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ORIGINAL PAPER

Impact of valvular resistance on aortic regurgitation after transcatheter aortic valve replacement according to the type of prosthesis

Masahiko Asami[1] · Thomas Pilgrim[1] · Stefan Stortecky[1] · Dik Heg[2] · Eva Roost[3] · Stephan Windecker[1] · Lukas Hunziker[1]

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Abstract

Background The impact of aortic valvular resistance (VR) on the degree of post-transcatheter aortic valve replacement (TAVR) aortic regurgitation (AR) remains unclear. The objective of the study was to investigate the relationship between VR and paravalvular AR after TAVR.

Methods Between August 2007 and December 2015, 708 TAVR patients had sufficient data to calculate VR before the intervention and were eligible for the present analysis. The patient population was dichotomized according to VR. The association between VR and post-TAVR AR was separately assessed by prosthesis type.

Results Among patients with low VR (LVR; < 238 dynes/cm^5), 176 (49.7%) patients were treated with balloon-expandable (BE) valves and 178 (51.3%) patients with self-expandable (SE) transcatheter valves. Among patients with high VR (HVR ≥ 238), 147 (41.5%) and 207 (68.5%) patients received BE and SE, respectively. Baseline characteristics were similar in both groups irrespective of the type of valve. Patients with HVR had a 2.5-fold risk of ≥ moderate post-TAVR AR compared to patients with LVR. Both, HVR (HR_{adj} 2.45, 95% CI 1.33–4.51) and the use of SE (HR_{adj} 3.11, 95% CI 1.66–5.82), emerged as independent predictors of ≥ moderate post-TAVR AR. Moderate or greater post-AR was consistently predicted in patients treated with SE (HR_{adj} 2.42, 95% CI 1.22–4.80) irrespective of the level of VR.

Conclusions HVR is associated with a nearly 2.5-fold increased risk of moderate or greater post-TAVR AR and is an independent predictor of post-TAVR AR.

Keywords Aortic stenosis · Post-procedural aortic regurgitation · Transcatheter aortic valve replacement · Right heart catheterization

Abbreviations

AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
BE	Balloon-expandable valve
BMI	Body mass index
MACCE	Major adverse cardiac and cerebrovascular events
RHC	Right heart catheterization
SE	Self-expandable valve
TAVR	Transcatheter aortic valve replacement
VARC	The valve academic research consortium
VR	Valvular resistance

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✉ Lukas Hunziker
lukas.hunziker@insel.ch

[1] Department of Cardiology, Swiss Cardiovascular Center, Bern University Hospital, Freibrugstrasse, 3010 Bern, Switzerland

[2] Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland

[3] Department of Cardiac Surgery, Swiss Cardiovascular Center, Bern University Hospital, Freibrugstrasse, 3010 Bern, Switzerland

Introduction

During the past decade, therapeutic options for the treatment of patients with severe, symptomatic aortic stenosis (AS) have considerably changed. Transcatheter aortic valve replacement (TAVR) has matured into an alternative strategy to surgical aortic valve replacement in symptomatic severe AS patients at increased surgical risk; however, several peri-procedural problems remain unresolved [1, 2]. Moderate or greater post-procedural aortic regurgitation (AR) is well recognized as an independent predictor of impaired prognosis [3–5]. With advances in delivery catheters and refinements of valve prostheses featuring skirts, cuffs, and sleeves, the rate of ≥ moderate post-procedural AR has significantly decreased, but appears to be higher with self-expandable valve (SE) compared to balloon-expandable valve (BE) prostheses [6–8]. In addition to valve type, male sex, diabetes, large prosthesis size, and mitral or aortic regurgitation at baseline have been identified as predictors of residual aortic regurgitation [4].

Aortic valvular resistance (VR), which can be calculated from the measurements obtained by routine right heart catheterization (RHC), has been shown to be exponentially inversely related with the aortic valve area (AVA) [9]. Therefore, we hypothesized that high VR (HVR) may be associated with restricted mobility of the annuli owing to the many obstacles (mainly calcification) around the cusps and moderate or greater post-procedural AR may be more likely to occur in patients with HVR than in those with low VR (LVR). The aim of this study was to investigate the impact of VR at baseline on post-TAVR AR according to the type of valve.

Methods

Patient population and study design

The Bern TAVI registry is a prospective registry that is part of the SWISS TAVI registry (ClinicalTrials.gov NCT01368250) [10]. Between August 2007 and December 2015, patients with symptomatic severe AS who underwent TAVR at the Bern University Hospital and had sufficient RHC data to calculate VR before the intervention were considered eligible for the present study.

Decisions regarding peri-procedural management including device selection were based on multidisciplinary planning and detailed imaging analysis. Data collection occurred at baseline, index procedure, discharge, 30-day, and 1-year follow-up for all subjects and data management was conducted by the Clinical Trials Unit at the University of Bern, Switzerland. An independent clinical event committee composed of an interventional cardiologist, a cardiac surgeon, and imaging and heart failure specialist adjudicated all clinical events that were observed throughout the study period, according to the updated criteria of the Valve Academic Research Consortium (VARC)–2 [11]. The study was approved by the local ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Furthermore, this article does not contain any studies with animals performed by any of the authors. All subjects provided a written informed consent for the procedure and the prospective follow-up.

Echocardiography

All subjects had detailed echocardiographic assessment within 3 months before TAVR and before hospital discharge after the intervention. Left ventricular ejection fraction was assessed using the biplane Simpson method. Echocardiographic measurements at baseline were performed according to the latest guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery [12]. The assessment of prosthetic aortic valve regurgitation after TAVR was evaluated according to the VARC–2 criteria [11]. In brief, color flow Doppler signal was performed, just below the valve strut for paravalvular regurgitation and at the coaptation point of the leaflets for transvalvular jets, for grading the severity of AR. In line with the VARC–2 criteria, the regurgitant volume (mild < 30 mL, moderate 30–59 mL, and severe ≥ 60 mL) and effective regurgitant orifice area (mild < 0.10 cm^2, moderate 0.10–0.29 cm^2, and severe ≥ 0.30 cm^2) were used as quantitative parameters, with the circumferential extent of prosthetic valve paravalvular regurgitation (mild < 10%, moderate 10–29%, and severe ≥ 30%) used as a semi-quantitative parameter useful in the classification of the severity of post-TAVR AR. If these parameters are contradictory, considering the presence of a prosthetic valve and the underlying clinical conditions, the components with the best quality and most precision based on technical and physiologic reasons to explain these discrepancies were prioritized over the other parameters. Paravalvular leak was mainly investigated in the current analysis. However, in some cases it was difficult to separation between central and paravalvular jets. For the main objective of the study, post-procedural AR as the pre-specified primary endpoint was compared between patients with HVR and LVR according to the type of implanted valve.

Right heart catheterization

According to our previous report [13], RHC was simultaneously performed at the time of pre-TAVR coronary angiography. VR was calculated using the following equation [14]:

$$VR = (1.333 \times \Delta Pm \times HR \times SEP)/CO,$$

where ΔPm indicates mean gradient, HR indicates heart rate, SEP indicates systolic ejection period, and CO indicates cardiac output. The median VR of this population was 237.86 dynes/cm^5. For the purpose of the present analysis, the LVR cut-off was, therefore, defined as a value of less than 238 dynes/cm^5 due to lack of an established cut-off value.

Multi-slice computed tomography

An ECG-gated multi-slice computed tomography (MSCT) angiography using dual-source 128-row MSCT (Somaton Definition Flash; Siemens Healthcare, Erlangen, Germany) was used for valve assessment. Scan parameters were as follows: reference tube voltage was set to 100–120kv and reference tube–current–time product 300 mAs_{ref}; rotation time 0.28 s; slice collimation 128 × 0.6 mm; pitch value 0.17 for spiral acquisition within 40–75% of RR. Scan direction was cranio-caudal. Automatic current modulation (CareDose4D) was used for raw data acquisition. Images were reconstructed with individually adapted FOV at a 2 mm slice thickness with an increment of 1.4 mm using an I30f kernel (SAFIRE, strength 3).

Contrast agent protocol was used as follows: 40–90 ml (Iopromide 370 mg iodine/mL; Ultravist 370, Bayer Healthcare, Berlin, Germany). Bolus tracking technique with the region of interest (ROI) placed at the proximal part of the ascending aorta was used.

All CT images were transmitted to a dedicated software customized for valve analysis (3mensio Valves, version 9.0, 3mensio Medical Imaging BV, Bilthoven, the Netherlands) and were blindly assessed by a board-certificated cardiologist in the Corelab. For valve analyses, a systolic phase was evaluated. Furthermore, aortic-valvar complex and left ventricular outflow tract calcium volume were quantified using a validated methodology to determine calcium volume in a contrast scan (850-Hunsfield Unit threshold) [15].

Procedure

The standardized TAVR procedure during the study period has been previously described in detail [10]. Transfemoral approach under local anesthesia and conscious sedation was selected as the default strategy. An alternative access approach under general anesthesia was reserved for patients with inadequate femoral access. Several valves were commercially available in Switzerland throughout the study period. In this study, SAPIEN XT and Sapien S3 (Edwards Lifesciences Inc., Irvine, CA) were used as the BE, whereas CoreValve and CoreValve Evolut R (Medtronic Inc., Minneapolis, MN), Symetis ACURAT E-TA and-TF (Boston/Symetis SA, Ecublens, Switzerland), Lotus (Boston Scientific, Natick, MA), St Jude Medical Portico (St. Jude Medical, Minneapolis, MN), and Direct Flow Medical (Direct Flow Medical, Santa Rosa, CA) were considered as the SE.

Statistical analysis

The HVR patients were compared descriptively against the LVR patients per valve type, using the following statistics: means with standard deviations with Student *t* tests (continuous variables); or counts with percentages with Fisher's exact test or chi-square tests (i.e., to compare baseline characteristics, echocardiography, RHC, procedural characteristics, complications). Interaction *p* values were reported accordingly testing for the interaction between the two main factors HVR/LVR patients x balloon-expandable/self-expandable valve type.

Predictive factors for post-TAVR AR moderate or greater were analyzed using univariable logistic regressions (reported are odds ratios [OR] with 95% confidence intervals [CI]). The multivariable logistic regression model retained the variables included stepwise if the *p* value of entry was < 0.1. Predictive factors explored where VR ≥ 238, use of SE, chronic obstructive pulmonary disease, body mass index (BMI) ≤ 20 kg/m^2, diabetes mellitus, atrial fibrillation, age, sex, history of cerebrovascular events, pre-dilatation, Society of thoracic surgeons Predicted Risk Of Mortality score, peripheral artery disease, coronary artery disease, and creatinine > 200 µmol/L. One patient with missing post-TAVR AR was not in these analyses. Single imputation of missing values was performed before the multivariable model was built (number of patients imputed): creatinine ($n = 1$ assumed ≤ 200), and chronic obstructive pulmonary disease ($n = 1$ assumed no). Similarly, predictive logistic regression models were constructed per valve type separately, with *p* value of stepwise inclusion < 0.1.

The first event of each event type per patient entered into the time-to-event analyses using Cox's regressions. Events according to VR group were compared and hazard ratios (HR) (with 95% CI) with *p* values are reported. All analyses were performed with Stata version 14 (StataCorp, College Station, TX, USA). Two-sided *p* values < 0.05 were considered statistically significant.

Results

Study population

Between August 2007 and December 2015, 1339 consecutive patients underwent TAVR at Bern University Hospital. Out of 824 (61.5%) patients who underwent RHC before TAVR, 708 (85.9%) patients had available data for VR calculation. BEs were used in 323 patients (LVR [169.8 ± 40.3 dynes/cm^5], 176 patients; HVR [384.3 ± 166.1 dynes/cm^5], 147 patients), and SEs were used in 385 patients (LVR [173.2 ± 44.4 dynes/cm^5], 178 patients; HVR [440.7 ± 215.7 dynes/cm^5], 207 patients).

The baseline characteristics are provided in Table 1. In both the valve groups, patients with HVR were older (BEs: 82.8 ± 6.0 years vs. 81.0 ± 5.9 years; $p = 0.007$; SEs: 83.4 ± 4.7 years vs. 81.6 ± 5.0 years; $p < 0.001$), and were more likely to be female (BEs: 66.7% vs. 35.8%, $p < 0.001$; SEs: 69.1% vs. 39.3%; $p < 0.001$) compared to those with LVR. Furthermore, with respect to the surgical risk, patients with HVR who received a BE showed a higher logistic EuroSCORE (21.8 ± 12.9% vs. 18.9 ± 13.0%; $p = 0.042$), whereas those who received a SE showed an increased STS score (6.9 ± 5.8% vs. 5.8 ± 3.4%; $p = 0.04$) compared with those with LVR. In addition, all variables showed negative interactions across the four groups.

Pre-procedural imaging assessments

Measurements of echocardiography before TAVR are described in Table 2. In both valve groups, patients with HVR were found to have a smaller AVA (BEs: 0.65 ± 0.20 cm^2 vs. 0.77 ± 0.21 cm^2, $p < 0.001$; SEs: 0.63 ± 0.19 cm^2 vs.

Table 1 Baseline characteristics

	Overall	Balloon-expandable valve			Self-expandable valve			Interaction *p* value
		LVR	HVR	*p* value	LVR	HVR	*p* value	
	N = 708	*N* = 176	*N* = 147		*N* = 178	*N* = 207		
Age, years	82.2 ± 5.4	81.0 ± 5.9	82.8 ± 6.0	0.007	81.6 ± 5.0	83.4 ± 4.7	< 0.001	0.98
Female gender, *n* (%)	374 (52.8)	63 (35.8)	98 (66.7)	< 0.001	70 (39.3)	143 (69.1)	< 0.001	0.90
Body mass index, kg/m^2	26.4 ± 5.1	27.8 ± 5.0	26.0 ± 5.2	0.002	26.3 ± 5.5	25.6 ± 4.7	0.22	0.13
Cardiac risk factors								
Diabetes mellitus, *n* (%)	192 (27.1)	66 (37.5)	41 (27.9)	0.08	46 (25.8)	39 (18.8)	0.11	0.92
Hypercholesterolemia, *n* (%)	462 (65.3)	132 (75.0)	89 (60.5)	0.006	123 (69.1)	118 (57.0)	0.02	0.65
Hypertension, *n* (%)	611 (86.3)	161 (91.5)	122 (83.0)	0.03	153 (86.0)	175 (84.5)	0.77	0.14
Past medical history								
Previous myocardial infarction, *n* (%)	94 (13.3)	30 (17.0)	17 (11.6)	0.21	30 (16.9)	17 (8.2)	0.01	0.43
Previous PCI, *n* (%)	193 (27.3)	57 (32.4)	31 (21.1)	0.02	61 (34.3)	44 (21.3)	0.006	0.83
Previous CABG, *n* (%)	60 (9.0)	23 (14.0)	6 (4.3)	0.005	19 (11.7)	12 (6.0)	0.06	0.35
Previous stroke or TIA, *n* (%)	74 (10.5)	21 (11.9)	20 (13.6)	0.74	14 (7.9)	19 (9.2)	0.72	0.97
Peripheral vascular disease, *n* (%)	114 (16.1)	38 (21.6)	20 (13.6)	0.08	35 (19.7)	21 (10.1)	0.009	0.61
Chronic obstructive pulmonary disease, *n* (%)	107 (15.1)	26 (14.8)	22 (15.1)	1.00	31 (17.4)	28 (13.5)	0.32	0.45
Renal failure (eGFR < 60 mL/min/1.73 m^2), *n* (%)	496 (70.2)	113 (64.2)	104 (70.7)	0.24	122 (68.5)	157 (76.2)	0.11	0.79
Baseline cardiac rhythm								
Atrial fibrillation, *n* (%)	229 (32.3)	56 (31.8)	39 (26.5)	0.33	64 (36.0)	70 (33.8)	0.67	0.62
Permanent pacemaker, *n* (%)	59 (8.3)	14 (8.0)	8 (5.4)	0.51	20 (11.2)	17 (8.2)	0.39	0.92
Symptoms								
NYHA classification III or IV, *n* (%)	467 (66.1)	112 (63.6)	101 (68.7)	0.35	112 (62.9)	142 (68.9)	0.24	0.90
CCS III or IV, *n* (%)	80 (11.3)	20 (11.4)	19 (12.9)	0.73	20 (11.2)	21 (10.2)	0.74	0.59
Syncope, *n* (%)	88 (12.4)	17 (9.7)	22 (15.0)	0.17	18 (10.1)	31 (15.0)	0.17	0.92
Risk assessment								
Logistic EuroSCORE, %	21.1 ± 13.4	18.9 ± 13.0	21.8 ± 12.9	0.042	21.7 ± 13.1	21.8 ± 14.0	0.92	0.16
STS score, %	6.3 ± 4.6	5.8 ± 4.2	6.6 ± 4.2	0.07	5.8 ± 3.4	6.9 ± 5.8	0.04	0.79

Values are means ± standard deviations or counts (percentages)

CABG coronary artery bypass grafting, *CCS* Canadian cardiovascular society, *NYHA* New York heart association, *PCI* percutaneous coronary intervention, *STS* Society of Thoracic Surgeons, *TIA* transient ischemic attack

Table 2 Baseline echocardiographic assessments

	Overall	Balloon-expandable valve			Self-expandable valve			Interaction *p* value
		LVR	HVR	*p* value	LVR	HVR	*p* value	
	N = 708	*N* = 176	*N* = 147		*N* = 178	*N* = 207		
Aortic stenosis severity								
Aortic valve area, cm^2	0.70 ± 0.23	0.77 ± 0.21	0.65 ± 0.20	< 0.001	0.81 ± 0.26	0.63 ± 0.19	< 0.001	0.20
Aortic maximal velocity, m/s	4.08 ± 0.80	3.60 ± 0.60	4.44 ± 0.56	< 0.001	3.57 ± 0.75	4.39 ± 0.78	< 0.001	0.88
Mean gradient, mmHg	43.1 ± 17.0	37.9 ± 14.4	47.3 ± 14.3	< 0.001	35.5 ± 15.2	51.2 ± 18.2	< 0.001	0.01
Valvular resistance calculated by TTE, $dyne.s.cm^{-5}$	338.2 ± 208.4	286.6 ± 169.5	387.9 ± 236.5	0.01	273.1 ± 151.6	408.0 ± 234.0	< 0.001	0.52
LV systolic function								
LV ejection fraction, %	54.9 ± 14.8	54.0 ± 14.2	56.4 ± 14.4	0.14	53.4 ± 15.6	55.8 ± 14.6	0.13	0.99
Stroke volume index, mL/m^2	33.9 ± 12.5	33.9 ± 11.7	33.3 ± 13.2	0.77	34.1 ± 12.9	34.2 ± 12.5	0.93	0.78
Evaluation of valvular abnormality								
Aortic regurgitation moderate or severe, *n* (%)	64 (10.0)	14 (8.0)	11 (8.0)	1.00	14 (8.0)	25 (13.0)	0.18	0.27
Mitral regurgitation moderate or severe, *n* (%)	137 (20.0)	25 (15.0)	31 (21.0)	0.14	41 (24.0)	40 (20.0)	0.45	0.09
Tricuspid regurgitation moderate or severe, *n* (%)	114 (17.0)	23 (14.0)	20 (14.0)	1.00	29 (17.0)	42 (21.0)	0.29	0.51

Values are means ± standard deviations or counts (percentages)

LV left ventricular

0.81 ± 0.26 cm^2, $p < 0.001$), a higher aortic maximal velocity (BEs: 4.44 ± 0.56 m/s vs. 3.60 ± 0.60 m/s, $p < 0.001$; SEs: 4.39 ± 0.78 m/s vs. 3.57 ± 0.75 m/s, $p < 0.001$), and a higher mean transvalvular gradient (BEs: 47.3 ± 14.3 mmHg vs. 37.9 ± 14.4 mmHg, $p < 0.001$; SEs: 51.2 ± 18.2 mmHg vs. 35.5 ± 15.2 mmHg, $p < 0.001$) compared to patients with LVR.

Furthermore, pre-procedural CT assessments are summarized in Table 3. Patients with HVR showed significantly higher aortic-valvar complex calcium volume than those with LVR (Supplementary Table 1). However, no significant differences were noted in the interaction *p* value for all variables across all arms.

Right heart catheterization assessment

RHC assessments at baseline are presented in Table 4. Notwithstanding no significant difference in systolic arterial pressure (BEs: 141.1 ± 28.5 mmHg vs. 138.7 ± 26.5 mmHg, $p = 0.45$; SEs: 139.6 ± 29.3 mmHg vs. 134.4 ± 27.5 mmHg, $p = 0.08$) with both valve types, lower stroke volume index (BEs: 25.1 ± 7.1 ml/m^2 vs. 32.6 ± 8.2 ml/m^2, $p < 0.001$; SEs: 24.1 ± 7.0 ml/m^2 vs. 30.6 ± 7.8 ml/m^2, $p < 0.001$) and higher left ventricular systolic pressure (BEs: 198.5 ± 31.9 mmHg vs. 181.7 ± 30.8 mmHg, $p < 0.001$; SEs: 202.7 ± 36.1 mmHg vs. 175.3 ± 32.1 mmHg, $p < 0.001$) were observed in patients with HVR than in those with LVR.

Procedural characteristics

Procedural details and complications for all subjects are provided in Table 5 and Supplementary Table 2. Patients with HVR who received a SE were more likely to undergo pre- and post-dilatation when compared to those with LVR (pre-dilatation: 86.0% vs. 73.6%, $p = 0.02$; post-dilatation: 36.2% vs. 23.0%, $p = 0.02$). This was not noted in patients who received a BE (Fig. 1). Furthermore, a significant difference in moderate or greater post-TAVR AR between patients with LVR and those with HVR was observed only in the SE group (BEs: 2.8% vs. 6.2%, $p = 0.18$; SEs: 7.9% vs. 15.9%, $p = 0.02$). No significant difference in new pacemaker implantation was noted within 30 days after TAVR (BEs: 22.2% vs. 15.0%, $p = 0.12$; SEs: 28.1% vs. 26.1%, $p = 0.73$) (Fig. 1). Overall, patients with HVR had a 2.5-fold higher risk of moderate or greater post-TAVR AR than those with LVR. In multivariable analysis, HVR (HR_{adj} 2.45, 95% CI 1.33–4.51), the use of SE (HR_{adj} 3.11, 95% CI 1.66–5.82), and lower BMI (HR_{adj} 2.73, 95% CI 1.29–5.77) were independent predictors of moderate or greater post-TAVR AR (Table 6). According to the type of valve, HVR was consistently associated with moderate or greater post-TAVR AR in patients treated with SE (HR_{adj} 2.42, 95% CI 1.22–4.80; $p = 0.01$), but not in those treated with BE (HR_{adj} 2.19, 95% CI 0.71–6.71; $p = 0.17$) (Supplementary Table 3). Furthermore, in patients with CT, predictive measurement of moderate or greater post-TAVR AR was investigated. The

Table 3 Computed tomography assessments according to the type of valve

	Overall	Balloon-expandable valve			Self-expandable valve			Interaction *p* value
		LVR	HVR	*p* value	LVR	HVR	*p* value	
	N = 551	*N* = 129	*N* = 117		*N* = 134	*N* = 171		
Aortic valve apparatus								
Maximum annulus diameter, mm	27.2 ± 2.5	27.9 ± 2.2	27.0 ± 2.3	0.001	27.5 ± 2.5	26.6 ± 2.5	0.003	0.85
Minimum annulus diameter, mm	20.7 ± 2.1	21.5 ± 2.0	20.5 ± 1.9	< 0.001	20.9 ± 2.2	20.1 ± 2.1	0.001	0.67
Mean annulus diameter, mm	24.0 ± 2.1	24.7 ± 1.9	23.8 ± 1.9	< 0.001	24.2 ± 2.2	23.4 ± 2.1	0.001	0.74
Annulus area, mm^2	446.6 ± 76.9	474.1 ± 75.0	437.2 ± 67.4	< 0.001	455.9 ± 80.8	425.0 ± 74.5	0.001	0.64
Annulus perimeter, mm	76.2 ± 6.5	78.4 ± 6.1	75.5 ± 5.8	< 0.001	77.0 ± 6.9	74.3 ± 6.5	< 0.001	0.83
Left coronary height, mm	14.6 ± 3.5	15.2 ± 3.7	14.5 ± 3.4	0.11	14.8 ± 3.5	14.2 ± 3.5	0.12	0.86
Right coronary height, mm	17.5 ± 3.3	17.7 ± 3.0	17.0 ± 3.2	0.08	18.2 ± 3.2	17.1 ± 3.4	0.005	0.50
Ascending aorta, mm	33.1 ± 3.2	33.3 ± 3.1	33.1 ± 3.3	0.71	33.2 ± 3.0	32.9 ± 3.5	0.39	0.75
Sinotublar junction, mm	27.7 ± 3.1	28.4 ± 3.2	27.1 ± 2.9	0.001	28.5 ± 3.0	27.0 ± 3.0	< 0.001	0.87
Sinus of valsalva, mm	33.2 ± 3.9	33.6 ± 3.4	32.7 ± 3.5	0.03	33.7 ± 4.2	32.9 ± 4.1	0.13	0.74
LVOT, mm	23.6 ± 3.1	24.0 ± 3.2	23.2 ± 3.2	0.05	24.0 ± 3.3	23.3 ± 2.9	0.08	0.75
Annulus eccentricity	0.76 ± 0.06	0.77 ± 0.05	0.76 ± 0.06	0.30	0.76 ± 0.06	0.76 ± 0.07	0.63	0.70
AVC calcium volume (Total), mm^3	322.2 ± 308.4	276.1 ± 260.9	393.2 ± 358.2	0.003	265.4 ± 263.8	352.9 ± 325.4	0.01	0.57
LVOT calcium volume (Total), mm^3	15.3 ± 38.2	12.4 ± 31.7	18.1 ± 43.4	0.24	13.6 ± 41.6	17.0 ± 36.2	0.46	0.72

Values are mean ± standard deviation where appropriate

AVC aortic-valvar complex, *LVOT* left ventricular outflow tract

Table 4 Measurements of right heart catheterization before TAVR

	Overall	Balloon-expandable valve			Self-expandable valve			Interaction *p* value
		LVR	HVR	*p* value	LVR	HVR	*p* value	
	N = 708	*N* = 176	N = 147		*N* = 178	*N* = 207		
Pressure measurements								
Systolic arterial pressure, mmHg	138.4 ± 28.0	138.7 ± 26.5	141.1 ± 28.5	0.45	134.4 ± 27.5	139.6 ± 29.3	0.08	0.51
Diastolic arterial pressure, mmHg	65.4 ± 13.5	63.4 ± 12.1	68.6 ± 13.4	< 0.001	62.6 ± 12.9	67.3 ± 14.6	0.001	0.76
Mean arterial pressure, mmHg	95.1 ± 17.7	93.5 ± 15.8	98.1 ± 17.2	0.02	91.9 ± 17.2	97.0 ± 19.4	0.008	0.85
LV systolic pressure, mmHg	189.7 ± 34.9	181.7 ± 30.8	198.5 ± 31.9	< 0.001	175.3 ± 32.1	202.7 ± 36.1	< 0.001	0.03
LV end diastolic pressure, mmHg	22.3 ± 8.3	21.9 ± 7.8	23.5 ± 8.8	0.09	21.9 ± 7.8	22.5 ± 8.8	0.46	0.45
PA systolic pressure, mmHg	50.8 ± 16.2	47.0 ± 14.4	53.2 ± 17.1	0.001	50.2 ± 14.4	53.0 ± 17.8	0.10	0.16
PA diastolic pressure, mmHg	19.8 ± 8.3	17.9 ± 7.6	20.8 ± 8.5	0.001	19.5 ± 7.2	21.1 ± 9.2	0.06	0.29
Mean PA pressure, mmHg	32.6 ± 11.6	29.4 ± 10.5	34.7 ± 12.4	< 0.001	32.0 ± 10.3	34.3 ± 12.3	0.053	0.09
Mean PCWP, mmHg	20.9 ± 8.7	19.8 ± 8.5	20.5 ± 10.1	0.65	22.0 ± 7.6	21.2 ± 8.9	0.55	0.46
Myocardial workload								
Heart rate, bpm	79.4 ± 16.9	74.1 ± 13.7	82.6 ± 18.5	< 0.001	75.4 ± 12.4	85.1 ± 19.2	< 0.001	0.61
Oxygen consumption, ml/min (scheduler)	197.3 ± 33.9	212.0 ± 31.5	191.1 ± 31.1	< 0.001	206.8 ± 32.1	182.6 ± 32.4	< 0.001	0.53
Systolic function								
Cardiac output, L/min	3.87 ± 1.06	4.45 ± 1.10	3.52 ± 0.98	< 0.001	4.11 ± 0.93	3.43 ± 0.88	< 0.001	0.09
Cardiac index, l/(min/m^2)	2.15 ± 0.51	2.35 ± 0.50	2.01 ± 0.51	< 0.001	2.25 ± 0.47	1.98 ± 0.45	< 0.001	0.37
Stroke volume, ml	50.6 ± 17.0	61.6 ± 17.5	43.9 ± 13.1	< 0.001	55.6 ± 15.4	41.8 ± 13.1	< 0.001	0.08
Stroke volume index, ml/m^2	28.1 ± 8.4	32.6 ± 8.2	25.1 ± 7.1	< 0.001	30.6 ± 7.8	24.1 ± 7.0	< 0.001	0.40
Systolic ejection periods, s	24.6 ± 4.6	23.5 ± 4.6	25.2 ± 4.1	< 0.001	23.8 ± 4.7	25.6 ± 4.7	< 0.001	0.96
Aortic valve assessment								
Aortic valve area (Gorlin), mm^2	0.59 ± 0.24	0.74 ± 0.24	0.46 ± 0.17	< 0.001	0.70 ± 0.21	0.45 ± 0.17	< 0.001	0.30

Values are means ± standard deviations or counts (percentages)

LV left ventricular, *PA* pulmonary artery, *PCWP* pulmonary capillary wedge pressure

calcium volume of both aortic-valvar complex and left ventricle outflow tract did not predict moderate or greater post-TAVR AR (Supplementary Table 4).

Discussion

The present study demonstrates the impact of VR at baseline on moderate or greater post-TAVR AR in patients undergoing TAVR according to the type of valve prosthesis. The key findings of the present analyses are as follows: (1) HVR was identified as an independent predictor of post-TAVR AR; (2) increased aortic-valvar complex calcium volume was recorded in patients with HVR compared to those with LVR; and (3) VR essentially affects the risk of post-procedural AR in patients treated with SE. In contrast, however, we found no association between post-procedural AR and VR in patients treated with BE.

During the balloon aortic valvuloplasty era, pronounced symptomatic improvement was observed in patients with AS who underwent a balloon aortic valvuloplasty, despite a small change in AVA [16]. Several previous studies have shown that VR may contribute to the hemodynamic assessment in patients with AS [9, 16, 17]. Indeed, Isaaz and coworkers revealed that hemodynamic improvement after balloon aortic valvuloplasty was more likely to be related to VR changes than AVA changes [9]. Furthermore, this small cohort showed that there was a significant exponentially inverse correlation between VR and AVA [9], which can also be calculated by transforming the Gorlin formula. As previously reported, there is a close relationship between AVA and aortic valve calcium. Annular aortic valve calcium was noted more commonly in patients with a narrow AVA than in those with a wider AVA [18]. Considering these studies, the annuli of patients with HVR may have a higher aortic valve calcium load compared to patients with LVR. In fact, our findings corroborate that the annuli of patients with HVR have a higher aortic valve calcium load as compared to those of patients with LVR (Supplementary Table 1). Furthermore, there is an association between aortic valve calcium and post-procedural AR after TAVR [15, 19]. Accordingly, patients with HVR are likely to show an association with post-TAVR AR. However, the clinical implications of VR have not been fully investigated yet. In the present analysis,

Table 5 Procedural characteristics

	Overall	Balloon-expandable valve			Self-expandable valve			Interaction *p* value
		LVR	HVR	*p* value	LVR	HVR	*p* value	
	N = 708	*N* = 176	*N* = 147		*N* = 178	*N* = 207		
Procedural characteristics								
Procedure time, min	66.8 ± 34.0	66.8 ± 26.6	64.9 ± 31.7	0.57	69.5 ± 38.8	65.6 ± 36.7	0.32	0.70
Length of hospital stay, days	9.3 ± 4.7	8.9 ± 4.2	9.0 ± 3.9	0.83	9.5 ± 5.5	9.8 ± 4.7	0.66	0.84
Access route				0.53			0.22	0.92
Femoral, *n* (%)	601 (84.9)	137 (77.8)	110 (74.8)	0.60	160 (89.9)	194 (93.7)	0.19	
Others, *n* (%)	107 (15.1)	39 (22.2)	37 (25.2)	0.60	18 (10.1)	13 (6.3)	0.83	
Valve type								
Balloon-expandable valve				< 0.001				
Sapien XT, *n* (%)	212 (29.9)	97 (55.1)	115 (78.2)	< 0.001				
Sapien 3, *n* (%)	111 (15.7)	79 (44.9)	32 (21.8)	< 0.001				
Self-expandable valve							0.02	
CoreValve, *n* (%)	283 (40.0)				124 (69.7)	159 (76.8)	0.13	
Evolut R, *n* (%)	37 (5.2)				13 (7.3)	24 (11.6)	0.17	
Symetis Acurate, *n* (%)	23 (3.2)				11 (6.2)	12 (5.8)	1.00	
BSC Lotus, *n* (%)	35 (4.9)				25 (14.0)	10 (4.8)	0.002	
SJM Portico, *n* (%)	6 (0.8)				4 (2.2)	2 (1.0)	0.42	
Direct Flow Medical, *n* (%)	1 (0.1)				1 (0.6)	0 (0.0)	0.46	
Balloon valvuloplasty								0.71
Pre-dilatation, *n* (%)	599 (84.7)	151 (86.3)	139 (94.6)	0.02	131 (73.6)	178 (86.0)	0.003	0.65
Post-dilatation, *n* (%)	161 (22.7)	26 (14.8)	19 (12.9)	0.75	41 (23.0)	75 (36.2)	0.005	0.045
Revascularization								
Concomitant PCI, n (%)	101 (14.3)	24 (13.6)	25 (17.0)	0.44	22 (12.4)	30 (14.5)	0.55	0.86
Procedural specifications								
Post-TAVR AR moderate or severe, *n* (%)	61 (8.6)	5 (2.8)	9 (6.2)	0.18	14 (7.9)	33 (15.9)	0.02	0.99
Post-TAVR need for PPM within 30 days, *n* (%)	165 (23.3)	39 (22.2)	22 (15.0)	0.12	50 (28.1)	54 (26.1)	0.73	0.31

Values are means ± standard deviations or counts (percentages %)

AR aortic regurgitation, *PCI* percutaneous coronary intervention, *TAVR* transcatheter aortic valve replacement, *PPM* permanent pacemaker implantation

TAVR patients had a 2.5-fold higher risk of moderate or greater post-procedural AR. Patients with HVR treated with a SE had a significantly higher rate of moderate or greater post-TAVR AR, but not those treated with a BE. BE can control post-TAVR AR through full expansion of the valve prosthesis due to balloon expansion. In contrast, it is difficult to control post-TAVR AR after implantation of a SE despite a higher rate of post-dilatation. Often, there is no complete expansion of the valve prosthesis owing to radial force or lack of circumferential skirt closing residual leaks between the annulus and the valve frame.

With respect to factors related to post-TAVR AR, our findings are consistent with a large registry from France. In the France2 Registry, the use of a SE had a 2.03-fold higher risk of grade 2 or higher post-procedural AR [4]. Similar to our results, the type of device did not affect mortality. In contrast, in two national TAVR registries from Germany and the United Kingdom, post-procedural AR was significantly associated with mortality, even for a longer term follow-up of more than 5 years [5, 20]. In the CoreValve US high-risk clinical study randomly assigned 1:1 to TAVR with CoreValve or surgical aortic valve replacement, patients with post-procedural AR ≥ mild had a twofold increased risk of death in the TAVR group [21]. The Sapien S3 BE valve, newer generation valve prosthesis, achieved reduction of post-procedural AR owing to the polyethylene terephthalate outer skirt [22]. Although the Sapien S3 decreases the rate of moderate-to-severe AR after TAVR compared with Sapien XT, no significant difference in mortality between groups was observed in an observational study of 209 intermediate–high-risk patients undergoing TAVR using Sapien S3 or XT [23]. These discrepancies with respect to clinical outcomes after TAVR might result from multifactorial etiologies of AS,

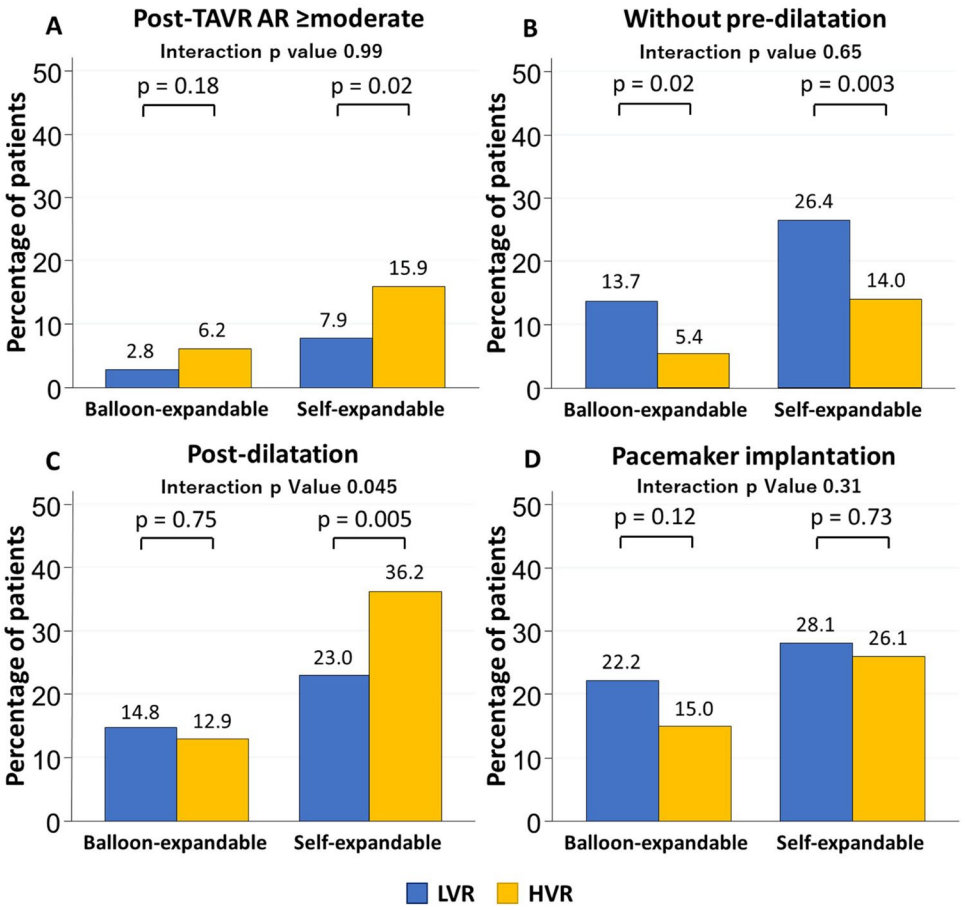

Fig. 1 Impact of valvular resistance on clinical outcomes after TAVR according to type of valve. Bar graph of cumulative incidence of **a** post-TAVR AR ≥ moderate, **b** no pre-dilatation, **c** post-dilatation, and **d** pacemaker implantation after TAVR

Table 6 Predictor of moderate or greater post-TAVR AR

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	Adj. OR (95% CI)	Adj. *p* value
VR ≥ 238	2.38 (1.36–4.18)	0.003	2.45 (1.33–4.51)	0.004
Use of self-expandable valve	3.06 (1.65–5.67)	<0.001	3.11 (1.66–5.82)	<0.001
BMI ≤ 20 kg/m^2	2.51 (1.23–5.12)	0.01	2.73 (1.29–5.77)	0.008
Female	0.85 (0.51–1.45)	0.56	0.58 (0.32–1.03)	0.06
Pre-dilatation	2.12 (0.83–5.43)	0.12	2.29 (0.87–6.01)	0.09
Diabetes mellitus	0.44 (0.21–0.91)	0.03		
Peripheral artery disease	1.31 (0.67–2.54)	0.43		
COPD	1.77 (0.94–3.35)	0.08		
Atrial fibrillation	1.29 (0.75–2.23)	0.35		
Age (years)	1.00 (0.95–1.05)	0.98		
History of CVEs	1.33 (0.60–2.91)	0.48		
Coronary artery disease	0.81 (0.47–1.39)	0.45		
STS-PROM score	1.03 (0.99–1.08)	0.16		
Creatinine > 200 µmol/L	1.19 (0.35–4.03)	0.79		

Multivariable logistic regression models include variables included stepwise if the *p* value of entry was < 0.1

One patient with missing post-TAVI AR is not in these analyses. Single imputation of missing values: creatinine ($n = 1$ assumed ≤ 200), COPD ($n = 1$ assumed no)

AR aortic regurgitation, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CVEs* cerebrovascular events; *STS-PROM* Society of Thoracic Surgeons Predicted Risk of Mortality, *TAVR* transcatheter aortic valve replacement, *VR* valvular resistance

the extent of cardiac dysfunction caused by severe AS (e.g., change in left ventricular geometry and function, right ventricular dysfunction, and other valvular diseases) [24], unmeasurable confounders, different analytic models, variations in the number of included patients and the difference in follow-up periods. However, as VR can be easily assessed during routine RHC, it may be included in the overall risk assessment to obtain better results with respect to post-TAVR AR. Furthermore, our manuscript included an additional clinical implication. In Table 6, in addition to VR, the use of a self-expandable valve or lower BMI was predictors of post-TAVR AR ≥ moderate. Therefore, when considering the use of a self-expandable valve or TAVR in patients have lower BMI, performing RHC prior to TAVR is an option.

Limitations

The present study has some limitations. First, all patients were from a single center, and we were unable to evaluate consecutive patients who underwent TAVR due to the lack of RHC data. Second, the present study is an observational registry study, and valve allocation was not prospectively based on VR. Third, the Lotus valve, which is well known to be capable to reduce post-TAVR AR, was implanted infrequently (4.9%) [25], and categorized as a SE, not as a mechanically expandable valve. Fourth, newer generation TAVR devices enforced a prophylaxis system of paravalvular leak after TAVR. [26] However, they were underrepresented in the present analysis due to the fewer number of events. Therefore, we did not stratify the analysis according to the individual valve type. Furthermore, the impact of newer generation devices on post-TAVR AR could not be adequately addressed. Finally, the long-term enrollment does include a bias due to a refinement of devices or techniques over the time.

Conclusions

HVR was associated with a nearly threefold higher risk of moderate or greater post-TAVR AR and was an independent predictor for moderate or greater post-TAVR AR. The findings were consistently observed in patients treated with SE, but not in those treated with BE. The measurement of VR may be added in the overall risk assessment before TAVR.

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Compliance with ethical standards

Conflict of interest Prof. Pilgrim has received research grants to his institution from Edwards Lifesciences, Symetis, and Biotronik; has received speaker fees from Boston Scientific; and has received reimbursement for travel expenses from St. Jude Medical. Prof. Windecker has received research grants to his institution from Abbott, Amgen, Boston, Biotronik, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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