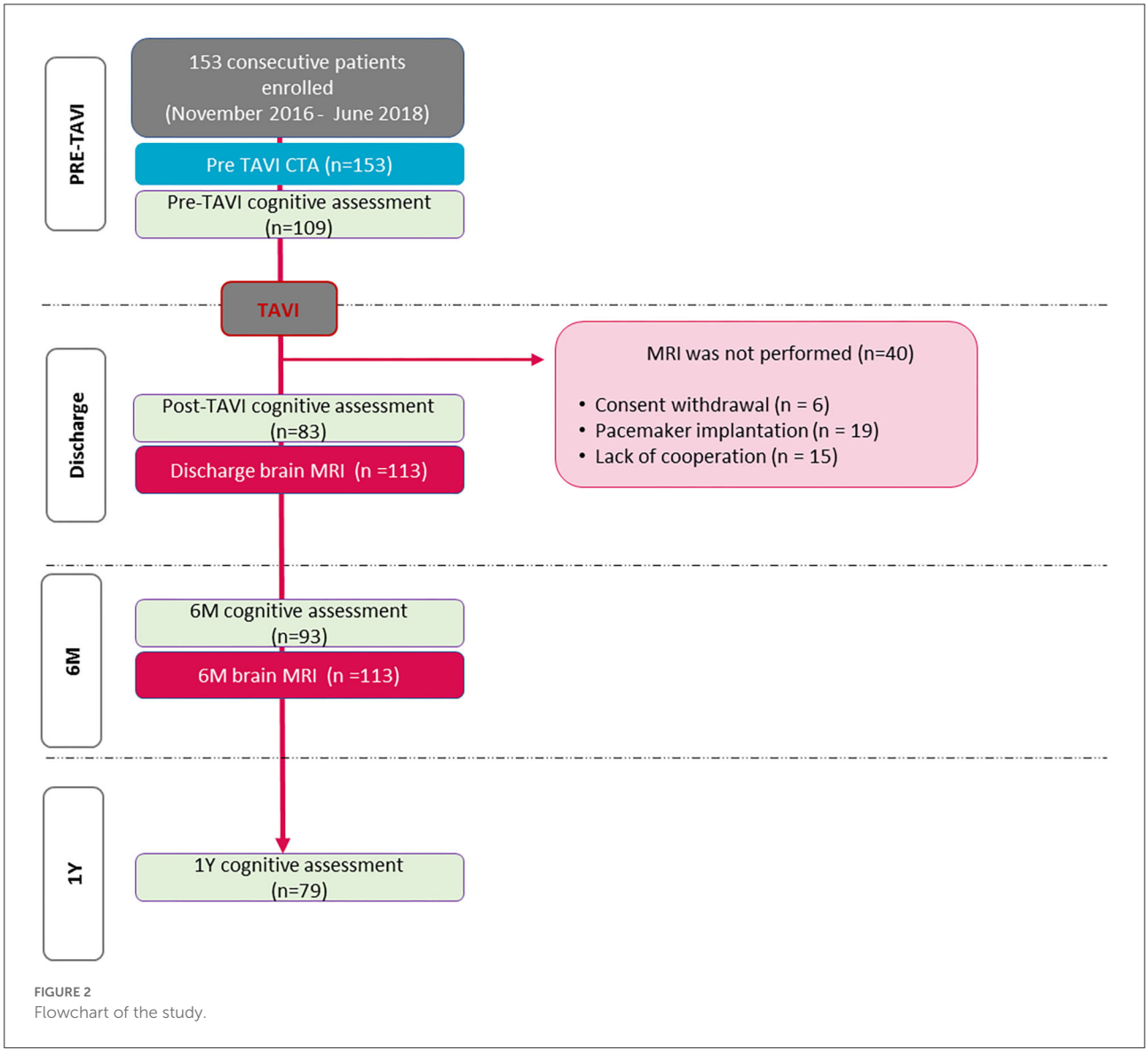

FIGURE 2
Flowchart of the study.

TABLE 2 Demographic parameters and cardiovascular risk factors.

Patient data ($N = 113$)	
Age (years)	79.2 ± 6.7
Female sex, *n* (%)	50 (44.2)
BMI (kg/m^2)	27.3 ± 4.7
Diabetes, *n* (%)	54 (47.8)
Hypertension, *n* (%)	102 (90.3)
Hyperlipidemia, *n* (%)	74 (65.5)
Previous AMI, *n* (%)	27 (23.9)
PAD, *n* (%)	57 (50.4)
Atrial fibrillation, *n* (%)	38 (33.6)
Previous TIA/stroke, *n* (%)	15 (13.3)
Chronic kidney disease	64 (56.6)
Antiplatelets, *n* (%)	84 (74.3)
Anticoagulants, *n* (%)	33 (29.2)

BMI, Body mass index; AMI, Acute myocardial infarction; PAD, Peripheral artery disease; TIA, Transient ischemic attack.
Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as numbers and percentages.

follow-up (6M) in order to assess the gliotic transformation of procedural ischemic lesions.

Diffusion MRI acquisitions were performed using a single shot spin echo, echo-planar imaging sequence in 32 diffusion encoding directions with b = 800 s/mm^2 and one b = 0 measurement. Whole brain coverage was obtained with 2 mm-thick contiguous axial slices. From the diffusion, MRI dataset averaged diffusion-weighted images commonly referred to as "trace", and mean diffusivity and ADC maps were automatically derived and used to calculate the ischemic lesion volume (ILV). New ischemic lesions were detected at postprocedural imaging on diffusion-weighted imaging (DWI), and they were considered completely resolved if neither DWI nor FLAIR positive lesions were detected in the same location at follow-up; gliotic transformation was considered if there was FLAIR hyperintensity in the same location of the discharge DWI positive lesion.

Ischemic lesion volume measurement

The number, localization, and three perpendicular diameters of all lesions with restricted diffusion images were recorded using an AGFA PACS workstation (Impax 6.5.2.657, Agfa HealthCare). ILV was calculated as the sum of lesion volumes using the formula of a x b x c x 0.52 (a, b, and c are the three lesion diameters) (33). The ILV measurements were performed in a random order and the investigator was blinded to the scan date and patient data.

Neurocognitive assessment

Patients underwent a serial evaluation of the cognitive status, pre-TAVI, and post-TAVI before hospital discharge, 6-month follow-up (6M), and 1-year follow-up (1Y) following TAVI. We used the Hungarian version of the Addenbrooke's Cognitive Assessment (ACE) test (34), which incorporated the Mini-Mental State Examination (MMSE), and the evaluation was performed by one of the two trained investigators blinded to CTA and MRI data. Among all enrolled patients, 113 participants completed the pre-TAVI, 83 subjects completed the post-TAVI, 93 subjects completed the 6M, finally 79 patients completed the 1Y cognitive tests. Patients with periprocedural stroke (6/113, 5.3%) were excluded from the further neurocognitive assessment.

Statistical analysis

Continuous variables are presented as mean and standard deviation, whereas categorical variables are presented as frequency with percentages. Categorical variables were compared using the chi-squared test. The Kruskal-Wallis test was used to analyze the association between ILV and the number of positioning of the valve during TAVI. Because of non-normal distribution of ILV, data were log-transformed. The univariate linear regression analysis was performed to detect the association between patient- and procedure-related risk factors and log-transformed ILV. The multivariate linear regression models were performed using the backward method.

We also aimed to identify predictors of periprocedural stroke using univariate and multivariate logistic regression. Repeated-measures analysis of variance was performed to evaluate changes in neurocognition over time; pairwise differences were assessed using Duncan's multiple comparison test. A p-value <0.05 was considered statistically significant. All calculations were performed using SPSS software (SPSS version 23; IBM Corp.).

Results

In total, 113 patients were included in the analysis (mean age: 79.2 ± 6.7 years, 44.2% women, and mean BMI: 27.3 ± 4.7 kg/m^2). Overall, 23.9% (27/113) of the patients had prior myocardial infarction, 90.3% (102/113) had hypertension, and 65.5% (74/113) had hyperlipidaemia. Oral anticoagulant medication was administered in 29.2% (33/113), while 74.3% (84/113) of the patients received antiplatelet therapy. Patient characteristics and imaging parameters are summarized in Table 2.

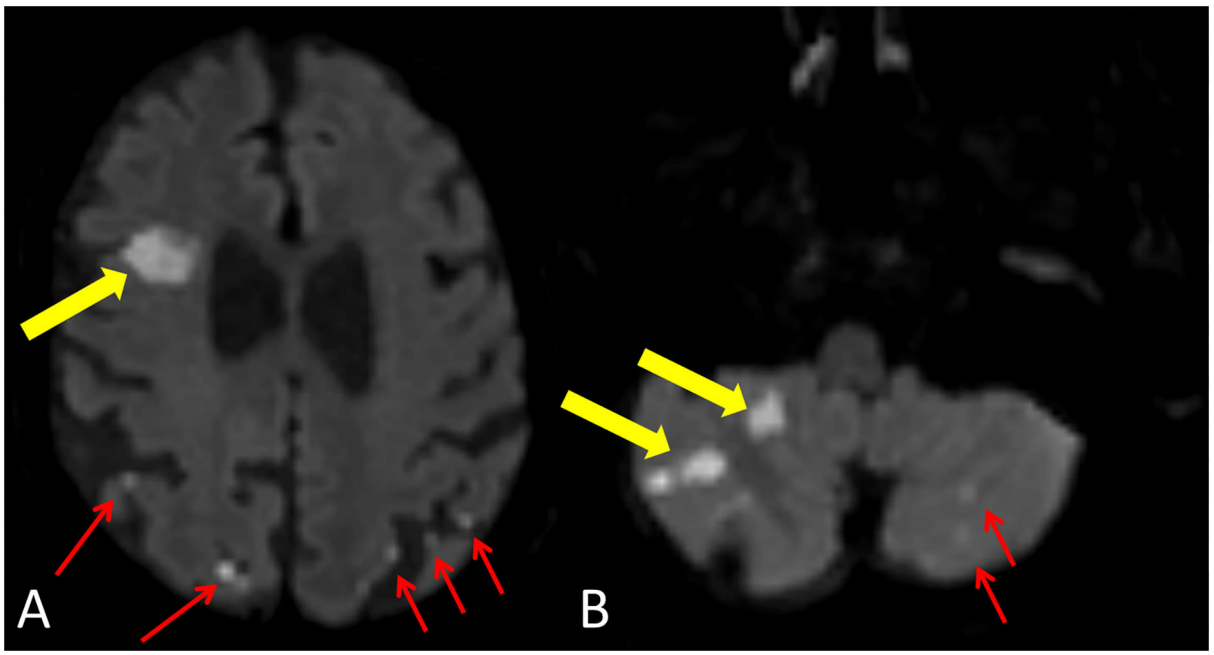

FIGURE 3
New ischemic lesion after TAVI. Yellow arrows demonstrate a larger lesion with restricted diffusion in the right frontal lobe **(A)** and in the right cerebellar hemisphere **(B)**. Red arrows show smaller cortical-subcortical lesions with restricted diffusion in the left and right parietal lobes **(A)** and in the left cerebellar hemisphere **(B)**.

Procedural characteristics

Procedural characteristics and procedural complications are summarized in Table 1. Prosthetic valves were implanted successfully in all patients (Medtronic CoreValve 8.0%, Medtronic CoreValve Evolut R 66.3%, Portico 25.7%). The mean AVCS was 3,332 ± 1,944, and 13.3% of the patients had a bicuspid aortic valve (BAV). The transfemoral approach was used in 105 patients (92.9%), the trans-subclavian access in six cases (5.3%), and the transcarotid route in two patients (1.8%). Balloon predilatation was performed in 15 patients (15.3%), while most of the valves (78.8%) were postdilated. Predilatation was performed in the case of the heavily calcified native aortic valve, according to the operators' visual judgment; however, no significant difference in AVCS could be observed in patients with predilatation compared to those without predilatation (median AVCS: 2,774 [IQR:1,885–4,271] vs. median AVCS: 3,612 [IQR:1,847.4–6,366]; $p = 0.44$). The mean number of positional attempts was 1.7 ± 0.9. In 60 (53.1%) cases, the implantation was successful at the first positional attempt, in 39 (34.5%) cases at the second, and in 14 patients (12.4%) at the third or fourth time. According to the VARC-3 criteria, nine patients had major and 17 patients had minor vascular and access-related complications.

Cerebral embolization after TAVI

A total of 104 patients (92.0%) had new cerebral ischemic lesions on discharge MRI (Figure 3), among them six patients had periprocedural stroke. The median number of lesions per patient was six (IQR: 2–10), and the median ILV was 257.3 μl (IQR: 97.1–718.8 μl). In addition, 944 new ischemic brain lesions were found on brain MRI, most of the lesions were supratentorial (781/944, 81.9%), and the majority were located in the cortical–subcortical area (796/944, 84.3%). The left and right cerebral and cerebellar hemispheres were equally affected (Table 3). On the 6M MRI, 46/113 (40.7%) patients had gliotic transformation on FLAIR images.

Predictors of ischemic lesion volume and stroke after TAVI

We evaluated clinical and imaging parameters for association with ILV and stroke. Age, cardiovascular risk factors, aortic calcification, access route, valve type and size, and postdilatation did not show any association with ILV (all non-significant see, $p > 0.05$ Table 4). On univariate analysis, sex,

TABLE 3 Results of postprocedural assessment with MRI.

Patient data ($N = 113$)	
Patients with new cerebral ischemic lesions, *n* (%)	104 (92.0)
Patients with periprocedural stroke, *n* (%)	6 (5.3)
Number of lesions per patient	6 (2–10)
Ischemic load per patient (μl)	257.3 [97.1–718.8]
Number of lesions: left vs. right, *n* (%)	500 (52.97) vs. 444 (47.03)
Volume of lesions: left vs. right (μl)	123.3 [29.7–357.9] vs. 89.1 [14.6–226.1]
Number of lesions: supra- vs. infratentorial, *n* (%)	781 (82.7) vs. 163 (17.3)
Volume of lesions: supra- vs. infratentorial (μl)	58.3 [14.58–215.6] vs. 0.0 [0.0–53.1]
Cortical-subcortical lesions, *n* (%)	796 (83.4)
Deep lesions, *n* (%)	158 (16.6)
Lesions <5 mm, *n* (%)	558 (59.1)
Lesions 5–10 mm, *n* (%)	332 (35.2)
Lesions > 10 mm, *n* (%)	54 (5.7)

Continuous variables are expressed as median and interquartile ranges [IQR] and categorical variables are expressed as numbers and percentages.

AVCS, number of valve positioning attempts, and predilatation showed an association with log-transformed ILV. AVCS was not an independent predictor of log-transformed ILV after adjustments. Regarding ILV, it seems that the manipulations during TAVI are more relevant than the AVCS: positioning the device three or more times resulted in a significant increase in ILV (Figure 4). On multivariate linear regression analysis, predilatation ($\beta = 1.13$, 95% CI:0.32–1.93; $p = 0.01$), and positioning attempts ($\beta = 0.28$, 95 % CI: 0.06–0.50; $p = 0.02$) were independent predictors of log-transformed ILV after adjusting for covariates using the backward method (Table 4).

On multivariate logistic regression analysis, we found that predilatation (OR:12.04; 95%CI: 1.46–99.07; $p = 0.02$) and alternative access route (OR: 7.84; 95%CI: 1.01–61.07; $p = 0.049$) were independent predictors of periprocedural stroke (Table 5).

Neurocognitive function

Among all patients, 79 out of 113 patients had a serial neurocognitive assessment and post-TAVI MRI, and these subjects were included in our subanalysis. The overall cognitive performance of the cohort was stable over the 1Y follow-up period (Figure 5), with mean baseline, discharge, 6M Addenbrooke's score, and 1Y Addenbrooke's score of 72.3 ± 13.1, 74.8 ± 14.2, 72.8 ± 16.6, and 73.4 ± 13.4 ($p = 0.32$) and an MMS score of 25.9 ± 2.8, 26.1 ± 3.5, 25.8 ± 4.1, and 26.3 ± 3.0, $p = 0.92$, respectively (Table 6). We found that neither ILV nor the presence of gliotic transformation of these procedural lesions was associated with neurocognitive change at any time during the follow-up period (at discharge, at 6M, at 1Y, $p > 0.05$ for all).

Discussion

The main findings of our study are as follows: (1) we found that 92% of the patients had new cerebral ischemic lesions; however, most of them were clinically silent; (2) balloon predilatation and the number of valve positioning attempts during the procedure were independently associated with a larger log-transformed ILV, whereas predilatation and alternative access route were associated with periprocedural stroke; and (3) the ILV was not associated with cognitive decline after TAVI.

Despite the extensive literature on CVE and SCIL risk factors during TAVI, the identified predictors differ from study to study, highlighting the great complexity of patient- and procedure-related factors (15, 17, 19–23, 28, 35–45). Although CVE is relatively rare, it is the most worrisome complication in this frail patient population with multiple comorbidities, which is linked to poor outcomes. Nombela-Franco et al. found that balloon postdilatation and valve dislodgement/embolization were predictors of acute CVE, and new-onset atrial fibrillation was a predictor of subacute CVE (15). Keiko et al. found that self-expandable valves were associated with an increased risk of acute cerebral embolization on MRI (39). A meta-analysis showed that female sex, chronic kidney disease, level of experience, and new-onset atrial fibrillation were predictors of CVE post-TAVI (19). Regarding the access site, Rodés et al. found no difference when comparing transfemoral vs. transapical approaches (23); however, Eggebrecht et al. (16) found an association between stroke and the type of approach, with transapical TAVI carrying the lowest risk of stroke. A meta-analysis from Lu et al. found that transcarotid access was associated with an increased risk of 30-day mortality and with an increased risk of 30-day neurovascular complications (46). A nationwide study from Sweden found that reduced renal function, diabetes, history of stroke, age, and male sex were risk factors for developing stroke after TAVI (47). Also, a recent meta-analysis showed that next-generation devices can decrease TAVI-related complications, including periprocedural stroke (18). We identified predilatation and valve positioning maneuver as important predictors of larger ILV, whereas predilatation and access route were risk factors of periprocedural stroke.

SCILs are more frequent after TAVI, but their impact on neurocognitive function still remains controversial (24, 27, 28, 36, 37). Various cerebral MRI studies showed a very high (58–91

TABLE 4 Multivariate linear regression analysis of the predictors of total ischemic volume.

	Univariate				Multivariate			
	β	95% CI, lower-upper		*p*	β	95% CI, lower-upper		*p*
Sex	***0.48***	***0.10***	***0.86***	***0.02***	0.25	−0.15	0.66	0.22
New-onset atrial fibrillation	0.65	−0.11	1.40	0.09				
Previous AF	0.39	−0.02	0.80	0.06	0.33	−0.04	0.71	0.08
Anticoagulant therapy	0.002	−0.008	0.01	0.65				
Previous stroke/TIA	0.14	−0.45	0.74	0.64				
Aortic valve ca score	***0.00***	***0.00***	***0.00***	***0.02***	0.00	0.00	0.00	0.055
Bicuspid aortic valve	−0.22	−1.03	0.59	0.59				
Alternative access route	0.50	−0.26	1.26	0.19	0.68	−0.04	1.40	0.06
Predilatation	***0.93***	***0.08***	***1.79***	***0.03***	***1.13***	***0.32***	***1.93***	***0.01***
Malposition	0.24	−0.71	1.19	0.62				
Postdilatation	−0.17	−0.65	0.31	0.49				
Number of attempts to position	**0.23**	**0.03**	**0.44**	**0.03**	***0.28***	***0.06***	***0.50***	***0.02***

AF, Atrial fibrillation; CI, Confidence interval; TIA, Transient ischemic attack. Numbers marked in bold are significant predictors of the outcome based on multivariate analysis ($p < 0.05$).

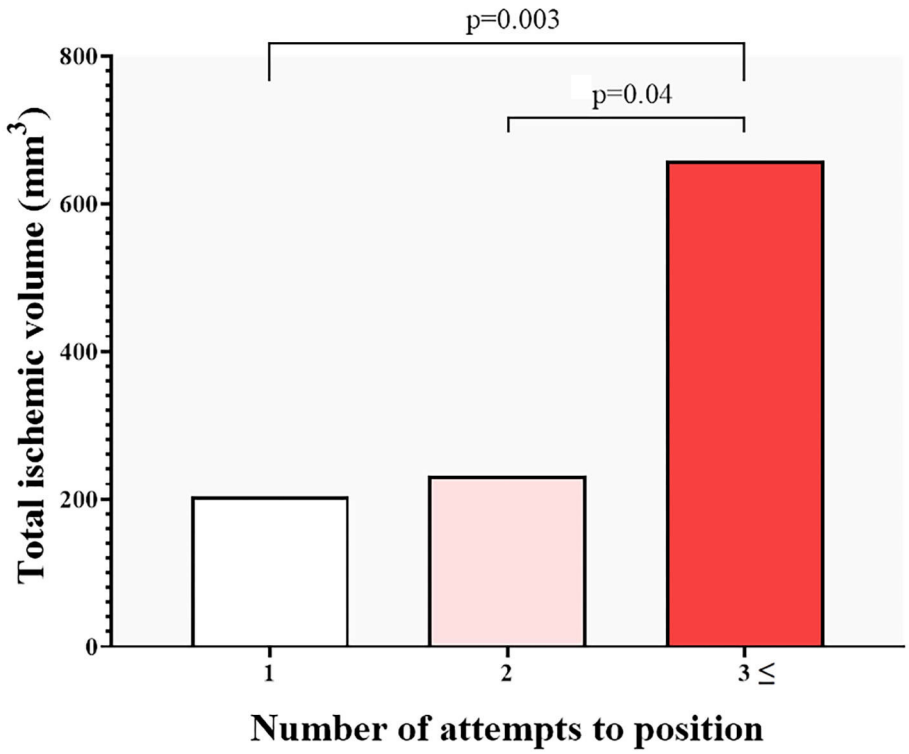

FIGURE 4
Total ischemic volume on MRI and the number of TAVI positioning attempts. The number of procedural manipulations shows a strong correlation with the ischemic lesion volume (ILV), Three or more positioning attempts of the device resulted in significantly increased ILV.

%) incidence of new ischemic lesions after TAVI, regardless of the transcatheter valve type and approach (22–24, 38). Several different predictors for SCIL have been identified: Carlo et al. showed that baseline age-related white matter damage was an independent predictor of the occurrence of SCILs together with the use of non-balloon-expandable prostheses (36). A

TABLE 5 Multivariate logistic regression analysis of the predictors of periprocedural stroke.

	Univariate			Multivariate		
	OR	95% CI, lower-upper	*p*	OR	95% CI, lower-upper	*p*
Sex	2.65	0.47–15.11	0.27			
New-onset atrial fibrillation	2.86	0.29–27.92	0.37			
Previous AF	−0.99	0.17–5.64	0.99			
Anticoagulant therapy	−0.04	−0.75–1.23	0.77			
PAD	0.98	0.19–5.08	0.98			
Previous stroke/TIA	1.58	0.17–14.72	0.69			
Aortic valve ca score	1.00	1.00–1.00	0.99			
Bicuspid aortic valve	3.62	0.60–21.74	0.21			
Alternative access route	***8.42***	***1.28–55.53***	***0.03***	***7.84***	***1.01–61.07***	***0.049***
Predilatation	***12.88***	***1.80–92.27***	***0.01***	***12.04***	***1.46–99.07***	***0.02***
Malposition	0.00	0.00–0.00	1.00			
Postdilatation	0.52	0.09–3.01	0.46			
Number of attempts to position	1.49	0.81–2.75	0.20			

AF: Atrial fibrillation; CI: Confidence interval; PAD: Peripherial artery disease; TIA: Transient ischemic attack Numbers marked in bold are significant predictors of the outcome based on multivariate analysis ($p<0.05$).

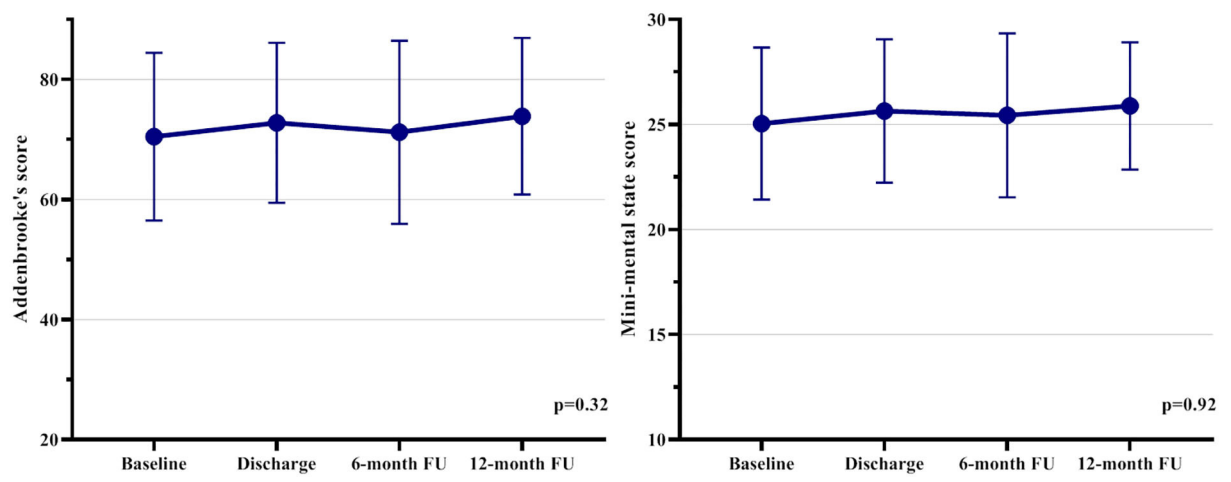

FIGURE 5
Neurocognitive examination results in the 79 patients based on serial assessments. The overall neurocognitive function was stable during the one-year follow-up.

recent meta-analysis showed that diabetes, kidney disease, and predilatation increased the overall risk for SCIL (28).

We found that the number of positioning maneuvers of the device resulted in a significantly increased log-transformed ILV. However, AVCS did not show a correlation with ILV. Importantly, the transcatheter valve type, access route, or the presence of BAV did not influence the log-transformed ILV either. Although alternative access route did not appear to be a significant predictor of ILV on multivariate analysis, an increasing tendency in ILV could be observed and the lack of statistical significance regarding the association between ILV and alternative access route could be explained by the relatively low number of alternative access. Notably, some studies found an association between AVCS and cerebral embolization, as well as acute periprocedural CVE (48, 49). According to our study, it appears that aortic valve calcification has limited associations with CVE.

In a recent study, Fan et al. published that patients with BAV had more cerebral ischemic lesions following TAVI (50). In our study, we found that AVCS was higher in patients with

TABLE 6 Results of serial neurocognitive assessments.

	Baseline	Discharge	6-month follow-up	12-month follow-up	*p*
Mini-mental state score	25.9 ± 2.8	26.1 ± 3.5	25.8 ± 4.1	26.3 ± 3.0	0.92
Adenbrook's score	72.3 ± 13.1	74.8 ± 14.2	72.8 ± 16.6	73.4 ± 13.4	0.32

Parameters are shown as mean ± SD.

TABLE 7 Procedural characteristics of patients with the bicuspid and tricuspid valves.

Patient data	Bicuspid	Tricuspid	*p*
(*n* = 113)	(*n* = 15)	(*n* = 98)	
Aortic valve calcium score	***4,913 ± 2,800***	***3,078 ± 1,668***	***<0.001***
Ischemic load (mm^3)	4,789 ± 2,1800	4,086 ± 1,7450	0.95
Access route (TF vs. TS vs. TC), *n* (%)	***12 (80.0) vs. 3 (20.0)***	***93 (94.9) vs. 5 (5.1)***	***0.04***
Predilatation, *n* (%)	3 (20.0)	12 (12.2)	0.41
CoreValve vs. portico, *n* (%)	13 (86.7) vs. 2 (13.3)	71 (72.4) vs. 27 (27.6)	0.24
Malposition/migration, *n* (%)	0 (0.0)	3 (3.1)	1.00
Postdilatation, *n* (%)	14 (93.3)	75 (76.5)	0.14
Stroke, *n* (%)	2 (13.3)	4 (4.1)	0.14
Vascular and acces-related complications *n* (%)			
Minor (according to VARC-3 criteria)	2 (13.3)	15 (15.3)	0.84
Major (according to VARC-3 criteria)	2 (13.3)	8 (8.2)	0.51

VARC-3, Valve Academic Research Consortium; TF, Transfemoral; TS, Transsubclavian; T, Transcarotid.
Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as numbers and percentages.
The bold values indicate the significant differences between the groups ($p < 0.05$).

BAV compared to patients with tricuspid valves; however, the procedural characteristics and ILV did not differ between the two groups (Table 7).

The results of our study showed that 5.3% of the patients had periprocedural stroke, which is concordant with the findings of Auffret and colleagues (19). Based on our results predilatation and alternative access route were associated with periprocedural stroke. Predilatation was usually performed if there was heavy leaflet calcification by the visual estimation of the interventional cardiologist, but AVCS did not differ between patients with or without predilatation. The association between the number of device positioning maneuvers and stroke could not be observed; however, the stroke incidence was low.

Some studies revealed a neurocognitive decline after TAVI (26, 28); however, Kahlert et al. found no significant changes in cognitive function (38). A subgroup analysis from a recent meta-analysis showed that, despite new cerebral lesions following TAVI, there is a cognitive improvement in 19% and impairment in only 7% (37) of the subjects. They found that using a cerebral embolic protection device was associated with a decreased prevalence of cognitive decline up to 1-week post-TAVI, and pre-TAVI cognitive impairment had an association with post-TAVI cognitive improvement at 6-month. It has to be acknowledged that studies with longer follow-up [i.e., Vermeer et al. with 3.6 years follow-up (26)] might better identify an association with cognitive dysfunction compared to studies with a shorter follow-up (28). In our study, the neurocognitive function was stable during the 1Y period, and we could not find any association between ILV or gliotic transformation of the procedural lesions and changes in neurocognitive function. To our knowledge, this is the largest patient population who underwent brain MRI and had a one-year-long serial neurocognitive assessment after TAVI, and this study is the first to report an association between the number of device positioning maneuvers and ILV.

Procedural complications such as CVE and SCILs still remain a problem, and the effect of SCIL on neurocognitive function is controversial; therefore, identifying the patient- and procedure-related risk factors for CVE and SCIL are crucial to achieve the best long-term outcome.

Limitations

Some limitations of the present study must be acknowledged. Our single-center study enrolled 153 patients for the current evaluation, but we included 113 patients with brain MRI. Patients who received a pacemaker post-TAVI or could not cooperate with the brain MRI were excluded, which might have led to selection bias. This together with a proportion

of patients who did not participate in the serial neurocognitive assessment could influence neurocognitive decline rates. Also, longer follow-up could better find the association between SCIL and neurocoginitive decline. Alternative access route and predilatation was used in a limited number of patients that could possibly limit the generalizability of our findings.

Conclusion

In the present study, we found that more procedural manipulations and predilatation resulted in larger log-transformed ILV on discharge MRI following TAVI. We identified a new procedural risk factor, namely, the number of positioning maneuvres of the valve that should be taken into consideration during TAVI. However, the clinically silent lesions did not influence the patient's neurocognitive function during 1Y. Predilatation and alternative access route were associated with stroke after TAVI in our study.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Institute of Pharmacy and Nutrition. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: FS, BS, PM-H, AA, and AN. Methodology: FS and BS. Software: FS and MN-V. Validation: FS, MN-V, AP, BS, and ÁJ. Formal analysis: BS, MN-V, and MK. Investigation and writing-original draft preparation: FS. Resources: LM and AP. Data curation: JK and AB. Writing-review and editing: AA, AN, JK, AB, ÁJ, MK, and AV. Visualization: FS and MN-V. Supervision: PM-H and BM. Project administration: AN, PM, and BM. Funding acquisition: BM and PM-H. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Research, Development and Innovation Office of Hungary (NKFIA; Project No. NVKP_16-1–2016-0017-'National Heart Program') and by the Thematic Excellence Programme (2020-4.1.1.-TKP2020) of the Ministry for Innovation and Technology in Hungary, within the framework of the Therapeutic Development and Bioimaging thematic programmes of the Semmelweis University. AN was supported by the János Bolyai Scholarship of the Hungarian Academy of Sciences.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 17 October 2022
DOI 10.3389/fcvm.2022.958732

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 31 May 2022
ACCEPTED 12 September 2022
PUBLISHED 17 October 2022

CITATION
Jimenez Diaz VA, Estevez Loureiro R, Baz Alonso JA, Juan Salvadores P, Bastos Fernandez G, Caneiro Queija B, Veiga Garcia C and Iñiguez Romo A (2022) Stroke prevention during and after transcatheter aortic valve implantation: From cerebral protection devices to antithrombotic management.
Front. Cardiovasc. Med. 9:958732.
doi: 10.3389/fcvm.2022.958732

Stroke prevention during and after transcatheter aortic valve implantation: From cerebral protection devices to antithrombotic management

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Since its conception, transcatheter aortic valve implantation (TAVI) has undergone important improvements both in the implantation technique and in transcatheter devices, allowing an enthusiastic adoption of this therapeutic approach in a wide population of patients previously without a surgical option and managed conservatively. Nowadays, patients with severe symptomatic aortic stenosis are typically managed with TAVI, regardless of their risk to surgery, improving the prognosis of patients and thus achieving an exponential global expansion of its use. However, thromboembolic and hemorrhagic complications remain a latent concern in TAVI recipients. Both complications can appear simultaneously in the periprocedural period or during the follow-up, and when minor, they resolved without apparent sequelae, but in a relevant percentage of cases, they are devastating, overshadowing the benefit achieved with TAVI. Our review outlines the etiology and incidence of thromboembolic complications associated with TAVI, the main current strategies for their prevention, and the implications of its pharmacological management at the follow-up in a TAVI population, mostly frail and predisposed to bleeding complications.

KEYWORDS

transcatheter aortic valve implantation (TAVI), stroke, cerebral embolic protection devices, complication, antithrombotic therapy, aortic stenosis (AS)

10.3389/fcvm.2022.958732

Introduction

The current American (1) and European (2) guidelines for the treatment of patients with valvular heart disease favor transcatheter aortic valve implantation (TAVI) by transfemoral access for patients with aortic stenosis (AS) who are at low to high risk for surgical aortic valve replacement (SAVR). Although the results of its pivotal clinical trials and reports of its clinical use were published, several concerns regarding its neurological safety arose soon afterward.

The expansion of TAVI indication to a younger and less comorbid population has prompted active research into the mechanisms involved in procedure-related stroke and the development of various devices to protect the brain from the passage of emboli during TAVI. Also, the determination of the most balanced antithrombotic strategy after TAVI in terms of ischemic protection and bleeding is a relevant clinical need and is under current quest. In this article, we provide an updated overview on stroke related to TAVI and its most relevant advances in devices aimed at stroke prevention, and on the ongoing clinical research in preventive pharmacological strategies.

Etiology, timing, and mechanism of transcatheter aortic valve implantation-related stroke

Despite great advances in patient management and latest iterations on TAVI devices occurred during the last decade, stroke has remained steady over time and continues to be a frequent TAVI complication with relevant prognostic implications (**Table 1**). In general, strokes related to TAVI can be divided into procedure-related strokes (acute) and patient- or prosthesis-related strokes (long-term). In addition, the clinical manifestations can be broad, ranging from silent or subclinical events detected as findings in brain imaging studies, to episodes of transitory delirium or acute confusional state, to a major stroke with manifest clinical expression and disabling sequelae. Overt stroke is one of the most fearful and catastrophic complication of TAVI, being strongly associated with morbidity and mortality (3), increasing the average 30-day mortality more than six times in patients who suffer from it than those who do not after TAVI (4). Also, bleeding complications remain a problem to be solved, not only those that occur periprocedural but also those that continue for a long-standing period, the former being more in relation to TAVI vascular access, and the latter to long-term post-TAVI antithrombotic management (5).

Clinical stroke

Stroke occurrence during and after TAVI is likely multifactorial and closely linked with the patients' risk profile (6). Ischemic stroke can happen during or after TAVI, either in periprocedural days or during the long-term follow-up; is strongly linked to morbidity; and can entirely nullify TAVI prognostic improvements (5–8). TAVI and transcatheter valve components induce a prothrombotic environment in the aortic root (9, 10). Mechanical disruption of atheromatous or calcific debris during different procedural steps of TAVI (crossing of catheters and devices in the aortic arch/valve, during balloon aortic valvuloplasty, during deployment, or during valve post-dilation) may account as the main mechanisms for most of the periprocedural strokes (11, 12). Also, suboptimal intraprocedural anticoagulation levels inducing the formation of thrombi in guidewires and catheters, air embolism, and severe hypotension states may also be involved in the stroke pathophysiology during TAVI. The use of cerebral embolic protection devices (CEPDs) during TAVI may contribute to decrease the procedural stroke risk. Different biological responses to the presence of an aortic bioprosthesis and its materials, such as increased platelet activation and an acute rise in prothrombotic factors, increased shear stress and endothelial injury, altered aortic flow dynamics in the neosinus, and suboptimal antiplatelet effect, may favor the formation of thrombi and embolic phenomena during the first year after TAVI, with the first 3 months being the period of greatest risk (9, 10, 12–14). Also, postprocedural subacute and late events can be at least partly explained by atrial fibrillation (AF), which has been reported in about 20–40% of patients admitted for TAVI, and by the development of new-onset atrial fibrillation (NOAF) in up to 8% of cases during or after the intervention (15–17). In addition to AF, it is likely that the mechanism of late events is also associated with other baseline characteristics known predictors of late cardiovascular events, such as cerebrovascular disease, peripheral artery disease, and/or renal disease, namely the baseline burden of the aged TAVI patient. Therefore, TAVI-related stroke seems to be linked to both increased platelet activation due to endothelial injury after valve deployment and to AF-related thromboembolic risk factors (**Figure 1**).

Subclinical stroke

Different studies have shown the presence of silent cerebral embolic lesions in most patients undergoing percutaneous and surgical aortic valve replacement detected by diffusion-weighted magnetic resonance imaging (DW-MRI) (18, 19). Increasing evidence indicates that these subclinical phenomena may be associated with progressive cognitive deterioration, leading to a neurocognitive decline and dementia (20, 21). The long-term relevance of these clinically "silent" brain lesions still remains unknown, but since they can be found in the vast majority of patients undergoing TAVI, they constitute the hidden part of the iceberg; so, the adoption of preventive measures will be of utmost importance. The recognition of overt strokes and asymptomatic brain lesions after TAVI is largely dependent

TABLE 1 Rates of stroke/TIA in the pivotal randomized TAVI trials.

Trial	Year	Sample size	STS-PROM score (mean ± SD)	Stroke or TIA (%)	
				30 days	1 year
PARTNER 1A	2007–2009	348	11.8 ± 3.3	5.5	8.3
PARTNER 1B	2007–2009	179	11.2 ± 5.8	6.7	10.6
U.S. CoreValve	2011–2012	390	7.3 ± 3.0	5.7	10.4
PARTNER 2A	2011–2013	1,011	5.8 ± 2.1	6.4	10.4
SURTAVI	2012–2016	864	4.4 ± 1.5	4.5	8.2
PARTNER 3	2016–2017	496	1.9 ± 0.7	0.6	2.2
Evolut Low Risk	2016–2018	734	1.9 ± 0.7	4.0	5.8

TAVI, transcatheter aortic valve implantation; STS-PROM, society of thoracic surgeons predicted risk of mortality; TIA, transient ischemic attack.

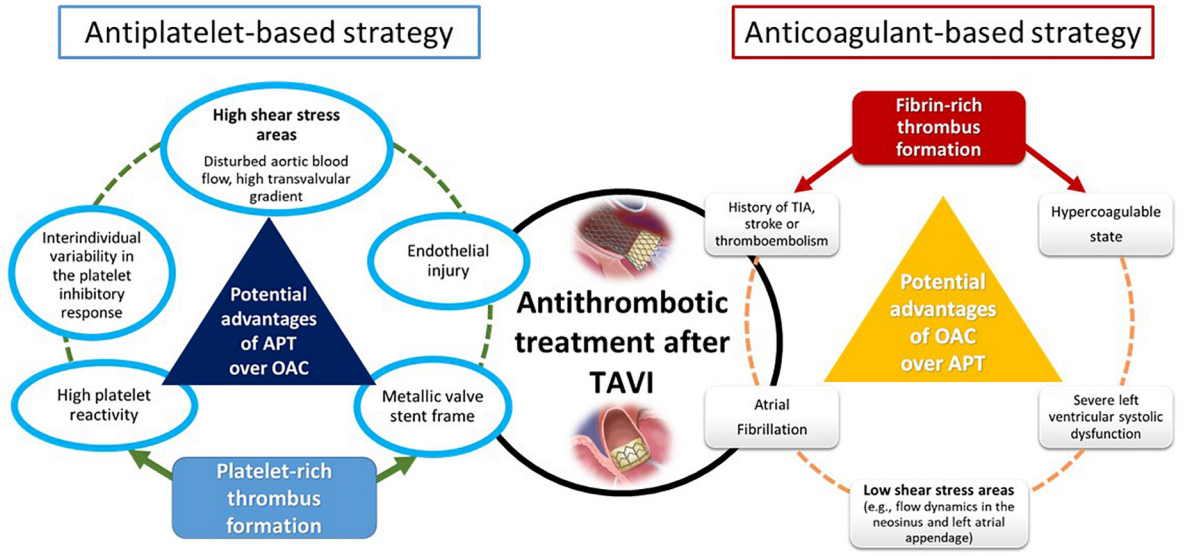

FIGURE 1
Potential mechanisms related to stroke after TAVI and main antithrombotic strategies. TAVI, transcatheter aortic valve implantation; APT, antiplatelet therapy; OAC, oral anticoagulation therapy; TIA, transient ischemic attack.

on the intensity of the neurological and imaging tests used. Therefore, the inclusion of an experienced neurologist in the heart team to assess the neurological integrity after TAVI and to detect any early subtle sign of brain damage is paramount.

Preventive strategies for acute and late strokes in transcatheter aortic valve implantation

Since manipulation of the transcatheter valve in the calcified aortic arch and native aortic valve plays an important role in the genesis of emboli and periprocedural acute stroke (procedure associated origin) (11, 12), cerebral protection devices may provide benefit (22–25). By contrast, strategies for the prevention of subsequent stroke are based on an optimal and balanced antithrombotic therapy to prevent ischemic events without substantially increasing the risk of long-term bleeding.

Cerebral embolic protection devices

Given that most CVEs in patients undergoing TAVI are embolic in nature, the use of CEPDs seems reasonable to reduce debris or embolic material that travels to the brain, subsequently minimizing the risk of stroke and lessen the extent of neurological damage. Previous studies have shown the feasibility and safety of CEPD use (22–25), but its efficacy remains to be clearly demonstrated (26).

Currently, there are four devices with published data, two of them under clinical use, and the other two under active investigation in early phase studies for their potential applications in TAVI and structural heart interventions

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(**Figure 2**). Basically, they are divided into two types based on their mechanism of action: devices that capture (totally or partially) debris before it reaches the brain arteries and devices that deflect the debris away from the main arterial branches of the aortic arch.

Another classification of devices is based on the brain protection they offer, being partial – covering two of the three main arteries of the aortic arch (brachiocephalic trunk or right common carotid artery and left common carotid artery) – or total (the former two plus the left vertebral artery originating from the left subclavian artery which merges with the right vertebral artery to form the basilar artery, the major supply to the posterior portion of the circle of Willis). The implications of leaving the left subclavian artery and thus the left vertebral artery unprotected are relevant.

Fanning JP and col (27) provided a detailed description of the anatomical distribution and the subsequent cerebral predilection for injury of the cerebral ischemic lesions occurring secondary to TAVI using DW-MRI. The authors observed that the distribution of lesions suggests the posterior circulation and the right hemisphere are particularly vulnerable to perioperative cerebrovascular injury. They found that 59% of all cerebral infarcts occurred in the posterior circulation, and around two-thirds of all lesions affected the right hemisphere. Interestingly, when considering the total volume of infarction, 10,255 μl (90%) occurred in the posterior compared with 1,192 μl (10%) in the anterior circulation (27).

Thus, embolic protection devices that lack coverage of the left subclavian artery also fail to completely protect the posterior circulation, resulting in potentially 19 of 28 cerebral vascular territories and 26% of the brain volume being completely unprotected. The authors hypothesized that the relatively impaired cerebral autoregulation in the posterior versus anterior circulation is a plausible explanation for the observed differences in vulnerability to injury, increasing the importance of providing complete cerebral protection in cases of cardiovascular procedures with risk of cerebral embolization (27).

Sentinel cerebral protection system

The Sentinel® Cerebral Protection System (Boston Scientific, Marlborough, MA, USA) consists of two polyurethane filters with 140-mm-diameter pores fixed in a flexible nitinol radiopaque frame, advanced from a 6-Fr sheath through the right radial or right brachial artery and deployed into the ostia of the brachiocephalic trunk and left common carotid artery (22). It is designed to capture emboli passing to the cerebral circulation in two of the three branches of the aortic arch, leaving the left subclavian open and potentially the left vertebral circulation unprotected (22, 28). The device has CE and FDA approval and is to date the most widely used CEPD in TAVI.

The MISTRAL-C trial (27) (n = 65 patients) and the CLEAN TAVI trial (22) (n = 100 patients) are randomized clinical trials that showed fewer new lesions and a smaller total lesion volumes in the protected group with Sentinel vs. no protection. Also, neurocognitive deterioration was more frequent in patients treated without protection (28).

The SENTINEL U.S. IDE trial (25) was a multicenter study (n = 363 patients) with a 1:1:1 randomization into a safety device arm (n = 123), an imaging device arm (n = 121), and an imaging control arm (n = 119). The authors found debris in 99% of the filters. Despite a reduction in all-cause strokes at 30 days, statistical significance was not met (5.6% for the EPD group vs. 9.1% in the control group; p = 0.25). Also, the decrease in the median total new lesion volume in protected territories (44%) evaluated by DW-MRI 2–7 days after TAVI was not statistically significant (102.8 mm^3, IQR 36.9–423.2 mm^3 in the device arm vs. 178.0 mm^3, IQR 34.3–482.5 mm^3 in the control arm; p = 0.33). It is noteworthy that using the procedural stroke classification by NeuroARC definition, the CEPD group showed a significant reduction in stroke within 72 h after TAVI when compared with the unprotected group (3.0 vs. 8.2%; p = 0.053).

In total, two large ongoing randomized trials will probably bring definitive evidence on the efficacy of Sentinel on stroke prevention in TAVI: Stroke PROTECTion With SEntinel During Transcatheter Aortic Valve Replacement (PROTECTED TAVR) (NCT04149535, N = 3,000) and British Heart Foundation Randomised Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation (BHF PROTECT-TAVI) (ISRCTN16665769, N = 7,730).

TriGUARD 3™ cerebral protection device

The TriGUARD 3™ Cerebral Protection Device (Keystone Heart, Tampa, FL, USA, a Venus Medtech Company) is a deflection device positioned in the aortic arch to provide protection to all three branches of the aortic arch, including the left subclavian artery (23). It is placed through a transfemoral access via a 9-Fr femoral arterial sheath, which also allows for concomitant use of a 6-Fr pigtail catheter. The device is composed of a semi-permeable nitinol mesh with pores of 115 × 145 mm, which deflects particles larger than 140 μ m (24).

The first and latest generation of the TriGUARD was assessed in four prospective clinical studies of TAVI recipients in the United States and Europe showing a numerical reduction (non-statistically significant) in stroke rates and a lower total lesion volume in cases who have complete coverage of all brain branches than in cases who were not protected in a combined analysis (23, 24).

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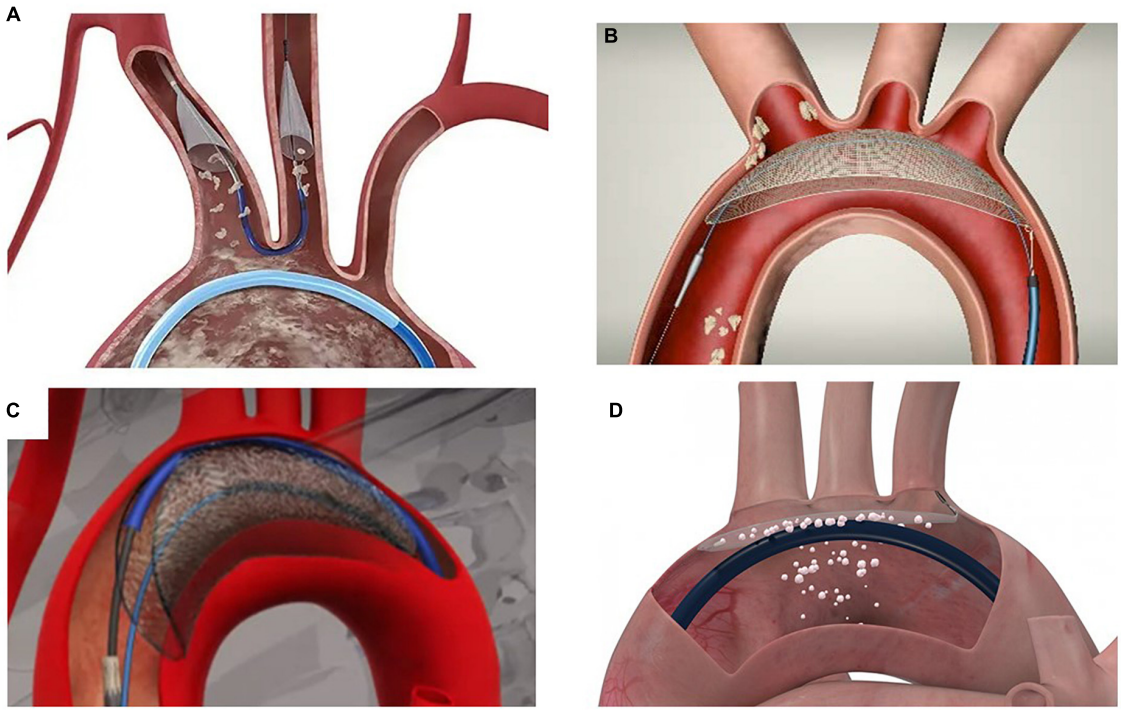

FIGURE 2
Cerebral embolic protection devices with published data. **(A)** Sentinel® Cerebral Protection System (Boston Scientific, Marlborough, Massachusetts). **(B)** TriGUARD 3 Cerebral Protection Device (Keystone Heart, Tampa, FL, USA, a Venus Medtech Company). **(C)** Emblok Embolic Protection System (Innovative Cardiovascular Solutions, Grand Rapids, Michigan). **(D)** ProtEmbo® Cerebral Protection System (Protembis GmbH, Aachen, Germany).

The feasibility and safety of this device were investigated in DEFLECT I (29) and DEFLECT II (30) trials, which were prospective, single-arm studies (n = 37 patients and 14 patients, respectively). Data on DW-MRI showed that in the DEFLECT I trial (28), the presence of new brain infarcts was comparable with those in historical controls (82 vs. 76%, p = NS). However, as compared with historical data, the total lesion volume per patient was 34% smaller (0.2 vs. 0.3 cm^3). Similarly, the DEFLECT II study (30) comparing the DWI-MRI of these patients with that of a historical control group revealed no significant reduction in the number of lesions [median 5.5 vs. 5.0, p = 0.857] but a substantial reduction in the mean lesion volume per patient [median 13.8 vs. 25.1, p = 0.049].

The DEFLECT III trial (31) (n = 85 patients) was a single-blind multicenter randomized trial in which patients with TAVI were randomized to either EPD (n = 46) with TriGUARD HDH or no CEPD (n = 39). DW-MRI was performed in all patients on days 4 ± 2 and 30 ± 7 after TAVI, as well as multiple serial neurological assessments. The dropout rate for DW-MRI assessment at 4 days was 30% (33 of 46 in the CEPD group and 26 of 39 in the no-CEPD group). Device success was achieved in 88.9% of the patients (40 of 45). The primary in-hospital procedural safety endpoints (death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute renal failure, or major vascular complications) did not differ statistically in TriGUARD HDH (21.7%) compared with the control group (30.8%, p = 0.34), but in cases with complete brain protection, TriGUARD HDH was associated with a higher rate of freedom from new cerebral lesions at 1 month (26.9 vs. 11.5%, p not reported) and less neurological damage assessed by the National Institutes of Health Stroke Scale (NIHSS) (3.1 vs. 15.4%, p = 0.16).

The REFLECT I trial (n = 258 patients of the initially planned 375 patients) was a multicenter (20 U.S. and 6 European centers), randomized controlled trial that evaluated the safety, efficacy, and performance of the TriGUARD™ HDH device in patients undergoing TAVI (23). There were 54 roll-in patients and 204 patients randomized 2:1 to TriGUARD HDH device (n = 141) or control (n = 63). The trial was suspended by recommendation of the data safety monitoring committee before patients' enrollment was completed. The primary efficacy endpoint was a hierarchical composite of (i) all-cause mortality or any stroke at 30 days, (ii) NIHSS worsening at 2–5 days or Montreal Cognitive Assessment worsening at 30 days, and (iii) total volume of brain ischemic lesions detected by DW-MRI at 2–5 days. Complete protection of all three cerebral vessels throughout the TAVI procedure was achieved in 57.3% (78/136).

Compared with the performance goal, the primary safety outcome was met (21.8 vs. 34.4%, $p < 0.0001$). The primary hierarchical efficacy endpoint was comparable between the groups, with a mean score (higher is better) of -5.3 ± 99.8 for TriGUARD and 11.8 ± 96.4 for controls ($p = 0.314$), corresponding to a win percentage of 44.6% for TriGUARD and 55.4% without protection. Comparable results were obtained in patients with complete cerebral coverage (mean score of -2.0 ± 71.4 for TriGUARD and 2.5 ± 70.1 for controls, $p = 0.766$, with a similar win percentage of 48 vs. 52%). When compared with the controls, covert central nervous system damage was reduced with TriGUARD both in-hospital (46.1 vs. 60.3%, $p = 0.0698$) and at 5 days (61.7 vs. 76.2%, $p = 0.054$).

In 18 U.S. sites, the REFLECT II U.S. trial (24) enrolled 220 of the 345 patients planned (63.8%), with 41 roll-in and 179 randomized patients (121 TriGUARD 3 and 58 control subjects). The study suffered an early discontinuation of the enrollment by the sponsor after the U.S. Food and Drug Administration advised for unblinded safety data assessment. Complete cerebral coverage (before, during, and after TAVI) was achieved in 59.7% (94/157), and device interaction was reported in 9.6% (15/157). The primary safety endpoint was met compared with the performance goal (15.9 vs. 34.4%; $p < 0.0001$), but the primary hierarchal efficacy endpoint at 30 days (death or stroke at 30 days, NIHSS score worsening in-hospital, and cerebral ischemic lesions on DW-MRI at 2 to 5 days) was not met (mean scores [higher is better]: −8.58 TG3 vs. 8.08 control; $p = 0.857$).

Emblok® embolic protection system

The Emblok Embolic Protection System (Innovative Cardiovascular Solutions, Grand Rapids, MI, USA) is a device designed to protect all supraaortic vessels by a full circumferential coverage of the aortic arch (32). The delivery system is an 11-Fr catheter compatible to be deployed through a single access site supported by 0.035 guidewire and integrates a 4-Fr radiopaque pigtail catheter for aortogram performance. Anatomical criteria for its use include an ascending aorta length $\geq$ 9 cm, an ascending aorta or aortic arch diameter between 30 and 35 mm, and an arterial femoral access suitable for an 11-Fr delivery system. The filter is made of a polyurethane mesh with a pore size of 125 μm, supported by a nitinol frame positioned just proximal to the brachiocephalic trunk. Once the transcatheter valve is deployed, the Emblok system must be recaptured to be able to retrieve the transcatheter delivery system from the body (32).

The Emblok device ($n = 20$ patients) was tested in a prospective, multicenter, non-randomized, first-in-man pilot study intended to evaluate its efficacy and safety during TAVI (32). The device was successfully positioned in all the cases, and no major adverse cardiovascular and cerebrovascular events occurred at the 30-day follow-up. Significant debris was captured in 18 (90%) filters, but 19 (95%) patients had new brain lesions at postprocedural DW-MRI. The median number of new lesions per patient was 10.00 (interquartile range [IQR]: 4.75 to 15.25), the total new lesion volume was 199.9 mm^3 (IQR: 83.9 to 447.5 mm^3), and the mean lesion volume per lesion was 42.5 mm^3 (IQR: 21.5 to 75.6 mm^3).

ProtEmbo® cerebral protection system

The ProtEmbo® Cerebral Protection System (Protembis GmbH, Aachen, Germany) is a temporary, intra-aortic embolic deflection filter used as an adjunct device during transcatheter heart interventions and is the only available device that can be positioned through a 6-Fr left radial access (33, 34). ProtEmbo is designed to provide complete cerebral protection and inserted in the beginning of the procedure prior to the TAVI device and removed following the completion of the TAVI procedure. The device consists of (1) a heparin-coated, 60-μm-pore size mesh (currently the smallest pore size of CEPDs), (2) a self-expanding nitinol frame that when expanded ensures sufficient coverage of all cerebral vessels of the aortic arch and includes radiopaque markers for fluoroscopic visualization and precise device placement, and (3) a delivery unit. The device is delivered unexpanded and deployed by unsheathing the self-expanding filter. A handle provides a simple user interface for preparation, delivery, deployment, and removal of the device. The device is loaded into a commercially available delivery catheter and placed into the aortic arch using a commercially available guiding sheath via the left radial artery (33, 34).

The first-generation ProtEmbo device was shown to be safe and feasible in the first-in-human PROTEMBO SF trial ($n = 4$ patients) in two clinical sites in Europe (33). The PROTEMBO C trial ($n = 41$ patients) was a prospective, non-randomized, multicenter (eight sites in Europe) study designed to evaluate the safety and performance of the second-generation ProtEmbo Cerebral Protection System in patients undergoing TAVI (34). The primary safety endpoint was the rate of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, as per the Valve Academic Research Consortium 2 definition, and the primary performance endpoint was the composite rate of technical success compared with performance goals (33). Secondary analyses included the brain DW-MRI new lesion volume and rate of death, or all strokes compared with historical data. Both primary endpoints were met early in this study. MACCE at 30 days were 8.1% (3/37) (upper limit of the 95% confidence interval [CI]: 21.3% versus performance goals 25%, $p = 0.009$), and technical success was 94.6% (35/37) (lower limit of the 95% CI: 82.3% versus performance goals 75%, $p = 0.003$). The new DW-MRI lesion volume with ProtEmbo was lower than that in historical data, and most patients who completed the MRI follow-up (87%, 27/31) were free of any single lesion larger than 150 mm^3.

Antithrombotic therapy in transcatheter aortic valve implantation

The current European (2) and American (1) guidelines for the management of valvular heart disease have modified their recommendation favoring the use of single antiplatelet therapy (SAPT) over dual antiplatelet therapy (DAPT) in TAVI patients without an underlying indication for oral anticoagulation (OAC), and in OAC alone over the association of OAC with antiplatelet therapy for TAVI patients requiring lifelong OAC. SAPT on top of vitamin K antagonists (VKAs) may be beneficial only in specific subsets (i.e., TAVI patients with recent acute coronary syndrome or recent coronary stenting). VKA or a direct-acting oral anticoagulant (DOAC) may be considered if OAC is indicated in the absence of contraindications. VKA is indicated in cases of clinical valve thrombosis, accompanied with symptoms or high transvalvular gradient, whereas its role in asymptomatic patients or with those with a normal transvalvular gradient (subclinical leaflet thrombosis) is currently not yet defined. A consensus document of the European Society of Cardiology Working Group on Thrombosis and the European Association of Percutaneous Cardiovascular Interventions (35) supports these recommendations.

Periprocedural antithrombotic management

The decision to start the antithrombotic therapy before TAVI is not standardized and is primarily left to the physicians' discretion. However, preprocedural DAPT with aspirin and clopidogrel has been linked to a two-fold increased risk of in-hospital bleeding and transfusions compared with SAPT or no antiplatelet medication, with no clear benefit in terms of ischemic protection (36, 37). Low-dose aspirin is the recommended pre-TAVI treatment in patients without OAC indication (35). Although most patients with TAVI have high residual platelet reactivity to clopidogrel (9, 38), no additional benefits on thromboembolic event reduction have been demonstrated with clopidogrel maintenance or with loading dose prior to TAVI (39).

Among patients on OAC, both VKAs and DOACs are usually stopped before the procedure. A bridging strategy with low-molecular weight heparin is optional and, based on local practice, is restarted for OAC after an uncomplicated intervention (36, 37). Recent evidence suggests that TAVI in patients with OAC may be as safe as and equivalent to an OAC interruption strategy (40–42).

During the intervention, unfractionated heparin is the most used strategy and may be reversed with protamine sulfate at procedure completion according to local practice (43). Although the use of protamine to reverse unfractionated heparin (UFH) after the procedure is not widespread in all TAVI centers and small studies have found no benefit in its use (44), some other evidence points in favor of this strategy after the procedure. In a prospective observational study of 873 patients undergoing TAVI (43), authors found lower rates of the primary composite outcome (a composite of 30-day all-cause mortality and major and life-threatening bleeding) in the group with UFH reversal using protamine (3.2%) than in the control group without heparin reversal (8.7%; $p = 0.003$). This finding was driven by a reduction in major and life-threatening bleeding complications (1.0 vs. 4.1%; $p = 0.008$; and 0.1 vs. 2.6%; $p < 0.001$, respectively). Also, in the control group, the hemoglobin level at 24 h was lower, need for transfusion was higher, and hospital stay was longer, suggesting the benefits for the prevention of clinically relevant complications by protamine administration. Another relevant observation was that thromboembolic complications were equal between the groups. These data are reassuring regarding one of the main concerns of protamine use, which are thrombotic complications, primarily at the transcatheter valve level or in patients with a recent coronary stent. The use of protamine was independently associated with the reduction of the primary composite outcome in the multivariate analysis. Hence, the EAPCI states that protamine sulfate may be used before vascular access closure to reverse anticoagulation with UFH to prevent vascular access site complications and bleedings (35).

The role of procedural bivalirudin is limited to patients who are unable to receive heparin (i.e., allergy and heparin-induced thrombocytopenia) (45). Ongoing studies [Periprocedural Continuation Versus Interruption of Oral Anticoagulant Drugs During Transcatheter Aortic Valve Implantation trial (POPular PAUSE TAVI), NCT04437303] will provide more evidence on this topic.

Antithrombotic management after transcatheter aortic valve implantation

From the latest ACC/AHA guidelines (1), a SAPT of aspirin (75–100 mg daily) is recommended after TAVI in the absence of other indications for oral anticoagulants (class of recommendation: 2a, level of evidence: B-R), while DAPT (aspirin 75–100 mg plus clopidogrel 75 mg daily) for 3 to 6 months has been retroceded to class of recommendation 2b.

In the same line, in the ESC/EACTS guidelines (2), lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC (class of recommendation: I, level of evidence: A), while the routine use OAC is not recommended after TAVI in patients with no baseline indication for OAC (class of recommendation: III, level of evidence: B) (**Figure 3**).

Previous observational studies and recent randomized control trials have demonstrated in patients undergoing TAVI

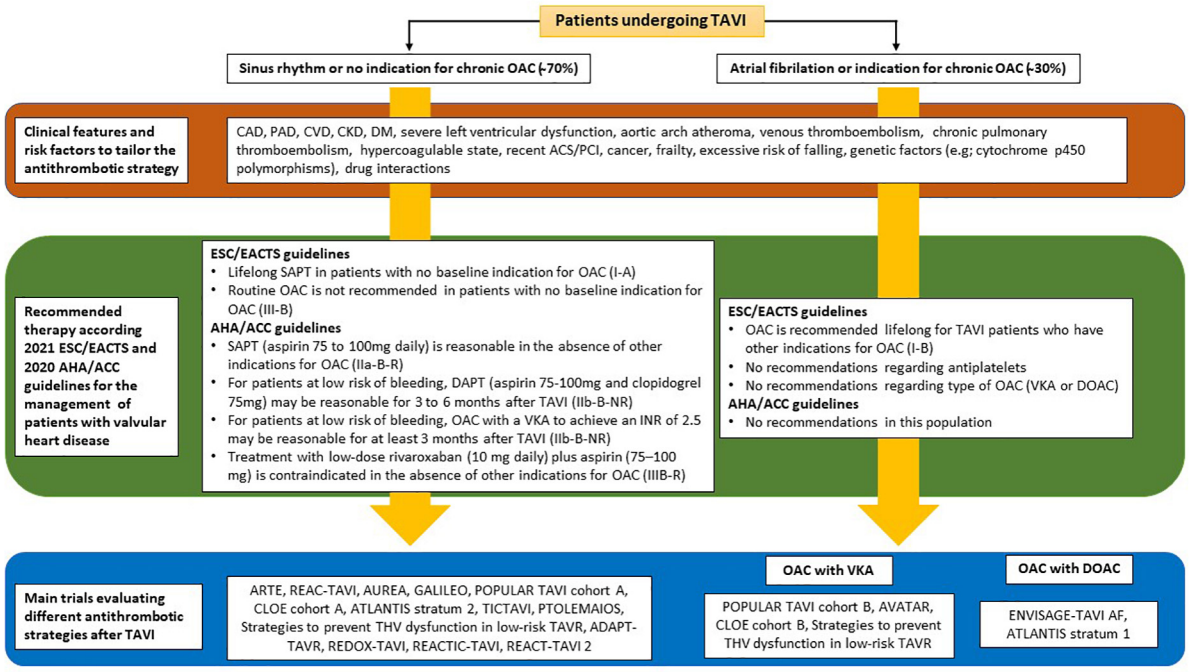

FIGURE 3
Summary of current recommendations of the European and American guidelines on the antithrombotic regimen after TAVI, including the main studies assessing a variety of antiplatelet and anticoagulant combinations. TAVI, transcatheter aortic valve implantation; OAC, oral anticoagulation; CAD, coronary artery disease; PAD, peripheral artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery; AHA, American Heart Association; ACC, American College of Cardiology; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; HBR, high-bleeding risk; VKA, vitamin K antagonist; LBR, low bleeding risk; DOAC, direct oral anticoagulant.

with no underlying indication of OAC, the use of DAPT has no advantage over SAPT for the prevention of ischemic events and increases the risk of bleeding. A total of three small-scale RCTs did not find differences between DAPT and SAPT after TAVI on ischemic outcomes (46–48). In the POPular TAVI trial cohort A (49), 665 patients undergoing TAVI without an indication for OAC were randomized to aspirin 100 mg or aspirin 100 mg + clopidogrel 75 mg for 3 months following TAVI (no loading dose prior TAVI). At 1 year, bleeding and the composite endpoint of bleeding or thromboembolic events were significantly less frequent with aspirin monotherapy than with DAPT (15.1 vs. 26.6%, respectively, relative risk [RR] 0.57; 95% CI: 0.42–0.77; p = 0.001 for bleeding); and non-procedure-related bleeding (15.1 vs. 24.9%; RR, 0.61 [95% CI, 0.44–0.83]; p = 0.005), and this benefit was driven by less major bleeding events, mostly due to periprocedural bleeding. In addition, the rates of ischemia events and valve function measurements were comparable in both groups. However, there are certain scenarios, where in the absence of increased bleeding risk, DAPT should be considered for a limited period (i.e., within 1–12 months), such as recent acute coronary syndrome, complex coronary stenting prior TAVI or during TAVI (chimney stenting), valve-in-valve procedures, large aortic arch atheromas, and previous non-cardioembolic stroke.

Also, the use of OAC (either VKA or DOAC) has not shown evidence to support its use. The GALILEO trial (n = 1,644 patients) tested rivaroxaban 10 mg/d (plus aspirin for the first 3 months) versus aspirin 75 to 100 mg/d (plus clopidogrel 75 mg/d for the first 3 months). The authors found a higher risk of thromboembolic complications (hazard ratio [HR], 1.35 [95% CI, 1.01–1.81]; p = 0.04), death (HR, 1.69 [95% CI, 1.13–2.53]), and major, disabling, or life-threatening bleeding (HR, 1.50 [95% CI, 0.95–2.37]; p = 0.08) with the OAC strategy (50). Notably, in the GALILEO-4D substudy (n = 231), patients treated with rivaroxaban plus aspirin showed a less frequency of subclinical leaflet motion anomalies and leaflet thrombosis than patients treated with a DAPT regimen (51). The ADAPT-TAVR (n = 229) was an open-label trial that evaluated the use of edoxaban for 6 months or DAPT with ASA plus clopidogrel on leaflet thrombosis assessed by 4DCT in patients without indication of OAC. At 6 months after TAVI, the researchers noted no link between subclinical leaflet thrombosis and an increased risk of cerebral thromboembolism or neurological impairment (52). Also, no statistically significant difference between edoxaban and DAPT in leaflet thrombosis incidents

were found, although edoxaban group patients did show a lower trend (9.8 vs. 18.4% for DAPT; absolute difference: −8.5%; 95% CI: −17.8 to 0.8%; $p = 0.076$). The edoxaban group had numerically more new cerebral lesions on DW-MRI than the DAPT group (25.0 vs. 20.2%, respectively; difference, 4.8%; 95% CI: −6.4 to 16.0%; $p = 0.40$). The median total new lesion number (1 for each group; $p = 0.85$) and volume (36.6 mm^3 for edoxaban and 43.9 mm^3 for DAPT; $p = 0.88$) were also not different between the two groups. Neurocognitive outcomes measured by the NIHSS, modified Rankin Scale, and Montreal Cognitive Assessment, and any or major bleeding events (11.7% of the edoxaban patients versus 12.7% on DAPT, hazard ratio 0.93; 95% CI: 0.44–1.96) were comparable between the two groups. Similar data on the potential lack of benefit on the prevention of silent cerebral lesions after TAVI with OAC (acenocoumarol) compared with DAPT (aspirin + clopidogrel) has been presented (53).

For patients undergoing TAVI with underlying indication of long-term OAC, definitive evidence supporting DOACs over VKAs after TAVI is currently lacking. Observational data have shown inconsistent results regarding the thromboembolic risk associated with DOACs in the post-TAVI population. A collaborative registry between German and Italian centers ($n = 962$) showed higher all-cause mortality, myocardial infarction, and cerebrovascular events at 1 year with DOACs (rivaroxaban, apixaban, or dabigatran) than with VKA, with a comparable 1-year event rates of bleeding (54), while in a nationwide observational cohort Danish study ($n = 735$), a similar risk of thromboembolism, bleeding, or all-cause mortality post-TAVI among DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) and VKAs (warfarin or phenprocoumon) was found (55). According to the data from the PARTNER 2 cohort, OAC alone was ineffective in reducing 2-year stroke, while antiplatelet therapy with or without anticoagulant therapy significantly lowered the risk of stroke at 2 years after TAVI. OAC, on the other hand, was linked to a lower risk of combined death and stroke when taken alone (56).

The POPular TAVI cohort B ($n = 326$) evaluated the safety and efficacy of OAC plus clopidogrel or OAC alone post-TAVI (57). The rate of non-procedural bleeding at 1 year was considerably higher in the OAC plus clopidogrel than in the OAC alone group (34 vs. 21.7%, $p = 0.02$), while the composite of cardiovascular death, stroke, or MI was comparable between the two treatment strategies non-inferior (17.3 and 13.4%, respectively; 95% CI for non-inferiority, −11.9 to 4.0).

The ENVISAGE-TAVI AF ($n = 1,426$) trial compared edoxaban with VKAs in patients with an indication for anticoagulation (58). Regarding NACE (death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding), edoxaban was non-inferior to VKA (17.3 vs. 16.5 per 100 person-years; HR, 1.05; 95% CI, 0.85 to 1.31; $p = 0.01$ for non-inferiority), but edoxaban was associated with a higher incidence of major bleeding (mostly gastrointestinal bleeds) than VKA, mainly among patients who received specified concomitant antiplatelet therapy (9.7 vs. 7.0 per 100 person-years; HR, 1.40; 95% CI, 1.03 to 1.91; $p = 0.93$ for non-inferiority). No valve thrombosis events were reported in the trial.

The recently published ATLANTIS trial ($n = 1,500$) tested apixaban 5 mg (2.5 mg if impaired renal function or concomitant antiplatelet therapy) ($n = 749$) two times daily, or standard of care ($n = 751$) (59). In stratum 1, patients in the standard-of-care group received a VKA, while in stratum 2, patients received antiplatelet therapy with aspirin and clopidogrel, if there was an indication for anticoagulation or not, respectively. The primary endpoint was the composite of death, myocardial infarction, stroke or transient ischemic attack, systemic embolism, intracardiac or bioprosthesis thrombosis, deep vein thrombosis or pulmonary embolism, and life-threatening, disabling, or major bleeding over the 1-year follow-up. The primary safety endpoint was major, disabling, or life-threatening bleeding. Apixaban was not superior to standard of care globally (18.4 vs. 20.1%; HR 0.92; 95% CI 0.73–1.16; P interaction = 0.57) and in each stratum arms (indication or not for OAC). Similar to observed in the GALILEO trials (50, 51), subclinical valve thrombosis was reduced with apixaban compared with the aspirin and clopidogrel regimen (HR 0.19; 95% CI 0.08–0.46), while a signal of higher non-cardiovascular mortality was observed with apixaban.

Ongoing trials (AVATAR, NCT02735902; Strategies to Prevent Transcatheter Heart Valve Dysfunction in Low Risk Transcatheter Aortic Valve Replacement, NCT03557242; REACTIC-TAVI, NCT04331145; REAC-TAVI 2, NCT05283356; and REDOX-TAVI, NCT04171726) will provide more information regarding the antithrombotic management on this complex field.

The conventional TAVI population carries a large burden of comorbidities that make them more susceptible to long-term cerebrovascular events. The incidence of diabetes mellitus, coronary artery disease, history of atrial fibrillation, previous stroke, or peripheral vascular disease raises up to 60–70% in TAVI recipients, including high- to intermediate-risk (60–64) to low-risk patients (65, 66).

In these patients, achieving an optimal long-term antithrombotic strategy that provides protection from future ischemic events (stroke, myocardial infarction, or valve thrombosis) without significantly increasing the cumulative risk of bleeding over time is crucial. This long-term treatment is very relevant primarily in the low-risk population and in younger patients with a long life expectancy in whom extending the durability of the aortic bioprosthesis as much as possible is essential to avoid repeat interventions, as well as in certain scenarios, such as bicuspid valve, valve-in-valve, or valve-in-TAV procedures. Also, it should be in line with

the optimal medical management of their comorbidities. Some studies are in this direction (NCT05283356, NCT03042104, NCT02825134, NCT03972644, NCT04204915, and NCT03094143), exploring the lifetime management of the TAVI population and will provide data in future.

Conclusion

In current TAVI practice, the rate of overt stroke during or early after TAVI is relatively low (2–4%) (5) but remain stable over the years (4). However, it may represent only the tip of the iceberg of cerebral cardioembolic events, being microembolization and cerebral "silent" injury more frequent phenomena, but still poorly understood with a potential substantial impact on mid- and long-term cognitive function. Although there is still not enough clinical evidence to conclusively establish a direct relationship between the use of CEPDs and stroke prevention, the available studies point to significant protection from periprocedural cerebrovascular events. Important studies are under way to clarify this point (NCT04149535 and ISRCTN16665769). Therefore, in light of TAVI expansion to lower risk patients and the younger population, measures to abate neurological risks during and after TAVI are warranted.

Author contributions

VJ, RE, and AI developed the concept, design, and drafted the manuscript. JB, PJ, GB, BC, and CV contributed substantially to the critical revision of the manuscript and add important intellectual content. All authors contributed to the article and approved the submitted version.

Funding

This research has been partially supported by the Axencia Galega de Innovación – GAIN through program code IN607B-2021/18.

Conflict of interest

VJ serves as clinical advisor for Protembis GmbH.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 02 November 2022
DOI 10.3389/fcvm.2022.922696

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 18 April 2022
ACCEPTED 30 September 2022
PUBLISHED 02 November 2022

CITATION
Monizzi G, Olivares P, Makmur G, Fabbiocchi F, Grancini L, Mastrangelo A, Ferrari C, Galli S, Montorsi P and Bartorelli AL (2022) Conduction disorders after transcatheter aortic valve implantation: A comparison between SAPIEN 3 and SAPIEN 3 Ultra balloon-expandable valves. *Front. Cardiovasc. Med.* 9:922696. doi: 10.3389/fcvm.2022.922696

Conduction disorders after transcatheter aortic valve implantation: A comparison between SAPIEN 3 and SAPIEN 3 Ultra balloon-expandable valves

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Background: Conduction disorders (CD) are the most common complications after Transcatheter Aortic Valve Implantation (TAVI). The last generation of Edwards balloon expandable valves, the SAPIEN 3 Ultra (S3U), is provided with an external sealing skirt that aims to further reduce paravalvular leakage (PVL) compared to SAPIEN 3 (S3) and could potentially lead to higher CD rate. We sought to investigate the rate of new-onset CD in patients undergoing TAVI with the S3 or S3U valve.

Methods: We included 582 consecutive patients undergoing TAVI in a single high-volume Center. Patients with previously implanted pacemaker and Valve in valve procedures were excluded. CD rate was evaluated early after implantation and at discharge.

Results: No significant difference in the overall CD rate was found between S3 and S3U patients both immediately after the procedure (S3 45.5% vs. S3U 41.8%, $p = 0.575$) and at discharge (S3 30.4% vs. S3U 35.6%, $p = 0.348$) with low rate of permanent pacemaker implantation (S3 6.3% vs. S3U 5.5%, $p = 0.749$). No significant differences were found also in patients with pre-existing atrial fibrillation (S3 8.2% vs. S3U 5%, $p = 0.648$). A significantly lower rate of PVL was found with S3U compared to S3 (S3 42% vs. S3U 26%, $p = 0.007$). According to the manufacturer's guidelines we confirmed that S3U were implanted in a significantly higher position compared to S3 (S3 4.89 $\pm$ 1.57 mm vs. S3U 4.47 $\pm$ 1.36 mm, $p = 0.001$).

Conclusion: No significant difference in the rate of CD, including the need for PPM implantation, was found in patients undergoing TAVI with the S3 compared to S3U. Moreover, S3U significantly reduced the PVL rate.

KEYWORDS

conduction disorders in new-generation balloon-expandable valves TAVI, conduction disorders, aortic stenosis, TAVI, pacemaker

Introduction

Transcatheter aortic valve implantation (TAVI) is nowadays a worldwide accepted option for treating patients with severe aortic valve stenosis in patients at all levels of surgical risk (1–3). Conduction disorders (CD) are one of the most common complications of TAVI. Indeed, about one third of patients present CD at discharge, with the left bundle branch block (LBBB) being the most frequent (4–6). The SAPIEN 3 Ultra transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, CA) is the latest iteration of the balloon-expandable Edwards THV family featuring an improved external sealing skirt that aims to further reduce paravalvular leakage (PVL) (7). A recent retrospective study comparing the Edwards SAPIEN 3 (S3) to SAPIEN 3 Ultra (S3U) valves did not find any difference in terms of 30-day clinical outcomes except for a lower rate of major vascular complications (11.4% vs. 4.5%, $p = 0.05$) and PVL with the S3U (8). Comparative studies specifically focusing on the evaluation of all types of CD after S3 or S3U valve implantation are not currently available. Thus, the primary endpoint of our study was to compare the rate of new-onset CD in patients undergoing TAVI with the S3 or S3U valve.

Materials and methods

Population

We prospectively included 582 consecutive patients with severe aortic valve stenosis undergoing TAVI after local Heart Team decision with a balloon-expandable S3 or S3U in a single high-volume TAVI Center (Centro Cardiologico Monzino, Milan, Italy) between January 2016 and November 2020. S3 valves were implanted from January 2016 until April 2019, and S3U valves from March 2019 onward. Experienced operators performed TAVI according to the local protocol. All subjects gave written informed consent. Exclusion criteria of the study were:

1. "Valve-in-valve" procedures (THV implantation into a previously surgical or percutaneous implanted aortic prosthesis);
2. Presence of a previously implanted pacemaker;
3. Electrocardiogram not available or not analyzable before TAVI.

The final population of our study consisted of 498 patients. Among them, 352 (70.5%) received a S3 and 146 (29.5%) a S3U (**Figure 1**).

Multislice CT scan evaluation

As recommended by the current guidelines, an ECG-gated multislice CT study (MSCT) was performed to obtain information about anatomical predictors of CD as previously demonstrated (9). For this reason aortic annulus dimension, degree of leaflet calcification, Left ventricle outflow tract (LVOT) calcifications, Membranous septum length (MSL) in addition to anatomy of the access site and peripheral vessels were collected (3, 9). A dedicated protocol was formulated, with 100–120 kV and tube current modified according to the patient's size.

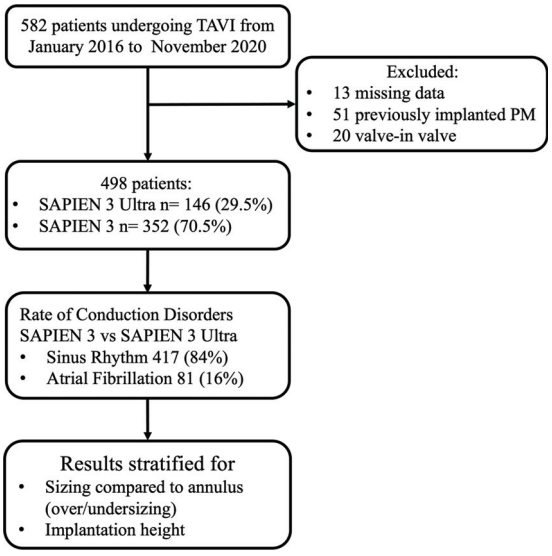

FIGURE 1
Study flowchart.

The following variables were analyzed for each patient:

1. Aortic valve calcification was quantified with MSCT according to current criteria (grade 1–4 calcification of the aortic cusps) (10).
2. The MSL was measured by two expert CT operators (PO, AM) determining the thinnest part of the interventricular septum on axial images as previously validated (11).
3. The THV implantation depth within the left ventricular outflow tract was evaluated by angiographic standard projections during the implantation. The distance between the inferior edge of the cobalt-chromium THV frame and the left and non-coronary cusps was assessed and the mean value of the two measurements was recorded (11, 12) (**Supplementary Figure 4**).
4. Prosthesis sizing was calculated as the ratio of THV nominal area and aortic annulus area measured with MSCT. Valve undersizing was defined as a prosthesis nominal area 5% smaller than the annular area measured with MSCT, while oversizing was defined as a nominal area 5% larger than the annular area measured with MSCT as previously validated (13). Values comprised in this interval were defined as matched THV sizing.

Procedural evaluation

Most of the patients were treated under general anesthesia, while in some selected cases deep sedation was used as deemed indicated by the Heart Team. All baseline, procedural, and post-operative data were retrospectively recorded. Post-TAVI transthoracic echocardiography (TTE) were performed by experienced echocardiographers who are independent from TAVI operators. PVL was graded as mild, moderate, and severe according to the Valve Academic Research Consortium 3 (VARC-3) criteria.

Periprocedural complications were defined according to the Valve Academic Research Consortium-3 criteria (VARC-3) (14).

Electrocardiographic analysis

Standard 12-lead ECG was recorded at a speed of 25 mm/s and a calibration of 1 mV/mm at baseline (within 24 h prior to the procedure), immediately after the procedure, and daily until hospital discharge. All ECGs were digitalized and reviewed by two expert cardiologists (PO, GM) blinded to the clinical data. The diagnosis of AV and intraventricular CD was based on the recommendations of the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) for the standardization and interpretation of ECG (15, 16).

Patients with atrial fibrillation (AF) were excluded from the evaluation of new-onset AV block and included in the assessment of permanent pacemaker (PPM) implantation rate.

The variables analyzed in each ECG were:

1. Atrial Fibrillation (AF);
2. First-, second- or third-degree AV block;
3. Left bundle branch block (LBBB);
4. Right bundle branch block (RBBB);
5. Left anterior fascicular block (LAFB).

Statistical analysis

Continuous variables are reported as means and standard deviations if normally distributed, and as medians and interquartile ranges otherwise. Normal distribution of the variables has been evaluated using Shapiro-Wilk test. Categorical variables are reported as absolute numbers and percentages of the total. To assess statistically significant differences for the comparison of categorical measures, the Chi-square test was used, while for continuous values the unpaired *t*-test was used. A p-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using R version 3.5.2.

Results

Baseline characteristics of the final population (498 patients) are shown in **Table 1**. The average age was 80.4 years, and 252 (50.6%) patients were women. Arterial hypertension was present in 81%, dyslipidemia in 53.5% and diabetes mellitus in 25%. A previous myocardial infarction occurred in 15% of the patients, 16% of the patients had persistent AF, 52% were in NYHA class III or IV and 23.5% presented a history of chronic obstructive pulmonary disease. The average ejection fraction was 59.2% and the mean and maximal aortic gradients were 45.82 ± 14 mmHg and 74.55 ± 21.4 mmHg, respectively. The risk profile was evaluated using Logistic Euroscore II and STS score that were 4.9 ± 4.1% and 4.7 ± 3.8, respectively. Regarding medical therapy, 48.7% of the patients were being treated with a beta blocker, 21% with a calcium channel blocker and 10.6% with amiodarone. The access site was femoral in 471 (94.4%) patients, while 20 cases were performed with a transapical approach (4%) and 7 (1.6%) with a transaortic approach.

Patients receiving a S3 were 352 (70.5%), while 146 (29.5%) received a S3U. **Table 2** shows the comparison of characteristics between the two groups. No significant differences were found in baseline characteristics, echocardiography parameters, and procedural data. Compared to S3U, S3 was implanted deeper into the outflow tract (S3 4.89 ± 1.57 mm vs. S3U 4.47 ± 1.36 mm, $p = 0.001$). Higher implantation was intentional

TABLE 1 Baseline characteristics.

Patients number, *n*	**498**
Edwards SAPIEN 3 Ultra, *n* (%)	146 (29.5%)
Age (years)	80.4 ± 5
Female, *n* (%)	252 (50.6%)
Height (cm)	165 ± 4.8
Weight (Kg)	71.8 ± 15.4
Body mass index (kg/m^2)	26.3 ± 7.13
Hypertension, *n* (%)	405 (81%)
Diabetes, *n* (%)	125 (25%)
Dyslipidemia, *n* (%)	266 (53.5%)
NYHA class III or IV, *n* (%)	258 (52%)
COPD, *n* (%)	117 (23.5%)
Previous MI, *n* (%)	75 (15%)
Glomerular filtration rate (mL/min/1.73 m^2)	53.77 ± 19.25
Logistic Euroscore II	4.9 ± 4.1
STS score	4.7 ± 3.8
Atrial fibrillation, *n* (%)	81 (16%)
Right bundle branch block at baseline, *n* (%)	51 (10%)
Echocardiographic data	
LV ejection fraction (%)	59.2 ± 11
Transvalvular mean aortic gradient (mmHg)	45.8 ± 14
Transvalvular maximum aortic gradient (mmHg)	74.5 ± 21.4
Previous medication	
Beta blockers, *n* (%)	243 (48.7%)
Calcium channel blockers, *n* (%)	105 (21%)
Amiodarone, *n* (%)	53 (10.6%)

in concordance with recent data indicating the benefits of implanting the valve in a higher position (12, 17).

Rate of conduction disorders

No significant difference in the overall CD rate was found between S3 and S3U patients both immediately after the procedure (S3 45.5% vs. S3U 41.8%, $p = 0.575$) and at discharge (S3 30.4% vs. S3U 35.6%, $p = 0.348$, **Figure 2**). **Figure 3** shows in detail the different types of CD found in the study patients. The rate of new-onset LBBB early after the procedure and at discharge was similar in the two groups (postprocedural LBBB: S3 33.5% vs. S3U 28.8%, $p = 0.406$; LBBB at discharge: S3 19.5% vs. S3U 19.4%, $p = 0.984$) (**Figure 3A**). Similarly, no difference was found in terms of AV block of different degree between the two groups (**Figure 3B**).

Permanent pacemaker rate

The incidence of high-degree AV block requiring PPM implantation was similar between groups (S3 patients 6.3% vs. S3U patients 5.5%, $p = 0.749$) (**Figure 2**). No significant difference was found in PPM implantation rate in patients with pre-existing AF (S3 8.2% vs. S3U 5%, $p = 0.648$) (**Figure 3C**). Finally, a subanalysis of AV block occurrence that excluded patients with I° AV block before the procedure did not show any difference among the two groups. Detailed results are shown in **Supplementary material**.

Other outcomes including adverse events and paravalvular leakage rate

In our cohort, we found that 101 (20%) patients were treated with an undersized prosthesis, 68 of whom received a S3 (67%) and 33 a S3U (33%). In 134 (27%) patients, the prosthesis was of matched size. Of them, 102 received a S3 (76%) and 32 a S3U (24%). In 263 (53%) patients, an oversized prosthesis was implanted. Of them, 182 were treated with an S3 (31%) and 81 with an S3U (69%). Stratification flowchart is shown in **Figure 4A**. The comparison between S3 and S3U stratified based on prosthesis size showed no difference (**Figure 4B**). However, the comparison between oversized und undersized S3 and S3U valves showed a significantly higher rate of CD at discharge in the "oversized" group (37.3%, vs. 23.8% in the "undersized" group, $p = 0.046$) (**Figure 4C**).

Based on the implantation depth of the THV in the outflow tract, patients were divided in tertiles defining three groups: "high positioning," "intermediate positioning" and "low positioning" (**Figure 5A**). A high-positioning was performed in 28% S3 vs. 47% S3U, an intermediate positioning in 37% S3 vs. 25% S3U, and a low positioning in 35% S3 vs. 29% S3U. This indicates that S3U were implanted in a higher position compared to S3 (**Figure 5B**). A significantly higher CD rate was found with lower implantation position. However, no difference was observed comparing S3 to S3U stratified for prosthesis implantation depth (**Figure 5C**).

In-hospital complications analysis (**Table 3**) showed low rate of adverse events for both valves with no difference between S3 and S3U except for a significantly lower PVL rate in the S3U patients [S3 148 cases (42%) vs. S3U 38 cases (22%), $p = 0.007$) (**Figure 6**).

Discussion

The main results of our study can be summarized as follows:

1. There was no significant difference in terms of CD rate comparing the two latest generations of the balloon-expandable Edwards valve;
2. The rate of PPM implantation was low and comparable between the two groups;

TABLE 2 Comparison of baseline characteristics and procedural data between groups.

Patient number, *n*	**498**		
	SAPIEN 3*n* = 352	**SAPIEN 3 Ultra*n* = 146**	***P-value***
Age (years)	80.6 ± 5.73	80.7 ± 5.29	0.864
Female, *n* (%)	171 (48.5%)	81 (55.5%)	0.324
BMI (kg/m^2)	26.7 ± 5.25	26.3 ± 4.8	0.921
Hypertension, *n* (%)	304 (86%)	101 (69.2%)	0.107
Diabetes, *n* (%)	94 (26%)	31 (21.2%)	0.791
Dyslipidemia, *n* (%)	176 (50%)	74 (51%)	0.887
NYHA class III or IV, *n* (%)	190 (54%)	76 (52%)	0.789
COPD, *n* (%)	91 (25.8%)	26 (17.8%)	0.146
Previous MI, *n* (%)	49 (14%)	23 (16%)	0.546
GFR (mL/min/1.73 m^2)	54.9 ± 19.85	52.2 ± 19.48	0.246
Logistic Euroscore II	4.8 ± 4.5	4.33 ± 4.7	0.2658
STS score	3.7 ± 3.5	3.2 ± 3.4	0.346
AF, *n* (%)	61 (17%)	20 (14%)	0.360
RBBB at baseline, *n* (%)	32 (9%)	19 (13%)	0.213
PR interval, ms	168 ± 38.9	175 ± 34.6	0.673
QRS duration, ms	101 ± 25.4	102 ± 23.8	0.854
Moderate or severe LVOT calcium *n* (%)	74 (21%)	32 (22%)	0.843
Membranous septum length (mm)	4.1 ± 2.4	4.2 ± 2.4	0.886
Calcification (grade)	2.35 ± 0.9	2.4 ± 0.94	0.577
Annulus area (mm^2)	461 ± 85.4	454 ± 83	0.401
Echocardiography data			
LV ejection fraction (%)	58.4 ± 10.9	60.6 ± 10.3	0.069
Transvalvular mean aortic gradient (mmHg)	45.6 ± 15.2	46.6 ± 13.5	0.501
Transvalvular maximum aortic gradient (mmHg)	74.3 ± 23	74.8 ± 20.3	0.933
Previous medication			
Beta blockers, *n* (%)	182 (51%)	61 (42%)	0.148
Calcium channel blockers, *n* (%)	81 (23%)	36 (24.7%)	0.730
Amiodarone, *n* (%)	39 (11%)	14 (9.5%)	0.642
Procedural data			
Percutaneous access			
Transfemoral	331 (94%)	140 (95.9%)	0.819
Transapical	16 (4.5%)	4 (2.7%)	0.270
Transaortic	5 (1.4%)	2 (1.4%)	0.923
Prosthesis size			
26 mm	207	71	0.166
23 mm	142	75	0.089
20 mm	3	0	0.264
Predilatation, *n* (%)	37 (10.5%)	16 (11%)	0.889
Postdilatation, *n* (%)	33 (9.3%)	12 (8%)	0.696
Postprocedural PR interval, ms	185 ± 39.4	178 ± 35.6	0.784
Postprocedural QRS duration, ms	111 ± 26.3	110 ± 28.6	0.811
Prosthesis implantation depth (mm)	4.89 ± 1.57	4.47 ± 1.36	0.001

3. CD were relatively frequent after TAVI, and LBBB was the most common CD followed by AV blocks;
4. The S3U valve was implanted in a higher position compared to the S3 valve;
5. The PVL rate was significantly lower with the S3U valve;
6. In-hospital clinical outcome was good and comparable between the two groups.

The primary end point of our study was the incidence of CD after implantation of the latest version of the Edwards balloon-expandable valve (S3U) compared with the previous generation (S3). The prosthesis, which is available in three sizes (20, 23, and 26 mm), features the same bovine pericardium tissue and process as the S3 valve but has a taller, textured polyethylene terephthalate (PET) outer skirt. The main objectives of the new design are the simplification of the procedure due to the

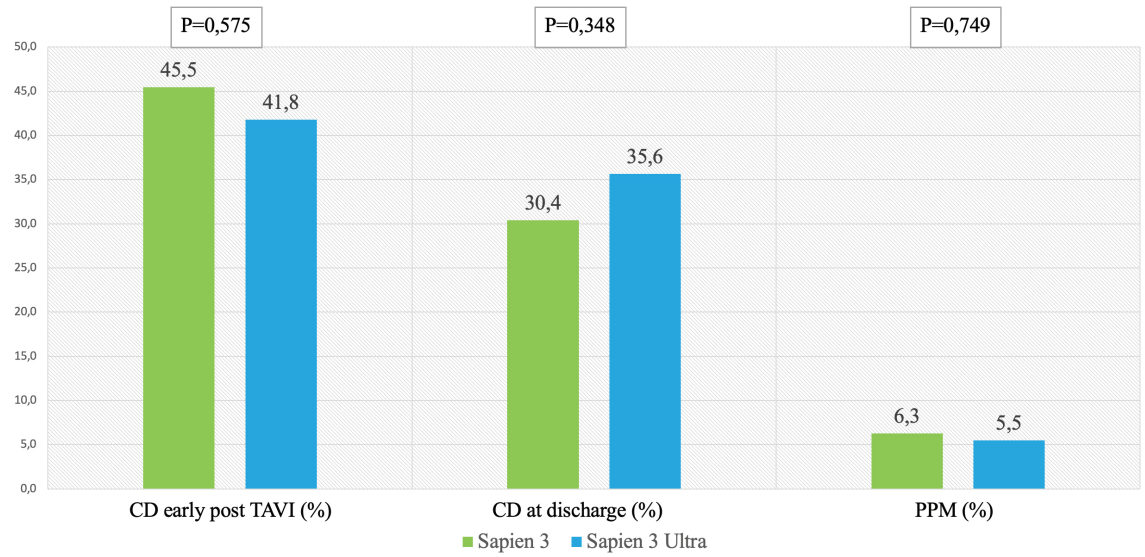

FIGURE 2
Rates of conduction disorders (CD) Left and central panel shows CD early after the procedure and at discharge with the SAPIEN 3 and SAPIEN 3 Ultra. Right panel shows rate of permanent pacemaker (PPM) implantation after TAVI with the SAPIEN 3 and SAPIEN 3 Ultra.

new delivery system and a further reduction of PVL risk (7). A recent retrospective study comparing S3 to S3U did not find any difference in terms of 30-day clinical outcomes except for a lower rate of major vascular complications (11.4% vs. 4.5%, p = 0,05) and PVL with the S3U (8). However, as the S3U has a "bulkier" and taller PET outer skirt, this could theoretically lead to a higher rate of CD after implantation such as new onset LBBB and high-grade AV block requiring PPM implantation. It is important to highlight that the rate of PPM implantation after TAVI is highly variable in literature and is dependent on many pre-existing anatomical and electrocardiographic factors other than only intraprocedural factors (9). Even if the new design of S3U valve could theoretically look "bulkier" and more risky, the results of our study seem to rule out this possibility showing that the two generation of Edwards balloon expandable valves had a similar CD rate after implantation (**Figure 2**). The explanation of this similarity could be due the fact that predictors of CD are other than the valve design as previously stated by Sammour et al. (9) Similarly, the need for PPM was low in both groups without any significant difference (6.3% for S3 and 5.5% for S3U, respectively) and slightly less than that reported in the HOMO-Sapien Registry designed for the approval of the S3U valve (8). The low PPM implantation rate observed in our real-world experience matches that of the PARTNER 3 trial designed to evaluate the procedural outcomes in low-risk patients (18).

It is noteworthy that the two patient groups were homogeneous and comparable in terms of baseline and echocardiographic characteristics, excluding selection bias that could affect the results. Moreover, no significant difference was found between groups regarding the grade of valve calcification that is one of the major predictors for new-onset postprocedural CD (19, 20).

Remarkably, if we consider THV sizing, no difference was found in the subanalysis of each of the three groups, "undersized," "matched" and "oversized," between the two valves even in presence of a statistically significant difference in the overall rate of CD in the "oversized" group compared to the "undersized" group both early post TAVI and at discharge (**Figure 4**). These results confirm what has been already reported in literature, i.e., valve oversizing is associated with higher CD rate (20).

The most common CD in our patients after TAVI was LBBB (19.5% in S3 and 19.4% in S3U at discharge), a finding similar to what has been already reported in two previous studies and in a large registry that assessed CD after S3 valve implantation and found a LBBB rate around 20% (19, 21). Although LBBB occurring in fragile patients undergoing TAVI has been shown to reduce 1-year death rate (3.3% vs. 13%, p = 0.014), other series gave controversial results suggesting that further studies will be needed to confirm this finding (20, 22, 23). Interestingly, LBBB in our patients was more frequently observed early after the procedure and showed a tendency to regress at discharge as already observed in previous studies (13, 21). Conversely, AV blocks showed a trend to increase at discharge as compared to the early postprocedural time.

There are some procedural aspects that may cause acute injury to the conduction system such as the prosthesis depth into the outflow tract with direct mechanical interaction with

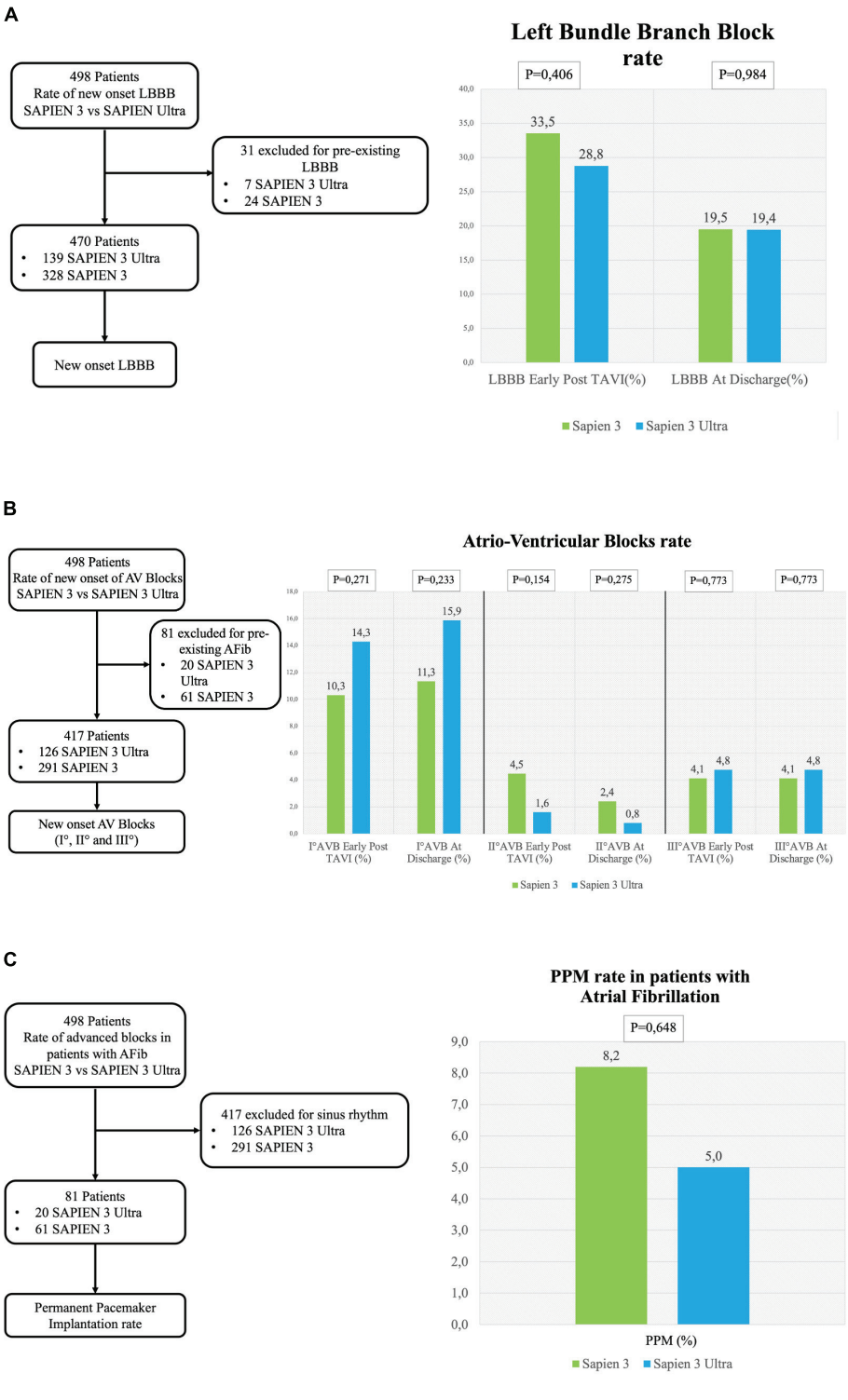

FIGURE 3
Conduction disorders subanalysis. **(A)** Left flowchart of the analysis for the rate of new-onset LBBB. Patients with pre-existing LBBB were excluded. **(A)** Right left bundle branch block (LBBB) rate early after TAVI and at discharge. **(B)** Left flowchart of the analysis for the rate of new-onset AV blocks. Patients with pre-existing atrial fibrillation were excluded. **(B)** Right rate of I° AV block early after TAVI and at discharge (right graph), II° AV block rate early after TAVI and at discharge (central graph) and III° AV block early after TAVI at discharge (left graph). **(C)** Left flowchart of the analysis for the rate of permanent pacemaker (PPM) implantation in patients with atrial fibrillation. Patients with sinus rhythm were excluded. The graph shows the rate of PPM implantation.

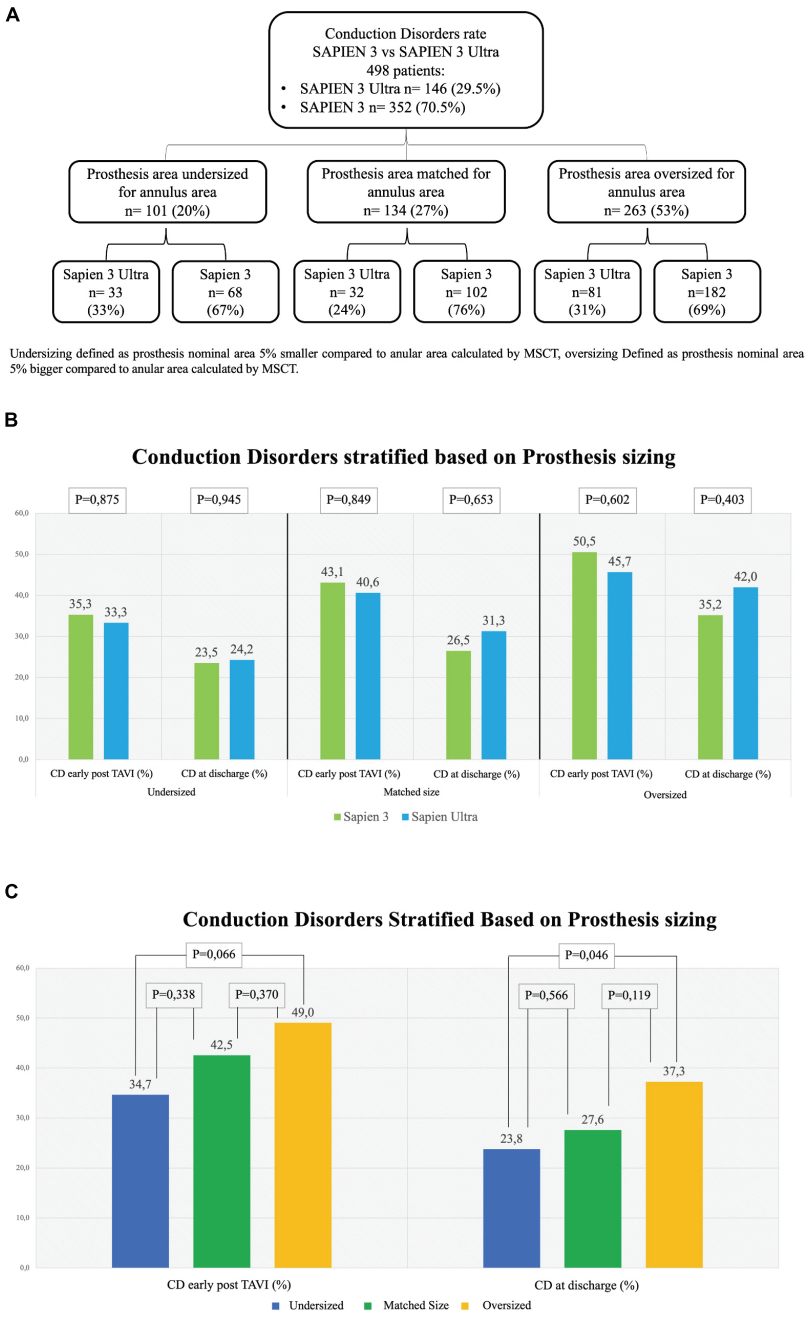

FIGURE 4
Rate of conduction disorders stratified based on prosthesis size. **(A)** Flowchart of stratification. Undersizing defined as prosthesis nominal area 5% smaller than the annular area calculated by multi-slice computed tomography (MSCT). Oversizing defined as prosthesis nominal area 5% bigger than the annular area calculated by MSCT. **(B)** Conduction disorders (CD) rate early after TAVI in undersized prostheses (left graph), in matched-sized prostheses (central graph) and in oversized prostheses (right graph). **(C)** CD rate based on prosthesis sizing combining together the two generations of valves S3 and S3U early post procedure (left) and at discharge (right). Dark Blue: Undersized group, Dark Green: Normosized group, Yellow: Oversized group.

the conduction system (19, 24). In our cohort, S3U valves were implanted in a higher position compared to the previous THV generation (Figure 5). A paper published recently by Sammour et al. demonstrated that aiming at a higher implantation position could reduce CD (25). A recent single center study evaluated the predictors of persistence of PM dependency at long term (30 days and 1 year after TAVI). They confirmed that pacemaker dependency after TAVI was strongly associated to implantation

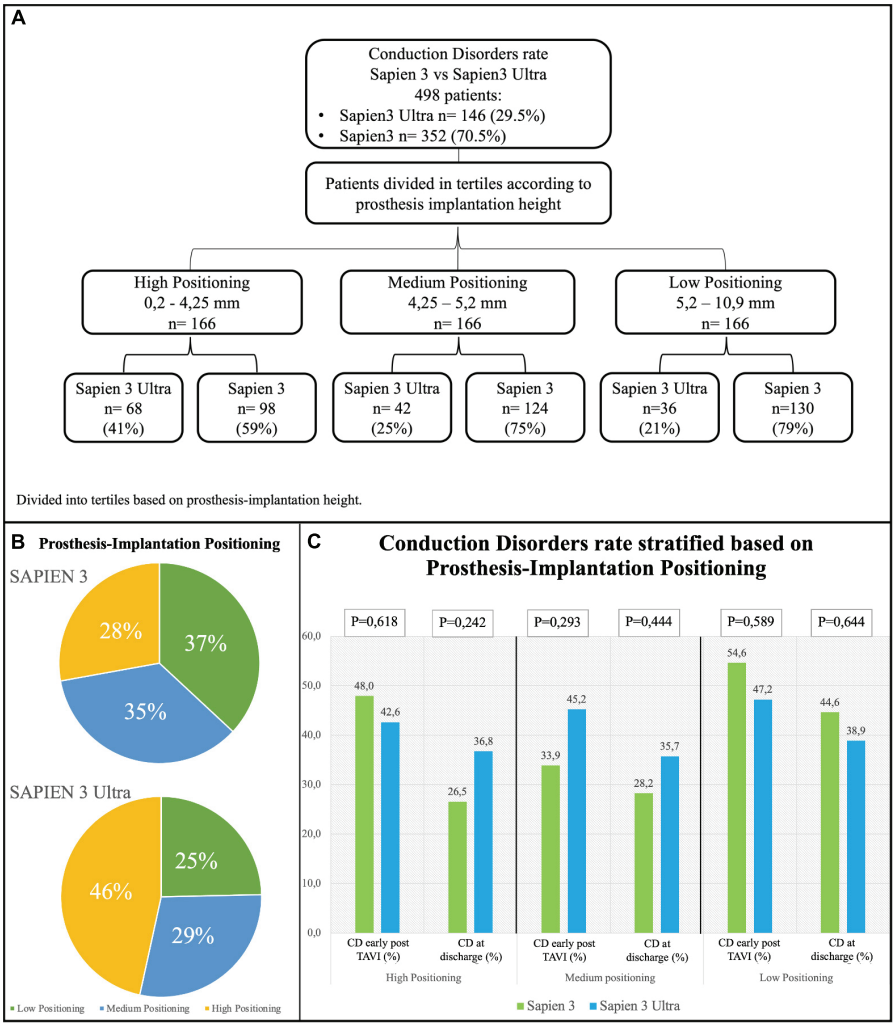

FIGURE 5
Conduction disorders rate stratified based on prosthesis implantation depth. **(A)** Flowchart of stratification. Prosthesis implantation height was calculated by evaluating angiographic projections during the implantation. The population was then divided into tertiles. **(B)** Distribution of the study population based on valve implantation depth. **(C)** Rate of conduction disorders (CD) early after TAVI and at discharge based on prosthesis implantation depth.

depth in relation to membranous septum. Conversely, the membranous septum itself and the type of implanted prosthesis, although previously associated with a higher risk of pacemaker implantation, were not predictive of CD persistence (26).

For the S3U valve, a higher implantation position is favored to the new PET outer skirt that increases the stability of the prosthesis and more importantly provides improved sealing even in a higher implantation position (8).

The reduction of PVL is of importance because several studies and meta-analyses showed decreased survival rates for patients even with mild PVL (13, 18). In the PARTNER trials with the S3, the rate of ≥ mild PVL ranged between 26.3 and 29.5%, while moderate or severe PVL ranged between 0.8 and 3.7% (2, 18). It is noteworthy that our study shows a lower rate of PVL for S3U as compared to S3 (**Figure 6**). This result is in agreement with the Saia et al. multicenter study that reported a significant PVL reduction with the S3U confirming the advantage of the new sealing skirt of the S3U over that of the S3 (27).

Even if the main objective of this study was to analyze CD occurrence, it should be noted that the clinical outcomes, defined according to VARC-3, were comparable between the two groups indicating the safety of the S3U.

Limitations

The main limitation of our study is the non-randomized, observational, and monocentric nature of the analysis. Nevertheless, we must state that patients were prospectively

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TABLE 3 In-hospital complications.

Patients number, *n*	**498**		
	Sapien 3*n* = 352	**Sapien 3 Ultra *n* = 146**	***P-value***
Procedural failure	5 (1.4%)	2 (1.3%)	0.965
In hospital death	2 (0.5%)	2 (1.3%)	0.363
Periprocedural myocardial infarction	4 (1.1%)	1 (0.6%)	0.647
Disabling stroke	2 (0.5%)	1 (0.6%)	0.943
Non-disabling stroke	4 (1.1%)	2 (1.3%)	0.791
Transient ischemic attack	12 (3.4%)	5 (3.4%)	0.993
Major bleeding	6 (1.7%)	3 (2%)	0.791
Major vascular complications	30 (8.5%)	10 (6.8%)	0.548
Paravalvular leakage (overall)	148 (42%)	38 (26%)	0.007
Trivial-mild PVL	121 (34%)	33 (22%)	0.031
> Mild PVL	27 (7.6%)	5 (3.4%)	0.088
Prosthesis thrombosis	4 (1.1%)	0	0.197
In-hospital stay (days)	6.42 ± 3.54	6.17 ± 2.98	0.436

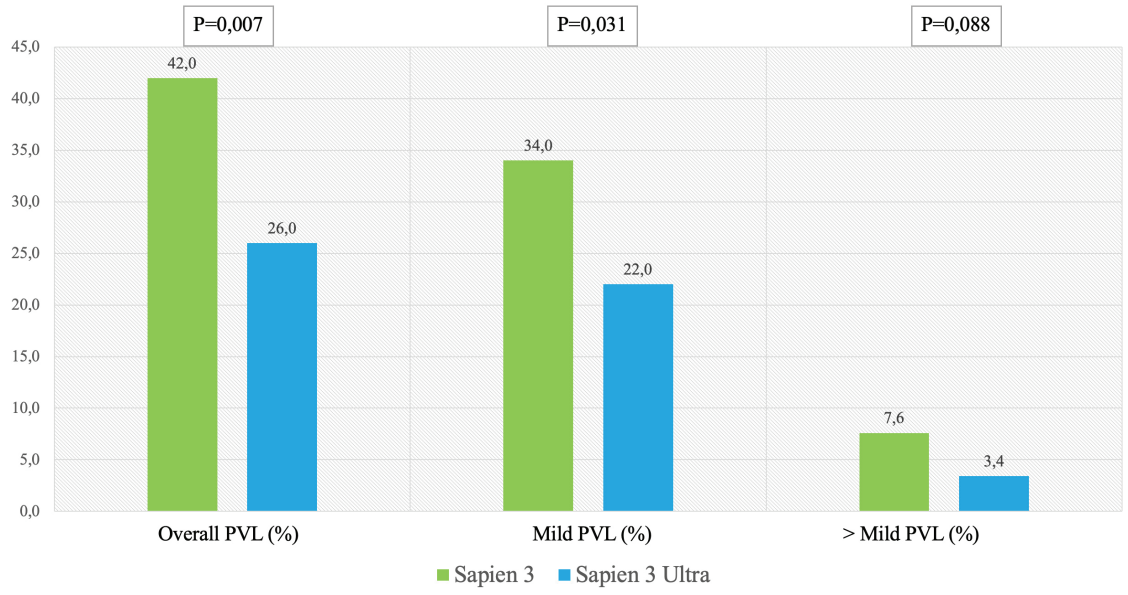

FIGURE 6
Paravalvular leakage rate. Rate of overall, mild and more than mild paravalvular leakage rate after SAPIEN 3 or SAPIEN 3 Ultra implantation.

and consecutively enrolled in the registry. Second, no statistical adjustment was performed to compare the groups. However, the comparison between the two groups showed very similar profiles with no statistically significant differences in any variable also for what concerns previous drug therapy that could affect the result. For these reasons, no adjustment was deemed necessary. Third, the study population was relatively small. It should be acknowledged that previous reports on CD after S3U implantation focused only on LBBB and PPM implantation rate and did not take in account RBBB and different grades of AV blocks.

Conclusion

In this retrospective, monocentric series, there was no significant difference in the rate of CD in patients undergoing TAVI with the S3 compared to S3U. Moreover, S3U further

reduced the PVL rate without increasing CD or the need of PPM implantation. However, further multicenter, prospective studies including a higher number of patients will be needed to confirm these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Centro Cardiologico Monzino. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GMo ideated the manuscript, analyzed the data, designed the figures, and wrote the draft. PO, GMa, and AM collected the data, analyzed the data, and reviewed the manuscript. FF, LG, and AB performed TAVI procedures and reviewed the manuscript. All authors contributed equally in reviewing the manuscript and contributed to the article and approved the submitted version.

Funding

Funding for open access fee, was granted by authors' institution IRCCS Centro Cardiologico Monzino.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.922696/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 21 November 2022
DOI 10.3389/fcvm.2022.971762

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 17 June 2022
ACCEPTED 31 October 2022
PUBLISHED 21 November 2022

CITATION
Kalogeropoulos AS, Redwood SR, Allen CJ, Hurrell H, Chehab O, Rajani R, Prendergast B and Patterson T (2022) A 20-year journey in transcatheter aortic valve implantation: Evolution to current eminence.
Front. Cardiovasc. Med. 9:971762.
doi: 10.3389/fcvm.2022.971762

A 20-year journey in transcatheter aortic valve implantation: Evolution to current eminence

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Since the first groundbreaking procedure in 2002, transcatheter aortic valve implantation (TAVI) has revolutionized the management of aortic stenosis (AS). Through striking developments in pertinent equipment and techniques, TAVI has now become the leading therapeutic strategy for aortic valve replacement in patients with severe symptomatic AS. The procedure streamlining from routine use of conscious sedation to a single arterial access approach, the newly adapted implantation techniques, and the introduction of novel technologies such as intravascular lithotripsy and the refinement of valve-bioprosthesis devices along with the accumulating experience have resulted in a dramatic reduction of complications and have improved associated outcomes that are now considered comparable or even superior to surgical aortic valve replacement (SAVR). These advances have opened the road to the use of TAVI in younger and lower-risk patients and up-to-date data from landmark studies have now established the outstanding efficacy and safety of TAVI in patients with low-surgical risk impelling the most recent ESC guidelines to propose TAVI, as the main therapeutic strategy for patients with AS aged 75 years or older. In this article, we aim to summarize the most recent advances and the current clinical aspects involving the use of TAVI, and we also attempt to highlight impending concerns that need to be further addressed.

KEYWORDS

TAVI, TAVR, aortic stenosis (AS), paravalvular aortic leak, bicuspid and tricuspid aortic valve, aortic valve calcification, minimalistic approach

Introduction

Since the first groundbreaking procedure in 2002, transcatheter aortic valve implantation (TAVI) has led to a pervasive transformation in the management of severe aortic stenosis (AS). TAVI has now been shown to be non-inferior or even superior to surgical aortic valve replacement (SAVR) in several important randomized clinical trials (RCTs) across the whole spectrum of surgical risks, including high-, intermediate-, and low-risk patients. The procedure streamlining with the introduction of new generation transcatheter heart valve (THV) design, the establishment of dedicated computed tomography (CT) TAVI analysis for pre-procedural planning (valve and arterial access selection), the better patient selection, the minimalization of the procedure (single arterial access and conscious sedation), the transition from dual to single antiplatelet therapy and several technical enhancements (cusp overlap technique for self-expanding THVs) have driven a dramatic improvement on outcomes and safety of the procedure and also an even more vivid reduction of procedural complications over time. These advances have opened the road to the use of TAVI in younger and lower-risk patients, leading to an expansion of current guideline recommendations for TAVI. As TAVI rapidly expands to younger and lower-risk patients with longer life expectancy, new concerns of paramount significance have emerged, such as THV durability in comparison with surgical bioprostheses, coronary access after TAVI, paravalvular regurgitation, the prognostic impact of conduction disturbances, and need for re-intervention after TAVI. In this review, we aim to summarize the most recent advances and the current clinical aspects involving the use of TAVI and we also attempt to highlight impending concerns that need to be further addressed.

Evolution and contemporary perceptions on transcatheter aortic valve implantation: Vascular access, the minimalist approach, and the fast-track discharge pathways

After two decades of clinical experience, the TAVI procedure has undergone a transformative evolution (**Figure 1**). The new generation THVs with improved sizing, deliverability, and positioning compared to their predecessors (**Figure 2**), the advent of new hydrophilic, small bore, expandable and atraumatic sheaths, as well as the introduction of intravascular lithotripsy have now made transfemoral TAVI feasible in > 95% of patients.

Pre-procedural planning including valve selection and vascular access has been refined by standardization of CT imaging, which has now been established as the ultimate imaging modality for evaluating vascular access, annular dimensions, and valve morphology, and predicting potential complications, such as acute coronary occlusion, annular rupture, and conduction disturbances (1). In addition, the introduction of newly developed and sophisticated 3D software simulating procedural outcomes such as the severity of the paravalvular leak and the need for pacemaker (PPM) implantation will help to further improve TAVI procedural outcomes (FEops HEART Guide^{TM}, Gent, Belgium) (2).

A growing proportion of TAVI cases worldwide are now performed using a "minimalist" approach, which incorporates conscious sedation (CS), local anesthesia, and a post-procedure transthoracic echocardiographic assessment. Conscious sedation is commonly used across Europe and has conceivable advantages including reduced procedural time, faster recovery, and reduced cost and it is also associated with a shorter hospital stay and reduced short-term mortality (3, 4). Moreover, the transition from secondary femoral to radial access for guiding valve deployment and assessing the vascular closure of the primary access has further simplified TAVI and has substantially reduced the risk of vascular complications (5). A newly introduced minimalistic technique incorporating a single arterial transfemoral access and the use of aortic valve leaflet calcifications as the fluoroscopic markers for THV positioning has shown promising results as a safe and effective approach associated with a lower rate of complications, procedural time, and contrast volume during the implantation of the Sapien 3 THV system (**Figure 3**) (6).

Over the last decade, different tools such as the micro-puncture kit, the ultrasound (US) guided vascular access, and the newly introduced intravascular lithotripsy has been associated with reduced peri-procedural vascular complications and has expanded the feasibility of transfemoral TAVI in patients with peripheral vasculopathy. Precise selection of the femoral cannulation site, pointing to avoid sites of anterior calcification, and successful implantation of percutaneous closure devices is of paramount importance in reducing vascular complications. US guidance allows a real-time examination of the vessel wall and the selection of the ultimate puncture area by identifying conventional landmarks, such as the femoral bifurcation (below) between the superficial femoral artery and the profunda femoris and the inguinal ligament (upper). The ultimate area of cannulation is in the horizontal segment of the common femoral artery (CFA), in the middle of the anterior wall in an area free of calcium. This technique has consistently been shown to improve puncture success rates at the first attempt, reduce accidental venipuncture rates, increase physician confidence, and reduce patients' life-threatening bleeding complications (7). In addition, the use of dedicated micro-puncture 21-gauge (G) needles with a US visible tip has been shown to reduce the rate of vascular complications with a significant decrease in the number of groin hematomas compared to standard large bore needles (8, 9).

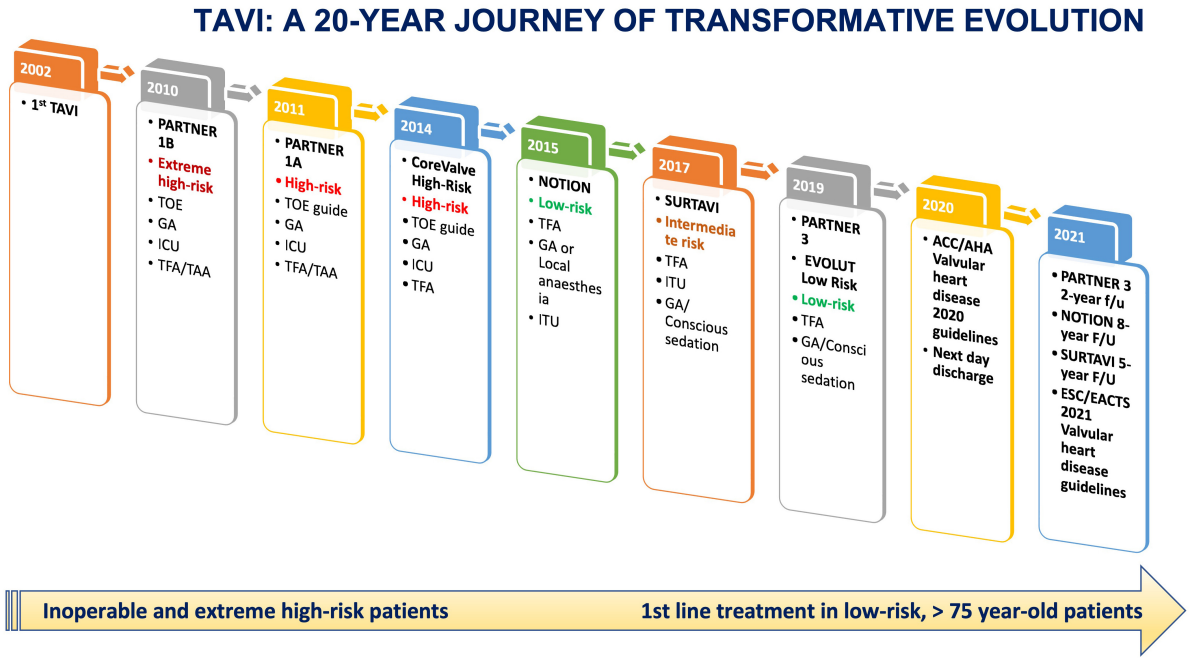

FIGURE 1
TAVI: A 20-year journey of transformative evolution from high-risk inoperable patients to the most recent European and US guidelines and low-risk younger patients along with landmark trials.

Commercially available THVs					
	Self-expanding THVs			Balloon-expandable THVs	
	Evolute PRO+	Acurate Neo2	Navitor	Myval	Sapien Ultra 3
					
Frame	Nitinol	Nitinol	Nitinol	Cobalt-Nickel	Cobalt-Chromium
Valve tissue	Porcine Pericardial	Porcine Pericardial	Bovine pericardial	Bovine pericardial	Bovine pericardial
Valve sizes (mm)	23, 26, 29, 34	23, 25, 27	23, 25, 27, 29	20, 21.5, 23, 24.5, 26, 27.5, 29, 30.5, 32	20, 23, 26, 29
Sheath sizes (Fr)	14 (23, 26, 29 mm) 18 (34 mm)	14	14 (23, 25 mm) 15 (27, 29 mm)	14	14 (20, 23, 26 mm) 16 (29 mm)
Design	Supra-annular	Supra-annular	Intra-annular	Intra-annular	Intra-annular
Repositioning	Yes	No	Yes	No	No

FIGURE 2
Commercially available transcatheter aortic valves.

Almost 35% of the elderly population undergoing TAVI procedures suffer from peripheral vascular disease with tortuous and heavily calcified vessels (10). Non-calcified arteries can be stretched, and successful insertion of TAVI delivery arterial sheaths can be achieved with an arterial lumen as small as 75% of the TAVI sheath's outer diameter. In contrast, for calcified and

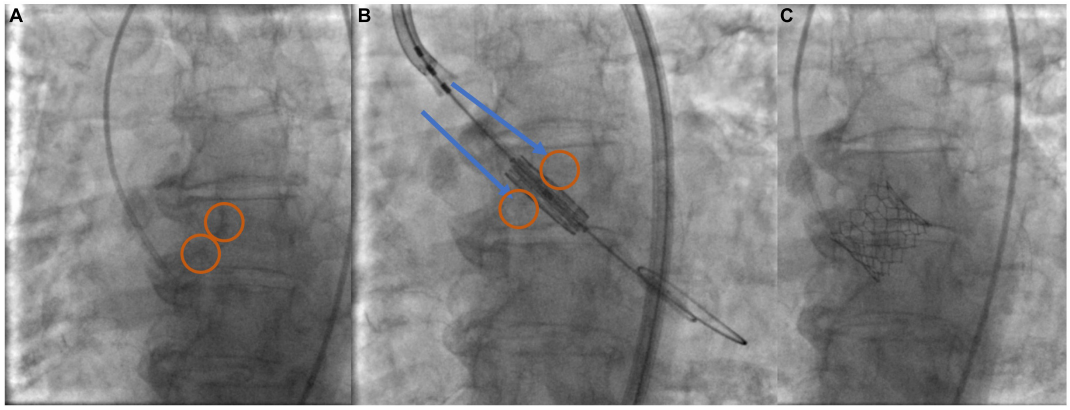

FIGURE 3
Minimalist—single arterial access technique implantation using aortic valve leaflet calcification for THV positioning and deployment. **(A)** Identify calcium markers and annular plane in 3-cusp view (circled). **(B)** Position Sapien ULTRA 3 central balloon marker—align with annular plane and calcium marker (arrows-circles). **(C)** THV deployment.

tortuous vessels, it is highly recommended that the minimum lumen diameter should be at least 1.25 mm bigger than the sheath. For the 14 or 16 F inner diameter sheaths of the contemporary miniaturized delivery systems, this is equal to minimum diameters of approximately 6–7 mm in non-calcified and calcified vessels, respectively (11). In this context, the newly introduced Shockwave intravascular lithotripsy balloon catheter (IVL) (Shockwave Medical Inc., Santa Clara, CA, USA) has emerged as a promising tool for lesion preparation as an elective or bailout strategy in patients with severe peripheral vascular disease intended for TAVI but considered ineligible for transfemoral access (12–14).

This transformational evolution of TAVI has led to a dramatic reduction in procedural mortality and major complication rates. Data from the UK TAVI registry have shown a dramatic reduction in in-hospital mortality after TAVI (9.09% in 2009 to 1.84% in 2016) (15). In addition, similar reductions in mortality and complication rates have been observed in large data series from other registries in France, Germany, Japan, and the USA (16–19). More particularly, the incidence of stroke dropped from 3.4 to 2.2%, acute kidney injury requiring dialysis from 6.4 to 0.9%, and cardiac tamponade from 5.3 to 1.4%. These improved outcomes were also associated with reduced in-hospital stay, with the median time from procedure to discharge falling from 130 h (2013) to 64 h (2016) (20). An all-corners patients' retrospective analysis has shown that a fast-track median length of post-TAVI in-hospital stay of 3-days compared to a standard 6-day in-hospital stay did not have any difference in all-cause mortality (1.3 vs. 1.9%), rate of rehospitalization after discharge (2.09 per patient-year vs. 2.09 per patient-year) and rate of permanent pacemaker implantation (PPI) in pacemaker naive patients at 90 days (15.8 vs. 21.9%) (21). In addition, two prospective studies the 3M-TAVR and FAST-TAVI have shown that next-day discharge is safe in judiciously selected patients who undergo uncomplicated transfemoral TAVI (22, 23). This is likely to further fall with dedicated and vigilantly structured early-discharge pathways as it has been brilliantly illustrated during the COVID-19 pandemic and the subsequent bed pressure to hospitals to further push their boundaries. Two recent studies have shown that in a selected population of TAVI patients with either *in situ* PPM or low risk for conduction abnormalities same-day discharge was feasible and safe (24, 25).

Patients' selection—The choice between transcatheter aortic valve implantation and surgical aortic valve replacement

Over the last decade, TAVI has led to a paradigm shift in the treatment of symptomatic severe AS and has now established itself as the treatment of choice in patients with symptomatic severe AS across all risk categories. The publication of the randomized trials PARTNER 3 (26) and the Evolut Low-Risk study (27) confirmed favorable outcomes of TAVI compared to SAVR even in patients with symptomatic AS at low surgical risk [Society of Thoracic Surgeons (STS) risk score < 4%]. The PARTNER 3 (Placement of Aortic Transcatheter Valve) trial highlighted the superiority of Transfemoral TAVR with the third-generation balloon-expandable SAPIEN 3 valve (Edwards Lifesciences LLC, Irvine California) over SAVR in 1,000 patients with mean STS risk score of 1.9%, for the primary endpoint of death from any cause, stroke, or rehospitalization (26). These results were also confirmed at a 2-year follow-up [TAVI: 11.5% vs. SAVR: 17.4%; Hazard Ratio (HR): 0.63; 95% CI: 0.45–0.88; $P = 0.007$]. TAVI was also associated with a lower incidence of disabling stroke at 30 days and new-onset atrial fibrillation

(AF), with no significant differences between groups in major vascular complications, new PPM implantation, and moderate or severe paravalvular regurgitation (28). However, this trial did not include patients with bicuspid aortic valve (BAV) or other complex high-risk aortic valve anatomies, significant coronary artery disease, low-flow low-gradient AS, concomitant valve disease, peripheral vascular disease precluding transfemoral access, and therefore, its findings cannot be extended or applied at these cohorts. In addition, at 2 years, the TAVI group demonstrated a signal for the significantly higher incidence of subclinical valve thrombosis (2.6 vs. 0.7%) and numerically higher mean gradients and lower effective orifice area. Whether these findings will reflect a more likely route of earlier valve failure, we will need to wait for more to see the results of the long-term follow-up outcomes of the study at 10 years.

The Evolut Low Risk study randomized 1,468 patients at low surgical risk to either TAVI with self-expanding supra-annular CoreValve, Evolute R, or Evolut PRO (Medtronic Inc. Minneapolis) or SAVR. At 2 years, the study showed non-inferiority of TAVI vs. SAVR for the primary composite endpoint of all-cause death or disabling stroke (TAVI: 4.3% vs. SAVR: 6.3%, $P = 0.084$ for superiority; $P < 0.001$ for non-inferiority). At 30 days, TAVI was associated with lower rates of disabling strokes, bleeding complications, acute kidney injury, and AF. As far as the THV performance is concerned, supraannular Evolut THV was associated with lower transvalvular gradients, larger effective valve area, and less frequent prosthesis-patient mismatch than SAVR, but more frequent mild and moderate PVL (27). In addition, at 8-years follow-up, in a low-risk population, the NOTION trial has shown comparable mortality between the Evolut self-expandable platform and surgery (51.8 vs. 52.6%, $p = 0.94$). Moreover, the rate of structural valve deterioration (SVD) was substantially lower with TAVI (13.9 vs. 28.3%; $p = 0.017$) (29). However, several issues should be considered before we attempt to extrapolate these results to the more general population with AS. The overall number of patients that were still alive at 8 years follow-up was very small, 133 patients from which 12 did not reach the 8-year follow-up visit. As the trial was initially designed to evaluate the primary outcome at 1-year follow-up, the results of the 8-year follow-up comprise an exploratory only and not conclusive analysis. In addition, in the SAVR group, 34% of the patients received Mitroflow and Trifecta bioprostheses, which have been consistently reported to have a higher risk of earlier SVD. Although the risk of SVD was significantly lower after TAVI, when compared with SAVR, the definition of SVD included several imaging findings that do not necessarily result in clinical symptoms or do impose further intervention. Besides, the rate of the more clinically important bioprosthetic valve failure (BVF) was comparable between TAVI and SAVR groups.

Further corroborating the results of the above RCTs that have demonstrated comparable or even superior clinical outcomes between TAVI and SAVR in the low-risk population with severe AS, a recent pooled meta-analysis of aggregated data of 8,020 patients showed that within a follow-up period of 2 years, TAVI was associated with a significant reduction of all-cause mortality compared to SAVR [Hazard Ratio (HR): 0.88, 95% CI: 0.78–0.99, $P = 0.030$; an effect that was consistent across the entire spectrum of surgical risk (P-for-interaction = 0.410) and irrespective of the type of the THV system (P-for-interaction = 0.674)]. The TAVI was also associated with a lower risk for stroke [Hazard Ratio (HR): 0.81, 95% CI: 0.68–0.98, $P = 0.001$] (30). In line with the new data, the 2021 ESC guidelines on the management of severe AS recommended transfemoral TAVI as the first-line therapy in patients older than 75 years old or those at high risk (STS PROM/EuroSCORE II > 8%) or unsuitable for surgery and it is recommended for remaining patients according to individual clinical, anatomic, and procedural characteristics (Class I) (31). The 2020 ACC/AHA guidelines recommend TAVI in preference to SAVR for patients with severe symptomatic AS aged > 80 years and in younger patients with a life expectancy < 10 years and no anatomic contraindication to transfemoral TAVI and have endorsed TAVI as Class I for patients with symptomatic severe AS aged 65–80 years from prohibitive to low-surgical risk patients (32). Considering the expanded indications of TAVI to lower-risk and younger patients, a shared decision-making process is strongly advised. The choice between TAVI and SAVR should be made after careful consideration on the patient's life expectancy and valve durability and should be based upon a meticulous evaluation of the patient's personal preference, and anatomical and procedural factors, weighing the risks and benefits of each approach for the individual patient (**Figure 4**).

Current transcatheter valve devices: Lifetime management and durability

The currently approved available THVs include the balloon-expandable and the self-expandable platforms. The decision-making process regarding the choice of a specific device over another one has become even more challenging after the commercialization of multiple platforms. Most recent platforms for both balloon-expandable (SAPIEN 3 ULTRA) and self-expanding (EVOLUT PRO and EVOLUT PRO +) have external sealing skirts that can effectively reduce paravalvular leak (PVL). Even though Edwards SAPIEN and Medtronic EVOLUT have been the most utilized systems, newer THVs have emerged as valuable alternatives. **Figure 2** provides a comparative synopsis of the currently commercially available transcatheter systems. Currently, scarce data are available regarding the direct head-to-head comparisons between different devices. In the CHOICE trial, SAPIEN XT and CoreValve THVs showed similar mortality rates but a higher incidence of more than

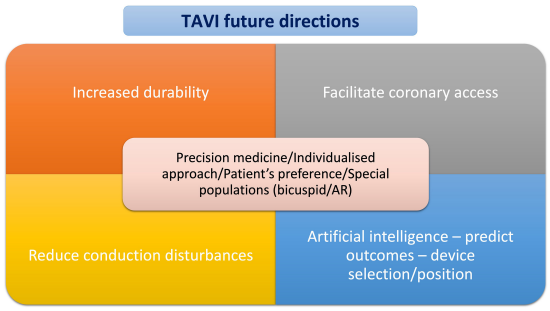

FIGURE 4
TAVI future directions.

mild PVL with CoreValve (33). In the PORTICO-IDE trial, the intra-annular Portico valve was found to have comparable rates of death or disabling stroke at 2 years compared to the Edwards SAPIEN and Medtronic EVOLUTE systems, but it was associated with higher rates of the primary composite safety endpoint including death at 30 days (34). A head-to-head comparison between the balloon-expandable SAPIEN 3 and the self-expanding EVOLUT R valves was performed in the recently published SOLVE-TAVI trial. Both valves were found to have statistically equivalent performance regarding all-cause mortality (2.3 vs. 3.2%). However, SAPIEN 3 was associated with numerically lower rates of PPM implantation (19.2 vs. 23.0%) and moderate to severe paravalvular leak (1.5 vs. 3.4%) but numerically higher rates of stroke (4.7 vs. 0.5%) (35). TAVI with the self-expanding ACURATE-neo did not meet non-inferiority compared to the balloon-expandable SAPIEN 3 (SCOPE I) and self-expanding Evolut (SCOPE II) in terms of early safety and clinical efficacy outcomes at 1 year (36, 37).

As the patients that were included in the early landmark TAVI trials were mostly elderly with short life expectancy, the THV performance was only evaluated at the short- and mid-term range of follow-up. As the TAVI has now been approved for the treatment of younger and low-risk patients, data collection regarding THV durability has become of utmost importance. SVD is defined as intrinsic permanent changes to the prosthetic valve, including wear and tear, leaflet disruption, flail leaflet, leaflet fibrosis and/or calcification, or strut fracture or deformation (38). The durability of valve bioprosthesis is determined by various physical aspects, such as THV tissue characteristics, anticalcification treatments, leaflet, and valve design and transvalvular gradients, and clinical factors such as patients' age and various metabolic abnormalities (end-stage kidney disease). In addition, the fundamental difference between SAVR, where the calcified valve is excised completely, and TAVI, where the THV frame is pressed into the calcified valve, may additionally lead to significant differences in fluid dynamics within the sinus of Valsalva affecting long-term bioprosthesis durability. The THVs are also exposed to crimping stress and to a different pattern of stent and leaflet stress.

In an echocardiographic follow-up of patients in the PARTNER 2A trial treated with the SAPIEN XT valve and in the SAPIEN-3 registry, there was inferior durability of the SAPIEN XT vs. the surgical valve with a 2.5-fold rate of SVD in the mid-term follow. Compared with SAVR, the SAPIEN XT TAVI cohort exhibited significantly higher 5-year incidence rates of SVD, SVD-related BVF, and all-cause (structural or non-structural) BVF. The results of the PARTNER 2A trial showed a higher rate of re-intervention within 5 years after the index procedure for the SAPIEN XT, 3.2 vs. 0.6%. In the SAPIEN-3 registry; however, the SAPIEN 3 bioprosthesis had similar rates of SVD (3.9 vs. 3.5%) and SVD-related BVF 1.1 vs. 0.8%) compared to SAVR at 5-year follow-up (39).

Data from the UK TAVI registry showed excellent THV performance and a low incidence of SVD 5–10 years after TAVI. Moderate SVD was noticed in 8.7% of the study population (regurgitation in 57% and stenosis in 43%), whereas severe SVD was noticed in only 0.4% of the study population (40). The investigators of the NOTION study reported sustained clinical outcomes at 8 years after TAVI with self-expandable CoreValve. All-cause death at 8-year follow-up was similar in both groups (TAVR 54.5% vs. SAVR 54.8%). In addition, moderate or severe SVD was significantly higher after surgery (28.3 vs. 13.9%) (29).

Given the absence of robust data regarding the long-term durability of either surgical or transcatheter BHVs, it is mandatory that in younger patients with life expectancy > 15–20 years, a careful life management plan should be incorporated as the likelihood of these patients undergoing two or more interventions is high (**Figure 5**). It is desirable that the number of surgical open-heart interventions should be minimized considering the tending preference of most patients for less invasive procedures and the higher operative mortality and morbidity of redo SAVR compared to SAVR in a native valve (41). In this line, incorporating TAVI in the sequence of long-term interventions makes this strategy more realistic and attractive. Redo SAVR and valve-in-valve (ViV) TAVI are both feasible options. If redoing SAVR is expected in patients in their 60s, a potential SAVR-SAVR-TAVI strategy with the TAVI taking place in 70s–80s is a reasonable approach. On the other hand, a less invasive approach with a single open-heart surgery as the initial strategy followed by ViV TAVI (SAVR-TAVI-TAVI) or TAVI-SAVR-TAVI as an alternative single surgery sequence are potential alternative scenarios with the need for only one open-heart surgery during a lifetime, which makes these options intuitively more attractive to the patients. However, in both these strategies, several issues should be considered and discussed with the patient before implementing a lifetime management plan. In the case of SAVR after TAVI, depending on the type of BHV implant at the index TAVI, surgical explantation of the valve may require additional procedural steps and more extensive surgery, such as root replacement

and/or replacement of the ascending aorta. The largest so far observational analysis with 5,756 patients with previous TAVI, the incidence of redo SAVR after TAVI was 0.5% with the most frequent indication being infectious endocarditis (67.8% of patients). For most patients, 60.7% required additional cardiac surgical procedures and the overall 12-month mortality was 33.5% (42). On the other hand, ViV TAVI is associated with several considerations, including the risk of coronary obstruction, prosthesis-patient mismatch, and the need for previous surgical bioprosthesis cracking. However, according to a recent large-scale meta-analysis and observational study, ViV TAVI was associated with lower 1-month mortality, a noteworthy threefold reduction in bleeding and respiratory complications, and less in-hospital stay with faster recovery compared to redo SAVR (43, 44). Novel technologies that will further improve the durability of BHVs will facilitate lifetime management plans for younger patients with severe AS. As such the recently presented RESILIA bioprosthetic leaflet tissue (Edwards Lifesciences), which has already been applied in surgical bioprostheses (INSPIRIS RESILIA aortic valve bioprosthesis, Edwards Lifesciences) and now has also been introduced in the new generation Sapien TAVI bioprosthesis has demonstrated excellent 5-year outcomes with no evidence of SVD after SAVR (45).

Transcatheter aortic valve implantation in particular patients' cohorts

Transcatheter aortic valve implantation in degenerated surgical bioprostheses (valve-in-valve transcatheter aortic valve implantation)

Mainly due to the aging population and increased use of bioprosthetic rather than mechanical valves, the need for redo intervention in the context of degenerative bioprosthetic valve disease has substantially increased over the last few years. ViV TAVI has emerged as an appealing alternative to the surgical approach for the treatment of failed surgical and transcatheter bioprosthetic valves, mainly due to the higher risk of periprocedural complications of redo SAVR compared to *de novo* surgery. The patients' frailty and the high burden of underlying comorbidities make ViV-TAVI a reasonable, less invasive, and much more attractive option for patients with degenerated bioprostheses. In the last few years, an incremental trend in both strategies has been observed with significantly more frequent utilization of TAVI ViV rather than redoing SAVR (46). Balloon expandable THVs showed higher rates of patient-prosthesis mismatch compared to self-expanding platforms in a registry of 459 patients undergoing ViV TAVI (46, 47). Therefore, self-expanding THVs should be considered a preferable option in patients with a small surgical bioprosthesis. Even though the difference was not statistically significant, a trend for lower mortality has been observed with ViV-TAVI compared to redo SAVR. Furthermore, ViV-TAVR has been associated with fewer in-hospital major adverse cardiovascular events (MACE) and reduced hospitalizations (46). These findings have been further confirmed in a large-scale metanalysis, including 23 studies and 8,509 patients. Compared to redo SAVR, ViV-TAVI was associated with no significant differences in 30-day mortality and stroke rates and 1-year mortality, suggesting a potential superiority of ViV-TAVI as the 1st line treatment for degenerative BVF. In the more recent 5-year follow-up of PARTNER II—Nested Registry/Valve in Valve study, TAVI for bioprosthetic aortic valve failure was associated with improved survival, valve hemodynamics, and, more importantly, sustained quality-of-life outcomes (48). Updated follow-up of the VIVID Registry reported the longest follow-up on a large scale of patients at high surgical risk with an estimated survival at 5 years of 38% (49). In a direct comparison of re-SAVR patients, ViV-TAVI patients had significantly lower 30-day mortality (2.7 vs. 5.0%), 30-day morbidity (66.4 vs. 79%), and rates of major bleeding (35.8 vs. 50%) (50). ViV TAVI was also associated with a shorter length of stay and higher odds of routine home discharges compared to re-SAVR (50). Another important issue in ViV TAVI is the risk for acute coronary obstruction, a life-threatening complication that can occur in 2.3% of patients undergoing TAVI ViV. The primary mechanism behind acute ostial coronary occlusion after ViV TAVI is a leaflet of the prior valve displacement toward coronary ostia, resulting in an obstruction of coronary blood flow. Even though multiple reports have demonstrated the feasibility of intentional bioprosthesis leaflet laceration with electrocautery wire (BASILICA) as a potential technique to prevent acute coronary occlusion after ViV TAVI, this technique is challenging, not widely adopted, and can be associated with potential risks. A novel dedicated device, the ShortCut (Pi-Cardia) device, is the first dedicated device specifically designed for the precise and controlled laceration of the bioprosthetic aortic valve leaflet imposing the risk for acute ostial coronary occlusion after ViV TAVI (51).

Optimal pre-procedural planning and then procedural execution, through a methodological and a step-by-step approach, have a fundamental role in achieving an optimal result after a ViV TAVI. Successful ViV TAVI requires correct identification of the previous surgical valve, the selection of an appropriate THV, and the implantation of the latter in the correct position (52). A ViV application tool (ViV Aortic) by Bapat (53) is available at online app stores and has been specifically developed to aid the interventionalist in choosing the transcatheter device suitable for the various surgical bioprostheses.

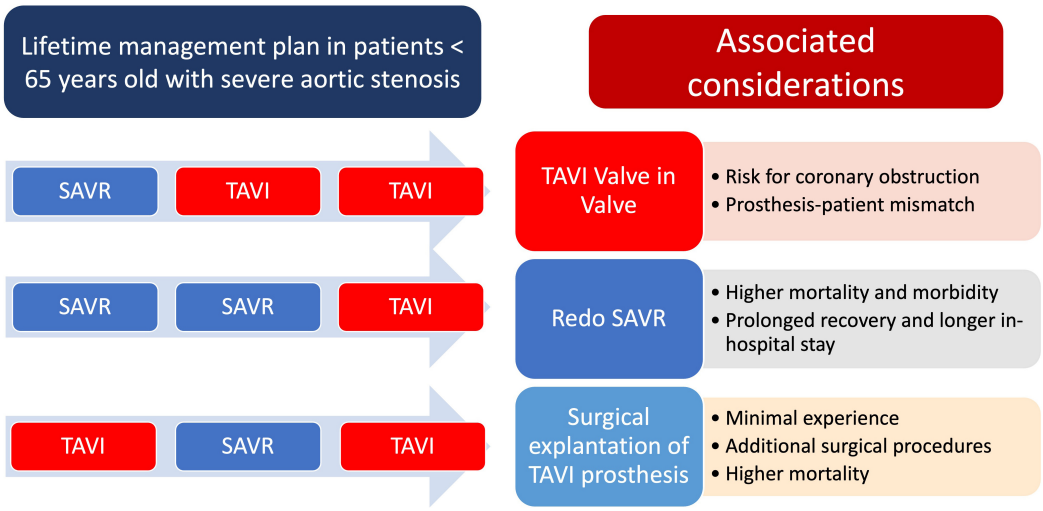

FIGURE 5
Lifetime management for younger patients < 65 years old with severe aortic stenosis. Potential interventional scenarios and associated considerations. SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Transcatheter aortic valve implantation in bicuspid aortic valve

BAV represents the most common congenital cardiac anomaly with an estimated incidence of 2% accounting for approximately 50% of cases requiring SAVR in younger patients (54, 55). BAV is known to exhibit a very heterogeneous morphology with considerable variations in leaflet geometry, leaflet orientation, presence, or absence of raphe, and especially in the severity of calcification of the aortic valve and the adjacent structures. Several schemes have been proposed so far to classify BAV—all of them addressing all these morphological aspects (56–59). Due to the presence of various morphological conditions, there are currently only limited data on which BAV anatomy favors a TAVI procedure, the implantation strategy, and device that will provide optimal results, the sizing strategy that should be applied, and the long-term THV durability in these very heterogeneous settings. However, it is unanimously accepted that severe and asymmetric leaflet and LVOT calcification, the presence of more elliptical aortic annulus that exceeds available sized THVs, a dilated ascending aorta > 45 mm, and the presence of raphe calcification can result in suboptimal THV frame expansion and potentially worsen outcomes.

A contemporary and optimal TAVI technology in a BAV morphology can mitigate the risk of PVL, annular rupture, and the need for second valve implantation (60). Historically, early-generation TAVI devices have performed worse in BAV anatomy, showing worse in-hospital outcomes, decreased device success, and increased incidence of device malpositioning, PVL, and aortic root injury (61). The recent refining of the device iteration has increased TAVI procedural success rates with noticeably improved short- and mid-term outcomes. Data from the STS/ACC TVT registry did not show any difference in 30-day (2.6 vs. 1.7%; $p = 0.18$) or 1-year mortality (10.4 vs. 12.1%; $p = 0.63$) between patients' propensity-matched cohorts of intermediate surgical risk with bicuspid vs. tricuspid AS undergoing TAVI with a self-expanding TAVI bioprosthesis. Valve hemodynamics appeared outstanding for both bicuspid and tricuspid patients up to 1-year, although post-procedure moderate or severe PVL was more frequent in BAV (5.6 vs. 2.1%; $p < 0.001$) (62). The presence of calcified raphe and excess leaflet calcification have been reported as robust predictors of increased intraprocedural risk and mid-term mortality, highlighting the need for further refinement in device technology and technical aspects to make TAVI a safer procedure for the treatment of BAV stenosis (59). Data from the BEAT registry has shown that new-generation balloon-expandable and self-expandable platforms had comparable clinical outcomes up to 1-year and similar device success. However, the balloon-expandable THV was associated with less PVL (0.8 vs. 10.8%; $p < 0.001$) and higher mean gradients 11.3 mmHg vs. 9.6 mmHg; $p < 0.001$) (63).

Currently, there is no standardized system for the sizing of THV in the setting of a TAVI BAV. In the BAVARD registry, THV sizing was based either on the size of the aortic annular plane or the intercommissural distance of the slit-shaped orifice 4 mm above the annular plane to appropriately select the device and predict the sealing. Annular sizing was recommended in 88% of patients with a tube- or flare-shaped BAV and sizing according to the intercommissural distance in a volcano-shaped BAV (64). On the contrary, other groups showed that supra-annular sizing was less reproducible and

did not find any difference in complication rates in patients in whom supra-annular sizing would have altered the device size used (65). Furthermore, an alternative modifying sizing algorithm incorporating the length and calcium load of the raphe combined with the overall volume of calcium in BAV morphology with a raphe has been proposed for TAVI in BAV (66). Based on advanced CT scan analysis, a promising concept of simulating the post-TAVI result, including information on frame deformation, paravalvular regurgitation, and major conduction abnormalities, in a small cohort of BAV patients has been applied with promising results. The investigators were able to accurately identify those patients with a hostile device landing zone for the THVs (67, 68). Even though undersized strategies seem to be more appropriate in some of the BAV patients, rapid, efficient, and reproducible algorithms for the optimal THV device selection do constitute an unmet clinical need and still need to be proven.

Transcatheter aortic valve implantation in patients unsuitable for transfemoral access

With the evolution of the pertinent equipment including thinner sheaths and improvements in the TAVI BHV delivery systems transfemoral TAVI is now feasible in more than 95% of cases. For those cases unsuitable for transfemoral TAVI, alternative access routes have been developed and adopted, including transapical, transaortic, transcarotid, transaxillary/subclavian, and transcaval approaches, each with different features.

Transapical TAVI was first performed in 2005 and during the early years of TAVI has rapidly emerged as the most frequently used alternative access route for patients with unsuitable iliofemoral arteries. However, due to the increased feasibility of the transfemoral approach, the complications related to the transapical access site as well as the advent of other access routes, transapical access has been substantially declining and it is now rarely used in clinical practice. The transapical approach is associated with increased invasiveness and direct injury to the myocardium, potential respiratory compromise, and an increased recovery time and chest discomfort. Furthermore, the THV choice is restricted only to antegrade delivery systems with an additional risk of apical rupture and pseudoaneurysm formation (69). Observational studies have shown a signal of higher mortality rates in patients treated with transapical compared to transfemoral TAVI (70, 71). Furthermore, propensity score-matched or score-adjusted analyses with a comparison between transapical and transfemoral TAVI after incorporating data derived from studies using an independent event adjudication process suggest a higher short- and long-term mortality, similar 30-day stroke rates, higher rates of major bleeding, and longer length of hospital stay for patients treated with a transapical TAVI approach (72, 73).

Transaxillary or TAVI *via* subclavian access route was first reported in the literature in 2008 (74). The transaxillary approach offers several advantages associated with percutaneous approaches, such as rapid recovery, no myocardial or chest wall injury, no restrictions in patients with prior cardiac surgery, and no interaction with descending or abdominal aorta. In addition, is an attractive approach for obese and extremely obese patients. On the other hand, compared to the femoral artery, the subclavian/axillary arteries are softer and more prone to injury and occlusive dissections. Furthermore, they are not accessible for effective manual compression in case of a bleeding complication and their proximity to the brachial plexus might be linked with a higher risk of upper limb compromise *via* peripheral nerve injury or distal embolism (69). The artery's minimum diameter should be 6 mm and specific conditions, such as LIMA graft or a pacemaker, should be considered but do not comprise absolute contraindications. A recent meta-analysis with nine observational studies and 2,938 patients showed comparable 30-day mortality between the transfemoral and transaxillary/subclavian access routes with less major vascular complications in the group with the subclavian approach (75). A previous feasibility study recruiting 100 patients undergoing a transaxillary TAVI, in whom access closure was performed with two Perclose ProGlide systems showed that a fully percutaneous transaxillary approach is safe and feasible with successful vessel closure in 94.8% and covered stent treatment in 11% of patients but without any major-access site adverse event being reported. Thirty-day mortality was 6%, life-threatening bleeding was 3%, and no strokes were reported (76).

A more recently introduced access route, the transcaval approach, has emerged as an alternative to the transfemoral and purely percutaneous approach to perform TAVI in patients with prohibitive iliofemoral access routes. The transcaval approach is based on obtaining percutaneous femoral venous access and entering the aorta through the inferior vena cava using an electrified stiff coronary guidewire. Subsequently, microcatheters in a mother and child setup, a stiff guidewire, and eventually, the delivery sheath is inserted. At the end of the procedure, a nitinol occluder device is implanted at the aortic entry site. Multi-sliced CT is crucial for the assessment of the feasibility of this approach as prerequisites involve a sufficiently large calcium-free target zone ($\geq$ 1 cm) of the right abdominal wall and a trajectory free of obstacles (bowel) (69, 77). A recent propensity-weighted analysis of transcaval vs. transaxillary TAVI in contemporary practice showed that patients undergoing transcaval TAVI had lower rates of stroke and similar bleeding compared to those with transaxillary access; however, both approaches were associated with more complications, including worse bleeding, vascular complications, stroke or TIA, intensive care unit and hospital length of stay, and 30-day and 1-year mortality (78). The

transcaval strategy has several advantages including the absolute percutaneous nature of the vessel access, no myocardial or chest wall injury and initial access through the distensible femoral vein allows the accommodation of all sheath sizes. In addition, it allows for a standard working position for the operator and thus less exposure to radiation (69). The shortcomings of this approach involve the risk of retroperitoneal bleeding and residual aorto-caval fistula, as well as bowel injury. The development of dedicated devices for aortic entry site closure will probably make this approach more attractive and increase its adoption in clinical practice.

Transcatheter aortic valve implantation and pertinent adverse events

Access-site and access-related vascular injury

With the ongoing technical improvements, the access-site and access-related vascular injuries (ASARVI) during TAVI have been substantially reduced over time. However, they remain the most frequent complications, and are associated with worse short- and long-term outcomes (79–82). Most of these complications affect the common femoral and external iliac arteries and among others, they predominantly include access-site bleeding mostly because of closure device failure, vessel dissection, or rupture (82). High body mass index and obese female patients usually have smaller caliber vessels and peripheral vascular disease with calcified atherosclerosis that can result in vascular closure device failure have been all independently correlated with a higher risk of ASARVI (82, 83). The Valve Academic Research Consortium Access-Site and Access-Related Vascular Injury (VARC-2-ASARVI) classification introduced by Sedaghat et al. is a useful tool to easily stratify the severity of vascular injury and proceed to appropriate management (80). The VARC-2-ASARVI is a modified classification model adapted from coronary perforation classification previously introduced by Ellis et al. and stratifies ASARVIs in four major categories: Type I involving blush or minimal dye extravasation; Type II with moderate extravasation (size < 5 mm); Type III with major extravasation (size > 5 mm); and finally, Type IV with acute vessel dissection or occlusion (80).

Prevention and management of vascular complications

Apart from the refining of arterial access with the introduction of the ultrasound-guided micro-puncture technique significant improvements have also been made regarding the vascular closure techniques and available equipment. Historically, suture-mediated percutaneous vascular closure devices (VCD) have been used for main access closure to avoid surgical cut-down. Among suture based VCD, the Perclose ProGlide (Abbott Vascular) has shown superior results compared to its predecessor Prostar XL (Abbott Vascular), and has become the most used suture-based VCD (84, 85). More recently, a novel large-bore plug-based VCD the MANTA (Teleflex) was introduced aiming to tackle difficult femoral anatomies such as those with higher atherosclerotic burden, where suture-based VCD are more likely to fail. Even though early feasibility trials and retrospective analyses showed promising results, the use of MANTA was associated with higher rates of vascular complications than the double ProGlide technique in two randomized controlled trials (86–89). Initially proposed as a bailout strategy to tackle excessive bleeding, the combined use of a suture-based VCD such as the ProGlide with a plug-based VCD such as the Angioseal (Terumo) has been reported to be safe and feasible (90). The technique involves the insertion of the ProGlide in the beginning before the large sheath insertion followed by the Angioseal insertion at the end of the procedure after the large sheath removal. A recent study has demonstrated a clear superiority of the technique compared to the dual ProGlide technique with significantly reduced main access-related major complications or bleeding $\geq$ Type 2 according to VARC-3 bleeding classification (3.0 vs. 11.4%) (91).

Early detection of access-related bleeding complications during TAVI remains challenging as clinical recognition relies on the manifestation of signs and symptoms, such as hematoma, pain, and hypotension and additional imaging confirmation with CT. By the time these bleeding complications become evident with symptoms or are confirmed with imaging, a considerable blood loss has typically already occurred with the subsequent substantial compromise of clinical prognosis. Accordingly, early bleeding detection post-TAVI has become fundamental for patients' prompt management and survival. A newly introduced device the Saranas Early Bird Bleed Monitoring System (EBMMS) has the capacity to detect bleeding through the continuous measurement of changes in the local bioimpedance (**Figure 6**). The EBBMS consists of the following parts: (1) A standard vascular access sheath (6 or 8 Fr); (2) four electrodes (two proximal and two distal) that are embedded within the sheath; and (3) a user interface display is integrated on the site of the port of the sheath. A recent study has shown excellent safety profile and accuracy of the device in early detection of bleeding with a high level of agreement with CT scan (Cohen's Kappa statistic of 0.84, with a sensitivity of 100%, specificity of 75%, a positive predictive value of 98%, and negative predictive value of 100% for bleed detection relative to CT scan findings) (92).

With the occurrence of vascular access, prompt and efficient management is mandatory for achieving adequate bleeding

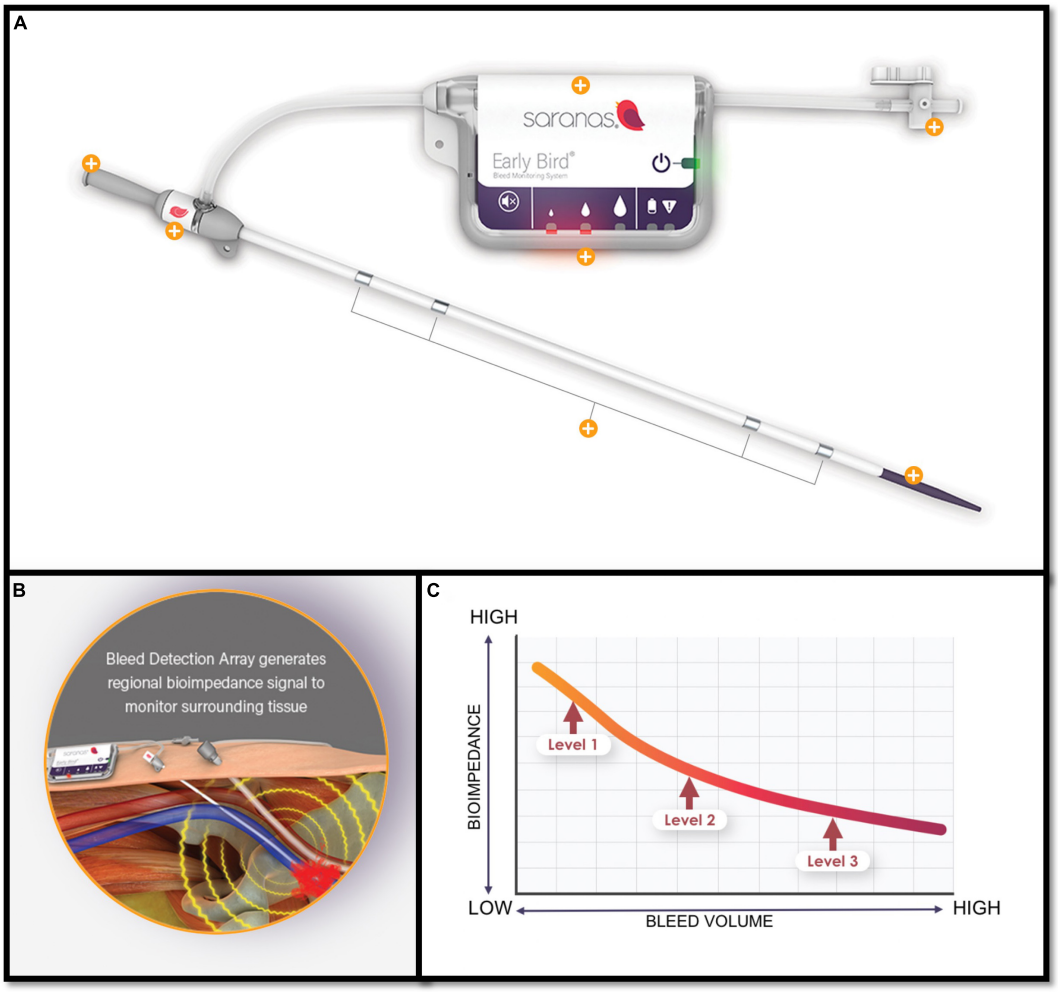

FIGURE 6
(A) The Saranas Early Bird Bleed Monitoring System. **(B)** By monitoring nearby tissue bioimpedance can offer early bleeding detection. **(C)** The lower the bioimpedance the higher the bleeding volume.

control and a good prognosis. A crossover angiography to assess for aortic/iliofemoral dissection, perforation, or VCD failure is currently the standard practice, and placement of a crossover wire from the contralateral femoral artery allows rapid vascular access with the delivery of the necessary equipment, such as appropriate size balloons to tamponade the area of interest of this deems necessary. Transradial secondary access has recently been demonstrated to be suitable for the management of peripheral vascular complications during TAVR and may reduce the rate of secondary contralateral femoral access complications (93, 94). Limited dissection or perforation can be well managed with prolonged occlusive balloon inflation. Percutaneous deployment of a covered stent or surgical repair is indicated for more extensive flow-limiting dissection or bleeding or in cases with hemodynamic instability or threatened limb circulation. Both options are associated with good outcomes, but the percutaneous option is usually preferred over surgical repair, especially when the injury is above the inguinal ligament as the latter might require laparotomy and TAVI patients are usually old, frail, and have high perioperative risk (80, 95, 96).

Stroke

Incidence of stroke

Despite the device refinements and procedural streamlining, stroke is still a feared and devastating complication of TAVI, which is associated with a 5–10-fold increased risk of mortality (97, 98).

Real-world registries have demonstrated that TAVI procedures have a similar incidence of stroke as SAVR with an in-hospital rate of 1–2% (99). In the STS/ACC TVT registry involving 101,430 patients treated with TAVI between 2011

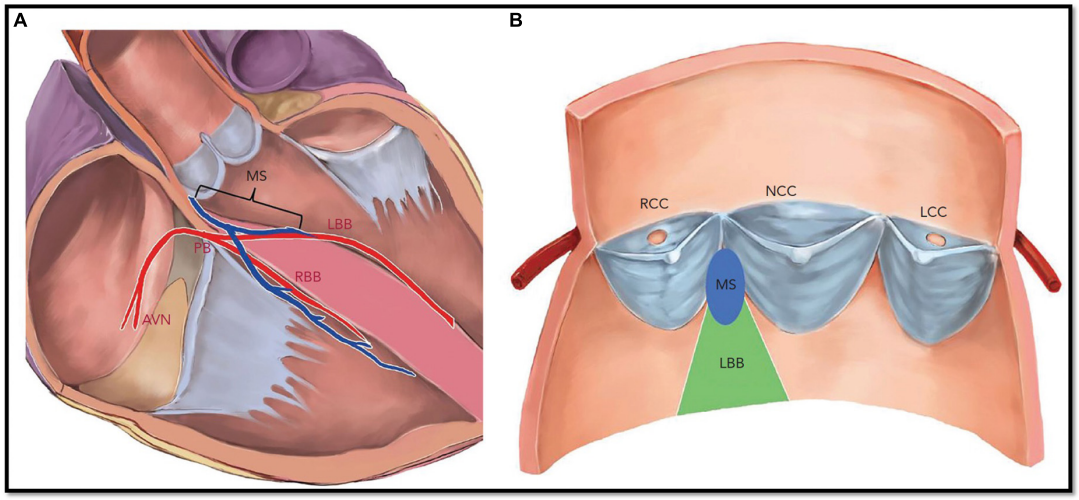

FIGURE 7
Native cardiac conduction system and its anatomical relations with aortic valve cusps and membranous septum. **(A)** The penetrating bundle of His emerges at the surface of the left ventricular outflow tract beneath the membrane septum (MS). The length of the MS is equal to the distance between the aortic annulus and the bundle of His. **(B)** The left bundle branch emerges beneath the MS and is positioned between the right coronary cusp and non-coronary cusp. AVN, atrioventricular node; LBB, left bundle branch; LCC, left coronary cusp; PB, penetrating bundle; MS, membrane septum; NCC, non-coronary cusp; RBB, right bundle. Reproduced from Lin et al. (159).

and 2017, the incidence of stroke was 2.3% (95% CI, 2.2–2.4%), while the transient ischemic attack was reported with a rate of 0.3% (95% CI, 0.3–0.4%) at 30 days. There was no decline in the incidence of stroke over time, indicating that the ongoing technical evolution did not have any positive impact on the prevention of cerebral embolic events. It is worth mentioning that 48.6% of stroke patients experienced a remarkable impairment of social and recreational activities, 34.5% suffered a neurocognitive impairment, and 41.2% required new aids or assistance at the time of event adjudication highlighting the debilitating consequences of stroke after TAVI. Occurrence of stroke was associated with a striking sixfold increased risk of 30-day mortality; HR: 6.1 (95% CI: 5.4–6.8; $P < 0.001$) (100).

In patients undergoing TAVI that belong to the low-risk group, the reported stroke rates appear to be lower. In the PARTNER-3 trial, the 1-year incidence of stroke after transfemoral TAVI was 1.2%, compared to 3.1% after SAVR (HR: 0.38; 95% CI: 0.15–1.00) (26). Interestingly, at 2-year follow-up, the investigators reported a convergence of stroke rates without a significant difference between TAVR and SAVR cohorts (2.4 vs. 3.6%, $p = 0.28$). This is more likely related to a plausible higher rate of THV thrombosis after TAVI (28). In the low-risk group treated with either the self-expandable platform CoreValve/Evolute or SAVR, the incidence of stroke was similar between TAVI and SAVR at 1-year follow-up namely 4.1 vs. 4.3% (27).

With regards to the rates of stroke specifically related to the device platform either the self-expandable or the balloon-expandable devices, the results are rather conflicting. A previous large propensity-matched population of 8,192 patients from the CENTER collaboration found a lower stroke incidence at 30-days in the balloon-expandable cohort for SAPIEN XT/3 vs. CoreValve/Evolute: 1.9 vs. 2.6% ($p = 0.03$) (101). In contrast, in the more recent SOLVE TAVI trial, a direct randomized comparison of 447 patients treated with transfemoral TAVI, with either Evolute-R or Sapien-3, a numerically lower stroke rate of 0.5% for self-expandable THVs compared with 4.7% for balloon-expandable was observed without reaching statistical significance in the superiority testing (35).

Intra-procedural measures to prevent stroke

The use of cerebral embolic protection devices has intuitively emerged as a new tool that could potentially reduce cerebral embolic events during and after a TAVI procedure. However, the currently available data have not demonstrated any robust and clear benefit from regular use of this specific equipment. A recent meta-analysis (102) failed to demonstrate a reduction in the incidence of stroke or the mean number of silent brain infarcts per patient. In addition, these devices appear to be used infrequently as this was shown in the German registry of 41,654 TAVIs, whereas cerebral embolic protection devices were used in 3.8% of cases. Moreover, the use of these devices did not reduce the risk of stroke or the risk of developing delirium as a sign of acute brain failure (103). In propensity-matched score analysis of patients undergoing TAVI, the use of cerebral protection devices demonstrated a significantly higher rate of stroke-free survival compared to unprotected patients (104). In contrast, the SENTINEL pivotal trial and the CLEAN TAVI trial failed to demonstrate a marked reduction in rates of clinically significant stroke associated with TAVI (105, 106).

Moreover, in the intention to treat analysis of the CLEAN TAVI trial the incidence of new neurological symptoms indicating an acute stroke was 10% in both the SENTINEL protection and the unprotected group of patients (105). In the largest so far RCT, including 3,000 patients, the PROTECTED TAVR trial, the use of the SENTINEL cerebral protection device was not associated with a significant reduction of periprocedural stroke during TAVI (107). Another ongoing RCT the BHF PROTECT TAVI trial (ISRCTN16665769) involving 7,730 patients undergoing TAVI with a direct comparison between patients with and without an intraprocedural SENTINEL cerebral protection device deployment will shed more light regarding the protective effect of the systematic use of cerebral protection devices in preventing the incidence of clinically evident stroke after TAVI.

To conclude, although cerebral protection devices have been proven efficient in drastically reducing the new ischemic brain lesions post-TAVI (105, 108), clear, robust, and groundbreaking results in preventing clinically evident strokes are still missing.

New conduction abnormalities and permanent pacemaker implantation after transcatheter aortic valve implantation

Pathophysiology

The aortic valve has a close spatial proximity to the intrinsic conduction system of the heart. In particular, the atrioventricular node (AVN) is near the subaortic region where the His bundle is running on the lower edge of the membranous septum in the left ventricular outflow tract (LVOT). TAVI prostheses are inserted in an intra-annular position and in contrast to surgical valves, which entail exerting pressure against the aortic annulus to maintain the stent frame in the desirable position (**Figure 7**). Excessive THV over-sizing can inadvertently compress the cardiac conduction system, which can subsequently cause transient or permanent mechanical damage to the surrounding tissue involving edema, hematoma, or necrosis of the conduction system. Almost half of these disorders may improve over time and will not require PPM due to the resolution of the associated trauma (109).

Incidence and risk factors associated with new conduction abnormalities after transcatheter aortic valve implantation

The most encountered conduction abnormalities after TAVI are a high degree or complete atrioventricular block requiring PPM implantation or new onset left bundle branch block (LBBB). Over the years, the incidence of PPM implantation and new conduction abnormalities have markedly decreased in line with the adoption of new-generation THVs and the implementation of novel implantation techniques. Historically, self-expanding Evolute R and PRO have demonstrated a higher percentage of conduction abnormalities compared to the balloon-expandable devices Sapien 3 and Sapien 3 ULTRA (12–20% PPM, 18–28% LBBB, vs. 4.4–6.5% PPM, and 13–24% LBBB) primarily due to different depths of implantation and mechanisms of expansion between the two types of valves (26, 27, 110, 111). Other more recent devices such as the Acurate-neo valve and the Portico with FlexNav system have shown acceptable PPM implantation rates of 10 and 14.6%, respectively. In the most recent PARTNER III Trial, 6.6% of the overall low-risk TAVI population required treatment with PPM implantation, which was found to be comparable with the corresponding rate of PPM implantation in the SAVR group. However, more patients in the TAVI group developed new LBBB than SAVR patients (22 vs. 8%) (26). In contrast, the Evolut Low-Risk TAVI Trial with self-expanding THVs showed that TAVI patients underwent postoperative permanent pacemaker (PPM) implantation much more frequently compared to SAVR individuals (17.4 vs. 6.1%, respectively) (27). It is felt that the unremittingly increased radial force applied on the wall of the left ventricular outflow tract associated with the self-expanding platforms might explain the higher rates of PPM implantation with the self-expanding THVs, compared to the balloon-expandable THVs (112).

Baseline electrocardiographic findings, anatomical features such as shorter membranous septum length (MSL), LVOT eccentricity, and severe annular calcification have been identified as potential risk factors for developing significant conduction abnormalities and subsequent need for PPM after TAVI (113–115). The presence of baseline right bundle branch block (RBBB) represents the most observed electrocardiographic predictor of PPI with an increased risk from 3 up to 47 times (115). With regard to other procedural factors, implant depth has been identified as the strongest and most consistent predictor among procedural factors. The adoption of a new THV implantation technique for the self-expanding system of EVOLUTE, known as the cusp-overlap view implantation technique (coplanar projection by overlapping the right and left coronary cusps) has enabled a higher implantation depth and compared to the conventional 3-cusp view implantation, has shown remarkable results with significant decrease in the 30-day new-onset LBBB (12.9 vs. 5.8%; $p = 0.005$) and PPM implantation rate (17.8 vs. 6.4%; $p = 0.004$), without any differences in MACE rate (116, 117). A similar approach with a high deployment technique for the balloon-expandable THV Sapien 3 has achieved a substantial decrease in a 30-day PPM implantation rate and the incidence of new-onset conduction abnormalities (118).

Two recent studies have evaluated the role of post-TAVI long-term monitoring with an implantable loop recorder (ILR) to appropriately recognize late clinically significant, high-degree conduction abnormalities or other arrhythmias, such as atrial fibrillation or ventricular tachycardia. In the first study, 98 patients undergoing a TAVI procedure (42% self-expanding THVs, 53% balloon-expandable valves) received an ILR (31% a median 20 days before TAVI and 69% a median 1 day after TAVI) with a follow-up at 1-year. Of the study participants, 7 and 10% had pre-existing right (RRBB) and LBBBs, respectively.

LBBB increased to 39% post-TAVI and decreased to 22% after 1 year. A PPM was implanted in 15 out of 98 (15%), of which nine (60%) received the PPM before discharge. Of the six patients receiving the PPM after hospital discharge, three patients (3% of the overall cohort) developed complete heart block and this occurred within maximum 14 days after TAVI. The other three patients received a PPM because of sick sinus syndrome. This study highlights that many conduction abnormalities related to TAVI occur within the first 2 days post TAVI usually before patients' discharge, while after 2 weeks post-TAVI high degree atrioventricular block related to TAVI is extremely unlikely to occur (119).

In the MARE study, 103 consecutive patients undergoing TAVI (50% balloon expandable BHV) and new persistent LBBB post-TAVI received an ILR. At 1-year follow up significant bradyarrhythmia, including severe bradycardia or high-degree AV block occurred in 20% of patients. In 10% of the patient, treatment with PPM implantation was required. Of those, 50% received the PPM due to high-degree AV block within the first 18 days after TAVI, while the rest 50% within 7 months post-TAVI highlighting that new persistent LBBB post-TAVI might require closer short and long-term monitoring due to a higher likelihood for advanced high-degree AV block.

Conduction disturbances after transcatheter aortic valve implantation and associated prognosis

The data regarding the impact of new conduction abnormalities and PPM implantation on prognosis after TAVI remain controversial. A recent study in intermediate-risk patients undergoing TAVI showed that new-onset LBBB was associated with a significant increase in all-cause and cardiovascular mortality, rehospitalization, PPM implantation, and decreased LV function at 2 years (120). Additional studies have shown that new-onset LBBB after TAVI is an independent predictor of all-cause mortality at more than 2 years of follow-up (121, 122). A recent meta-analysis of 12 studies reported an increased risk of all death at 1 year of follow-up in patients with a new persistent LBBB post-TAVI [RR: 1.32; 95% CI (1.17–1.49); $P < 0.001$]. In addition, new LBBB was associated with a higher risk of cardiac death [RR: 1.46; 95% CI (1.20–1.78); $P < 0.001$], heart failure requiring hospitalization [RR: 1.35; 95% CI (1.05–1.72); $P = 0.02$), and 1-year PPM [RR: 1.89; 95% CI (1.58–2.27); $P < 0.001$] at 1-year follow up (123). In contrast, two other studies and a meta-analysis did not show any relation of new-onset LBBB with 1-year all-cause mortality (124–126). Rodes-Cabau et al. recently proposed an algorithmic approach to the management of new LBBB post-TAVI. Patients with persistent LBBB at day 2 with QRS $\leq$ 150 ms and PR $\leq$ 240 ms could be safely discharged and continuous ECG monitoring (2–4 weeks) could be considered. Patients with QRS $>$ 150 ms and PR $>$ 240 ms are at increased risk of delayed high-degree AV Block and continuous ECG monitoring or electrophysiology studies might be considered to guide a decision for prophylactic PPM insertion. If further QRS or PR interval prolongation of $\geq$ 20 ms within 24 h was observed, then evaluation with an electrophysiology study followed by continuous ECG monitoring or direct PPM insertion might be considered (127).

Similarly, the clinical impact of PPM insertion after TAVI remains also controversial. Right ventricular pacing has been associated with inter- and intraventricular desynchrony and can intuitively result in detrimental effects on cardiac structure and overall myocardial contractility and function. RV pacing has been shown to cause left ventricular remodeling heart failure and death (128, 129). Results from the TVT registry have consistently shown that PPM implantation after TAVI has been associated with increased mortality (112, 120, 130). Furthermore, Costa et al. have shown that post-TAVI patients with PPM dependence showed higher overall mortality compared to the non-dependent patients (131). In contrast, a meta-analysis of 7,032 patients showed that periprocedural PPM after TAVI was not associated with an increased risk for all-cause mortality at 1-year (126). In another multicenter trial with 1,629 patients undergoing TAVI 19.8% required a PPM insertion. Even though PPM insertion is associated with a higher risk for heart failure hospitalization, there were no differences in all-cause and cardiovascular mortality between those with and without a PPM (132). These contradictory results can be attributed on one hand to the detrimental effects of pacing dependence on overall cardiac structure and function with patients that are not pacing dependent being less likely prone to develop adverse outcomes and on the other hand the protective effect of pacemakers against sudden cardiac death.

Coronary access and occlusion after transcatheter aortic valve implantation

Coronary access after transcatheter aortic valve implantation

The high prevalence of concomitant coronary artery disease in patients with AS, almost 50% (133), as well as further expansion of TAVI indications in low-risk and younger patients are critical factors that should be taken into account in all TAVI candidates. In this regard, it is critical to aim for seamless and uncomplicated coronary access after TAVR allowing for future diagnostic coronary angiograms, as well as percutaneous coronary intervention. In a recent study evaluating the impact of acute coronary syndromes (ACS) in 779 patients following TAVI, approximately 10% of the overall cohort of patients were readmitted with ACS after a median follow-up of 2 years. The presentation involved type 2 MI in 36% of patients, unstable angina in 35%, NSTEMI in 28%, and STEMI in 1% with associated mortality at 2 years post-ACS of 37% (134). The difficulty of coronary re-access post-TAVI is correlated with the implanted bioprosthesis design: it is considerably easier with the short-stent frame and sub-coronary position balloon-expandable platforms, and it is more difficult with

the supra-annular THVs with the tall stent frames and small struts. However, previous reports have shown unsuccessful coronary cannulation in 9–13% of patients treated with SAPIEN THV as well, which is not negligible, especially in low-risk young patients that might require coronary intervention in the future (135). In the REVIVAL (Revascularization After TAVI) study, PCI was successfully executed after TAVI in 96.6% of patients, without any significant differences between THV designs (136). In the RE-ACCESS (Reobtain Coronary Ostia Cannulation Beyond TAVI) study among 300 patients that were enrolled, unsuccessful coronary cannulation following TAVI was seen in 7.7% of cases. The use of Evolut R/PRO THVs, the THV implant depth, and the oversizing of the THV in relation to the sinus of Valsalva diameter were independent factors associated with unsuccessful cannulation of the coronaries (137). On the other hand, data from the RESOLVE registry with a real-world cohort of patients have shown unfavorable coronary access in up to 35% of patients after TAVI, as assessed with post-implantation CT angiograms in 66 patients. The authors concluded that THVs with a low skirt and commissural height pattern and large open cells that are specially designed to achieve commissural alignment with the native aortic valve may facilitate future coronary access (138). In addition, a simulation study predicted that sinus of Valsalva sequestration and resultant coronary obstruction will occur in up to 23% of patients treated with Evolut-Pro during future TAVI in TAVI procedures (139). That was the case for SAPIEN prostheses as well, where the most challenging anatomies for post-TAVI coronary cannulation including THV stent frame above the coronary ostia and commissural suture position in front of a coronary ostium were observed in 9–13% of patients (135). The alignment of Transcatheter Aortic-Valve Neo-Commissures (ALIGN TAVR) studies first evaluated the impact of THV deployment orientation on neo-commissural overlap with coronary arteries. In this pilot imaging study 828 TAVR implants (SAPIEN 3 = 483, Evolut = 245, ACURATE - neo = 100) were analyzed using pre-procedural multidetector row CT and coplanar fluoroscopy co-registration. While different crimping orientations of the SAPIEN 3 THV did not result in consistent commissural alignment, specific flush port positioning significantly influenced the rate of neo-commissural alignment with Evolut THV. Evolut flush port positioned at 3 o'clock improved "hat" marker orientation to the outer curve or center front at the annulus, thus reducing the rate of coronary artery overlap from 60 to 36%; $p < 0.05$ compared to that marker positioned toward the inner curve or center back. ACURATE-neo commissure positioning at the center back/inner curve significantly improved commissural alignment compared to the center front or outer curve (140, 141).

In line with the application of TAVI in younger patients with a potential need for coronary intervention, the implanting team should focus on three major technical aspects:

1. A THV with a sub-coronary frame position is generally preferable.
2. Commissural alignment is mandatory when a supra-annular valve design is used especially in narrow roots.
3. THVs with large open cells are beneficial for stents that cover the coronary ostia.

Acute coronary occlusion after transcatheter aortic valve implantation

Since the introduction of dedicated CT TAVI as gold-standard in the routine pre-procedural planning of TAVI, acute coronary occlusion is an uncommon complication following TAVI, with a reported incidence of < 1% (142, 143). The left main is mostly involved, encountered in approximately 87% of cases of coronary obstruction (142, 143). Well-recognized risk factors include the short distance between the annulus and coronary ostia < 10 mm and a narrowed aortic root < 28 mm at the level of sinuses of Valsalva (142, 143). Both these factors increase the risk of displacement of the native aortic valve leaflets over the coronary ostia with subsequent acute or late coronary occlusion. This risk becomes even higher during ViV TAVIs with a risk of acute coronary occlusion of 2.3% with a rate of 30-day mortality up to 50% (144). Different strategies have been developed to prevent this dreadful complication. In selected patients, the preventive strategy of placing an under-deployed stent in coronary artery ostia (Chimney stenting) has been reported as a simple and effective technique to prevent acute coronary occlusion after TAVI in patients at high-risk (145). Although the data regarding the efficacy of chimney stenting are reassuring, there are concerns regarding the risk of late stent failure (3.5% at 1 year). The Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction (BASILICA) has emerged as a novel technique to prevent post-TAVI acute or late coronary artery occlusion. Based on intentional laceration of preexisting native or bioprosthetic aortic valve leaflet in front of the threatened coronary artery, BASILICA appears achievable with a procedural success rate of 87% and relatively safe with a 30-day mortality of 2.8% (146). However, the extensive toolbox that is required to perform the procedure and the complex and high-risk nature of the procedure itself dictates the need for further refinement of this technique to facilitate its wider clinical adoption.

Paravalvular leak

Paravalvular leak is generally a result of inappropriate valve sealing and incomplete apposition between the THV and the aortic annulus and is contingent on specific THV designs. Since the introduction of TAVI, the rate of PVL used to be frequent. Moreover, moderate, or severe PVL has been recognized as a strong independent predictor of mortality (147, 148). Risk factors for PVL include severe native aortic valve calcification,

leaflet asymmetry, prosthesis malapposition or undersized, and self-expanding valves. Self-expanding valves exert less radial force compared to balloon-expandable valves, whereas excessive annular calcification has a more prominent effect on the final configuration of self-expanding valves, with frequent under-expansion and eccentric post-deployment shape of the latter (149). The evolution in THV and the subsequent improved operator experience has led to a remarkable decline in rates of PVL over time. A progressive reduction for moderate and severe PVL has been observed throughout RCTs up to 0.8% in the PARTNER 3 trial and 3.5% in the Evolut low-risk trial at 30 days (26, 27). On the contrary, no discernable change has been demonstrated regarding mild PVL, whose prognostic impact remains undefined. Recent data have shown a reduction for mild PVL with the latest generation balloon-expandable SAPIEN 3 Ultra compared to SAPIEN 3 THV (none-trace PVL 90.9 vs. 85.7%; $p < 0.01$ and mild PVL 8.9 vs. 13.9%; $p < 0.01$). Similarly, newer generation Evolut PRO had lower rates of mild PVL compared to Evolut R THV (none-trace PVL: 70.3 vs. 63.2% and mild PVL 27.8 vs. 34.8%; $p = 0.007$). In the SCOPE I trial ACURATE-neo showed higher rates of moderate-severe PVL compared to SAPIEN 3 THV (9.4 vs. 2.8%; $p < 0.001$). These findings were further confirmed in the SCOPE 2 trial where ACURATE-neo was compared to EVOLUT R (10 vs. 3%; $p = 0.002$). Balloon post dilatation or TAVI in TAVI has been described as a potential option to treat moderate-severe PVL. Other options include the percutaneous closure with plugs, with good overall results in terms of safety and efficacy (150).

Subclinical transcatheter heart valve thrombosis

Since TAVI introduction and subsequent wider adoption for the treatment of symptomatic severe AS several concerns were raised regarding the thrombogenicity of the THVs and therefore the systematic treatment with antiplatelet therapy was endorsed. In 2015, the ongoing success of TAVI was intercepted by the worrisome report of the phenomenon of subclinical leaflet thrombosis (151). A systematic protocol based on 4D high-resolution CT imaging is currently available for the evaluation and classification of the different patterns of subclinical THV leaflet thrombosis. The key CT features that were noted involved the hypoattenuating leaflet thickening (HALT) associated with reduced leaflet motion (RELM) leading to hypoattenuation affecting motion (HAM). The stratification of severity of RELM was further allocated to moderate (50–69%), severe (70–99%), and immobile (152). So far, no significant clinical implications of these CT findings have been shown, while the incidence of subclinical leaflet thrombosis appears to be comparable between TAVI and SAVR. In the pre-specified analysis of the Evolut Low-Risk CT sub-study among 179 patients undergoing TAVI, not oral anticoagulation therapy, HALT and RLM occurred frequently (HALT, 17.3% at 30 days and 30.9% at 1 year; RLM, 14.6% at 30 days, and 31% at 1 year) without any significant difference with SAVR patients. The detection of subclinical leaflet thrombosis was not associated with THV gradient or any clinical events (153). In a similar CT sub-study from the PARTNER 3 trial subclinical bioprosthetic valve leaflet thrombosis occurred more frequently in the TAVI group compared to the SAVR group at 1 month (TAVI: 13% vs. SAVR: 5%, $p = 0.03$), with a convergence of the incidence of subclinical leaflet thrombosis between the two groups at 1 year (TAVI: 28% vs. SAVR: 20%; $p = 0.19$) with no significant difference in the transvalvular gradient between the two groups. In addition, no association of HALT with death, stroke, or MI was observed. However, patients with more excessive HALT demonstrated an increase in thromboembolic events, while 1-year persistent HALT was associated with a higher mean transvalvular gradient ($\sim$ 5 mmHg) (154). The lower incidence of subclinical valve leaflet thrombosis in the SAVR group might at least in part be explained by the potentially higher proportion of these patients on oral anticoagulation therapy due to other clinical conditions, such as atrial fibrillation. In the GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial, the group of patients on rivaroxaban demonstrated significantly less HALT compared to those on antiplatelet only therapy (155). However, patients on anticoagulation showed higher mortality rates, a warning sign indicating that patients with severe AS represent a heterogenous group of patients with multiple underlying comorbidities and a complex interaction between high bleeding and ischemic risk that makes the choice of the appropriate antithrombotic treatment even more complex. In the ENVISAGE study, a multicenter RCT with 1,426 patients undergoing TAVI with atrial fibrillation and a primary indication for anticoagulation the patients were randomized to either therapeutic treatment with edoxaban or warfarin. Patients on edoxaban had higher rates of major bleeding compared to patients on warfarin (hazard ratio: 1.4; 95% CI: 1.03–1.91; $p = 0.93$ for non-inferiority) without any significant difference regarding the rates from any cause or stroke (156). In the most recent ATLANTIS trial, 1,500 patients undergoing TAVI were randomized to either oral anticoagulation with apixaban 5 mg od or standard-of-care therapy, which included either a vitamin-K antagonist if there was a primary indication for anticoagulation or antiplatelet therapy. There was no difference between the groups regarding the primary composite endpoint of death, myocardial infarction, stroke or transient ischemic attack, systemic embolism, intracardiac or bioprosthesis thrombosis, deep vein thrombosis or pulmonary embolism, and life-threatening, disabling, or major bleeding over 1-year follow up (18.4 vs. 20.1%) without any evidence of interaction between any treatment (apixaban, vitamin-K antagonist or antiplatelet therapy—p interaction = 0.57). Moreover, the

primary safety endpoint of major, disabling, or major bleeding over 1-year follow-up was not different between the groups. Interestingly, in the study stratum of 1,049 patients where apixaban was compared to antiplatelet therapy only, therapeutic apixaban was associated with significantly less obstructive valve thrombosis (HR: 0.19, 95%CI: 0.08–0.46), while a signal of higher non-cardiovascular mortality that was observed with apixaban (157). Finally, in the ADAPT-TAVR study with 229 patients undergoing TAVI and without any indications for anticoagulation, edoxaban resulted in numerically twofold lower subclinical THV leaflet thrombosis at 6 months (9.8 vs. 18.4%). However, the rates of death, stroke, transient ischemic attack, blood clotting in the brain and neurocognitive dysfunction were not different between the groups (158). Until further long-term follow-up results become available to further elucidate whether the reduction of THV thrombosis with oral anticoagulation will eventually be translated to overt clinical benefits, the primary antithrombotic therapy unless there is another indication for oral anticoagulation should include a single antiplatelet regimen with aspirin or clopidogrel.

Conclusion and future directions

Twenty years after the first breakthrough procedure, TAVI underwent a transformative evolution and currently can be unanimously considered the most striking development in the field of interventional cardiology for the twenty-first century. A lifesaving procedure that was initially developed to treat inoperable and terminal patients with critical AS has now established itself as the treatment of choice for most patients with severe symptomatic AS. As the number of patients that will have an indication for TAVI is likely to further grow with broader expansion and timing for intervention in currently ambiguous scenarios, including moderate AS with heart failure (TAVR UNLOAD trial, NCT02661451), asymptomatic severe AS (EARLY TAVR study, NCT03042104), bicuspid AS and native aortic regurgitation further refinements in the technology behind the THVs and implanting techniques will be necessary to completely eliminate adverse events such as the need for PPM implantation and further improve other aspects such as THV durability and post-TAVI coronary access (**Figure 4**).

Author contributions

AK and TP made the initial manuscript conception and structure and the initial manuscript draft and further edited and approved the final version of the manuscript. SR, CA, HH, OC, RR, and BP edited and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to thank Mizuki Miura (Department of Cardiovascular Medicine, University of Tokyo Hospital) for kindly providing **Figure 7** (native cardiac conduction system and its anatomical relations with aortic valve cusps and membranous septum).

Conflict of interest

Author SR received speaker fees from Edwards Lifesciences and served as an International Advisory Board Member for Medtronic. Author BP received institutional educational and research grants from Edwards Lifesciences, and speaker/consultancy fees from Abbott, Anteris, Microport, and Edwards Lifesciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Mini Review
PUBLISHED 01 December 2022
DOI 10.3389/fcvm.2022.1007139

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 30 July 2022
ACCEPTED 08 November 2022
PUBLISHED 01 December 2022

CITATION
Brito J, Raposo L and Teles RC (2022) Invasive assessment of aortic stenosis in contemporary practice. *Front. Cardiovasc. Med.* 9:1007139. doi: 10.3389/fcvm.2022.1007139

Invasive assessment of aortic stenosis in contemporary practice

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The authors review the current role of cardiac catheterization in the characterization of aortic stenosis, its main clinical applications, its pitfalls, and its additional value to the information provided by echocardiography. Discrepancies that may arise between these two modalities are discussed and further explained. Hemodynamic variables besides transvalvular pressure drop are described, and emphasis is given to an integrative approach to aortic stenosis assessment, that includes invasive and noninvasive evaluation.

KEYWORDS

aortic stenosis, invasive assessment, echocardiography/catheterization discrepancies, pressure drop, low-flow, integrative approach

Introduction

Aortic valve stenosis (AS) is increasingly prevalent in developed countries, and its etiologies include congenital, degenerative (the most common), and rheumatic disease (1). Degenerative AS is a complex process of progressive inflammation, fibrosis, and calcification, affecting an otherwise structurally normal valve at the macroscopic level, which eventually leads to leaflet restriction and related hemodynamic consequences (2), and constitutes the main indication for aortic valve intervention. Regardless of etiology, stenosis of the aortic valve causes obstruction of the blood flow from the left ventricle (LV) to the aorta, which generates a systolic flow-dependent pressure drop (ΔP, a more accurate term for the widely used *gradient*) across the valve and chronic overload of the LV. Understanding the hemodynamic principles behind AS assessment allows us to critically integrate all the information provided by noninvasive diagnostic modalities and to acknowledge the important role of invasive hemodynamic studies in this setting.

Essential anatomic and functional concepts underlying the measurements of aortic stenosis severity

In degenerative senile AS, calcification induces progressive leaflet immobility and obstruction, leading to a decrease in the aortic valve area (AVA). The narrowed AV

orifice leads to the acceleration of blood through the valve, from a lower velocity in the LV outflow tract (LVOT) to the peak velocity at the vena contracta (VC) of the jet. The area between the free edges of the valve leaflets is the true anatomical measure of AVA and is known as the geometric orifice area (GOA). Although it can be measured by planimetry by using either computed tomography (CT) or echocardiogram (usually transesophageal echo), its assessment is challenging, namely due to dependence on image quality and difficulty to locating the exact plane of maximal leaflet opening in a tridimensional structure. The area of flow convergence at the VC is the echocardiographic-obtained AVA, i.e., the effective orifice area (EOA). The latter is smaller than the GOA and corresponds to the smallest measure of AVA. The pressure drop between the LVOT and the EOA is ΔP_{max}. This decrease in pressure just distally to the valve, in the proximal ascending aorta, is primarily driven by the spatial acceleration of the blood flow (3). As the bloodstream flows to the distal ascending aorta, its kinetic energy is partially converted back into potential energy, resulting in an increase in local pressure. This phenomenon, known as the pressure recovery effect (**Figure 1A**), has implications for measurements and their interpretation, as will be further discussed below.

Invasive and echocardiographic assessment of aortic stenosis severity

Current guidelines define severe AS as an AVA < 1.0 cm^2 or indexed AVA (iAVA) < 0.6 cm^2/m^2, mean transvalvular pressure drop (ΔP_{mean}) ≥ 40 mmHg, and/or peak transaortic velocity ≥ 4 m/s assessed by Doppler echocardiography (4). Indeed, AS is accurately diagnosed in a significant proportion of patients by Doppler echocardiographic assessment and this is mandatory to guarantee that only suitable patients are referred to valve intervention, considering that a faulty evaluation may prevent a patient from receiving the recommended treatment. In the past, invasive hemodynamic studies were critical for understanding the physiology and pathophysiology of valvular heart disease, but this role was downgraded with the advent of echocardiography, a noninvasive modality. Currently, cardiac catheterization for hemodynamic evaluation of AS is only recommended to accommodate any perceived inconsistencies between clinical and echocardiographic data or if non-invasive imaging is inconclusive (4).

It should be noted that a fundamental difference between these two techniques is that cardiac catheterization can directly measure actual pressure and pressure drops (ΔP), whereas Doppler ultrasound measures velocities that are converted into ΔP by applying the modified (and oversimplified) Bernoulli equation: $\Delta P = 4v^2$, where v is the peak velocity measured by continuous Doppler through the LVOT and the aortic valve, in m/s. AVA can then be estimated from the velocities across the aortic valve and LVOT using the continuity equation:

$$AVA = \frac{LVOT\ area \times LVOT\ VTI}{AV\ VTI}$$

where *VTI* is velocity time integral, measured by pulsed Doppler.

Although Doppler echocardiography has been established as the gold standard for assessing AS severity, it should be emphasized that echo parameters were initially derived as surrogates of invasive measurements and that there are important pitfalls that may jeopardize their accuracy. Echocardiography is highly operator-dependent, and image quality may be occasionally mediocre; a lack of alignment between the Doppler beam and the direction of the aortic jet can result in underestimation of the pressure drop and, on the other hand, the pressure drop may be overestimated in severe anemia or conditions associated with high output; AVA calculation relies on the accurate measurement of LVOT diameter, which is challenging and prone to intraobserver and interobserver variability (ranging from 5 to 8%) (5). Since the square of the radius is used to derive the area of the LVOT in the continuity equation, a small measurement error causes a significant error in AVA. Moreover, the LVOT shape is elliptical rather than circular in most of the patients, which may further result in underestimation or overestimation of echo-derived areas (5). Finally, the use of the simplified Bernoulli formulation may introduce a variable source of error, as further discussed in the following section.

For the assessment of AS severity in the cardiac catheterization laboratory, it is essential to accurately measure both the transvalvular pressure drop and cardiac output (CO; flow). ΔP can be obtained by simultaneous measurement of LV and ascending aorta pressures, either by using two arterial accesses, dual lumen fluid-filled catheters, multitransducer micromanometer catheters, or common pressure wires (PWs) (6). Care must be taken with the potential damping of aortic pressure with double-lumen catheters, which may falsely increase the pressure drop. Also, the cross-sectional area of a catheter crossing the aortic valve may increase the measured pressure drop, especially in very tight stenoses, and there is *in vitro* evidence that catheter geometry may produce significant measurement bias in both the peak pressure and the waveform shape (7). In our experience, 4-to-5 French catheters (pigtail or multipurpose shapes with side holes) will be adequate for most cases. The use of a PW in the LV for pressure measurement further obviates these issues, however, at the expense of a higher procedural cost and the possible need for post-procedure analysis, as some polygraphs will not co-register both PW and fluid-filled signals simultaneously. Non-disposable multitransducer micromanometer catheters are very accurate but costly and are less often used in clinical laboratories (6). Catheterization should allow for the

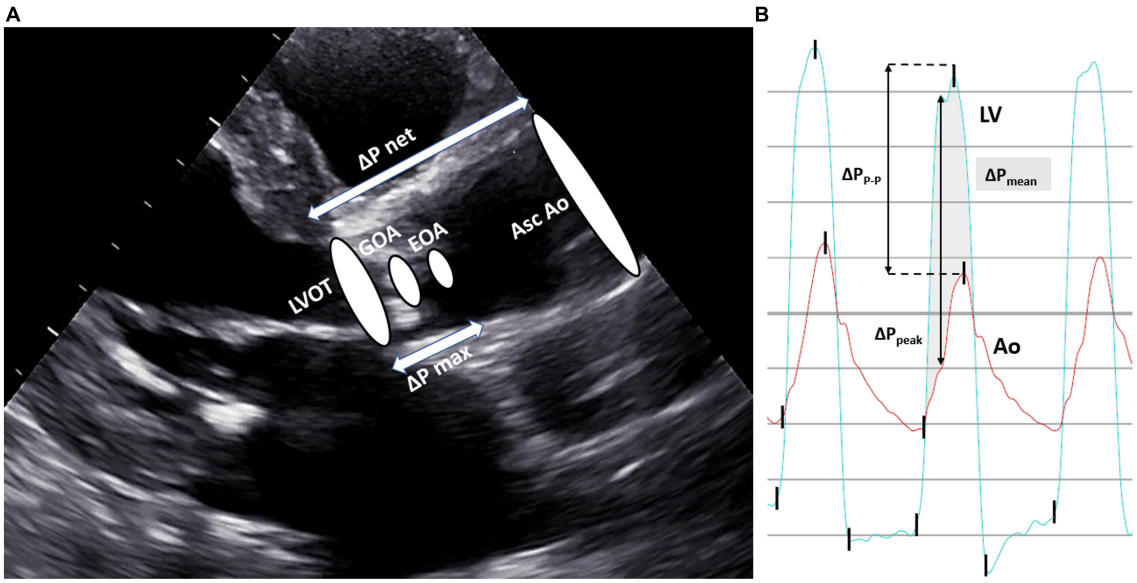

FIGURE 1
Echocardiographic and invasive characterization of aortic stenosis. Panel **(A)** The geometric orifice area *(GOA)* is the true anatomical area of the aortic valve and the area of the flow jet at the vena contracta, which occurs downstream of the valve orifice, is the effective orifice area *(EOA)*, and corresponds to the calculated AVA by the continuity equation. GOA is always larger than EOA (they will be equal if GOA has the same size as LVOT). The pressure difference between the LVOT and EOA is known as ΔP_{max}. The pressure difference between the ascending aorta and LVOT is ΔP_{net}, as it is recorded after the occurrence of pressure recovery, and corresponds to the measured pressure drop in the catheterization laboratory. In the presence of the pressure recovery phenomenon, ΔP_{max} is higher than ΔP_{net}, which partially explains the discrepancies between Doppler and invasive metrics. Panel **(B)** The shaded area represents the mean transaortic pressure drop (ΔP_{mean}); peak-to-peak pressure drop (ΔP_{P-P}) is the difference between the peak LV pressure and the peak aortic pressure at two different points in time; maximum instantaneous pressure drop (ΔP_{peak}) is the maximum recorded difference between the LV and aortic pressure at the same point in time. *Ao indicates aortic pressure; Asc Ao, ascending aorta; LV, left ventricle pressure; LVOT, left ventricular outflow tract.*

measurement of both ΔP_{P-P}, i.e., the peak-to-peak systolic pressure drop (the difference between the peak LV pressure and the peak aortic pressure), and ΔP_{mean}, i.e., the invasive mean pressure drop (average of instantaneous pressure drops over the ejection period) (**Figure 1B**). It is important to emphasize that single-catheter pullback curves from the LV to the aorta provide an approximation of the peak-to-peak systolic pressure drop, which is not a physiological measurement since it is obtained at two different points in time and, as such, may be imprecise for diagnostic purposes. The mean pressure drop should be used for diagnosis and measured from at least 3 consecutive beats in patients with sinus rhythm or 8–10 consecutive beats when a rhythm is irregular (8). CO is usually assessed invasively by the Fick method or thermodilution. The Fick method is the gold standard and requires the measurement of real-time oxygen consumption using dedicated equipment, which can be time-consuming and unpractical in the catheterization laboratory. Alternatively, oxygen consumption may be estimated from gender- and age-specific nomograms (indirect Fick method), which constitutes a potential source of error, as the impact of disease states is not accounted for. When thermodilution is used, inaccuracy may result from severe tricuspid regurgitation, cardiac shunts, very low output states, and highly irregular rhythms (8).

Finally, AVA can be calculated from ΔP and CO using the Gorlin equation (9):

$$AVA\ (cm^2) = \frac{\text{CO (l/min)/[HR (bpm) x SEP (mSec)]}}{44.3 \times \sqrt{\Delta P (mmHg)}}$$

where SEP is the systolic ejection period, K = 44.3 (empirical constant), and ΔP is the mean pressure drop. It must be noted that this equation has several inherent limitations (mainly stemming from the fact that it has not been primarily derived for the aortic valve) and that accuracy may be lower in patients with bradycardia, tachycardia, aortic regurgitation, or low output states (10).

Thorough invasive evaluation of a patient with AS is multiparametric. It must include measurement of transvalvular pressure drop, CO, and calculation of AVA, but also an appraisal of left ventricular contractility and peripheral vascular resistance. In addition, other indexes can be used to arbitrate inconsistency. Aortic valve resistance can be easily calculated using the same essential parameters and has been suggested to be less flow-dependent than the Gorlin-derived AVA (11). In the end, critical interpretation and integration of all the obtained values are mandatory for a correct diagnosis.

Questions have been raised regarding the risk of embolic stroke resulting from aortic root manipulation and retrograde

aortic valve crossing, with one study showing a high frequency of magnetic resonance imaging (MRI) defects in this context (12). However, a subsequent study failed to corroborate these findings (13). One further study showed that the time required for crossing the aortic valve was the most important independent predictor of silent cerebral infarction (14). In this context, the increasing number of transcatheter aortic valve interventions (TAVI) has brought technical and device improvements which have reduced the procedure time and increased its efficacy and safety (15). Besides this potential issue, one should also notice other known complications of cardiac catheterization, such as local vascular injury, bleeding complications, and also the exposure of both patients and operators to ionizing radiation. Taking all these aspects into consideration, the decision for invasive assessment of AS should be judiciously made, when a gain of diagnostic ability is expected, as unnecessary cardiac surgery and TAVI are themselves associated with a risk of neurologic and other systemic complications (16, 17). It is wise to recommend that this procedure should be performed by experienced operators.

Discrepancies between echocardiographic and catheterization findings

There is evidence that the correlation between noninvasive and invasive AS assessments is weaker than previously reported (18, 19). This observation should be highlighted and critically appraised since the values used in guidelines to define severe AS are derived from outcome studies using invasive hemodynamics, whereas echo values are recommended to evaluate AS (20). As previously discussed, several sources of error exist in both echocardiographic and invasive evaluation that can contribute to this discrepancy, starting with the essential assumptions inherent to both techniques. Transvalvular pressure drops derived from catheterization are lower than echo-derived values, and traditionally, this observation has been mainly explained by the pressure recovery phenomenon (21, 22). While Doppler echocardiography measures ΔP from the velocity obtained at the *VC*, catheterization directly measures the pressure drop between LVOT and the ascending aorta, after the conversion of some kinetic energy back into potential energy (ΔP_{net}) (**Figure 1A**). The degree of pressure recovery depends on many factors, including the ratio of actual AVA/ascending aorta area, with more pressure recovery typically observed in patients with larger valve orifice and smaller ascending aorta (22). Therefore, in the presence of significant pressure recovery, invasive pressure drops are lower and the estimated AVA is higher than the corresponding echocardiographic values. However, the exact anatomic point where the pressure is fully recovered is not known and differs from subject to subject, which potentially introduces a source of error in invasive estimations.

Moreover, the very use of the modified Bernoulli equation for the noninvasive assessment of ΔP provides an additional and important explanation for these discrepancies. It relies on two assumptions: (1) the pressure drop is entirely due to spatial acceleration of blood flow, neglecting the impact of unsteady and viscous components, and (2) the blood flow is considered a single streamline, which neglects the velocity distribution across the aortic valve plane (3). While it is known that the first assumption is indeed accurate as the spatial acceleration of blood is the dominant pressure component, there is evidence that the use of a single peak velocity value to the detriment of a complete velocity profile results in consistent overestimation of transvalvular pressure drop and is a source of uncontrolled variability (3, 23).

A comparison of the most important features of these two modalities for AS severity assessment is summarized in **Table 1**.

Role of cardiac catheterization in low-flow states

Low-flow, low-gradient aortic valve stenosis

A subset of patients with severe AS presents with low CO, $\Delta P_{mean} < 40$ mmHg, and reduced LV ejection fraction. The challenge in this setting is to ensure that the small, calculated AVA is due to true severe AS or "pseudo-aortic stenosis". In the latter, the aortic valve has the moderate disease, but the leaflet opening is insufficient due to a weak LV, with reduced inotropy. As the Gorlin formula is flow-dependent, the severity of AS may be overestimated in this situation. Dobutamine infusion (whether during catheterization or echocardiography) is the gold standard to differentiate true AS from pseudostenosis, as it induces an increase in inotropy and, consequently, increases CO. In true AS, ΔP_{mean} rises to $\geq$ 40 mmHg. If CO normalizes but ΔP_{mean} remains low ($<$ 30 mmHg), with an increase in AVA, then pseudostenosis is present. Some patients will not be able to increase CO due to a lack of contractile reserve (defined as an increase in stroke volume <20%). These subjects have indeterminate AS and will require the integration of clinical, imaging, and laboratory parameters for a comprehensive evaluation, bearing in mind that the long-term prognosis after valve intervention is poorer in this group of patients (24).

Paradoxical low-flow, low-gradient aortic valve stenosis

This group of patients presents with iAVA < 0.6 cm^2/m^2, $\Delta P_{mean} < 40$ mmHg, LVEF $> 50\%$, and indexed stroke volume

TABLE 1 Comparison of cardiac catheterization and Doppler echocardiography for AS evaluation.

Modality	Direct measurements	Advantages	Pitfalls
Cardiac catheterization	Mean transaortic pressure drop (ΔP_{mean}) Maximum instantaneous transaortic pressure drop (ΔP_{peak}) Peak-to-peak transaortic pressure drop (ΔP_{P-P}) Cardiac Output	Direct pressure measurement	Invasive Radiation exposure Potential risk of embolic stroke Unknown exact anatomic point where full pressure recovery occurs
Doppler echocardiography	Instantaneous VC velocity Peak VC velocity (V_{max}) Instantaneous transaortic pressure drop (through modified Bernoulli equation) Mean transvalvular pressure drop (Doppler ΔP_{mean})	Noninvasive Anatomic Evaluation Widely accessible	Requires good imaging window Does not provide pressure directly LVOT measurement may decrease AVA calculation accuracy Assumption of a single peak velocity value in Bernoulli equation may overestimate the pressure drop

AS indicates aortic stenosis; AVA, aortic valve area; LVOT, left ventricular outflow tract; VC, vena contracta.

(SVI) < 35 ml/m^2. Despite the preserved ejection fraction, the low-flow state may generally be explained by higher LV filling pressures, reduced systolic longitudinal myocardial shortening, and increased afterload on the LV through decreased systemic arterial compliance and increased systemic vascular resistance causing higher vascular impedance. This pattern may lead to an underestimation of AS severity and prevent appropriate valve intervention. Cardiac catheterization has an important role in the evaluation of this entity when noninvasive metrics are inconclusive or if there is a discrepancy between clinical and echocardiographic findings. One approach in this setting is to evaluate the global LV hemodynamic burden by determining the valvulo-arterial impedance (Z_{va}) by the following equation (25):

$$Zva = \frac{\text{SBP} + \Delta\text{Pmean}}{\text{SVI}}$$

where SBP is systolic blood pressure and SVI is indexed stroke volume.

Patients with paradoxical low-flow, low-gradient AS tend to have $Z_{va} \geq 5.5$ mmHg/ml/m^2, and these values are associated with a worse prognosis (26). In this setting, a nitroprusside challenge may be further helpful to assess the fixed component of total left ventricular afterload, unmask true aortic stenosis (27), and ideally predict symptomatic response to hemodynamic relief of aortic stenosis.

Clinical application of invasive assessment of Aortic valve stenosis

To illustrate the previously outlined concepts, we present the case of an 81-year-old overweight woman with a history of chronic obstructive lung disease, deep vein and pulmonary thromboembolism, and reactive depression, who was evaluated in the outpatient clinic with complaints of fatigue and effort dyspnea (New York Heart Association class II). The echocardiogram showed preserved ejection fraction (LVEF 57%) and calcified AS, with a mean pressure drop of 26 mmHg, AVA 0.36 cm^2/m^2, and SVI 26 ml/m^2. These findings were consistent with the diagnosis of paradoxical low-flow, low-gradient AS. However, doubts persisted regarding the severity of AS, and the presence of significant comorbidities suggested that the functional limitation might be due to other causes. Further investigation by CT scan revealed an aortic valve calcium score of 569 AU, which suggested that severe AS was less likely (28). An invasive hemodynamic assessment was performed to reconcile these discrepancies: ΔP_{mean} was 20 mmHg, CO was 5.1 L/min, and SVI was 32.1 ml/m^2. AVA estimated by the Gorlin equation was 1.16 cm^2. Zva was not elevated (4.4 mmHg.ml^{-1}.m^2) as would be expected in paradoxical low-flow low-gradient AS and the intrinsic valve resistance was < 120 dynes.s.cm^{-5}. The usefulness of this latter variable remains controversial, although one study postulates that in low-flow, low-gradient aortic stenosis, such a value identifies pseudo stenosis, while the values of > 180 dynes.s.cm^{-5} identify truly severe AS (11). Integration of all these invasive parameters allowed us to exclude severe AS and reclassify it as moderate.

Conclusion and future perspectives

Currently, invasive hemodynamic evaluation of AS is indicated to clarify inconsistencies between clinical and echocardiographic findings, or when those findings are not conclusive. Although AS severity assessment relies mostly on the echocardiographic evaluation, one should be aware that the obtained metrics often differ from invasive parameters. While catheterization allows for direct measurement of pressure drop, Doppler echocardiography measures velocities that are converted into pressure drops. This is an essential and distinguishing feature between these two modalities that must be accounted for when interpreting the whole clinical picture. It is critical to understand the hemodynamic concepts behind AS evaluation to identify potential inconsistencies in diagnosis and the subsets of patients that benefit from an integrated approach that includes cardiac catheterization.

Also, although AS is a valve disease, looking exclusively at the valve may be deceiving and it should be noted that

understanding the coupling between the valve and the LV is equally essential. Thus, investigation of the extent of myocardial fibrosis (by using cardiovascular magnetic resonance (CMR), echocardiography, or quantification of brain natriuretic peptide levels) may be useful in determining the prognostic impact of AS and potential valve intervention (29, 30). Recent advances in CMR have also proven to provide more precise and accurate values of pressure drop by addressing the limitations of the simplified Bernoulli formulation (3, 31). Interestingly, imaging modalities such as 4D flow CMR have the advantage of acquiring three-dimensional blood velocity vector fields, which have been validated against gold-standard techniques, and potentially overcome a previously discussed limitation of Doppler echocardiography (31). Unanswered questions, whether 4D flow CMR-derived pressure computations correlate accurately with transduced pressure data and whether these measures prove to have a strong prognostic impact, are a field of promising current and future research.

Finally, AS has increasingly become a disease of the elderly and is likely accompanied by multiple comorbidities including LV dysfunction, coronary artery disease, lung disease, and frailty. As such, their symptoms might arise from causes other than aortic stenosis, and establishing this link is often complicated and ambiguous. While cardiac catheterization has a role in clarifying AS severity, a noninvasive test such as a cardiopulmonary exercise test may help to define the symptomatic status and the functional capacity of such patients.

In the current era of expanding TAVI, we have observed a trend for an increased referral of AS patients with different degrees of severity and different hemodynamic states. The role of cardiac catheterization in the accurate hemodynamic characterization of the disease should be considered at a lower threshold, and this integrated, multimodality approach should become the cornerstone of patients' evaluation for treatment decisions and the best counseling.

Author contributions

JB wrote the first draft of the manuscript. JB, LR, and RT wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 08 December 2022
DOI 10.3389/fcvm.2022.1002071

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 24 July 2022
ACCEPTED 16 November 2022
PUBLISHED 08 December 2022

CITATION
Wang Y, Yu S, Qian D, Li J, Fang Z, Cheng W, Li X, Liu T, Zeng Y, Xia H and Jin J (2022) Anatomic predictor of severe prosthesis malposition following transcatheter aortic valve replacement with self- expandable Venus-A Valve among pure aortic regurgitation: A multicenter retrospective study.
Front. Cardiovasc. Med. 9:1002071.
doi: 10.3389/fcvm.2022.1002071

Anatomic predictor of severe prosthesis malposition following transcatheter aortic valve replacement with self-expandable Venus-A Valve among pure aortic regurgitation: A multicenter retrospective study

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Background: Transcatheter aortic valve replacement (TAVR) in the treatment of patients with pure native aortic valve regurgitation (NAVR) has been based on the "off-label" indications, while the absence of aortic valve calcification and difficulty in anchoring was found to significantly increase the risk of prosthesis malposition. The aim of this study was to explore the anatomical predictors of severe prosthesis malposition following TAVR with the self-expandable Venus-A Valve among patients with NAVR.

Methods: A total of 62 patients with NAVR who underwent TAVR with Venus-A Valve at four Chinese clinical centers were retrospectively observed. The clinical features, aortic multidetector computed tomography (MDCT) data, and clinical outcomes were compared between non-/mild malposition and severe malposition groups. Univariate logistic regression analysis was used to identify the risk factors of severe prosthesis malposition, and the receiver operating characteristic (ROC) curve was used to explore the predictive value of the risk factors.

Results: Valve migration to ascending aortic direction occurred in 1 patient, and the remaining 61 patients (including 19 severe malposition cases and 42 non-/mild malposition cases) were included in the analysis. The diameter and height of the sinotubular junction (STJ) and STJ cover index (STJCI,

calculated as 100%*STJ diameter/nominal prosthesis crown diameter) were all greater in the severe malposition group (all $p < 0.05$). Logistic regression showed that STJ diameter (OR = 1.23, 95% CI 1.04–1.47, $p = 0.017$), STJ height (OR = 1.24, 95% CI 1.04–1.47, $p = 0.017$), and STJCI (OR = 1.08, 95% CI 1.01–1.16, $p = 0.032$) were potential predictors for severe prosthesis malposition. The area under the ROC curve was 0.72 (95% CI 0.58–0.85, $p = 0.008$) for STJ diameter, 0.70 (95% CI 0.55–0.86, $p = 0.012$) for STJ height, and 0.69 (95% CI 0.55–0.83, $p = 0.017$) for STJCI, respectively. The cutoff value was 33.2 mm for STJ diameter (sensitivity was 84.2% and specificity was 65.8%), 24.1 mm for STJ height (sensitivity was 57.9% and specificity was 87.8%), and 81.0% for STJCI (sensitivity was 68.4% and specificity was 68.3%), respectively.

Conclusion: Larger and higher STJ, as well as greater STJ to valve crown diameter ratio, may help identify patients at high risk for severe prosthesis malposition among patients with NAVR undergoing TAVR with Venus-A prosthesis valve.

KEYWORDS

pure native aortic regurgitation, computed tomography, malposition, self-expandable, transcatheter aortic valve replacement

Introduction

Compared to Western countries, aortic regurgitation (AR) is more prevalent than aortic stenosis among the elderly in China (1). As transcatheter aortic valve replacement (TAVR) came into use for lower-risk patients with severe aortic stenosis, and "off-label" indications for TAVR in the treatment of patients with pure native aortic valve regurgitation (NAVR) have also been explored (2–4). When left untreated, NAVR is associated with high mortality risk. There are also many patients at high surgical risk or unwilling to undergo surgery, for whom less invasive trans-catheter treatment continues to present a feasible option. However, the absence of aortic valve calcification and difficulty in anchoring the prosthesis valve significantly increase the risk of valve migration/embolization, additional valve implantation, and significant residual regurgitation (2, 4).

The Valve Academic Research Consortium-3 (VARC-3) defines prosthesis malposition as valve migration, valve embolization, and ectopic valve deployment (5). In a previous study, the incidence of device malposition has been reported to amount to 33.0% using early-generation devices (2). Furthermore, the incidence of residual AR and the need for implanting a second valve (valve-in-valve procedures) were found to remain high in the NAVR population who received TAVR (6, 7). Several devices have shown favorable results in NAVR, such as JenaValve THV (JenaValve Technology, Inc., Irvine, CA, USA) and Acurate neo (Boston Scientific, Marlborough MA, USA), while none of which were approved for use in Mainland China. Transapical J-valve (JieCheng Medical Technology, Suzhou, China) has been verified as safe and effective for use in patients with NAVR (8); however, transfemoral access TAVR continues to be the first choice instead of the transapical approach. Given that there are currently no suitable artificial transcatheter heart valves available for NAVR, and there are a large number of patients requiring treatment who are unsuitable or unwilling to undergo surgery, identifying the high-risk anatomic feature of prosthesis malposition could help with the selection of more suitable NAVR candidates for transfemoral TAVR.

In their study, Li et al. (9) revealed that conical left ventricular outflow tract and tall aortic sinuses were strong predictors of prosthesis malposition during self-expandable TAVR in patients with aortic stenosis. However, there is still limited data on anatomic risk factors for prosthesis malposition in patients with NAVR, especially among those implanted with the most widely used Venus-A Valve (Venus MedTech, Hangzhou, China) in China. Therefore, considering the different anchoring conditions of patients with NAVR, we aimed to explore the anatomical predictors of prosthesis malposition following TAVR with the self-expandable Venus-A Valve among Chinese patients with NAVR.

Materials and methods

Study population and design

A total of 62 consecutive patients with symptomatic severe pure NAVR who underwent TAVR using a self-expandable Venus-A Valve at one of the four Chinese centers between

January 2019 and December 2021 were enrolled in this multicenter, retrospective study. All four experienced centers performed more than 100 TAVR cases per year. Venus-A Valve is the first approved transcatheter heart prosthesis valve and the most widely used one in Mainland China. The design characteristics of Venus-A Valve have been previously reported in detail (9). The second-generation Venus-A Plus Valve is resheathable and morphologically consistent with the first-generation valve (10). Patients with high/prohibitive surgical risk or those who rejected surgery were considered eligible candidates, and those with aortic stenosis defined as a peak aortic jet velocity $\geq$ 250 cm/s or mean transvalvular gradient $\geq$ 20 mmHg were excluded (11). The indication for TAVR was discussed by each heart team, and the size of the prostheses was independently determined by the individual centers based on aortic root multidetector computed tomography (MDCT). Lunderquist extra-stiff wire was used concerning its appropriate stiffness. The valve size selection and the decision on whether to implant an additional prosthesis valve were all individually decided in each heart center.

Among the 62 patients, there was 1 case of valve embolization to ascending aortic direction due to slender ascending aorta (AA) and narrow sinotubular junction (STJ) [STJ diameter was 27.2 mm, STJ cover index (STJCI) was 72.5%, and STJ height was 23.0 mm]. Given the contrasting anatomic features of aortic root among patients with upward and downward migration, there was only one case in the aortic migration group; therefore, only the downward migration patients were introduced in statistical analysis, resulting in 61 cases included in the final analysis. The patient flowchart is shown in **Supplementary Figure 1**, and description of surgical risk detail was shown in **Supplementary Figure 2**.

This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Army Military Medical University, and informed consent was waived because of the retrospective design.

Data collection

Baseline clinical information, echocardiographic and MDCT data, as well as procedural data and postprocedure 30-day clinical follow-up data were collected. All patients underwent echocardiography and electrocardiography before discharge and at a 30-day follow-up. Clinical events and 30-day endpoints were all recorded according to VARC-3 criteria. Impaired anterior mitral leaflet (AML) movement was defined as significant interference with the prosthesis frame and mitral valve, thus leading to limited AML movement shown by echocardiography. The valve implantation depth was measured as the distance from the native aortic annulus plane on the side of the non-coronary cusp (or right cusp for bicuspid) to the most proximal edge of the implanted prosthesis by an instant angiogram after implantation. The recommended implantation depth for the Venus-A prosthesis was 4–8 mm below the aortic annulus. Three marker points above 5 mm from the proximal edge were designed for identifying the implantation depth during device delivering (**Figures 1A,C**, shown by white arrow).

Multidetector computed tomography

Multidetector computed tomography data were retrospectively analyzed using 3mensio software (Pie Medical, Bilthoven, Netherlands) by two independent researchers who were blinded to all other clinical data. Inconsistencies were resolved by measuring again and consulting a local experienced interventional cardiologist. The aortic root structure was measured by the 40% systolic phase. Perimeter-derived diameter for annulus and average diameter of the left ventricular outflow tract, sinus of Valsalva, STJ, and AA were measured, respectively. STJ height was measured on the central line between STJ and annulus dimension automatically. The aortic valve calcification volume was automatically measured with a calcification threshold set at 850 HU. The oversize valve ratio was calculated as 100%*[(prosthesis size − annulus diameter)/annulus diameter − 1]. The STJCI was calculated as 100%*STJ diameter/nominal prosthesis crown diameter.

Grouping

Patients were divided into an optimal position group, mild malposition group, and severe malposition group based on the modified VARC-3 criteria (**Figure 1**). Optimal position referred to patients with implantation depth ranging from 0 to 8.0 mm. Mild malposition was defined as >8.0 mm but with acceptable implantation depth. Severe malposition referred to very deep implantation that is prone to cause hemodynamically relevant consequences (residual transvalvular gradient $\geq$ 20 mmHg or more than moderate paravalvular regurgitation). To define mild and severe malposition groups, the receiver operating characteristic (ROC) curve was then used to explore the optimal threshold of implantation depth. As a result, 15.0 mm was shown to be a good cutoff value to predict residual stenosis or more than moderate paravalvular regurgitation (area under the ROC curve, AUC, = 0.996, 95% CI 0.93–1.01, $p < 0.001$, **Figure 2A**). Given the similar aortic root anatomic construction and clinical outcomes of the optimal implantation group and mild malposition group (**Supplementary Tables 1**, **2**), we classified them as the non-/mild malposition group. Comparisons were made between the non-/mid malposition group and the severe malposition group.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation; those with skewed

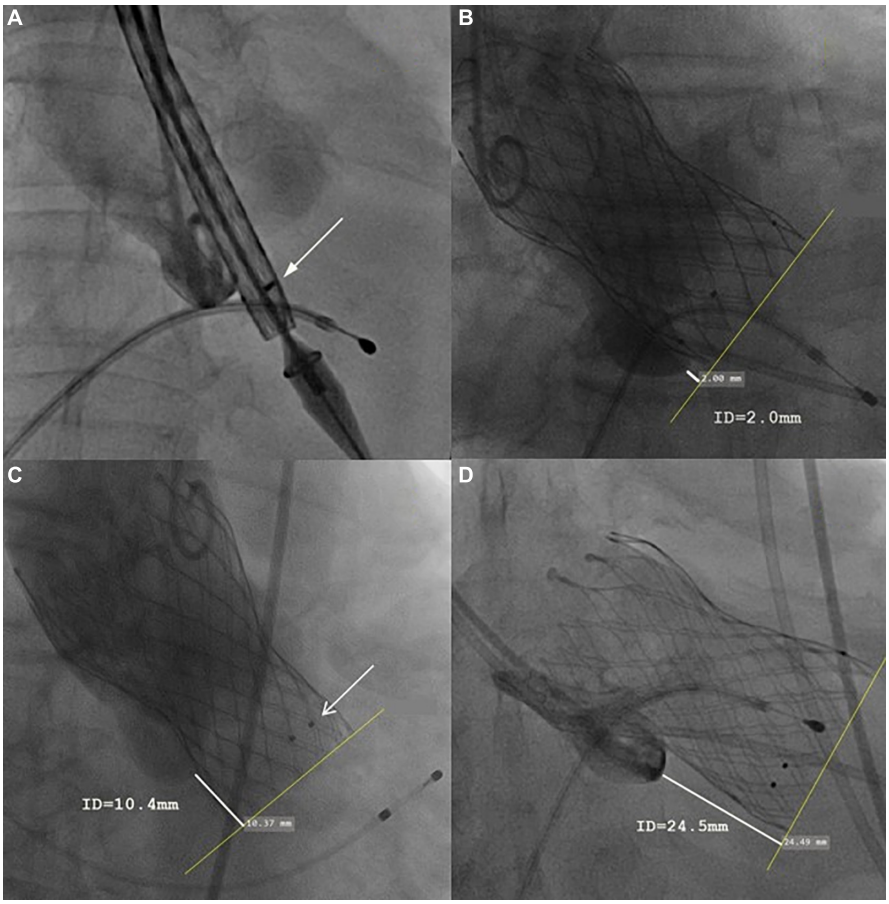

FIGURE 1
Representative case of each group. **(A)** The initial position of the prosthesis. **(B)** In optimal implantation, the implantation depth (measured as the distance from the native aortic annulus plane on the side of the non-coronary cusp to the most proximal edge of the implanted prosthesis) was 2.4 mm. **(C)** In the mild malposition case, the implantation depth was 10.4 mm, no perivalvular leakage or residual stenosis was found. The three black dots indicated by the white arrow were 5 mm from the proximal edge. **(D)** In severe malposition cases, the prosthesis migrated toward the ventricular direction during release, causing very deep implantation (implantation depth = 24.5 mm). Severe residual regurgitation was found and then a second Venus-A Valve was implanted (valve-in-valve TAVR).

distribution are expressed as median (lower and upper quartile), while categorical variables are reported as numbers (percentages). The independent-sample *t*-test or the Mann–Whitney *U*-test was used to compare the means between two groups, and the chi-square test or Fisher's exact test for categorical variables. The clinical, anatomic, and procedural indicators, which were regarded as candidate risk factors for severe valve malposition, are listed in Tables 1–3. Variables with $p < 0.10$ in inter-group comparisons or anatomical variables of interest were entered into the binary logistic regression model. Given the small sample size, only univariate analysis was performed in this study. ROC curve was used to analyze each predictor's discriminative performance and identify the optimal cutoff value. All statistical tests were two-tailed, with $p < 0.05$ being considered statistically significant. Statistical analyses were performed using SPSS (version 26.0; Chicago, IL, USA).

Results

Among 61 patients, 33 underwent TAVR with Venus-A and 28 with Venus-A Plus prosthesis valve. Sixty approaches were transfemoral and 1 was performed using the transcarotid approach. The non-/mid malposition group included 20 optimal position cases and 22 mild malposition cases. Among the 19 severe malposition cases, obvious valve migration toward the left ventricle causing residual stenosis or more than moderate paravalvular regurgitation was identified in 17 patients; in 15 patients (88.2%), it occurred during the TAVR procedure, and in 2 patients (11.8%), it occurred later. Both patients with delayed migration received successful single-valve implantation with acceptable hemodynamics immediately after the TAVR procedure. One complained of dyspnea 3 days after the TAVR procedure, and valve migration toward the ventricle was confirmed by transthoracic echocardiography, accompanied

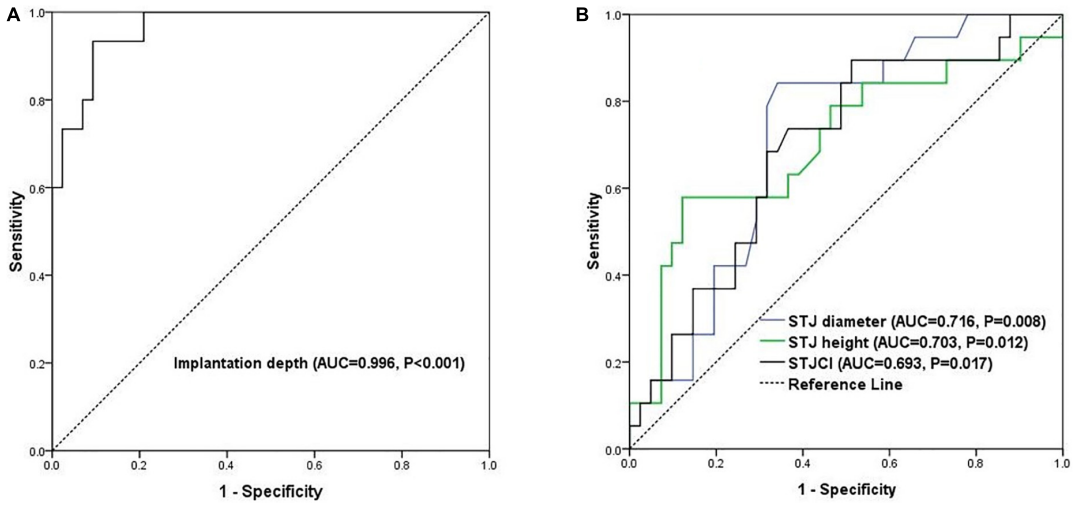

FIGURE 2
The ROC curves of **(A)** prediction of hemodynamically relevant consequences by implantation depth and **(B)** prediction of severe malposition by the three STJ indicators. AUC, area under the curve; ROC, receiver operating characteristic.

TABLE 1 Baseline characteristics of study population.

	Total population (n = 61)	Severe malposition (n = 19)	Non/mild malposition (n = 42)	P-value
Clinical data				
Age, years	72.8 ± 6.7	72.5 ± 7.4	73.0 ± 6.4	0.778
Male gender	38 (62.3)	15 (78.9)	23 (54.8)	0.071
BMI, Kg/m^2	23.3 ± 4.3	23.0 ± 3.3	23.5 ± 4.7	0.700
STS score, %	5.8 ± 1.8	6.0 ± 2.0	5.7 ± 1.8	0.683
Hypertension	41 (67.2)	13 (68.4)	28 (66.7)	0.892
Diabetes	9 (14.8)	1 (5.3)	8 (19.0)	0.128
Coronary heart disease	18 (29.5)	5 (26.3)	13 (31.0)	0.771
Atrial fibrillation	18 (29.5)	6 (31.6)	12 (28.6)	0.811
NYHA class III/IV	50 (82.0)	15 (78.9)	35 (83.3)	0.683
Echocardiographic assessment				
LVEF, %	54.3 ± 12.4	53.4 ± 12.6	54.7 ± 12.4	0.707
LVEDD, mm	58.0 ± 6.3	59.0 ± 4.6	57.6 ± 6.9	0.416
Mean aortic valve gradient	9.1 ± 4.8	9.5 ± 5.6	9.0 ± 4.5	0.732
Transaortic peak velocity	195.5 ± 50.6	198.4 ± 55.5	194.3 ± 49.2	0.795
≥Moderate mitral regurgitation	22 (36.1)	8 (42.1)	14 (33.3)	0.509
Cause of regurgitation				0.424
Leaflet degeneration	54 (88.5)	16 (84.2)	38 (90.5)	
Leaflet prolapse	6 (9.8)	2 (10.5)	4 (9.5)	
Leaflet injury	1 (1.6)	1 (5.3)	0	

Data are presented as mean ± standard deviation or n (%).
STS, Society of Thoracic Surgeons; BMI, body mass index; NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

by new-onset severe perivalvular leakage. Subsequently, the patient received valve-in-valve TAVR. The other patient was asymptomatic at his 30-day follow-up, while transthoracic echocardiography revealed prosthesis much deeper than before discharge (implantation depth changed from 15.8 to 21.5 mm), followed by perivalvular leakage, which progressed from mild to severe. This patient refused invasive treatment and insisted on medication. As shown in Table 1, the baseline characteristics such as age, body mass index, and echocardiographic assessment parameters were comparable between the two groups (all $p > 0.05$).

The anatomic characteristics are shown in Table 2. According to the CT parameters, the study population was without calcification in aortic cusps. The diameter and height

TABLE 2 Anatomic characteristics of the patients.

	Total population (n = 61)	Severe malposition (n = 19)	Non/mild malposition (n = 42)	P-value
Types of aortic valve				0.588
Type 0 bicuspid	2 (3.3)	0	2 (4.8)	
Tricuspid	56 (91.8)	19 (100)	37 (88.1)	
Quadricuspid	3 (4.9)	0	3 (7.1)	
Prosthesis size				0.092
L26	13 (21.3)	2 (10.5)	11 (26.2)	
L29	30 (49.2)	8 (42.1)	22 (52.4)	
L32	18 (29.5)	9 (47.4)	9 (21.4)	
Annulus				
Maximum diameter, mm	27.5 ± 2.8	27.8 ± 2.0	27.3 ± 3.1	0.577
Minimum diameter, mm	21.7 ± 2.0	22.2 ± 2.0	21.4 ± 1.9	0.188
Mean diameter, mm	24.6 ± 2.2	25.0 ± 1.7	24.4 ± 2.4	0.356
Perimeter, mm	78.5 ± 7.1	79.8 ± 4.9	77.9 ± 7.8	0.316
Area, mm^2	474.1 ± 85.5	488.6 ± 61.9	467.6 ± 94.3	0.379
LVOT				
Mean diameter, mm	25.5 ± 3.2	25.6 ± 2.7	25.4 ± 3.5	0.774
STJ				
Mean diameter, mm	33.1 ± 3.6	34.8 ± 3.4	32.3 ± 3.4	**0.009**
Height, mm	22.8 ± 4.0	24.9 ± 5.3	21.9 ± 2.9	**0.030**
AA diameter, mm	37.4 ± 3.5	38.3 ± 3.1	37.1 ± 3.7	0.228
Calcification volume, mm^3	0 (0, 5.65)	0 (0, 21.5)	0 (0, 4.6)	0.563
Aortic root angulation, degree	55.9 ± 10.3	56.4 ± 9.7	55.7 ± 10.7	0.814
Ratio within aortic root				
LVOT perimeter/Annulus perimeter	1.04 ± 0.07	1.03 ± 0.07	1.04 ± 0.07	0.691
STJ diameter/Annulus diameter	1.32 ± 0.14	1.36 ± 0.15	1.30 ± 0.13	0.118
AA diameter/STJ diameter	1.14 ± 0.09	1.10 ± 0.10	1.15 ± 0.08	0.075
AA diameter/Annulus diameter	1.52 ± 0.18	1.54 ± 0.17	1.52 ± 0.18	0.744
Ratio between aortic root and prosthesis				
Valve oversize ratio, %	17.4 ± 6.7	18.5 ± 5.7	16.9 ± 7.2	0.385
STJ cover index, %	80.3 ± 85.8	84.0 ± 8.5	78.7 ± 8.2	**0.027**
Prosthesis crown diameter/AA diameter	1.11 ± 0.11	1.09 ± 0.08	1.12 ± 0.11	0.373

Data are presented as mean ± standard deviation, median (interquartile range), or n (%).
LVOT, left ventricular outflow tract; STJ, sinotubular junction; AA, ascending aorta.
Bold values indicates $p < 0.05$.

of STJ of the severe malposition group were both significantly greater compared with the non-/mild malposition group (both $p < 0.05$). Furthermore, the severe malposition group was associated with a greater STJCI ($p = 0.027$). Procedural characteristics and 30-day clinical outcomes are listed in Table 3. The proportion of resheathable valve application showed no significant difference between the two groups; however, the implantation depth was significantly deeper in patients with severe prosthesis malposition (19.0 ± 3.2 vs. 7.7 ± 5.7 mm, $p < 0.001$). A total of 63.2% (12/19) cases received additional valve implantation in the severe malposition group and one case (2.4%) in the non-/mild malposition group. All the valve-in-valve procedures were implanted with the same size Venus-A prosthesis as the first valve. One patient received open surgery 2 days after the TAVR procedure due to severe residual AR and new-onset moderate stenosis of the mitral valve after very deep implantation. One patient received post-dilation because of the high residual transvalvular gradient after severe ventricular migration of the first valve.

Regarding 30-day clinical outcomes, there were no significant differences in mortality, permanent pacemaker implantation, major vascular complication, and major bleeding between the two groups, while the device success rate (21.1 vs. 97.6%, $p < 0.001$) and early safety rate (21.1 vs. 64.3%, $p < 0.001$) were significantly lower in the severe malposition group. These differences were mainly driven by residual moderate or more AR and reintervention (valve in valve TAVR). Furthermore, the incidence of impaired AML movement was higher in the severe malposition group (52.6 vs. 9.5%, $p < 0.001$). At 30-day follow up, the proportion of New York Heart Association (NYHA)

TABLE 3 Procedural characteristics and clinical outcomes.

	Total population (n = 61)	Severe malposition (n = 19)	Non/mild malposition (n = 42)	P-value
Procedural characteristics				
Device generation				0.785
Non-resheathable Venus-A	33 (54.1)	11 (57.9)	22 (52.4)	
Resheathable Venus-A Plus	28 (45.9)	8 (42.1)	20 (47.6)	
Reposition time(s)				0.813
Without reposition	20 (71.4)	7 (87.5)	13 (65.0)	
Once	6 (21.4)	1 (12.5)	5 (25.0)	
Twice	2 (7.1)	0	2 (10.0)	
Transfemoral approach	60 (98.4)	19 (100)	41 (97.6)	1.000
General anesthesia	60 (98.4)	18 (94.7)	42 (100)	0.311
Rapid pacing	61 (100)	19 (100)	42 (100)	NA
Post dilation	1 (1.6)	1 (5.9)	0	0.311
Implantation depth, mm	11.4 ± 7.3	19.0 ± 3.2	7.7 ± 5.7	**<0.001**
Valve-in-valve implantation	13 (21.3)	12 (63.2)	1 (2.4)	**<0.001**
Convert to open surgery	1 (1.6)	1 (5.3)	0	0.311
Device success (at 30 days)	45 (73.8)	4 (21.1)	41 (97.6)	**<0.001**
Technical success	48 (78.7)	7 (36.8)	41 (97.6)	**<0.001**
Mortality	2 (3.3)	1 (5.3)	1 (2.4)	0.530
Re-intervention related to device	14 (23.0)	13 (68.4)	1 (2.4)	**<0.001**
Intended valve performance	45 (73.8)	5 (26.3)	40 (95.2)	**<0.001**
MG < 20 mm Hg and PV < 3 m/s	60 (98.4)	18 (94.7)	42 (100)	0.311
No moderate or severe AR	45 (73.8)	5 (26.3)	40 (95.2)	**<0.001**
Early safety (at 30 days)	31 (50.8)	4 (21.1)	27 (64.3)	**0.002**
All-cause mortality	2 (3.3)	1 (5.3)	1 (2.4)	0.530
Stroke	2 (3.3)	0	2 (4.8)	1.000
Major bleeding	6 (9.8)	3 (15.8)	3 (7.1)	0.364
Access or cardiac complication	2 (3.3)	1 (5.3)	1 (2.4)	0.530
Acute kidney injury	0	0	0	NA
Moderate or severe AR	16 (26.2)	14 (73.7)	2 (4.8)	**<0.001**
New PPM	12 (19.7)	3 (15.8)	9 (21.4)	0.602
Re-intervention related to device	14 (23.0)	13 (68.4)	1 (2.4)	**<0.001**
Other 30-day clinical outcomes				
MG, mmHg, at 30-day	8.0 ± 4.0	7.8 ± 3.7	8.1 ± 4.1	0.807
PV, cm/s, at 30-day	192.8 ± 41.0	199.9 ± 44.0	189.7 ± 39.7	0.404
≥mild perivalvular leakage	29 (47.5)	19 (100)	10 (23.8)	**<0.001**
Impaired AML movement				**<0.001**
Significant impaired	14 (23.0)	10 (52.6)	4 (9.5)	
Not impaired	25 (41.0)	1 (5.3)	24 (57.1)	
Uncertain/Unkown	22 (36.1)	8 (42.1)	14 (33.3)	
NYHA class III/IV at 30 days	8 (13.1)	6 (31.6)	2 (4.8)	**0.006**
Re-hospitalization due to HF	4 (6.6)	4 (21.1)	0	**0.002**
All cause re-hospitalization	5 (8.2)	4 (21.1)	1 (2.4)	**0.018**

Data are presented as mean ± standard deviation or n (%).
NA, not applicable; MG, mean gradient; PV, peak velocity; PPM, permanent pacemaker implantation; HF, heart failure; AML, anterior mitral leaflet; NYHA, New York Heart Association.
Bold values indicates $p < 0.05$.

class III/IV (p = 0.006) and incidence of rehospitalization due to heart failure (p = 0.002) or all-cause rehospitalization (p = 0.018) were higher in the severe malposition group. One patient was rehospitalized in the non-/mild malposition group due to major gastrointestinal bleeding.

Table 4 shows the results of the univariate analyses of predictors of severe prosthesis malposition. The diameter (OR = 1.23, p = 0.003) and height (OR = 1.24, p = 0.017) of STJ were positively correlated with severe prosthesis malposition, as well as STJCI (OR = 1.08, p = 0.032). Large prosthesis (L32 size)

implantation has the tendency of severe malposition regarding the marginal statistical significance (OR = 5.50, $p = 0.059$). As shown in **Figure 2B**, the AUC was 0.72 (95% CI 0.58–0.85, $p = 0.008$) for STJ diameter, 0.70 (95% CI 0.55–0.86, $p = 0.012$) for STJ height, and 0.69 (95% CI 0.55–0.83, $p = 0.017$) for STJCI, respectively. The cutoff value was 33.2 mm for STJ diameter (sensitivity was 84.2% and specificity was 65.8%), 24.1 mm (sensitivity was 57.9% and specificity was 87.8%) for STJ height, and 81.0% (sensitivity was 68.4% and specificity was 68.3%) for STJCI, respectively. The three factors correlated with each other significantly (correlation coefficient 0.42–0.88, all $p < 0.05$, **Supplementary Table 3**).

Discussion

In this study, we investigated how the anatomic factors affected TAVR procedure performance among patients with NAVR from four large volume centers in China. Our results showed that the incidence of severe prosthesis malposition/embolization was 32.3% (20/62) following TAVR with self-expandable Venus-A Valve among patients with NAVR, most (19/20) of whom were with downward migration in the ventricular direction. Furthermore, the STJ diameter > 33.2 mm, height > 24.1 mm, and STJCI > 81.0% could predict severe prosthesis malposition. Finally, severe prosthesis malposition was associated with worse early safety, as well as impaired AML movement, heart failure, and rehospitalization at a 30-day follow-up.

TABLE 4 Logistic regression analysis of predictors of severe valve malposition.

	Univariate logistic regression analysis		
Parameter	**OR**	**95% CI**	***P*-value**
Male gender (1 = yes, 0 = no)	3.098	0.879–10.913	0.078
Annulus perimeter, mm	1.040	0.963–1.123	0.318
Valve oversize ratio, %	1.040	0.953–1.135	0.380
Valve oversize ratio > 20% or <10% (1 = yes, 0 = no)	1.200	0.404–3.563	0.743
LVOT mean diameter, mm	1.025	0.868–1.210	0.769
LVOT perimeter/Annulus perimeter	0.198	0–495.052	0.685
STJ mean diameter, mm	1.234	1.039–1.467	**0.017**
STJ height, mm	1.237	1.039–1.473	**0.017**
STJCI, %	1.080	1.007–1.159	**0.032**
Ascending aorta diameter, mm	1.103	0.941–1.292	0.226
Ascending aorta diameter/STJ*100	0.942	0.880–1.007	0.081
Implanted prosthesis size			
L26 (Reference)			
L29	2.000	0.362–11.060	0.427
L32	5.500	0.939–32.205	0.059
Venus A plus Implication (1 = yes, 0 = no)	0.800	0.268–2.388	0.689

LVOT, left ventricular outflow tract; STJCI, sinotubular junction.
Bold values indicate $p < 0.05$.

To the best of our knowledge, this is the first report to explore anatomic risk factors of prosthesis malposition among patients with NAVR who received self-expandable TAVR. Previous studies reported a low incidence (∼3%) of prosthesis malposition among the aortic valve stenosis population (12–14), while it reached up to approximately 20% in patients with NAVR who underwent TAVR with self-expandable devices (2, 15). This proportion is close to our data, partially because these studies used morphologically similar CoreValve prostheses (Medtronic, Minneapolis, USA) (2, 15). Valve migration or embolization may occur upward in the aortic direction and downward in the ventricular direction (13, 15). De Backer et al. (2) found that among patients with NAVR who underwent TAVR with CoreValve and Evolut R prosthesis, 13 out of 40 sizing error cases occurred in the ventricular direction valve migration and 6 were up toward the aortic direction. In the current study, 95.0% (19/20) of severe prosthesis malpositions were toward the ventricular direction, and there was only one case of valve embolization toward the ascending aortic aorta. Consistent with our findings, Yin et al. (6) reported that the malposition rate of the CoreValve device in patients with pure NAVR was 62%, all of which were caused by too-low implantation. In another study involving Chinese patients with aortic stenosis who underwent TAVR with Venus-A Valve, all valve malpositions were toward the ventricular direction (9), which may be partly explained by greater radial force at the bottom section of the Venus A-valve that could enhance the downward pushing force during delivering the prosthesis (16). Another possible reason is that the operator deliberately selected a somewhat deeper position to avoid prosthesis embolization to the aorta (6). Nevertheless, in a patient with the upward valve migration, the AA and STJ were quite slender, and the strong interaction between the prosthesis crown and STJ/AA was deemed to generate the upward force, which ultimately led to upward skipping of the prosthesis valve. Given the contrasting anatomic features of aortic root among patients with upward and downward migration, there was only one case in the aortic direction group; therefore, only 19 patients with downward migration were included in the final analysis.

As the absence of calcification hinders prosthesis anchoring and increases the risk of valve migration, careful evaluation of the aortic root anatomy for selecting suitable patients is of great importance. It is generally believed that suitable candidates should not have too large an annulus. Also, at least a 15–20% device oversize ratio is recommended (6, 11, 17). In the present study, the mean diameter of the annulus was 24.6 mm and the oversize ratio was 17.4%, which certainly represented a "selected" patient population. In fact, more patients with severe NAVR were considered for TAVR but were turned down because of anatomy or other reasons (15). Yet, even in this selected population, the rate of severe prosthesis malposition remained at 32.3%. In particular, among those who received 32-mm valve

implantation, the rate was as high as 50.0% (9/18). Undeniably, a larger annulus could hardly provide enough supporting force to prevent the downward migration of the prosthesis. Based on our data, large prosthesis (32 mm) implantation has the tendency of severe malposition according to the marginal statistical significance in logistic regression (OR = 5.50, $p = 0.059$). Large cohort research could be performed to explore a threshold of annulus size for predicting severe malposition in the future. Moreover, the interaction of STJ and prosthesis crown could also provide force against downward valve migration, thus explaining why smaller STJCI and STJ diameter were associated with greater force to prevent ventricular migration, while too small STJCI might lead to upward valve migration in the context of the slender AA. To the best of our knowledge, this study first reported the ratio of STJ size and prosthesis crown (STJCI) related to prosthesis malposition. In view of the intrinsic correlation of STJ diameter, STJ height, and STJCI, we prefer to choose an index that combines valve size and STJ morphology, thus we further identified the best threshold value of STJCI > 81.0% as a predictor of severe prosthesis malposition. Because only the Venus-A Valve was used in this study, the predictive performance of these indicators should be further evaluated in different prosthesis heart valves. It is worth mentioning that in Li's study (9), a "conical LVOT" was associated with deep implantation, while we did not detect the difference in LVOT perimeter/annulus perimeter between the malposition and non-malposition group. It is possible that in the absence of an adequate anchor the prosthesis valve has a tendency to move down during releasing, and the upward force of STJ against valve migration was significantly stronger than that of LVOT in patients with pure NAVR; hence, the effect of LVOT was covered, especially in this small sample.

Surprisingly, we noticed that the new-generation Venus-A Plus application did not reduce the incidence of severe malposition (42.1 vs. 57.9%, $p = 0.785$), which is inconsistent with previous studies (2, 4, 6, 18). The reason remains speculative, while a possible explanation may be that the stronger radial force of Venus-A Valve enhanced the downward migration tendency, even after repositioning with a resheathable delivery system. Also, the self-expanding valve was "self-adaptive" to match the best position within the native aortic root that could provide the most appropriate force against ventricular direction migration. In a sense, the uselessness of resheathable Venus-A Plus to minimize malposition introduced more strict requirements for patient selection before making final treatment strategy decisions.

As for the clinical impact of prosthesis malposition, we found no significant difference in mortality, need for permanent pacemaker implantation, or other VARC-3 defined endpoint events between the two groups at 30-day follow-up, while the device success and early safety were significantly lower in the severe malposition group. Moreover, the rates of heart failure and rehospitalization (mainly driven by heart failure) were higher in the severe malposition group. Residual AR may be responsible for the worse heart function. Besides, too-deep prosthesis implantation could also impair adequate AML movement (52.6 vs. 9.5%, $p < 0.001$), thus resulting in worse hemodynamics and cardiac function (19, 20).

Study limitations

There are several limitations in the present study. First, given the relatively small sample and retrospective observational design, we must be cautious when drawing firm conclusions due to unmeasured confounders. Second, we only discussed anatomic risk factors when implanting the Venus-A Valve in this study, while various other reasons may be responsible for prosthesis malposition, such as improper post-dilation, sizing errors, and fast-rate pacing failures. Other limitations are patient selection bias, short follow-up duration, and no independent core laboratory or adjudication of clinical events. Consequently, further studies aiming to explore more predictors on a larger scale using different types of prosthesis valves are needed to verify reported results.

Conclusion

Our data suggest that larger and higher STJ and greater STJ to valve crown diameter ratio (STJCI > 81.0%) are potential predictors of severe prosthesis malposition in patients with NAVR who underwent TAVR with Venus-A prosthesis valve.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of The Second Affiliated Hospital of Army Military Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YW and SY contributed equally to study design, data acquisition, statistical analysis, and drafted the manuscript. JJ approved the submission of the final version. DQ, JL, ZF, WC, XL, TL, YZ, and HX contributed greatly to data collection and

the revision of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by the Chongqing Talents Project (JJ) and Young Doctor Incubation Program of Xinqiao Hospital (2022YQB094).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1002071/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 20 December 2022
DOI 10.3389/fcvm.2022.977006

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 24 June 2022
ACCEPTED 18 November 2022
PUBLISHED 20 December 2022

CITATION
Kachel M, Buszman PP, Milewski KP, Michalak M, Domaradzki W, Pruski M Jr, Sobota M, Fernandez C, Konopko M, Nożyński J, Kaźmierczak P, Włodarczyk J, Stojko M, Bochenek A and Buszman PE (2022) Temporal, biomechanical evaluation of a novel, transcatheter polymeric aortic valve in ovine aortic banding model. *Front. Cardiovasc. Med.* 9:977006. doi: 10.3389/fcvm.2022.977006

Temporal, biomechanical evaluation of a novel, transcatheter polymeric aortic valve in ovine aortic banding model

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Objectives: The aim of the study is to evaluate the functionality, durability, and temporal biocompatibility of a novel, balloon-expandable polymeric transcatheter heart valve (ATHV) system (InFlow, CardValve Consortium, Poland). Along with expanding TAVI indications, the demand for new transcatheter valves is increasing.

Methods: A surgical ascending aortic banding model was created in 20 sheep. Two weeks later, 16 sheep were implanted with ATHV systems (15–16F). Three animals were euthanized after a 30-day follow-up, four animals after a 90-day follow-up, and six animals after a 180-day follow-up. A follow-up transthoracic echocardiography (TTE) was performed.

Results: There was one procedure-related (6,25%) and two model-related deaths (12,5%; banding site calcification with subsequent infection originating externally from banding). TTE revealed the flow gradients (max/average) of 30,75/17,91; 32,57/19,21; and 21,34/10,63 mmHg at 30, 90, and 180 days, respectively. There were two cases of low-degree regurgitation after 180 days with no perivalvular leak observed. Histopathological analysis showed no valve degeneration at terminal follow-up with optimal healing. Small thrombi were present at the aortic wall adjacent to the base of the leaflets, and between the aortic wall and the stent in most of the valves; however, leaflets remained free from thrombi in all cases. Scanty calcifications of leaflets were reported in three animals evaluated 180 days after implantation.

10.3389/fcvm.2022.977006

Conclusion: This preclinical study in the aortic banding model showed good hemodynamic performance, durability, and biocompatibility of the novel ATHV. Furthermore, regulatory studies with longer follow-ups are warranted.

KEYWORDS

aortic valve stenosis, transcatheter aortic valve replacement (TAVR), heart valve prosthesis, polymeric valve, preclinical "*in vivo*" study

Introduction

Transcatheter aortic valve implantation (TAVI) marked a beginning of a new era in aortic valve disease treatment (1). TAVI has come a long way from the last call technique for inoperable patients, through an equal measure in high-risk patients, to recent expansion of indications, becoming a favorable option in elderly patients and confirming its non-inferiority in moderate and low-risk patient subsets (2, 3). However, of note, the long-term results in these groups are still missing. This new reality creates more challenges for new TAVI technologies and increases the pressure to further improve outcomes and overcome current limitations of TAVI, including paravalvular leaks, vascular complications, and long-term durability by introducing novel solutions and upgrades to currently available technologies. However, the main limitation, the cost of TAVI combined with its accessibility, is yet to be answered. Currently, approximately 180,000 patients can be considered potential TAVI candidates in the European Union and Northern America annually. Even highly developed and wealthy countries struggle to cover the need. This situation might be further aggravated, as the potential future expansion of indications to lower-risk groups is expected to increase demand for transcatheter valves up to 270 000 (4).

Nowadays, long-term evaluation in the preclinical setting of new THV technologies has been limited to acute feasibility studies and very limited to long-term evaluation due to a lack of calcifications and anchoring mechanisms in the healthy animal aortic valve. The only available model of THV implantation in descending aorta with the creation of aortic valve insufficiency was related to high mortality (5).

Most recently, we introduced a novel ovine model of aortic banding and TAVI, which allows for stable valve anchoring and long-term evaluation, including mechanical performance and biological response (6).

Abbreviations: ATHV, artificial transcatheter heart valve; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; ACT, activated clotting time; AS, aortic stenosis; LCC, left coronary cusp; RCC, right coronary cusp; NCC, non-coronary cusp; SVD, structural valve deterioration.

Bearing in mind the above-mentioned limitations, an innovative polymeric ATHV would outrun the biological counterpart in terms of durability and become more affordable and thus attainable. Herein, we present the results of a short-, mid-, and long-term evaluation of mechanical performance, durability, and biological response of a low-profile, polymeric THV (InFlow, CardValve consortium) based on the novel ovine model of aortic banding.

Materials and methods

Study design

The study protocol has been accepted by the local ethics committee for animal research, Decision No. 150/2016. All animals received the standard of care outlined in the study protocol and in accordance with the act of animal welfare and the "Guide for the Care and Use of Laboratory Animals" (7). Slight ascending aorta stenosis (AS) was created by fixing a surgical band around the aorta. After AS creation, animals were allowed a recovery period of at least 10 days. Subsequently, an InFlow ^{TM} transcatheter heart valve was implanted *via* TAVI techniques and a carotid artery approach. Follow-up echocardiography and complete blood works were performed at 30-, 90-, and 180-day follow-ups. Twenty blackface crossbreed sheep, approximately 2 years old, weighing 40 to 80 kg were included. Animals received an acclimation period of at least 21 days.

Study device

An InFlow^{TM} Artificial Transcatheter Heart Valve (ATHV) comprises a proprietary balloon-expandable, radiopaque, cobalt–chrome alloy frame, and a tri-leaflet polymeric valve connected with a cuff, made from a combination of different polymers (**Figures 1**, **2**). The copolymers of ChronoFlex Ar 22% (polyurethane-co-carbonate) (PU) and ChronoSil AL80A 5% (polycarbonate-co-silicone) (PUS) manufactured by AdvanSource (Wilmington, MA, USA) were used for heart

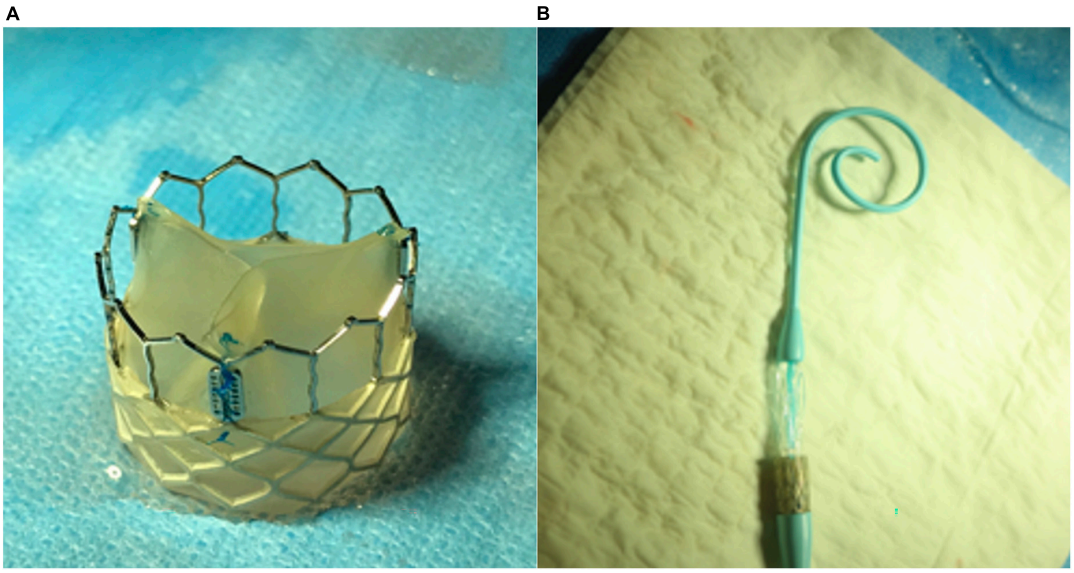

FIGURE 1
(A) Polymeric InFlow artificial heart valve prototype—lateral view and **(B)** InFlow valve crimped on the balloon.

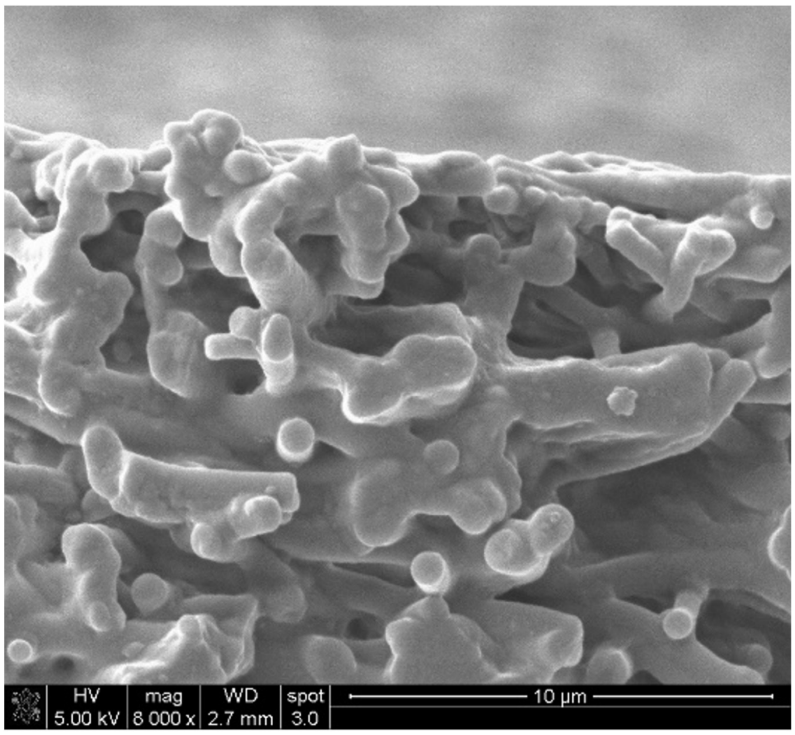

FIGURE 2
A cross-section of a single leaflet was imaged using scanning electron microscopy (SEM) (mag. 8000x).

valve leaflets preparation. Using the electrospinning unit model NEW-BM (NaBond), these polymers were processed to the multilayer fibrous and semi-fibrous layers mounted on stents. Polymeric materials are attached to the metal frame using the electrospinning method enabling the limited use of standard suturing and thus reducing the possible damage done to the material and plausible subsequent complications. The ATHV is a terminally sterilized (radiation), single-use device, indicated

for relief of AS in patients with symptomatic heart diseases due to severe native calcified AS in patients at high or greater risk for open surgical valve replacement. For the study purpose, the InFlow^{TM} transcatheter heart valve was available in diameter equaling 23 mm and used with a dedicated delivery system including a pig-tail catheter and a dog-bone-shaped balloon for better control and landing accuracy. After proper crimping, the outer diameter of the device is 15–16F. Devices are stored in a glutaraldehyde solution. This transcatheter artificial heart valve and delivery system are covered with five international patents issued (no. P.426429, P.426432, P.426433, P.426434, and P.426463).

The study device was previously subjected to bench testing. Six artificial heart valves were tested using BDC Laboratories VDT-3600i pump, dedicated equipment for the durability test. According to ISO 5840, the temperature of the test was 36, 6°C. Waveform, frequency, and stroke conditions (4,5 ml–10,46 ml) were all adjusted in the same manner for all tested prototypes. To meet preclinical study purposes and 6-month follow-up, all valves passed 40 million cycles. Further tests are ongoing and warranted.

Aortic banding model

Sheep were anesthetized using a combination of ketamine 10 mg/kg IM/IV + xylazine 0.05–0.2 mg/kg IM + atropine 0.1–0.2 mg/kg IM. Propofol 2–4 mg/kg IV was administered to facilitate intubation. Following successful intubation, sheep were placed in the right lateral recumbency. Aortic banding was achieved by means of a minimally invasive left-side thoracotomy. An incision was made between the fourth and fifth intercostal space, and the ascending aorta was exposed. The target site for the banding implantation was mid-way from the native aortic valve and the common carotid trunk. With the help of sizer kits, the Dacron sleeve was measured, and the diameter of the aorta decreased between 2 and 4 mm. A surgical stainless-steel wire was sutured in the mid-line of the banding tissue to allow identification under fluoroscopy. After the procedure completion, the wound was closed, and the sheep moved to post-op recovery.

Transcatheter aortic valve implantation

Two weeks after the aortic bending, TAVI procedures were performed starting with anesthesia using the same procedures outlined for the banding. Sheep were placed in dorsal recumbency with the legs stretched caudally. The left carotid artery was surgically exposed and prepared, as close to the thoracic inlet as possible. A 6fr arterial sheath was placed in the carotid artery. A J wire 0,035" was advanced through the arterial sheath in the left ventricle, and a 5fr pig-tail catheter with 10 mm markers was advanced over the J wire. Ventriculography and aortography along with invasive pressure evaluation were performed to assess the banding site and measure the target implantation site diameter. The pig-tail catheter markers were used to calibrate the distance. After all the measurements were finished, the pig-tail catheter and the J wire were removed. The ATHV valve was crimped on a balloon matching the valve size (a 23-mm balloon for a 23-mm valve) and the natural direction of blood flow from the heart (aortic position). The 6fr arterial sheath was removed and replaced with an arterial sheath bigger than the measured profile of the valve (usually 18–22F). Once the large arterial sheath was inserted, heparin was administered at a dose of 300 IU/kg (3 mg/kg), IV, to achieve an activated clotting time (ACT) over 300 s. A super stiff Amplatz wire was advanced through the arterial sheath into the left ventricle. The valve crimped on the balloon was advanced over the Amplatz wire and through the arterial sheath to the aortic banding. The valve was expanded with the help of a 50-ml syringe filled with a 70:30 ratio of saline and contrast. Once the implantation was complete, the Amplatz wire and the balloon were removed. Post-implantation control ventriculography and aortography were performed as outlined earlier without changing the arterial sheath. The arterial sheath was removed, the carotid artery ligated, and the tissues and skin sutured in three layers. The sheep were then transferred to post-op recovery.

Echocardiography

Transthoracic echocardiography (TTE) was performed at 30, 90, and 180-day follow-ups. Transoesophageal echocardiography (TEE) was performed at 180 days as a complement to TTE, while under anesthesia. All routine parameters were evaluated (left ventricle end-diastolic volume, aortic diameter, left ventricle end-systolic diameter, ejection fraction, cuspids' separation, among others), and valve functionality, deployment, and any other visual findings were documented in the echo reports.

Pathological evaluation

The independent, pathology core lab (Silesian Centre for Heart Diseases, Poland) received fixed, explanted hearts and ascending aorta for histopathology. Hearts were trimmed and the segment of tissue containing the explants was excised, grossly examined, and radiographed. Aortic roots with valve implants (AV) were dehydrated in a graded series of ethanol, cleared in xylene, and infiltrated and embedded in SPURR plastic resin. After polymerization, the device with the frame was sectioned radially two times to capture each cusp (LCC = left coronary cusp; RCC = right coronary cusp; NCC = non-coronary cusp) and stained with hematoxylin and eosin (H&E).

In addition, the portion of the plastic block containing each of the three valve cusps (radial planes) was separated from the frame, cut serially two times (thin sections), and stained with Movat's pentachrome (MP) and Von Kossa (VK). The block remnants were reassembled with appropriate spacers and cut crosswise (transverse plane) at two levels. All ground sections were ground and micro-polished to an optical finish using the Exakt cutting/grinding system. Resulting sections were stained with H&E. Trackable gross lesions submitted separately were processed, embedded in paraffin or SPURR resin as appropriate, sectioned, and stained with H&E and/or Masson's trichrome (MT) (paraffin only). All resulting slides were evaluated via light microscopy by the study pathologist. In the event of identifying problems with valve function, the harvested tissues were passed to the histopathology analysis. If no correlation between reported death and valve function was revealed, further analysis was abandoned.

Statistics

This is a prospective, observational, and experimental study; therefore, no study hypothesis was made. Data are presented as medians (25th–75th percentile). To test for temporal differences in echocardiographic parameters, a repeated measures ANOVA has been performed followed by a pairwise comparison with the Bonferroni modified paired *t*-test. A *p*-value of <0.05 was considered statistically significant. MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium[1]) was used for analysis.

Results

The study flowchart is shown in **Figure 3**. All 20 sheep survived the banding procedure, from which 16 were preselected according to banding location and size for the testing of ATHV. There was one procedure-related death within 7 days after TAVR. Three designated animals were euthanized after a 30-day follow-up, four animals after a 90-day follow-up, and six animals after a 180-day follow-up. There were additional two deaths during the follow-up (detailed description later). The detailed cause explanation is shown in **Table 1**.

Echocardiographic results

Echocardiographic analyses were conducted according to the protocol at respective time points of 30, 90, and 180 days. Representative images are shown in **Figure 4**. At the time

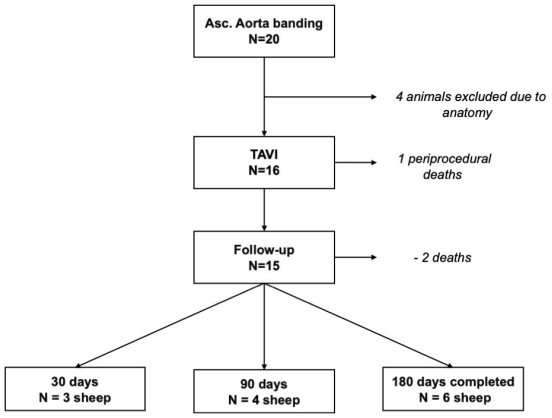

FIGURE 3
Study flowchart.

TABLE 1 Causes of premature death.

Cause of death	Number of animals
Death in post-operational care (inability to resume respiratory function after anesthesia) – day 0	1
Calcification and vegetation in banding site – day 18 and 62	2

of terminal control, TTE was utilized complementary to the standard transthoracic echo after the previous induction of anesthesia (at the time point of 30 and 90 days, only transthoracic echo was performed). Examination showed good hemodynamic results for all the valves at respective time points. Maximal and mean transvalvular gradients were typical for percutaneously implanted valves indicating proper valve deployment. At follow-up in TTE, the maximum and average flow gradients [median (IQR) – presented as max/average] for 30-, 90-, and 180-day observation were 26,4(18,9–34,7)/14(12,1–20,1); 30,7(23–35,5)/16,6(13,9–22,4); and 22,2(19,3–23,7)/11,4(9,3–12,1) mmHg, respectively. Serial measurements performed in five animals (one was disqualified because of a lack of available results at 30 days due to difficult examination conditions) showed that the valve hemodynamic was stable through the whole observation period (**Figure 5**). Valvular regurgitation was rare with no episodes of severe valvular regurgitation; however, one case of moderate-grade valvular regurgitation was reported. No perivalvular leaks were reported. Detailed ECHO parameters are shown in **Table 2**.

Histopathology results

Histopathological analyses showed good positioning of the valve in all cases. In each case, X-ray studies at lateral and craniocaudal projections showed a lack of stent deformations (**Figure 6**).

1 http://www.medcalc.org

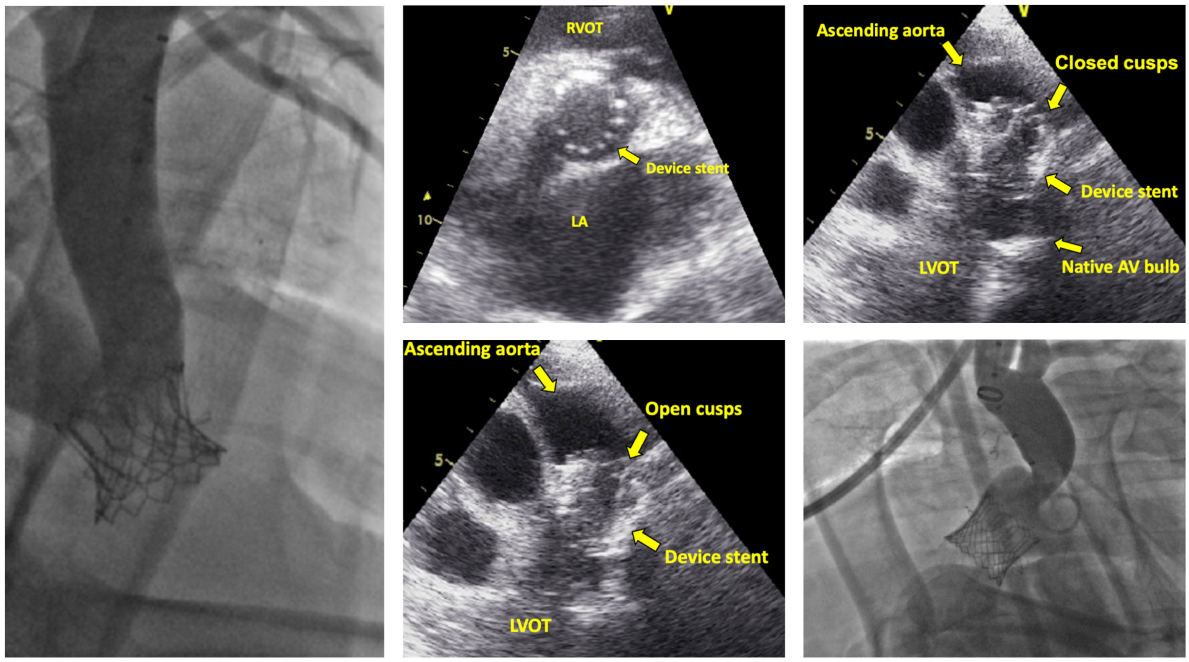

FIGURE 4
Fluoroscopy and echocardiography images of the implanted prosthesis.

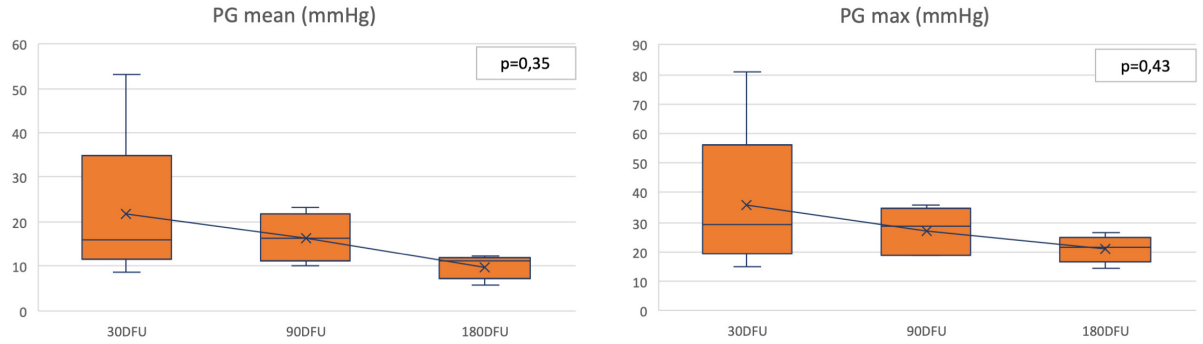

FIGURE 5
Pressure gradients—serial measurements. DFU: days follow-up; PG: pressure gradient.

In the 30 days group (three cases), the gross inspection showed elastic leaflets, without tears, fenestrations, or other pathologies. Metallic stent elements and the base of the leaflets were covered by a thin layer of neointima. The leaflets were free of thrombi. Only between the base of the leaflets and the aortic wall, a thin layer of clots was formed. X-ray analysis showed no calcifications of leaflets in all cases, free margins, and commissures. Pannus was well recognized at the lower part of the implanted prosthesis as the immature tissue with an abundance of extracellular matrix and hemosiderin deposits.

Similarly, in the 90-day group (four cases), the analysis showed thin elastic leaflets with no tears, fenestrations, or focal thickenings. A thin thrombus was visible on the ventricular surface in three animals, presenting as surface deposits, well delineated, and firmly attached to the base of the leaflets and adjacent stent elements contacting the aortic wall. X-ray observations indicated only one case of focal punctiform calcifications in place of commissures. Generally, stent struts were covered by immature and early matured neointima at above 75% of their surface. Sutures were also covered partially with neointima. In all cases, the absence of inflammatory infiltrations was obvious. Translucent leaflets showed no other foreign elements. It should be pointed out that the penetration of cellular elements into the polymer was never reported. Fibrous pannus was present only at the bases of leaflets. Histology of

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TABLE 2 Echocardiography findings.

	30 DFU		90 DFU		180 DFU	
Doppler measurements	**Median**	**Q1–Q3**	**Median**	**Q1–Q3**	**Median**	**Q1–Q3**
V max (m/s)	2,6	2,2–3,0	2,8	2,4–3,0	2,4	2,2–2,4
PG max (mmHg)	26,4	18,9–34,7	30,7	23,0–35,5	22,2	19,3–23,7
PG mean (mmHg)	14,0	12,1–20,1	16,6	13,9–22,4	11,4	9,3–12,1
ECHO findings	***n* = 15**	**%**	***n* = 10**	**%**	***n* = 6**	**%**
Mild regurgitation	2	13,33	2	20	2	33,33
Moderate regurgitation	1	6,66	1	10	0	0
Possible calcification	2	13,33	1	10	1	16,6
Present calcification	2	13,33	0	0	1	16,6
Probable vegetation	0	0	0	0	1	16,6
Mean pressure gradient > 30 mmHg	1	7,14	1	10,0	0	0

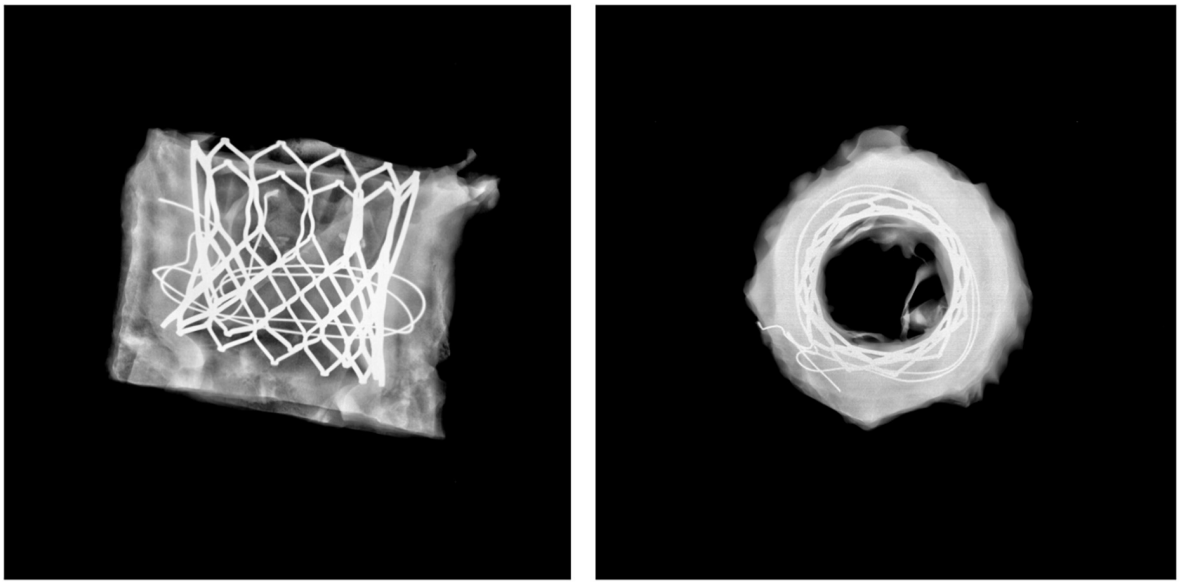

FIGURE 6
X-ray image. No deformations or damages in stent geometry.

leaflets showed linear and focal cellular covering in three cases. In one case, thin fibrin deposits were present.

The 180-day group consisted of six cases. In one case, there was firm vegetation with outflow stenosis, but no thrombi. Small thrombi were found at the aortic wall adjacent to the base of the leaflets and between the aortic wall and the stent in two cases. The leaflets were free from thrombi. The surface of the leaflets was elastic and smooth, without tears or fenestrations. Neointima was present covering only the stent and the sutures (leaflets were left uncovered). Punctiform calcifications of leaflets and commissures were present in three cases subjected to the analysis. Histopathology of leaflets showed a translucent structure of the polymer, focally with cells adjacent to the leaflet surface (Figure 7). No inflammation inside the polymer structure was reported.

The analysis of two animals that died prematurely on days 18 and 62 has shown banding site calcification with subsequent infection originating externally from the aortic banding. A discussion of this is provided below.

Discussion

The preclinical assessment of the InFlow polymeric THV demonstrated the feasibility of implantation, functionality, durability, and biocompatibility of a novel prosthesis both

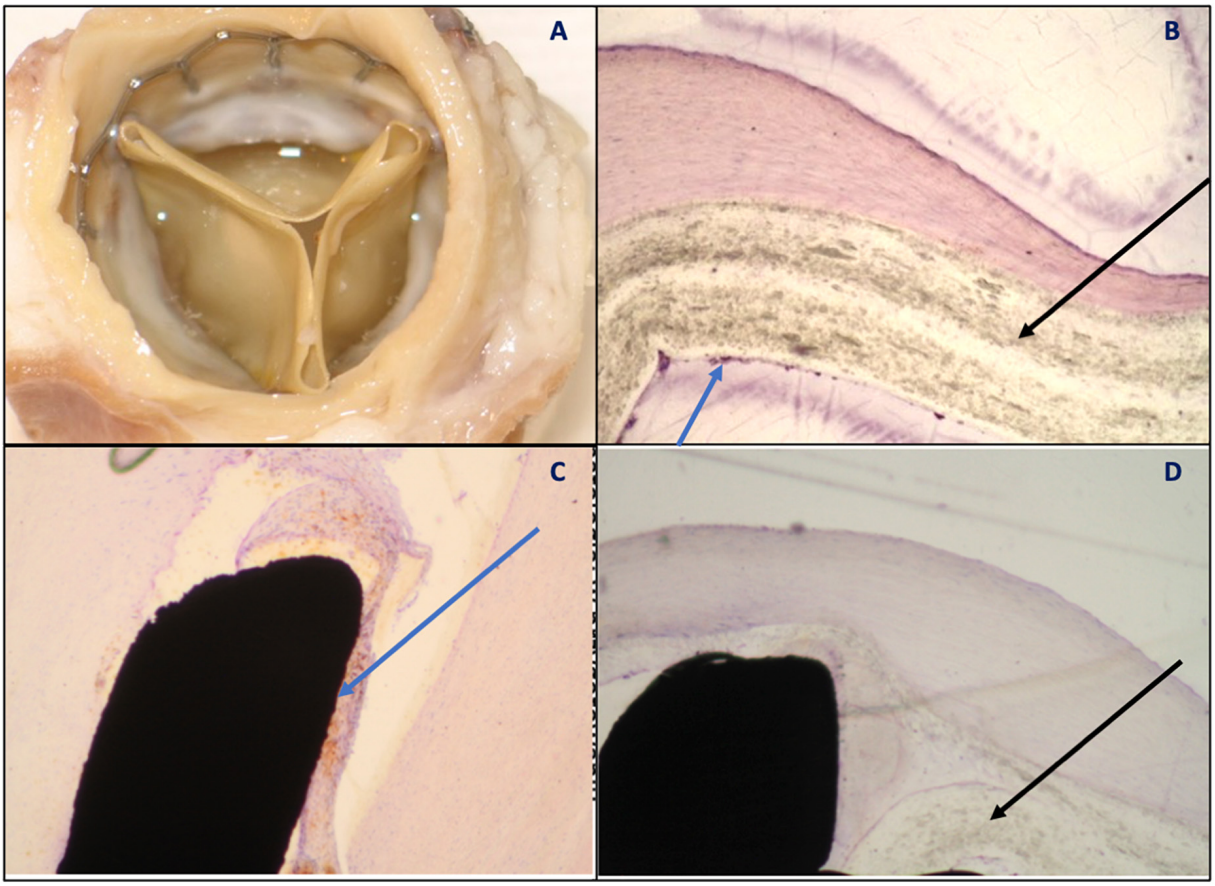

FIGURE 7
(A) Vascular surface—thin cusps, unchanged, metal frame covered with relatively thick neointimal tissue indicating pannus formation. No thrombus visible; **(B)** polymer (black arrow) partially covered with neointima (blue arrow) encompassing single cells; **(C)** stent-tissue contact zone (blue arrow) with no signs of inflammation; and **(D)** polymer (black arrow) with no signs of resorption or penetration of cellular elements into the polymer.

in short- and mid-term observation in an ovine model of aortic banding and THV implantation. The utilization of this innovative model resulted in a repeatable anchoring process that allowed for the successful implantation of the tested valves as well as temporal evaluation for up to 6 months. The mortality rate at follow-up was minor, and the reasons for death were not device-related, but procedure- or model-related. At terminal follow-up, histopathological analyses confirmed good positioning of the prostheses in all cases, good biocompatibility, and with early endothelialization.

The echocardiographic evaluation showed good hemodynamic results in respective time points with transvalvular gradients and velocities within normal limits. This is significant, given the fact that, as stated in the histopathology report, the presence of neointimal pannus covering the stent surface and leaflets to varying degrees (as seen in the 30- and 90-days follow-up) could have also influenced the gradient by inducing relative vessel stenosis and slightly impairing leaflet mobility. The pannus tissue showed maturation increased with time but in all cases, the pannus never formed a stenotic "collar" visible in implanted orthotopically valves. This phenomenon was reported in other studies of the biological valve utilizing surgical aortic banding and thus is considered model-related (8). Importantly, no severe cases of prosthesis insufficiency were reported, with only two cases of moderate regurgitation. Good anchoring capabilities of the landing zone and sustainable radial force generated by the metal stent frame resulted in proper sealing, and no perivalvular leakage was observed throughout the study. In addition, the innovative polymeric material was developed and used to create the leaflets, and the cuff of the prosthesis was proved to be biocompatible and non-thrombogenic with neointima covering the majority of the surface of the stent from 90 days on as seen in the pathology.

In our study, we reported two animals that died during the observation period. Every single case was thoroughly evaluated in search of a possible explanation and any potential prosthesis malfunction that could influence the outcome. The above-mentioned animals were found dead after 18 and 62 days,

respectively. The post-mortem analysis unveiled that in both cases the possible cause was a heavy calcification of the banding region with subsequent infection and vegetation on the prosthesis that immobilized the valve and resulted in heavy cardiac insufficiency (one of the animals was found with hydrothorax). Interestingly, as seen in the histopathology, the calcification process originated externally from the prosthesis and then penetrated the valve itself. Presumably, this can be attributed to the potential infection of the banding site that developed after the initial surgical procedure and turned into a chronic inflammatory process that resulted in calcium deposition, hindered hemodynamics, and vegetation that led to valve failure. Independent pathological analysis qualified this event as banding model-related. Our reports of harvested and analyzed bandings without TAVI implantation show that calcification and osseous metaplastic processes are occurring in this region, supporting our above rationale. Apart from these, no other adverse events were reported.

The above-described mortality rate of the polymeric InFlow valve equaled 6,25% in the periprocedural period (1 out of 16) and 13,3% in the observation period (2 out of 15), respectively. The mortality is similar to our most recent study utilizing biological THV in the banding model (8). However, these numbers are significantly lower when compared to previous studies of THV technologies utilizing either the descending aorta model or implantation in the native position (5, 9, 10). This is mostly due to improvements in the animal model design, which resulted in improved valve anchoring, no valve dislocation, and, as a result, improved survival.

Another important aspect is valve durability and biological response. Structural valve deterioration (SVD) is a gradual process defined by permanent intrinsic changes in the valve (calcification, pannus, and leaflet failure) leading to degeneration and/or dysfunction, which in turn may result in valvular stenosis or intra-prosthetic regurgitation (11). Although SVD is well documented in surgical valves (12, 13), TAVI studies such as PARTNER 1 with 5-year follow-up failed to demonstrate the importance of this phenomenon (around 0,2% deteriorated prostheses requiring management) (14). Despite reassuring results in the midterm, the lack of longer observations available constitutes a serious limitation as SVD events were hardly reported in transcatheter heart valves in the first 10 years after the initial procedure due to insufficient follow-up (15). Therefore, obtaining convincing data about the durability of current THV already at the experimental stage is of high importance. At long-term follow-up in the current preclinical study of the InFlow ATHV, there were two of 15 (13,3%) degenerated valves, but in pathology, the calcifications originated from the banding and were qualified as model-related. In a study in which no THV was implanted, the banding site itself created calcification and ossification originating from the graft (**Supplementary Figure 1**) (6). Therefore, to the best of our knowledge, no device-related SVDs were identified in this study. The evidence from the preclinical studies of currently available THV is very limited. The currently evaluated ATHV InFlow system shows similar healing with no degeneration at the comparable period to biological balloon-expandable THV counterparts (5, 8–10).

Limitations

The presented study includes several limitations that have to be considered: First, although the aortic model banding model was created, the included animals were young and healthy, with no calcific native valve stenosis.

Finally, as mentioned in the methodology section, the prostheses were implanted in the ascending aorta region, pre-prepared with the banding procedure. Such a scenario did not require the removal of the native aortic apparatus, and thus a potential bias attributed to the proper function of a native valve and different hemodynamics could be perceived.

Conclusion

The study showed a proper hemodynamic performance and acceptable biocompatibility of the novel artificial polymeric InFlow ATHV, similar to biological counterparts, as evaluated in the same follow-up in the ovine banding model. Given the presence of micro-calcifications and microthrombi on several valves, a finding was also reported in other preclinical studies including biological valves (8). Further studies with longer follow-ups are warranted. The presented prosthesis may be a viable alternative to the currently used biological technologies and add up to the widespread utilization of TAVR procedures and long-term durability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by Local Ethics Comittee in Katowice.

Author contributions

KM, AB, PK, MM, and PEB were responsible for planning the whole study. WD, MP, CF, and MKo were responsible

for conducting procedures of creating aortic banding model and transcatheter aortic valve implantation. MS and JN were liable for reporting the work described in the article. MKa and PPB were being responsible for the overall content as guarantors and they took part in planning, conducting, and reporting results of the study. All authors contributed to the article and approved the submitted version.

Funding

This study was funded with the scientific grant from the National Centre for Research and Development – STRATEGMED1/233166/6/NCBR/2014.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.977006/full#supplementary-material

SUPPLEMENTARY FIGURE 1
(A) Visible growths from the heart or vessel wall, extending over the stent, including the cusps and narrowing the opening. **(B)** Visible calcifications with formation of concretions near the edges of free cusps. **(C)** Radiological magnitude of the concretions reveals a trabecular fibrous structure presumably associated with the tissues of the annulus.

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 21 April 2023
DOI 10.3389/fcvm.2023.1035736

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 03 September 2022
ACCEPTED 27 March 2023
PUBLISHED 21 April 2023

CITATION
Kure Y, Okai T, Izumiya Y, Yoshida H, Mizutani K, Yamaguchi T, Ogawa M, Shibata A, Ito A, Takahashi Y, Shibata T and Fukuda D (2023) Impact of cystatin C-derived glomerular filtration rate in patients undergoing transcatheter aortic valve implantation. Front. Cardiovasc. Med. 10:1035736. doi: 10.3389/fcvm.2023.1035736

Impact of cystatin C-derived glomerular filtration rate in patients undergoing transcatheter aortic valve implantation

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Background: Chronic kidney disease (CKD) impacts prognosis in patients undergoing transcatheter aortic valve implantation (TAVI). While estimated glomerular filtration rate (eGFR) calculated from serum creatinine [eGFR (creatinine)] is affected by body muscle mass which reflects frailty, eGFR calculated from serum cystatin C [eGFR (cystatin C)] is independent of body composition, resulting in better renal function assessment.
Methods: This study included 390 consecutive patients with symptomatic severe aortic stenosis (AS) who underwent TAVI, and measured cystatin C-based eGFR at discharge. Patients were divided into two groups, with or without CKD estimated with eGFR (cystatin C). The primary endpoint of this study was the 3-year all-cause mortality after TAVI.
Results: The median patient age was 84 years, and 32.8% patients were men. Multivariate Cox regression analysis indicated that eGFR (cystatin C), diabetes mellitus, and liver disease were independently associated with 3-year all-cause mortality. In the receiver-operating characteristic (ROC) curve, the predictive value of eGFR (cystatin C) was significantly higher than that of eGFR (creatinine). Furthermore, Kaplan–Meier estimates revealed that 3-year all-cause mortality was higher in the CKD (cystatin C) group than that in the non-CKD (cystatin C) group with log-rank $p = 0.009$. In contrast, there was no significant difference between the CKD (creatinine) and non-CKD (creatinine) groups with log-rank $p = 0.94$.
Conclusions: eGFR (cystatin C) was associated with 3-year all-cause mortality in patients who underwent TAVI, and it was superior to eGFR (creatinine) as a prognostic biomarker.

KEYWORDS
TAVI, aortic stenosis, cystatin c, CKD, creatinine

1. Introduction

Aortic stenosis (AS) frequently causes left ventricular outflow impairment and is a common public health problem in an aging society (1, 2). Transcatheter aortic valve implantation (TAVI) has demonstrated comparable outcomes with surgical aortic valve replacement, and is the preferred treatment option for AS patients from all surgical risk

categories considered for a bioprosthetic valve (3–6). Although clinical outcomes after TAVI are generally good, there are some patients at a higher risk of short- and long-term mortality and morbidity. The remnant problem in treating AS is to investigate the relationship between potential risk to the patients and their long-term prognosis.

One of the prognostic factors impacting patients who undergo TAVI is CKD (7–9). Although the global index of renal function is eGFR (creatinine), serum creatinine can be affected by muscle mass and dietary protein intake, which decreases with increasing age (10). However, serum cystatin C level is another marker of renal function that is considered potentially superior to serum creatinine level for estimating renal function because it is produced constantly by most nucleated cells (11). Moreover, cystatin C production has been reported to be unaffected by age, gender, or muscle mass. Thus, renal function can be assessed more accurately using eGFR (cystatin C) than eGFR (creatinine) (12–15). However, the prognostic value of eGFR (cystatin C) has not been explored in patients who underwent TAVI. Therefore, this study aimed to evaluate the 3-year prognostic impact of CKD calculated from cystatin C after TAVI.

2. Methods

2.1. Study population

This single-center prospective observational study included 474 consecutive patients with symptomatic severe AS who underwent TAVI at Osaka Metropolitan University Hospital between January 2016 and December 2021 (**Figure 1**). The inclusion criteria were presence of symptomatic and degenerative AS, mean aortic valve pressure gradient (mAVPG) > 40 mmHg or jet velocity > 4.0 m/s, or aortic valve area (AVA) 1.0 cm^2 (or aortic valve area index < 0.6 cm^2/m^2), according to the guidelines for valvular heart disease by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (16). The indications for TAVI were determined based on the clinical consensus of a multidisciplinary team, including cardiac surgeons, interventional cardiologists, anesthesiologists, and imaging specialists. We excluded patients who died in the hospital due to peri-procedural complications. In addition, we excluded patients with active cancer because cancer may be an independent risk factor for death and patients without serum cystatin C data at the time of discharge. The protocol of this study was in accordance with the guidelines of the Declaration of Helsinki and was approved by our institutional ethics committee (approval number: 2021-064). All patients gave informed written consent for participating in the study.

2.2. TAVI procedure

We selected transfemoral approach as our first option and an alternative access (transapical, transaortic, transsubclavian) for patients with excessively narrow access routes or aortic arch atheroma. We performed TAVI in a hybrid operating room under general anesthesia, except for eight patients who

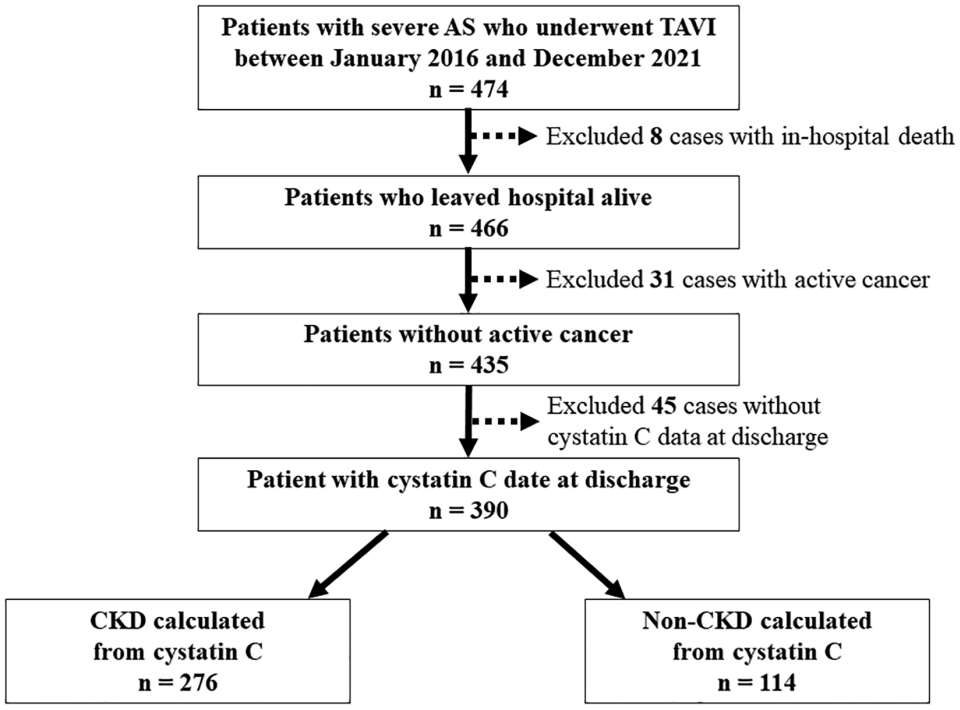

FIGURE 1
Flowchart of patient selection. AS, aortic stenosis; CKD, chronic kidney disease; TAVI, transcatheter aortic valve implantation.

underwent conscious sedation because of pulmonary dysfunction. Transcatheter heart valves were used either balloon-expandable (Edwards Sapien XT or Sapien 3 Transcatheter Heart Valve; Edwards Lifesciences, Irvine, CA, USA) or self-expandable (Medtronic classic CoreValve or CoreValve Evolut R/Pro/Pro+; Medtronic, Inc., Minneapolis, MN, USA). We chose Balloon-expandable valves as the first option, while self-expandable valves were reserved for patients with a narrow aortic annulus.

2.3. Data collection

All data were collected prospectively from patient records. Pre-procedural enhanced multi-slice computed tomography data were obtained to evaluate the annulus area, perimeter of the annulus, and diameter of the ST junction. The data were measured using the SYNAPSE VINCENT (Fujifilm, CO., Ltd, Japan). Blood test screens including serum creatinine and serum cystatin C were performed upon admission. The follow-up protocol in this study includes at discharge, 1 month, 3 months, 6 months, and every 6 months thereafter following TAVI. Patients who did not attend the regular follow-up visits were contacted by phone to confirm their survival. We measured serum creatinine and cystatin C in all patients at discharge and calculated eGFR (creatinine) and eGFR (cystatin C). The formula for calculating the eGFR is as follows: eGFR (creatinine) = $194 \times \text{Serum creatinine (mg/dl)}^{-1.094} \times \text{Age (year)}^{-0.287} \times 0.739$ (if female), eGFR (cystatin C) = $104 \times \text{Serum cystatin C (mg/dl)} \times 0.996^{\text{Age (year)}} \times 0.929$ (if female) −8 (17, 18). CKD was defined as eGFR < 60 ml/min/1.73 m^2, which was estimated from both serum creatinine and cystatin C (19). We divided the study population into two groups (CKD or non-CKD) calculated from serum creatinine and cystatin C, respectively. Other complications during TAVI, including the procedural, were evaluated according to the Valve Academic Research Consortium-3 criteria (20).

2.4. Study endpoint

The primary endpoint of this study was 3-year all-cause mortality after TAVI.

2.5. Statistical analysis

Categorical variables were expressed as summarized using means of counts and percentages, and continuous variables were expressed as summarized using medians and interquartile ranges (quartiles 1 to 3).Continuous and categorical variables between the two groups were compared with the Wilcoxon rank sum and chi-square tests, respectively. We evaluated the impact of eGFR (creatinine) and eGFR (cystatin C) on the endpoint using univariable and multivariable Cox regression analyses with 95% CI. To avoid the issue of multicollinearity, we used four models, one including eGFR (cystatin C) and the other including eGFR (creatinine). This multivariate model was built by selecting variables that satisfied the entry criterion of $p < 0.05$ and a 95% CI that exceeded 1 in the univariate analysis. The other two were multivariate models including eGFR (cystatin C) or eGFR (creatinine) and age and male sex. Three-year all-cause mortality was estimated using the Kaplan–Meier method, and the difference between the two groups (CKD calculated from serum creatinine and cystatin C, respectively) was evaluated using the log-rank test. The validity of the eGFR (creatinine) and eGFR (cystatin C) for estimating the 3-year all-cause mortality was evaluated using receiver-operating characteristic (ROC) curves, and area under the curve (AUC) of the eGFR (creatinine) and eGFR (cystatin C) were assessed using an ROC analysis tool based on DeLong's method (21). The statistical analyses were performed using the R software package (version 4.2.0; R Development Core Team, Vienna, Austria). The significance level of a statistical hypothesis testing was set at 0.05 and that of the alternative hypothesis was two-sided.

3. Results

3.1. Baseline patient characteristics, peri- and post-procedural findings

Among 474 possible TAVI candidates, we excluded 8 patients who died in the hospital and 31 patients with active cancer and 45 patients without serum cystatin C data at the time of discharge (**Figure 1**). Baseline patient characteristics are listed in **Table 1**. The median patient age was 84 years (interquartile range, 81–88 years), and 32.8% patients were men. The median society of thoracic surgeons (STS) risk and Clinical Frailty Scale scores were 6.46% (4.63–9.29%) and 4 (3–5), respectively. The median eGFR (cystatin C), eGFR (creatinine), and brain natriuretic peptide (BNP) on admission were 49.0 (36.1–60.1), 49.3 (39.5–63.5), and 180.3 (76.7–434.1), respectively. Evaluation of preoperative transthoracic echocardiograms showed that the median left ventricular ejection fraction (LVEF) was 61% (55%–65%) and the median aortic valve area with Doppler method was 0.66 cm^2/m^2 (0.57–0.73 cm^2/m^2), with a mAVPG of 45 mmHg (36–60 mmHg).

Table 2 displays information about the peri- and post-procedural outcomes. Among the total study population, 91.0% patients underwent transfemoral TAVI, while 67.9% underwent balloon-expandable TAVI. Peri-procedural complications included permanent pacemaker implantation, disabling stroke, acute kidney injury, and bleeding in 4.1%, 2.8%, 4.1% and 8.5% patients, respectively. Echocardiography revealed that post-procedural mAVPG and EOA were 9 mmHg and 1.56 cm^2/m^2, respectively.

3.2. The 3-year prognostic impact of CKD calculated from cystatin C after TAVI

The total study population was divided into two groups (CKD or non-CKD), which was estimated by eGFR (cystatin) at the time

TABLE 1 Baseline clinical characteristic of study patients.

Baseline Clinical Characteristic	Total $n = 390$	CKD calculated from cystatin C $n = 276$	Non-CKD calculated from cystatin C $n = 114$	p-value
Age, years	84 (81–88)	85 (82–88)	83 (80–87)	<0.001
Male sex, *n* (%)	127 (32.8)	85 (30.8)	43 (37.7)	0.19
BSA, m^2	1.43 (1.31–1.55)	1.42 (1.30–1.54)	1.47 (1.33–1.59)	0.08
NYHA Class III or IV, *n* (%)	85 (21.8)	71 (25.7)	14 (12.3)	0.003
STS score	6.46 (4.63–9.29)	7.16 (5.04–10.22)	5.42 (3.64–6.98)	<0.001
CFS	4 (3–5)	4 (3–5)	4 (3–4)	0.07
Comorbidity, *n* (%)				
Diabetes mellitus	100 (25.6)	70 (25.4)	30 (24.6)	0.90
Hypertension	348 (89.2)	248 (89.9)	100 (87.7)	0.59
Dyslipidemia	222 (56.9)	154 (55.8)	68 (59.6)	0.50
Coronary artery disease	110 (28.2)	80 (29.0)	30 (26.3)	0.62
Peripheral artery disease	65 (16.7)	55 (19.9)	10 (8.8)	0.006
Atrial fibrillation	67 (18.5)	60 (21.7)	12 (10.5)	0.009
Previous stroke	47 (12.1)	37 (13.4)	10 (8.8)	0.23
Liver disease	16 (4.1)	14 (5.1)	2 (1.8)	0.17
Pulmonary disease	36 (9.2)	31 (11.2)	5 (4.4)	0.03
Preprocedural laboratory data				
Albumin, g/dl	3.8 (3.5–4.1)	3.7 (3.4–4.0)	4.0 (3.7–4.2)	<0.001
eGFR from cystatin C, ml/min/1.73 m^2	49.0 (36.1–60.1)	40.0 (31.5–49.6)	68.1 (58.5–76.8)	<0.001
eGFR from creatinine, ml/min/1.73 m^2	49.3 (39.5–63.5)	44.0 (35.8–53.0)	66.4 (56.9–75.0)	<0.001
Natrium, mEq/L	140 (138–142)	141 (138–142)	140 (139–141)	0.03
Hemoglobin, g/dl	11.5 (10.3–12.6)	11.1 (10.0–12.4)	12.2 (10.8–13.0)	<0.001
BNP, pg/ml	180.3 (76.7–434.1)	234.1 (105.9–496.0)	99.9 (49.6–195.5)	<0.001
Preprocedural echocardiographic data				
LVEF, %	61 (55–65)	60 (54–65)	63 (60–65)	0.03
Peak AV velocity, m/s	4.5 (4.1–5.1)	4.4 (4.1–5.1)	4.6 (4.1–5.0)	0.63
Mean AVPG, mmHg	45 (36–60)	44 (35–61)	46 (39–59)	0.49
AVA, cm^2	0.66 (0.57–0.73)	0.65 (0.57–0.73)	0.66 (0.59–0.73)	0.53
Moderate or severe AR, *n* (%)	36 (9.2)	25 (9.1)	11 (9.6)	0.85
Moderate or severe MR, *n* (%)	44 (11.3)	35 (12.7)	9 (7.9)	0.22
Preprocedural CT data				
Annulus area, mm^2	393 (342–443)	392 (342–448)	394 (345–438)	0.78
Perimeter, mm	70.6 (66.1–75.3)	70.5 (66.0–75.6)	70.7 (66.5–74.4)	0.98

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75th percentiles).
BSA, body surface area; NYHA, New York heart association; STS, society of thoracic surgeons predictive risk of mortality; CFS, clinical frailty scale; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricle ejection fraction by modified simpson methods; AV, aortic valve; AVPG, aortic valve pressure gradient; AVA, aortic valve area; AR, aortic regurgitation; MR, mitral regurgitation; CT, computed tomography.

of discharge. There were significant differences in age, STS risk score, prevalence of New York Heart Association functional class III or IV, peripheral artery disease, atrial fibrillation, and pulmonary disease between the two groups. In pre-procedural investigations, plasma albumin level, plasma natrium level, plasma hemoglobin level, plasma BNP level, and LVEF showed significant differences between the two groups. Additionally, at the time of discharge, there were significant differences in the two groups regarding the duration of the procedure, life-threatening/major bleeding, BNP, and eGFR calculated from both cystatin C and creatinine (Tables 1, 2). The total number of all-cause deaths was 46 (non-CKD group 5, CKD group 41).

The results of the univariate Cox regression analysis for the association between cumulative mortality and clinical findings are presented in Table 3. The analysis indicated that eGFR (cystatin C), diabetes mellitus, liver disease, plasma albumin level on admission, and plasma BNP level at discharge were associated with 3-year all-cause mortality. Table 4 shows the multivariate Cox regression analysis for two models—model 1 includes eGFR (cystatin C) and model 2 includes eGFR (creatinine). In model 1, the multivariate Cox regression analysis indicated that eGFR (cystatin C) (HR, 0.972; 95% CI, 0.953–0.990; $p = 0.003$), diabetes mellitus (HR, 2.090; 95% CI, 1.149–3.811; $p = 0.02$), and liver disease (HR, 2.813; 95% CI, 1.089–7.266; $p = 0.03$) were independently associated with 3-year all-cause mortality. In contrast, model 2 showed that the 3-year all-cause mortality was not independently associated with eGFR (creatinine) (HR, 1.002; 95% CI, 0.985–1.019; $p = 0.82$); diabetes mellitus (HR, 1.954; 95% CI, 1.072–3.564; $p = 0.03$), liver disease (HR, 2.960; 95% CI, 1.142–7.764; $p = 0.03$), plasma albumin level on admission (HR, 0.398; 95% CI, 0.212–0.744; $p = 0.004$), and plasma BNP level at discharge (HR, 1.001; 95% CI, 1.000–1.001; $p = 0.02$) were independently associated. Figure 2 shows a comparison between the predictive value for the 3-year all-cause mortality for eGFR (cystatin C) and eGFR (creatinine) using a ROC curve, which demonstrated that the predictive value of eGFR (cystatin C) is

TABLE 2 Peri– and postprocedural outcome information.

Procedural and Outcome Information	Total $n = 390$	CKD calculated from cystatin C $n = 276$	Non-CKD calculated from cystatin C $n = 114$	p-value
Transfemoral, n (%)	355 (91.0)	250 (90.6)	105 (92.6)	0.70
SAPIEN XT, n (%)	18 (4.6)	13 (4.7)	5 (4.4)	1.0
SAPIEN 3, n (%)	247 (63.3)	175 (63.4)	72 (63.2)	1.0
Core valve, n (%)	3 (0.8)	3 (1.1)	0 (0.0)	0.56
Evolut R, n (%)	41 (10.5)	30 (10.9)	11 (9.6)	0.86
Evolut Pro/ Pro+, n (%)	81 (20.8)	55 (19.9)	26 (22.8)	0.58
Valve size, mm	26 (23–26)	26 (23–26)	26 (23–26)	0.74
Periprocedural variable				
Procedual time, min	55 (40–80)	60 (45–86)	50 (40–70)	0.004
Local anesthesia, n (%)	8 (2.1)	7 (2.5)	1 (0.9)	0.45
Contrast, ml	62 (54–76)	60 (53–73)	65 (54–78)	0.06
Periprocedural Complications, n (%)				
Coronary obstruction	8 (2.3)	6 (2.2)	3 (2.6)	0.72
Permanent pacemaker implantation	16 (4.1)	12 (4.3)	4 (3.5)	1.0
Disabling stroke	11 (2.8)	7 (2.5)	4 (3.5)	0.74
Acute kidney injury	16 (4.1)	16 (5.8)	0 (0.0)	0.004
All bleeding	33 (8.5)	28 (10.1)	5 (4.4)	0.07
Life–threatening/Major bleeding	18 (4.6)	17 (6.2)	1 (0.9)	0.03
All vascular complications	18 (4.6)	13 (4.7)	5 (4.4)	1.0
Cardiac tamponade	2 (0.5)	2 (0.7)	0 (0.0)	1.0
Postprocedural laboratory data				
eGFR from cystatin C, ml/min/1.73 m^2	48.0 (35.9–63.1)	40.6 (33.1–49.8)	71.1 (64.7–77.1)	<0.001
eGFR from creatinine, ml/min/1.73 m^2	52.8 (42.0–66.0)	47.2 (37.2–55.6)	69.7 (61.9–79.0)	<0.001
BNP, pg/ml	95.5 (48.2–204.8)	120.0 (58.6–234.8)	56.6 (32.4–106.3)	<0.001
Postprocedural echocardiographic data				
Peak AV velocity, m/s	2.1 (1.8–2.5)	2.1 (1.8–2.5)	2.1 (1.8–2.5)	0.95
Mean AVPG, mmHg	9 (7–12)	9 (7–12)	9 (7–13)	0.89
EOA, cm^2	1.56 (1.37–1.78)	1.56 (1.38–1.77)	1.58 (1.33–1.80)	0.90
Moderate or severe AR, n (%)	20 (5.1)	14 (5.2)	6 (5.4)	1.0
Moderate or severe MR, n (%)	17 (4.4)	14 (5.2)	3 (2.7)	0.40

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75th percentiles).
eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; AV, aortic valve; AVPG, aortic valve pressure gradient; AVA, aortic valve area; AR, aortic regurgitation; MR, mitral regurgitation; EOA, effective orifice area.

significantly higher than that of eGFR (creatinine) (AUC 0.701 vs. 0.566; $p < 0.001$). In model 3, the multivariate model with age and male sex indicated that eGFR (cystatin C) (HR, 0.963; 95% CI, 0.946–0.980; $p < 0.001$), was independently associated with 3-year all-cause mortality. In contrast, model 4 showed that the 3-year all-cause mortality was not independently associated with eGFR (creatinine) (HR, 0.993; 95% CI, 0.977–1.010; $p = 0.43$); male sex (HR, 1.801; 95% CI, 1.007–3.224; $p = 0.047$) was independently associated.

Kaplan–Meier estimates revealed that 3-year all-cause mortality were higher in the CKD (cystatin C) group than that in the non-CKD (cystatin C) group with log-rank $p = 0.009$. In contrast, there was no significant difference between the CKD (creatinine) and non-CKD (creatinine) groups with log-rank $p = 0.94$ (Figure 3).

4. Discussion

In this study, we demonstrated that CKD estimated by cystatin C (not by creatinine), predicted the 3-year all-cause mortality in patients undergoing TAVI. Our study showed that eGFR (cystatin C), diabetes mellitus, and liver disease were independently associated with 3-year all-cause mortality in the TAVI cohort. In addition, eGFR (cystatin C) presented good calibration, and better discrimination than eGFR calculated from serum creatinine. Furthermore, the estimated 3-year mortality rate was significantly higher in the CKD group, for which eGFR was calculated from cystatin C, as compared to that in the CKD group where eGFR was calculated from serum creatinine. To the best of our knowledge, this is the first study to demonstrate that CKD (calculated from cystatin C-based eGFR) is associated with long-term mortality in the TAVI cohort.

4.1. Comparison of the 3-year prognostic impact of CKD calculated from cystatin C and serum creatinine

CKD is a major risk factor for death and disability following TAVI, and is common in patients undergoing TAVI. Multiple studies suggest that approximately 91% patients have stage ≥ 2

TABLE 3 Cox regression univariate analysis for the association between cumulative mortality and clinical findings.

Parameter	Univariate		
	Unadjusted HR	95% CI	*p*–value
eGFR from cystatin C, ml/min/1.73 m^2	0.963	0.946–0.981	<0.001
eGFR from creatinine, ml/min/1.73 m^2	0.994	0.977–1.010	0.44
Age	1.001	0.944–1.060	0.98
CFS	1.371	0.964–1.950	0.08
NYHA Class III or IV	1.258	0.660–2.397	0.49
Diabetes mellitus	2.037	1.126–3.687	0.02
Hypertension	0.532	0.237–1.193	0.13
Liver disease	3.527	1.389–8.955	0.008
Pulmonary disease	1.564	0.699–3.499	0.28
Albumin on admission	0.344	0.190–0.626	<0.001
BNP at discharge	1.001	1.000–1.002	<0.001
Preprocedural LVEF	0.995	0.969–1.022	0.72
Postprocedural EOA	1.388	0.561–3.436	0.48
Hemoglobin on admission	0.884	0.735–1.065	0.19
Transfemoral	0.989	0.306–3.196	0.98

eGFR, estimated glomerular filtration rate; CFS, clinical frailty scale; NYHA, New York heart association; BNP, brain natriuretic peptide; LVEF, left ventricle ejection fraction by modified simpson methods; EOA, effective orifice area; HR, hazard ratio; CI, confidence interval.

CKD (7–9, 22–24). eGFR (creatinine) is generally used to assess renal function in clinical settings; however, it is well known that the non-GFR determinants of serum creatinine, including muscle mass, diet, and physical activity can confound the associations between creatinine-based eGFR and outcomes (25). The TAVI cohort is predominantly older; therefore, using creatinine in this cohort to calculate eGFR may lead to an overestimation of the GFR. However, serum cystatin C is not a blood test measurement used in all clinical settings, but it is unaffected by age, gender, or muscle mass; thus, renal function calculated from serum cystatin C can be more accurately evaluated in TAVI patients (11–15). Consistent with these findings, we demonstrated that CKD estimated by cystatin C (and not creatinine) predicted the 3-year all-cause mortality in patients undergoing TAVI. It was previously reported that assessment of CKD with serum cystatin C did not improve mortality prediction compared to serum creatinine in older community dwelling British men (median age 78.4 years) (26). In addition, although previous studies have reported that CKD assessed by creatinine is a poor prognostic factor following TAVI (7–9), eGFR (creatinine) was not shown to be associated with 3-year all-cause mortality following TAVI in this study. We speculate that this discrepancy is due to patient characteristics. Our study cohort included many older patients (median age 84.0 years) and a significant number of women, with the percentage of men being 32.8%, moreover a smaller body size (median BSA 1.43 m^2). These characteristics significantly affect body composition and frailty and serum creatinine may underestimate renal function. In conclusion, we believe that eGFR (cystatin C) is useful for predicting mortality following TAVI, and that it is superior to eGFR (creatinine), particularly for the older cohort, which includes many frail and undernourished patients.

4.2. Potential clinical implications

In this study, serum creatinine and cystatin C at discharge following TAVI were used for evaluation. Cubeddu RJ, et al. reported that in patients with severe aortic stenosis undergoing TAVI, renal function is more likely to stay the same or improve than worsen (24). They also reported that renal function following TAVI is associated with all-cause mortality at one year (24). Mizutani K, et al. reported that BNP at discharge would be more favorable for risk stratification of long-term prognosis than that on admission in patients who had undergone TAVI because the TAVI procedure releases the left ventricle from pressure overload immediately after the valve replacement (27). We thought renal function at discharge, as well as BNP, to be more useful in assessing its relationship to prognosis. Therefore, we considered renal function following TAVI to be suitable for assessing the relationship to prognosis. The prevalence of

TABLE 4 Cox regression multivariate analysis for the association between cumulative mortality and clinical findings; model 1, 2, 3 and 4.

Parameter	Model 1			Model 2		
	Adjusted HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
eGFR from cystatin C, ml/min/1.73 m^2	0.972	0.953–0.990	0.003	–	–	–
eGFR from creatinine, ml/min/1.73 m^2	–	–	–	1.002	0.985–1.019	0.82
Diabetes mellitus	2.090	1.149–3.811	0.02	1.954	1.072–3.564	0.03
Liver disease	2.813	1.089–7.266	0.03	2.960	1.142–7.674	0.03
Albumin on admission	0.509	0.258–1.005	0.051	0.398	0.212–0.744	0.004
BNP at discharge	1.001	1.000–1.001	0.10	1.001	1.000–1.001	0.02
Parameter	**Model 3**			**Model 4**		
	Adjusted HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
eGFR from cystatin C, ml/min/1.73 m^2	0.963	0.946–0.980	<0.001	–	–	–
eGFR from creatinine, ml/min/1.73 m^2	–	–	–	0.993	0.977–1.010	0.43
Age	0.985	0.929–1.045	0.62	1.002	0.944–1.063	0.96
Male	1.732	0.960–3.123	0.68	1.801	1.007–3.224	0.047

eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; HR, hazard ratio; CI, confidence interval.

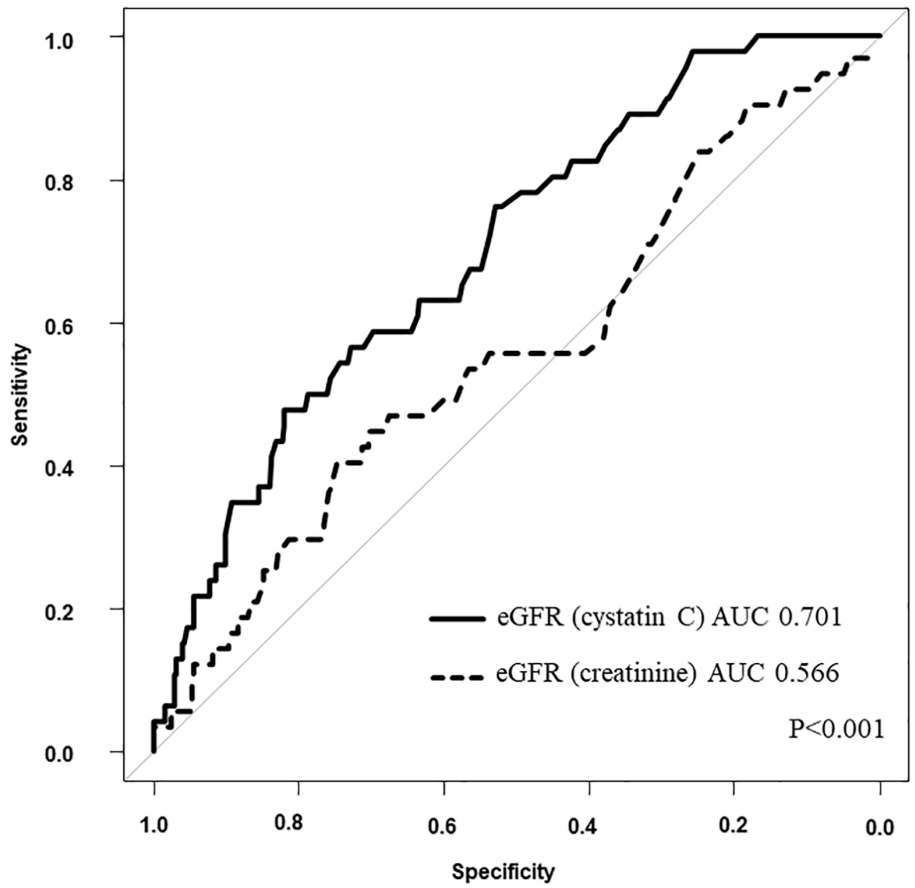

FIGURE 2
Comparison between eGFR (cystatin C) and eGFR (creatinine). AUC, area under the curve; eGFR, estimated glomerular filtration rate.

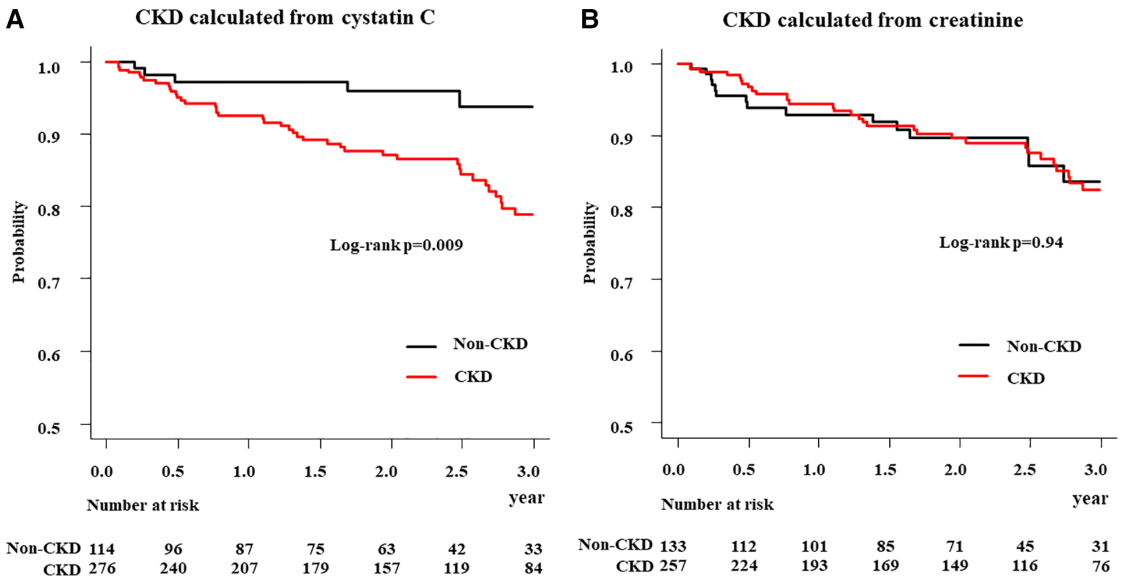

FIGURE 3
Kaplan–meier analysis of all-cause mortality in patients in CKD and non-CKD groups. (A) CKD calculated from cystatin C (B) CKD calculated from creatinine; CKD, chronic kidney disease.

postoperative AKI was low (4.1% of the total) and did not appear to influence the prognostic analysis. Serum cystatin C also has a greater diagnostic sensitivity than that of serum creatinine, especially in the pre-CKD area of serum creatinine (eGFR 75 ml/min/1.73 m^2 to 88 ml/min/1.73 m^2) (28). These characteristics may affect the predictive value of long-term mortality in patients with cardiovascular disease. Additionally, it has been reported that cystatin C is a predictor of long-term prognosis and rehospitalization in patients with heart failure and percutaneous coronary intervention (29–31). With the expanded indication of TAVI for a subset of lower-risk patients, TAVI could be considered as the first-line treatment choice for patients with AS. This would show improvement in pre-procedural, short-term, and long-term endpoints. Cystatin C could be easily monitored with blood tests. Accordingly, CKD patients should be followed-up carefully.

4.3. Study limitations

This study has several limitations. First, this study was a single-center design, and the small study population ($n = 390$) for the time period reduced the statistical power of the study. Second, the median follow-up period was 808 (368–1145) days, with some cases having a shorter follow-up period. Third, the patients whose data regarding the cystatin C level at discharge were not available were excluded, which could have led to a selection bias. Fourth, cystatin C is not a test commonly measured in clinical practice and has limited use.

4.4. Conclusion

eGFR calculated from cystatin C at the time of discharge was associated with the 3-year all-cause mortality in patients undergoing TAVI. Thus, serum cystatin C is superior to serum creatinine as a prognostic biomarker for the TAVI cohort.

Author's note

This study used the same TAVI study population as in the "Kihon checklist is useful for predicting outcomes in patients undergoing transcatheter aortic valve implantation" (32) reported previously by Kure Y, Okai T, et al. The period covered in this study was from January 2016 to December 2021, a different time period than in paper (32). Paper (32) included a cohort of TAVI patients who had undergone TAVI at Osaka Metropolitan University Hospital and were able to be evaluated for frailty, while the current study includes all TAVI patients who underwent TAVI at Osaka Metropolitan University Hospital. (peri-complicated in-hospital deaths, patients with active cancer, and cystatin C deficiency at discharge were excluded).

The TAVI procedure was the same as in paper (32), and the TAVI procedrure at Osaka Metropolitan University Hospital has been consistently the same in the present study.

The same analysis methods and software were used as in paper (32). The present study is a two-group comparison, whereas paper (32) is a three-group comparison.

Paper (32) investigated the impact of frailty on prognosis in TAVI patients, and reported the effectiveness of the Kihon checklist as one of the evaluation methods. The current study investigated the relationship between renal function calculated from cystatin C and prognosis after TAVI. From the above points, this study is different from the paper (32).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The protocol of this study was in accordance with the guidelines of the Declaration of Helsinki and was approved by our institutional ethics committee (approval number: 2021-064).

Author contributions

YK, TO, YI, HY, KM, TY, MO, AS, AI, YT, TS, DF made effort to enroll the patients. YK, TO, and YI were major contributors in writing the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to express our heartfelt gratitude to heart team members at our hospital.

Conflict of interest

KM is a clinical proctor of Edwards Lifesciences and Medtronic. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors disclose that there have been no previous studies with the same content and that transparency is not an issue.

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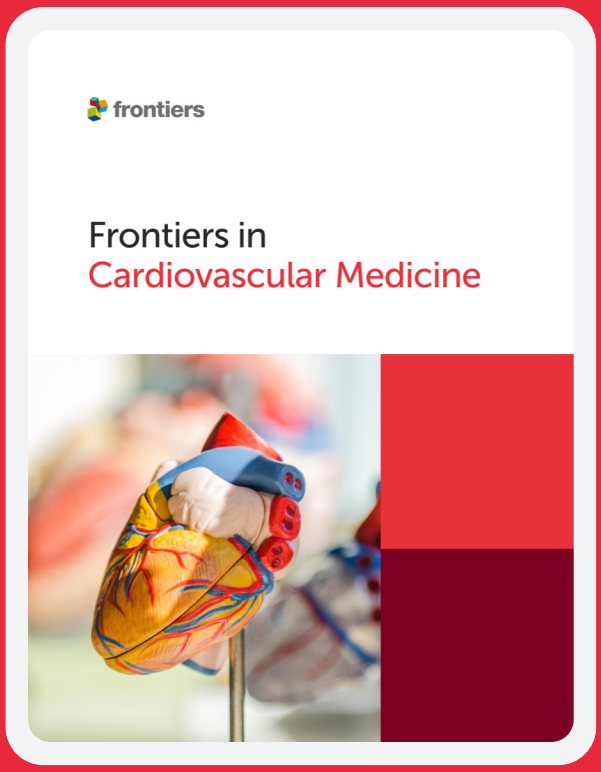

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