ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

SCIENZE CARDIO NEFRO TORACICHE

Ciclo 36

Settore Concorsuale: 06/D1 - MALATTIE DELL'APPARATO CARDIOVASCOLARE E MALATTIE DELL'APPARATO RESPIRATORIO

Settore Scientifico Disciplinare: MED/11 - MALATTIE DELL'APPARATO CARDIOVASCOLARE

OFF-LABEL USE OF BALLOON-EXPANDABLE TRANSCATHETER VALVES TO TREAT PURE AORTIC REGURGITATION

Presentata da: Mateusz Orzalkiewicz

Coordinatore Dottorato
Niccolò Daddi

Supervisore
Nazzareno Galiè

Esame finale anno 2024

Index

1. Graphical abstract **3**

2. Abstract **4**

2.1 Background **4**

2.2 Aims **4**

2.3 Methods **4**

2.4 Results **5**

2.5 Conclusions **5**

3. Background **6**

4. Methods **10**

4.1 Study design **10**

4.2 Study population and pre-procedural evaluation **10**

4.3 Pre-procedural CT **11**

4.4 TAVI procedure **12**

4.5 Post-procedural CT analysis **12**

4.6 Study endpoints **13**

4.7 Statistical analysis **13**

5. Results **14**

5.1 Procedural outcomes **14**

5.2 Post-procedural CT **19**

5.3 LVOT morphology and outcomes **22**

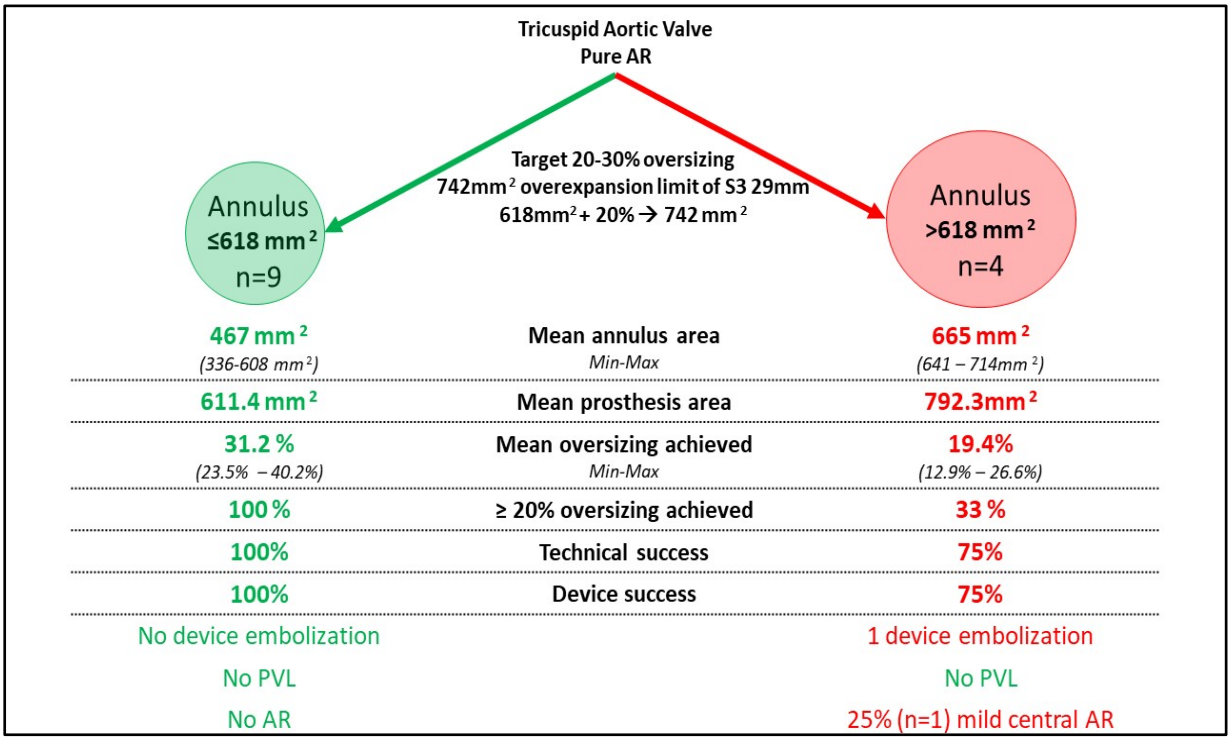
5.4 Echo follow-up **23**

5.5 Clinical outcomes **25**

6. Discussion **27**

7. Bibliography **32**

1. Graphical abstract



1. Graphical abstract. AR – aortic regurgitation, S3 – Sapien 3 prosthesis, PVL paravalvular leak

2. Abstract

2.1 Background

Transcatheter aortic valve implantation (TAVI) in pure severe native aortic regurgitation (AR) is challenging, as dedicated devices are not widely available. Compassionate, off-label use of transcatheter heart valves (THVs) approved for the treatment of aortic stenosis has been reported, mainly with self-expanding THVs. When balloon-expandable valves (BEV) are preferred, oversizing with respect to the annulus is necessary, but there is scant data regarding optimal oversizing and its safety.

2.2 Aims

To assess BEV oversizing and outcomes of TAVI with BEV in pure AR.

2.3 Methods

Consecutive patients undergoing transfemoral TAVI in pure AR with Sapien BEV at our centre between 2019 and 2023 were included. Bicuspid (BAV) and tricuspid (TAV) aortic valves were analyzed separately. The assure anchorage the aim was to implant a valve with 20-30% oversizing with respect to the annulus. TAV were divided into small annulus group (≤618mm^2, SA) where ≥20% oversizing is achievable based on published data on BEV overexpansion and larger annulus group (LA, >618mm^2). Overexpansion and actual oversizing were measured on post-procedural CT scan. Procedural and clinical outcomes during follow-up were analyzed using the Valve Academic Research Consortium-3 criteria.

2.4 Results

Seventeen patients were identified (76.5% males, mean age 79.2 years, STS 3.8%, TAV 13 patients). Mean aortic valvular calcium volume was: TAV=15.4mm^3 and BAV=171.0mm^3 (p=0.001). Technical success was 94.1% with one valve embolisation in TAV LA group. Mild paravalvular leak (PVL) was more frequent in BAV (p=0.0088). There were no cases of AR > grade 1.

The post-procedural CT in TAV patients showed a mean 28.3% oversizing, significantly higher in SA (31.2%) then in LA group (19.4%), p= 0.0092. Oversizing ≥20% was achieved in 100% SA vs 33.3% LA patients (p=0.046). In LA patients the implanted BEVs were significantly more overexpanded than in SA group (10.8% vs 22.3%, p=0.0119)

In-hospital mortality was 5.9% (1 TV patient). There was no difference in 1-year mortality between groups. Echocardiographic follow-up showed stable gradients without PVL. One patient developed endocarditis with bioprosthetic valve failure.

2.5 Conclusions

TAVI in pure AR with oversized Sapien BEV showed good procedural and short-term outcomes when ≥20% oversizing was predictably achievable. Prosthesis overexpansion does not affect valve function at short-term follow-up.

3. Background

Severe aortic valve regurgitation (AR) is a common valvular disease, increases with age, occurring in up to 2% of individuals over 65 years of age (1,2). AR may be associated with aortic stenosis (AS) in calcific aortic valve (AV) disease or pure AR caused by the malcoaptation of the non-calcified AV cusps due to primary disease of the cusps, the abnormalities of the aortic root (dilatation or geometric distortion of the aortic root) or due to a combination of both mechanisms (3):

The causes of AR due to primary valve disease include:

- congenital leaflet abnormalities degeneration like bicuspid AV where abnormal valve structure predisposes it to wear and tear, leading to regurgitation;
- acquired leaflet abnormalities due to rheumatic fever which causes scarring and thickening of valve leaflets preventing coaptation and causing insufficiency or due to infective endocarditis with damage and perforations of the leaflets;
- other rarer acquired causes: chest trauma with traumatic rupture or avulsion of an aortic cusp, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and many others.

The causes of AR due to primary aortic root abnormalities:

- age-related changes with or without chronic systemic hypertension;
- cystic medial necrosis associated with Marfan syndrome or osteogenesis imperfect;
- inflammatory disorders as ankylosing spondylitis, Behcet syndrome, psoriatic arthritis, arthritis associated with reactive arthritis, ulcerative colitis;
- acute or chronic retrograde dissection of the aorta that involves and disrupts the aortic annulus.

Untreated severe AR leads to left ventricular (LV) volume overload, increase ventricular wall stress, chamber dilatation and LV dysfunction. (4). Current guidelines recommend surgical valve replacement (SAVR) or surgical valve sparing procedures for severe AR for patients who are symptomatic with heart failure or develop LV dysfunction or dilatation (5).

However, in the aging population, a significant number of patients with symptomatic severe AR are not eligible for surgery due to comorbidities and prohibitive surgical risk and are often treated conservatively (4,6). Once symptoms develop, in patients without surgical treatment annual mortality is up to 20% (4,6,7) which is even higher for patients with reduced LV function (8).

Transcatheter aortic valve implantation (TAVI) has been developed for and revolutionised the treatment of severe AS in the recent years. Numerous studies show progressive improvements in procedural outcomes and, despite expanding indications towards younger and lower risk patients, TAVI shows durable benefits compared with SAVR with respect to all-cause mortality or disabling

stroke (9,10). However, the results achieved in AS patients cannot be directly translated to pure non-calcified AR patients. The available TAVI devices can be dived into balloon-expandable valves (BEV) and self-expanding valves (SEV) and all are designed to anchor on the thickened calcified leaflets of the AV. In the treatment of pure AR TAVI might represent an alternative to SAVR but, given the AR specific anatomical features that can compromise device success and procedural safety, until now there are no randomised clinical trials of TAVI for pure AR. The only two dedicated transcatheter devices for pure AR with unique anchoring mechanism which does not require a calcified anchoring zone are the J-Valve (JCMedical) and the JenaValve (JenaValve Technology) have been used in the past via the transapical approach (11,12) and demonstrated satisfactory outcomes and low rates of THV embolisation, residual AR and permanent pacemaker implantation. These devices they have been recently replaced with transfemoral systems and start showing promising procedural and short-term results in pure AR (13–16) but they are currently not widely available outside the clinical trials setting.

Off-label use of oversized THV prosthesis dedicated for AS is feasible and has increased over the years (17) with results getting progressively better with operators' experience and newer generations of devices (18,19). The procedure, however, faces challenges for valve positioning and anchoring (lack of calcium, large annuli, dilated aortic root and increased stroke volume) and the risks of the greater degree of oversizing required resulting in unpredictable outcome with increased the risk of complications (embolisation, migration or annular rupture) (20). In the majority of published series the operators preferably used SEV probably due to the possibility of recapturing, repositioning and the perceived

benefit of continuous radial pressure on the annulus facilitating anchorage of the prosthesis (21–27). However available SEV may not be able to achieve sufficient oversizing in large annuli patients and, in the absence of head-to-head comparisons, the device choice depends on clinical factors, root anatomy and local expertise. There is a growing interest in the use of oversized BEV in pure AR (28–30) with favourable short term results, even in very large annuli patients (31). BEV final size can be modulated with overfilling and underfilling the balloon to achieve the desired oversizing. There is a paucity of data regarding optimal oversizing and its safety. In the current manuscript, I report our experience of TAVI with a BEV in consecutive inoperable patients with native pure AR focused on the oversizing and overexpansion achieved and related outcomes.

4. Methods

4.1 Study design

Single-centre observational study that enrolled all consecutive patients with symptomatic severe pure AR who underwent compassionate TAVI with a BEV (SAPIEN 3, Edwards Lifesciences) performed between January 2019 and September 2023.

Tricuspid aortic valve (TAV) and bicuspid aortic valve (BAV) patients were analyzed separately. Data was collected in a dedicated hospital database, which captures baseline clinical, laboratory, echocardiographic and CT data as well as procedural data and clinical follow-up.

4.2 Study population and pre-procedural evaluation

All patients were evaluated by our Heart Team consisting of cardiologists, cardiovascular surgeons and (when needed) cardiac anaesthesiologists on the basis of routine laboratory test, transthoracic and transoesophageal echocardiography, coronary angiography and ECG-gated contrast enhanced computed tomography (CT) and were deemed not eligible for SAVR due to prohibitive operative risk. Severe AR was defined according to ESC guidelines criteria. (5) Patients with AS defined as a mean aortic valve gradient >20 mm Hg were excluded. If no AS was reported for a patient, then mean gradient and aortic valve area were not available.

4.3 Pre-procedural CT and BEV sizing

The quantification of aortic valve calcification was performed from contrast-enhanced CT using an automatic Aortic Valve Calcium Score (AVCS) on a 3mensio Valves™ workstation (version 10.2, 3mensio Medical Imaging B.V., Netherlands) and reported as a calcification volume (in mm^3) with the threshold for correct calcium identification depending on the contrast enhancement of aortic and cardiac structures (in patients with left ventricular outflow tract of >300 Hounsfield units [HU] the threshold was set at 850 HU). (32,33)

The LVOT morphology (tapered, tubular or flared) was determined on the pre-procedural CT based on the difference in area between the annular plane and 3 mm below the annulus as previously described (34).

BEV size and expansion volume were chosen by the operator based on the annulus measurement [systolic virtual basal ring (VBR) area] and in order to achieve 20-30% oversizing. Based on the ex-vivo studies the Sapien 29 mm valve with additional 4 mls of contrast achieves the area of 742 mm^2 and this would provide a sufficient oversizing of at least 20% for the annulus of 618 mm^2. Therefore TAV patients were divided in two groups based on the annulus area: smaller annulus (SA, ≤618mm^2) with expected least 20% oversizing and larger annuli (LA, >618mm^2) with less predictable achievement of at least 20% oversizing.

4.3 TAVI procedure

All procedures were performed in the hybrid catheterization laboratory with full cardiac surgery back-up. Femoral artery access via the femoral artery using ultrasound-guided puncture and Seldinger technique was used for all cases. BEV choice was based on operator preference (Sapien 3/3 Ultra). The implantation itself did not differ from our standard TAVI procedure for AS with the exception of slightly lower intended implantation depth ranging up to 5 mm below the annular plane in cases with expected shortening of the inflow part due to overexpansion. In cases with significant overexpansion the extra volume of contrast (5-8 mls) was delivered by a syringe attached on the side port of the stopcock of the delivery system and was injected before the nominal volume from the inflator.

4.4 Post-procedural CT

Following a successful TAVI all TAV patients underwent ECG-gated CT scan to assess the BEV overexpansion and oversizing achieved. The BEV dimensions were assessed at the native annulus level. Achieved area oversizing (%) was calculated as: (BEV outer area/VBR area – 1) x 100. Achieved valve overexpansion (%) was calculated as: (BEV outer area/nominal BEV area – 1) x 100. We did not perform the post-procedural CT in the BAV patients as the sizing algorithms and oversizing are not based only on VBR area.

4.5 Study endpoints

The main outcome was assessment of the oversizing achieved and effectiveness and safety of our sizing strategy aiming at 20-30% oversizing in TAV patients with SA and LA based on post-procedural CT and using the Valve Academic Research Consortium-3 (VARC-3) definitions (35) for procedural and follow-up outcomes. MACE were defined as cardiovascular death, stroke and myocardial infarction. Secondary outcome was to evaluate the effects of valve overexpansion in follow-up. Follow-up was obtained through clinical visits and/or by telephone.

4.6 Statistical analysis:

Continuous variables were assessed for normality, prior to the analysis, using Shapiro-Wilk test. Normally distributed variables were reported as mean ± standard deviation (SD) and compared using independent samples t-tests. Repeated, longitudinally measured values were compared with paired-samples t-test. Non-normal and ordinal variables were compared using non-parametric Mann-Whitney tests and reported as means, whilst categorical variables were reported as absolute numbers and percentages and were compared using chi-square test or Fisher's exact test. In addition, a Kaplan-Meier approach was used to estimate the outcome rates at different points of follow-up and compared using a log-rank test. All tests were two sided and $p<0.05$ considered significant. All analyses were performed using the STATA 14.2.

5. Results

5.1 Procedural outcomes

Seventeen consecutive transfemoral TAVI for pure AR with Sapien BEV at our institution were identified. The mean age was 79.2 ± 7.3 years with 76.5% males, mean STS PROM 3.8 ± 1.6 %, n=13 patients in TAV and n=4 in BAV group (**Table 1**). The TAV and BAV patients' baseline characteristics were similar except for significantly worse rental function in TAV than BAV patients (eGFR 37.4 vs 72.4 ml/min/1.73m^2 respectively, p=0.0013). Mean left ventricular ejection fraction (LVEF) (44.8% vs 42.5, p=0.75) and mean AV gradient (9.1 vs 12.8 mmHg, p=0.17) did not differ significantly between TAV and BAV patients but BAV patients had a significantly higher mean aortic valve calcium volume than TAV patients (171 vs 15.4 mm^3 respectively, p=0.001).

The prevalent etiology of AR in the TAV patients was functional (38%) whereas in the majority of BAV patients the etiology was degenerative (75%).

All patients were in functional class NYHA III. BEVs implanted were: 70.6% (n=12) Sapien 3 29mm and 29.4% (n=5) Sapien 3 Ultra. No major vascular complications occurred.

	All patients (n=17)	TAV patients (n=13)	BAV patients (n=4)	p-value*
Age , yrs	79.2 ±7.3	80.8±5.6	73.9±10.5	0.10
Males	76.5% (13)	69.2% (9)	100% (4)	0.21
BMI (kg/m²)	24.9 ±3.9	23.9±2.5	28.3±6.1	0.043
STS score	3.8 ±1.6	4.0±1.7	3.2±1.6	0.445
Diabetes	35.3% (6)	38.5% (5)	25% (1)	0.62
Atrial fibrillation	29.4% (5)	30.8% (4)	25% (1)	0.82
Permanent PM	29.4% (5)	30.8% (4)	25% (1)	0.82
Prior PCI	17.6 % (3)	15.4% (29	25% (1)	0.66
Prior MI	17.6 % (3)	15.4% (2)	25% (1)	0.66
COPD	41.2% (7)	38.5% (5)	50% (2)	0.68
Haemoglobin (mg/dl)	12.3 ± 0.9	12.4±1.6	12.1±2.0	0.74
eGFR (ml/min/1.73m²)	45.6±21.3	37.4±11.7	72.3±25.7	0.0013
Mean AVG (mmHg)	9.9 ±4.6	9.1±4.6	12.8±3.6	0.17
LVEF, (%)	44.2 ± 12.1	44.8 ±12.0	42.5 ±14.2	0.75
LVEF ≤35%	23.5% (4)	23.1% (3)	25% (1)	0.94
LVEDD (mm)	56.9±8.9	56.2±9.5	59.3±6.8	0.56
LVEDV (ml)	187±68.1	184.5±69.2	197.0±73.7	0.76
LVEDVi (ml/m²)	102.2 ± 33.5	102.2 ±35.6	102.3 ±30.2	0.99
>moderate MR	11.8%% (2)	15.4% (2)	0	0.40
AR etiology:				0.20
Degenerative	41.2% (7)	30.8% (4)	75% (3)	
Functional	29.4% (5)	38.4% (5)	0	
Mixed	17.6% (3)	23.1 %(3)	0	
Other**	11.8% (2)	7.7% (1)	25% (1)	
Aortic annulus area, mm²	551.9 ±136.7	528.9±130.9	627.0±146.2	0.22
Aortic annulus perimeter, mm³	83.7 ±10.7	81.9±10.6	89.5±9.9	0.22
ICD, mm	-	-	29.5±3.5	-
Mean AV calcium volume, mm³	52.0 ±93.9	15.4±28.6	171.0±138.2	0.001
AV calcium volume, mm³				0.047
0	47.1% (8)	53.9% (7)	25% (1)	
1-25	23.5% (4)	30.8% (4)	0	
25-50	5.9% (1)	7.7% (1)	0	
>50	23.5% (4)	7.7% (1)	75% (3)	
Valve implanted				0.42
Sapien 3 Ultra 23 (+1-2mls)	17.6% (3)	23.1% (3)	0	
Sapien 3 Ultra 26 (nominal, +1mls)	11.8% (2)	7.7% (1)	25% (1)	
Sapien 3 29 (+5-8mls)	70.6% (12)	69.2% (9)	75% (3)	

Table 1. Baseline and procedural characteristics. Values are mean±SD or % (n).
*difference between BV an TV patients
**previous endocarditis (1), acute traumatic aortic regurgitation (1)
AR –aortic regurgitation, AV – aortic valve, AVG – aortic valve gradient, BMI –body mass index, BV – bicuspid valve, COPD- chronic obstructive pulmonary disease, eGFR - estimated glomerular filtration rate; ICD-intercommissural distance, LVEDD/i left ventricular end-diastolic diameter; LVEDV/i – left ventricular end-diastolic volume/indexed, LVEF - left ventricular ejection fraction; MI - myocardial infarction; MR – mitral regurgitation, PCI - percutaneous coronary intervention; PM- permanent pacemaker, STS - Society of Thoracic Surgeons, TV – tricuspid valve

Overall technical success (94.1%, 1 device embolisation in TAV LA group) and device success (88.2.%) did not differ significantly between TAV and BAV patients (p=0.57 and p=0.35, respectively). BAV patients had a significantly higher prevalence of mild paravalvular leak (PVL) with respect to TAV patients (2 vs 0, p=0.0088). One TAV patient had a mild central intraprosthetic AR. Five patients had a preexisting permanent pacemaker (PM) and 3 TAV patients needed a PM implantation after TAVI. There were no statistically significant differences in procedural outcomes between SA and LA TAV patients but the only one BEV embolisation occurred in TAV LA group **(Table 2 and 3).** The BEV embolised into the LV within few beats after implantation. After the initial unsuccessful attempt of percutaneous retrieval from the LV using a balloon recapture, the patient underwent emergency surgical extraction of the embolised prosthesis and surgical aortic valve replacement.

	All patients (n=17)	TAV patients (n=13)	BAV patients (n=4)	p-value*
Technical success VARC-3	94.1% (16)	92.3% (12)	100% (4)	0.57
Device success VARC-3	88.2% (15)	92.3% (12)	75% (3)	0.35
Early safety VARC-3	94.1% (16)	92.3% (12)	100% (4)	0.57
New PM implantation	17.6% (3)	23.1% (3)	0	0.29
BEV embolisation	5.9% (1)	7.7% (1)	0	0.57
AVA, cm^2	1.83 ± 0.4	1.80±0.3	1.91±0.42	0.62
AVAi, cm^2/m^2	1.03±0.2	1.05±0.24	0.99±0.2	0.67
Mean BEV gradient, mmHg	9.6 ±4.9	8.4±3.4	13.0±7.6	0.11
Mild PVL	2	0	50% (2)	0.0088
Mild central AR	5.9% (1)	7.7% (1)	0	0.55

Table 2. TAVI procedural outcomes.

*difference between BV an TV patients

Values are mean**±**SD or % (n).

AR – aortic regurgitation, AVA/i – aortic valve area/indexed, BEV – balloon expandable valve, BAV – bicuspid aortic valve, PM- permanent pacemaker, PVL – paravalular leak, TAV – tricuspid aortic valve, VARC – valve academic research consortium

	TAV smaller annulus (≤618mm²) (n=9)	TAV larger annulus (>618 mm²) (n=4)	p-value
Technical success VARC-3	100% (9)	75% (3)	0.12
Device success VARC-3	100% (9)	75% (3)	0.12
Early safety VARC-3	100% (9)	75% (3)	0.12
New PM implantation	22.2% (2)	25% (1)	0.91
BEV embolization	0	25% (1)	0.12
AVA, cm²	1.7 ±0.3	2.3±0.1	0.018
AVAi, cm²/m²	1.0 ±0.3	1.2 ±0.2	0.30
Mean BEV gradient, mmHg	9.0±3.3	6.7±3.5	0.32
Mild PVL	0	0	1
Mild central AR	0	25% (1)	0.12

Table 3. TAVI procedural outcomes.

Values are mean±SD or % (n).

AR – aortic regurgitation, AVA/i – aortic valve area/indexed, BEV – balloon expandable valve, BAV – bicuspid aortic valve, PM- permanent pacemaker, PVL – paravalular leak, TAV – tricuspid aortic valve, VARC – valve academic research consortium

5.2 Post-procedural CT

Twelve successfully treated TAV patients underwent post-procedural CT scan **(Figure 1).** The mean prosthesis oversizing achieved with respect to the annulus achieved was 28.3% (±7.8%) with a significantly bigger mean oversizing achieved SA patients (31.2%) than LA patients (19.4%), p=0.0092.

83.3% (10/12) of patients achieved ≥20% oversizing and 41.7% (5/12) an oversizing of ≥30%.

≥20% oversizing was achieved in 100% (9/9) SA patients group vs only in 33.3% (1/3) in LA group (p=0.046) despite significantly higher prosthesis overexpansion with respect to nominal area than in LA than in SA group (10.8% vs 22.3% respectively, p=0.0119). **(Table 4, Figure 2)**

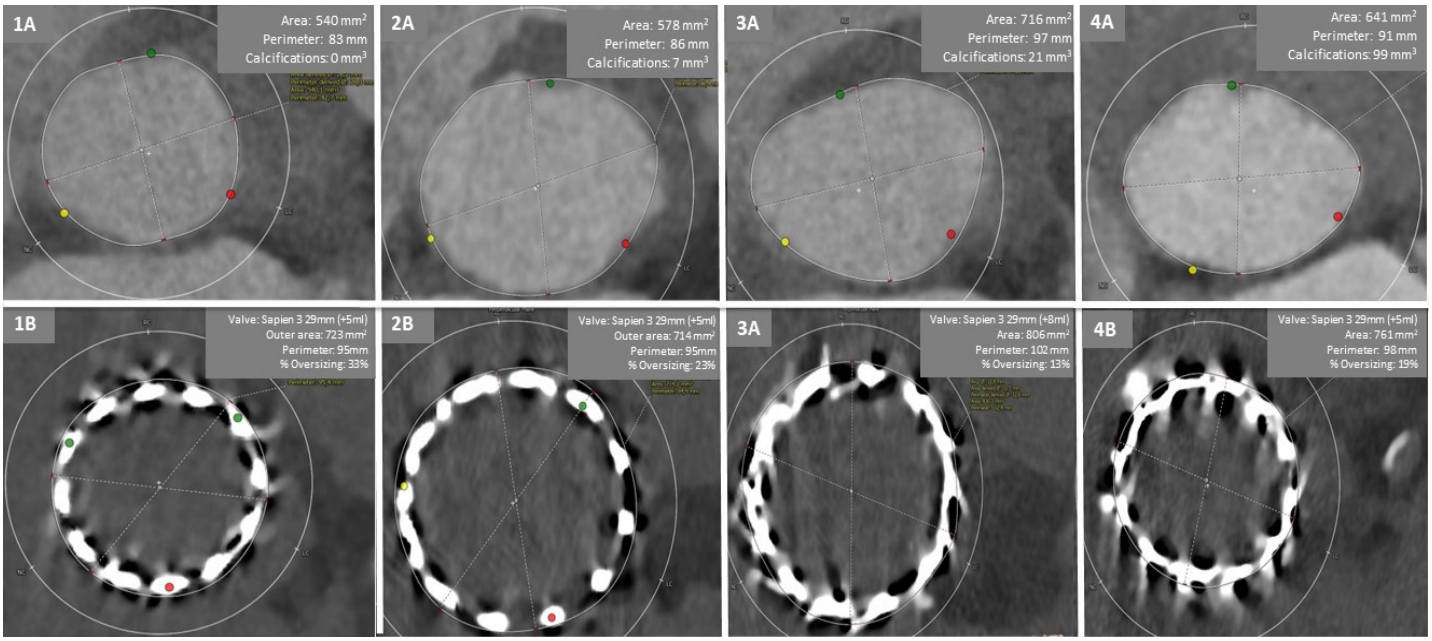


Figure 1. Four examples of pre- and post-TAVI CT with measurement of oversizing achieved.

	TAV smaller annulus (n=9)	TAV larger annulus (n=3)	P-value
Mean annulus area (mm^2)	467.3 ± 107	665.0 ±42	0.012
Mean oversizing achieved (%)	31.2±5.1	19.4±6.9	0.0092
≥20% oversizing achieved	100% (9)	33.3% (1)	0.046
Mean prosthesis area (mm^2)	611.4±132.6	792.3±27.2	0.046
Mean BEV overexpansion (%)	10.8±5.9	22.3±4.2	0.0119

Table 4. Oversizing and overexpansion after successful TAVI between study group based on post-procedural CT.

Values are mean**±**SD or % (n).

BEV – balloon expandable valve, TAV – tricuspid valve,

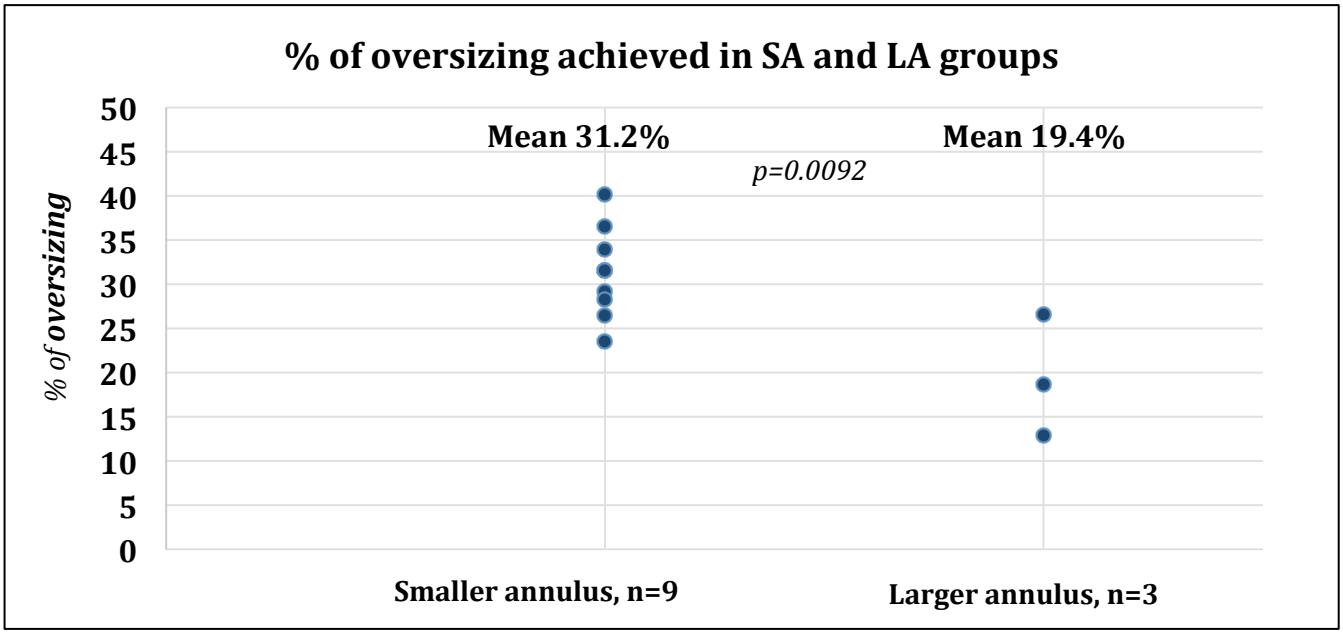


Figure 2. % of oversizing achieved in smaller annulus (SA) and larger annulus (LA) groups.

5.3 LVOT morphology and outcomes

The most common LVOT morphology in our series was a tapered type in 52.9 % of patients (n=9), followed by the tubular shape (6 patients, 35.3%) and flared (2 patients, 11.8%). The only valve embolisation in our series occurred in a patient with a flared shape LVOT anatomy. **(Figure 3)**

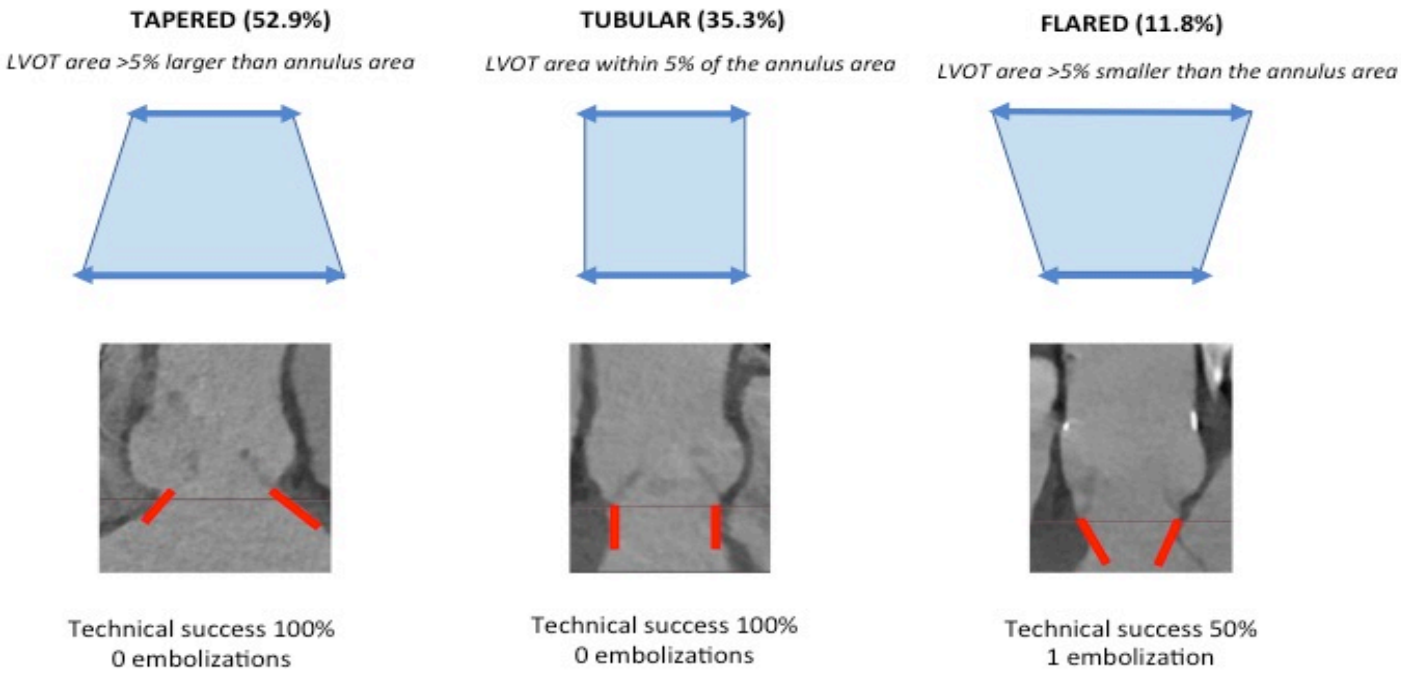


Figure 3. Left ventricular outflow tract (LVOT) morphology and related outcomes.

5.4 Echocardiographic follow-up

Over the mean follow-up of 329 days in 12 patients who underwent follow-up echocardiogram there was no statistically significant change in mean LVEF (41.8% vs 42.8%, p=0.8) or mean AV gradient AV gradient (9.8 vs 9.4 mmHg, p=0.82). One PVL in a BAV patient worsened from mild to moderate. No new PVL occurred. Two TAV patients developed mild intra-prosthetic regurgitation. One structural valve failure occurred due to acute endocarditis. **(Table 5)**

All patients (n=12)			
	Baseline	**Follow-up**	**p-value**
LVEF, (%)	41.8 +13.2	42.8 +17.5	0.80
Mean AVG (mmHg)	9.8 +4.0	9.4+2.7	0.82
AVAi (cm^2)	1.1 + 0.2	1.1+0.3	0.76
PVL, % (n)	16.7% (2 mild)	16.7% (1 mild, 1 moderate)	1
Intraprosthetic AR	8.3% (1 mild)	33.3% (3 mild, 1 severe*)	0.13

* severe AR due to acute infective endocarditis

Table 5. Echocardiographic follow-up.

Values are mean±SD or % (n).

AVAi – aortic valve area indexed, AVG – aortic valve gradient, AR – aortic regurgitation,

LVEF – left ventricular ejection fraction, PVL – paravalular leak

Among TAV patients who underwent follow-up echo (n=10) the changes in prosthesis function were irrespective of the degree of BEV overexpansion (<15% or ≥15%) **(Table 6).**

	BEV with <15% overexpansion (n=6)			BEV with ≥ 15% overexpansion (n=4)		
	Baseline	**Follow-up**	**p**	**Baseline**	**Follow-up**	**p**
LVEEF, (%)	46.2 ±12.8	45.2 ± 13.0	0.73	37.3 ± 12.6	46.3 ± 26.2	0.31
Mean AVG (mmHg)	7.7±2.3	10.0±1.5	0.11	7.3 ± 3.1	9.0 ± 3.8,	0.35
AVAi (cm^2)	1.09 ±0.2	1.3±0.2	0.40	1.2 ± 0.3	1.0 ± 0.4	0.34
PVL	0	0	-	0	0	-
Intraprosthetic AR	0	33.3% (1 mild, 1 severe*)	0.12	25% (1 trace)	50% (2 mild)	0.47

*severe AR due to acute infective endocarditis

Table 6. Echocardiographic follow-up depending on BEV overexpansion.

Values are mean**±**SD or % (n).

AVAi – aortic valve area indexed, AVG – aortic valve gradient, AR – aortic regurgitation,

LVEF– left ventricular ejection fraction, PVL – paravalular leak

5.5 Clinical outcomes

In-hospital mortality was 5.9% (1 patient). The overall estimated one-year survival for all patients was 87.8% and estimated one-year MACE rate was 24.7% (**Figure 3 and 4).** Two patients in the TAV group underwent successful elective mitral transcatheter edge-to-edge repair in follow-up.

Figure 3. Survival curve for 1-year all-cause mortality

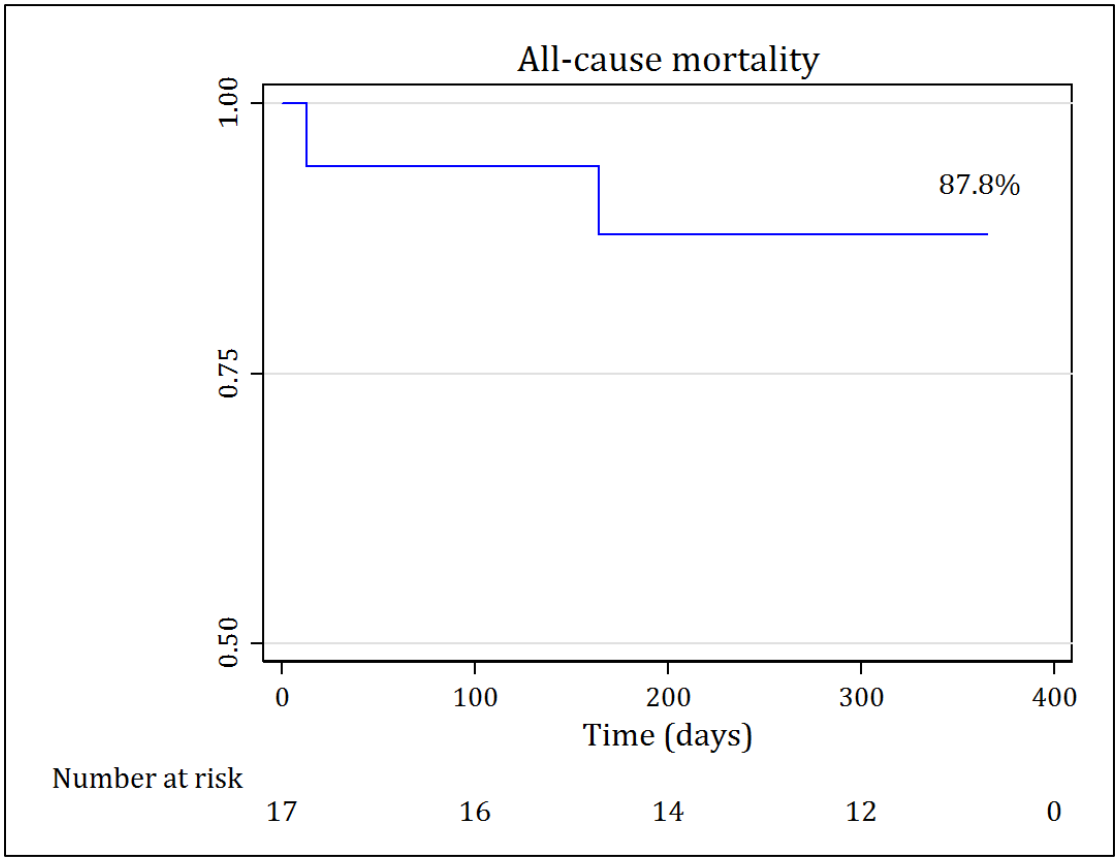
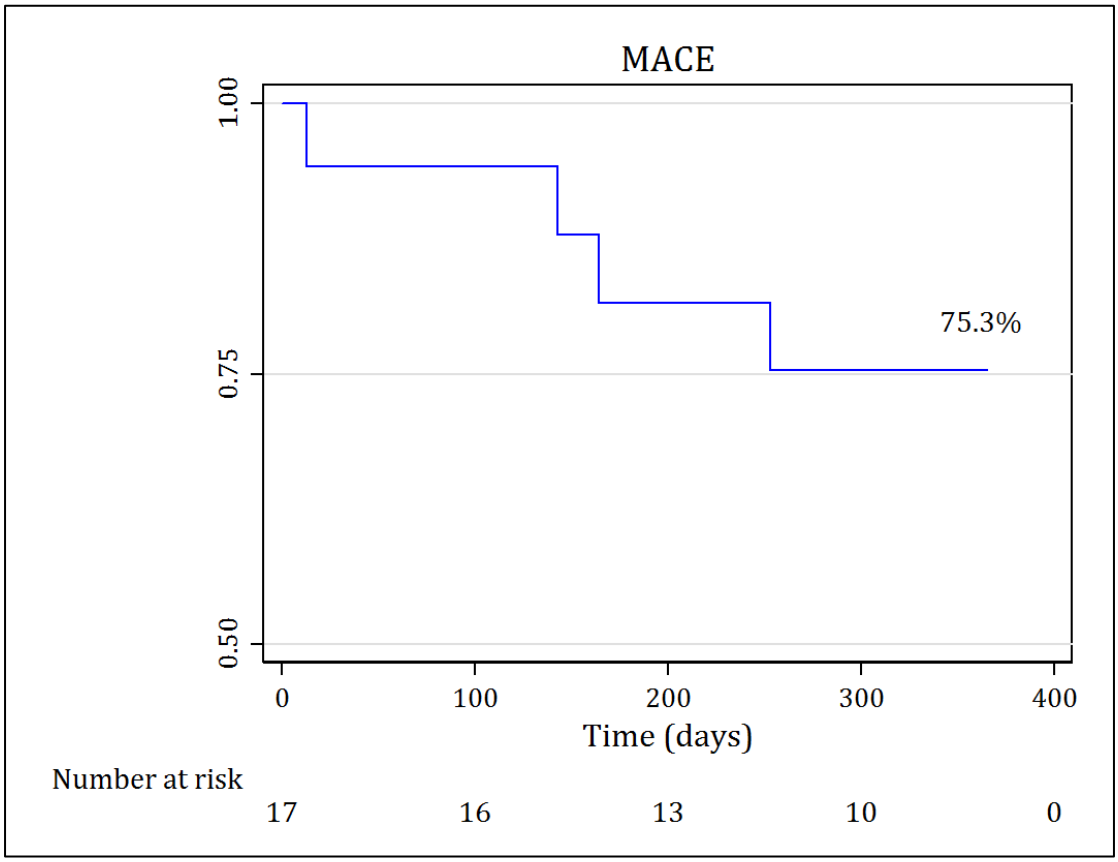


Figure 4. Survival curve for 1-year MACE.



5. Discussion

The principal findings of our study are the following:

1) TAVI with BEV in inoperable patients with pure AR is feasible with acceptable procedural and short-term results;

2) the annulus area of ≤618 mm^2 provides a safe and predictable margin for achieving at least 20% Sapien BEV oversizing;

3) a degree of valve overexpansion with respect to nominal size appears a good method to achieve appropriate oversizing when needed and does not seem to be associated with structural valve degeneration in short-term follow-up in pure AR patients.

In calcific AS a 5-15% of oversizing is generally recommended in order to balance the risk of embolisation, PVL and annual rupture whereas oversizing of ≥20% is associated with a risk of annular rupture (36–38). In pure AR being an off-label indication there are no official recommendations for oversizing but in the light of the lack of calcium for anchorage, the higher 20 – 30% oversizing is commonly adopted (28). AR valves are more elastic than calcified stenotic valves and can expand to a greater degree during deployment in cases of BEV implantation (39). The maximal degree of annular distensibility is unpredictable – a case report of an implanataion of 29 mm Sapien BEV in a patients with pure AR and annulus of 443mm^2 resulted in a 49% oversizing without signs of aortic root injury (40). In patients with large anatomies the oversizing needed can be achieved with balloon overfilling. Feasibility of BEV overexpansion has been demonstrated in bench testing with a corresponding gain on prosthesis area (34)

and non-nominal BEV expansion showed excellent durability (35) and overexpansion does not seem to have any negative clinical impact in short- to mid-term follow-up in patients with calcific AS (41,42). This has not been studied in pure AR patients. This study shows no signs of overexpanded prosthesis degeneration in the short- term follow-up in pure AR patients. There were no new PVLs but the occurrence of mild intraprosthetic AR needs further follow-up.

The CT assessment of achieved oversizing and overexpansion in pure AR patients has not been assessed to date in larger patient series. This study confirms the highly predictable overexpansion of the Sapien prosthesis with non-nominal inflations and the >15-20% overexpansion probably reaching the limits of balloon compliance.

Moreover, in our study we showed that ≥20 % oversizing is achievable in all patients with the annulus area of ≤618 mm^2 and was sufficient to ensure technical success. In LA patients only 33% achieved >20% oversizing and the only one device embolisation occurred in this group.

The use of larger BEVs (up to 32 mm) available from other manufacturer showed good procedural and mid-term outcomes in treatment of pure AR in a recently published registry (34). In this study the mean annulus area was 638.5 mm^2 (above our cut-off for achieving predictable ≥20% oversizing with Sapien BEV) and hence large valve sizes were used in 80% of patients. Larger BEVs might be useful in these patients but as the use of BEV in the setting of pure AR remains off-label a randomised comparison with Sapien BEV is unlikely. It is also worth noticing that even the novel dedicated the Trilogy JenaValve prostehsis does not cover annuli with diameters greater than 27 mm which corresponds to an area of around 576 $mm^{2.}$.

LVOT morphology may play a role in predicting device embolisation risk as the anchorage plane and the degree of oversizing needed may differ according to the type. In a recently published series with a different BEV type a tapered type LVOT was present in all 4 embolisations that occurred and this morphology was significantly related to the risk of embolisation (34). In the present study the only one embolisation occurred in the flared type LVOT and does not confirm the finding but the patients number is to small to perform statistical analysis and draw any definite conclusions.

In terms of clinical outcomes our study confirms the good procedural results of transfemoral TAVI with Sapien BEV in pure AR with high device success rate and low in-hospital mortality. Observational studies of TAVI in pure AR show a higher risk of complications than TAVI in AS with reported in-hospital mortality of 2-3 % (43–45), a device success rate of 80.4%, ≥moderate aortic regurgitation (AR) in 7.4% of patients, and a 30-day mortality rate of 9.5%, with up to 3% requiring conversion to open surgery (23) but the outcomes are improving with new generation of devices. (25,46) It is worth noticing that TAVI in pure AR is performed as an off-label indication in inoperable patients and the high early mortality mirrors the outcomes of initial TAVIs performed in inoperable patients with AS (in PARTNER 1 trial 30-day mortality was 3.4% for inoperable and high risk patients)(47). Patients with pure AR represent a population with different pathologies often including exclusively surgical and high-risk indications like acute infective endocarditis, aortic dissection or aortic root aneurisms and in fact even SAVR as the gold standard treatment for AR also carries a high in-hospital mortality up to 5.7% in some series even significantly higher than off-label TAVI in pure AR (43,48).

Our study shows that, in selected inoperable patients, TAVI for pure AR using Sapien BEV results in low in-hospital mortality and low complication rates, especially in patients with the annulus of ≤618 mm^2 in whom at least 20% oversizing is predictably achievable. Off-label use of Sapien BEV represents a good option for these patients as dedicated devices are not widely available and non-randomized clinical trials are ongoing to confirm their safety and effectiveness.

Study limitations:

The study has several limitations. This is a single centre observational study with data collected prospectively. The decision of final BEV size and inflation volume was based on operators' decision. Due to the low number of patients and low number of events the study is not powered for clinical outcomes. The data must be confirmed in large prospective multicentre cohorts.

Bibliography:

1. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). The American Journal of Cardiology. 1999 Mar 15;83(6):897–902.

2. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study†. European Heart Journal. 2016 Dec 14;37(47):3515–22.

3. Boodhwani M, de Kerchove L, Glineur D, Poncelet A, Rubay J, Astarci P, et al. Repair-oriented classification of aortic insufficiency: Impact on surgical techniques and clinical outcomes. The Journal of Thoracic and Cardiovascular Surgery. 2009 Feb 1;137(2):286–94.

4. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and Morbidity of Aortic Regurgitation in Clinical Practice. Circulation. 1999 Apr 13;99(14):1851–7.

5. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2022 Feb 14;43(7):561–632.

6. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European Heart Journal. 2003 Jul 1;24(13):1231–43.

7. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation. 1991 Oct 1;84(4):1625–35.

8. Kamath AR, Varadarajan P, Turk R, Sampat U, Patel R, Khandhar S, et al. Survival in Patients With Severe Aortic Regurgitation and Severe Left Ventricular Dysfunction Is Improved by Aortic Valve Replacement. Circulation. 2009 Sep 15;120(11_suppl_1):S134–8.

9. Forrest John K., Deeb G. Michael, Yakubov Steven J., Gada Hemal, Mumtaz Mubashir A., Ramlawi Basel, et al. 3-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients With Aortic Stenosis. Journal of the American College of Cardiology. 2023 May 2;81(17):1663–74.

10. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, et al. Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years. N Engl J Med. 2023 Nov 23;389(21):1949–60.

11. Silaschi M, Conradi L, Wendler O, Schlingloff F, Kappert U, Rastan AJ, et al. The JUPITER registry: One-year outcomes of transapical aortic valve implantation using a second generation transcatheter heart valve for aortic regurgitation. Catheterization and Cardiovascular Interventions. 2018 Jun 1;91(7):1345–51.

12. Tung M, Wang X, Li F, Wang H, Guo Y, Wang C, et al. A versatile transapical device for aortic valvular disease: One-year outcomes of a multicenter study on the J-Valve system. Journal of Cardiology. 2018 Nov 1;72(5):377–84.

13. Garcia S, Ye J, Webb J, Reardon M, Kleiman N, Goel S, et al. Transcatheter Treatment of Native Aortic Valve Regurgitation: The North American Experience With a Novel Device. JACC: Cardiovascular Interventions [Internet]. 2023 May 17; Available from: https://www.sciencedirect.com/science/article/pii/S1936879823008440

14. Hensey Mark, Murdoch Dale J., Sathananthan Janarthanan, Alenezi Abdullah, Sathananthan Gnalini, Moss Robert, et al. First-in-human experience of a new-generation transfemoral transcatheter aortic valve for the treatment of severe aortic regurgitation: the J-Valve transfemoral system. EuroIntervention. 2019 Feb 7;14(15):e1553–5.

15. Yokoyama Hiroaki, Tamm R. Alexander, Geyer Martin, Munzel Thomas, Treede Hendrik, von Bardeleben Ralph Stephan. Treatment of severe aortic valve regurgitation with the Trilogy TAVI system. EuroIntervention. 2023 Apr 24;18(17):1444–5.

16. Schäfer Ulrich, Schirmer Johannes, Schofer Niklas, Harmel Eva, Deuschl Florian, Conradi Lenard. First-in-human implantation of a novel transfemoral self-expanding transcatheter heart valve to treat pure aortic regurgitation. EuroIntervention. 2017 Dec 20;13(11):1297–300.

17. Hira RS, Vemulapalli S, Li Z, McCabe JM, Rumsfeld JS, Kapadia SR, et al. Trends and Outcomes of Off-label Use of Transcatheter Aortic Valve Replacement: Insights From the NCDR STS/ACC TVT Registry. JAMA Cardiology. 2017 Aug 1;2(8):846–54.

18. De Backer O, Pilgrim T, Simonato M, Mackensen GB, Fiorina C, Veulemanns V, et al. Usefulness of Transcatheter Aortic Valve Implantation for Treatment of Pure Native Aortic Valve Regurgitation. The American Journal of Cardiology. 2018 Sep 15;122(6):1028–35.

19. Chetan P Huded, Keith B Allen, Adnan K Chhatriwalla. Counterpoint: challenges and limitations of transcatheter aortic valve implantation for aortic regurgitation. Heart. 2021 Dec 1;107(24):1942.

20. Poletti Enrico, De Backer Ole, Scotti Andrea, Costa Giuliano, Bruno Francesco, Fiorina Claudia, et al. Transcatheter Aortic Valve Replacement for Pure Native Aortic Valve Regurgitation. JACC: Cardiovascular Interventions. 2023 Aug 28;16(16):1974–85.

21. Franzone A, Piccolo R, Siontis GCM, Lanz J, Stortecky S, Praz F, et al. Transcatheter Aortic Valve Replacement for the Treatment of Pure Native Aortic Valve Regurgitation: A Systematic Review. JACC: Cardiovascular Interventions. 2016 Nov 28;9(22):2308–17.

22. Sawaya FJ, Deutsch MA, Seiffert M, Yoon SH, Codner P, Wickramarachchi U, et al. Safety and Efficacy of Transcatheter Aortic Valve Replacement in the Treatment of Pure Aortic Regurgitation in Native Valves and Failing Surgical Bioprostheses: Results From an International Registry Study. JACC: Cardiovascular Interventions. 2017 May 22;10(10):1048–56.

23. Takagi H, Hari Y, Kawai N, Ando T. Meta-Analysis and Meta-Regression of Transcatheter Aortic Valve Implantation for Pure Native Aortic Regurgitation. Heart, Lung and Circulation. 2020 May 1;29(5):729–41.

24. Anwaruddin S, Desai ND, Szeto WY, Hermiller JB, Sorajja P, Kodali S, et al. Self-Expanding Valve System for Treatment of Native Aortic Regurgitation by Transcatheter Aortic Valve Implantation (from the STS/ACC TVT Registry). Am J Cardiol. 2019 Sep 1;124(5):781–8.

25. Yoon SH, Schmidt T, Bleiziffer S, Schofer N, Fiorina C, Munoz-Garcia AJ, et al. Transcatheter Aortic Valve Replacement in Pure Native Aortic Valve Regurgitation. J Am Coll Cardiol. 2017 Dec 5;70(22):2752–63.

26. Schneeberger Y, Seiffert M, Schaefer A, Bhadra OD, Schofer N, Pecha S, et al. TAVI for Pure Non-calcified Aortic Regurgitation Using a Self-Expandable Transcatheter Heart Valve. Frontiers in Cardiovascular Medicine [Internet]. 2022;8. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2021.743579

27. Zheng HJ, Cheng YB, Yan CJ, Lin DQ, Yu SJ, Li J, et al. Transfemoral transcatheter aortic valve replacement for pure native aortic regurgitation: one-year outcomes of a single-center study. BMC Cardiovascular Disorders. 2023 Jun 29;23(1):330.

28. Urena M, Himbert D, Ohlmann P, Capretti G, Goublaire C, Kindo M, et al. Transcatheter Aortic Valve Replacement to Treat Pure Aortic Regurgitation on Noncalcified Native Valves. J Am Coll Cardiol. 2016 Oct 11;68(15):1705–6.

29. Orzalkiewicz M, Taglieri N, Palmerini T, Saia F. Overinflation of balloon-expandable valves for transcatheter treatment of pure noncalcified native aortic regurgitation: How much oversizing is needed and achievable? Catheterization and Cardiovascular Interventions. 2023 Feb 1;101(2):481–4.

30. Oechslin Luca, Biaggi Patric, Wenaweser Peter, Wyss Christophe, Fritschi Daniel, Gaemperli Oliver, et al. Transcatheter Aortic Valve Implantation With

Balloon-Expandable Valve Prostheses in Patients With Pure Native Non- or Mildly Calcified Aortic Regurgitation: A Case-Series and Literature Review. J Invasive Cardiol. 2023 05;35(5):E254–64.

31. Orzalkiewicz Mateusz, Bruno Antonio Giulio, Taglieri Nevio, Ghetti Gabriele, Marrozzini Cinzia, Galiè Nazzareno, et al. Transcatheter Aortic Valve Replacement for Pure Aortic Regurgitation in a Large and Noncalcified Annulus. JACC: Cardiovascular Interventions. 2021 Oct 11;14(19):e271–3.

32. Jilaihawi H, Makkar RR, Kashif M, Okuyama K, Chakravarty T, Shiota T, et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. European Heart Journal - Cardiovascular Imaging. 2014 Dec 1;15(12):1324–32.

33. Angelillis M, Costa G, De Backer O, Mochi V, Christou A, Giannini C, et al. Threshold for calcium volume evaluation in patients with aortic valve stenosis: correlation with Agatston score. J Cardiovasc Med (Hagerstown). 2021 Jun;22(6):496–502.

34. Sanchez-Luna Juan Pablo, Martín Pedro, Dager Antonio E., Charry Pablo D., Beltrán Javier R., Sánchez-Recalde Ángel, et al. Clinical outcomes of TAVI with the Myval balloon-expandable valve for non-calcified aortic regurgitation. EuroIntervention. 2023 Sep 18;19(7):580–8.

35. VARC-3 WRITING COMMITTEE, Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. European Heart Journal [Internet]. 2021 Apr 19 [cited 2021 Apr 22];(ehaa799). Available from: https://doi.org/10.1093/eurheartj/ehaa799

36. Blanke P, Reinöhl J, Schlensak C, Siepe M, Pache G, Euringer W, et al. Prosthesis Oversizing in Balloon-Expandable Transcatheter Aortic Valve Implantation Is Associated With Contained Rupture of the Aortic Root. Circulation: Cardiovascular Interventions. 2012 Aug 1;5(4):540–8.

37. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, et al. Anatomical and Procedural Features Associated With Aortic Root Rupture During Balloon-Expandable Transcatheter Aortic Valve Replacement. Circulation. 2013 Jul 16;128(3):244–53.

38. Blanke P, Pibarot P, Hahn R, Weissman N, Kodali S, Thourani V, et al. Computed Tomography–Based Oversizing Degrees and Incidence of Paravalvular Regurgitation of a New Generation Transcatheter Heart Valve. JACC: Cardiovascular Interventions. 2017 Apr 24;10(8):810–20.

39. Noble S, Mauler-Wittwer S. TAVR as an Alternative to SAVR for Pure Native Aortic Regurgitation. Canadian Journal of Cardiology [Internet]. 2023 Nov 26; Available from: https://www.sciencedirect.com/science/article/pii/S0828282X23019505

40. Le Ruz R, Plessis J, Guimbretiere G, Roussel JC, Piriou PG, Cueff C, et al. Sapien 3 Embolization From Ventricle to Aorta in the Setting of Noncalcified Aortic Regurgitation. JACC: Case Reports. 2021 Jan 1;3(1):64–8.

41. Basman C, Kodra A, Pirelli L, Mustafa A, Wang D, Li A, et al. Comparison of clinical outcomes between use of overexpanding an undersized versus nominal-sized SAPIEN 3 ultra transcatheter heart valve in patients with borderline annulus area. Catheterization and Cardiovascular Interventions. 2022 Sep 1;100(3):415–21.

42. Ishizu K, Shirai S, Tashiro H, Kitano K, Tabata H, Morofuji T, et al. Mid-term impact of underfilling and overfilling of the SAPIEN 3 balloon-expandable transcatheter aortic valve implantation on mortality and valve function. Heart and Vessels. 2022 Dec 1;37(12):2067–82.

43. Oettinger V, Hilgendorf I, Wolf D, Stachon P, Heidenreich A, Zehender M, et al. Treatment of pure aortic regurgitation using surgical or transcatheter aortic valve replacement between 2018 and 2020 in Germany. Frontiers in Cardiovascular Medicine [Internet]. 2023;10. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1091983

44. Arora S, Lahewala S, Zuzek Z, Thakkar S, Jani C, Jaswaney R, et al. Transcatheter aortic valve replacement in aortic regurgitation: The U.S. experience. Catheterization and Cardiovascular Interventions. 2021 Jul 1;98(1):E153–62.

45. Isogai T, Saad AM, Ahuja KR, Shekhar S, Abdelfattah OM, Gad MM, et al. Short-term outcomes of transcatheter aortic valve replacement for pure native aortic regurgitation in the United States. Catheterization and Cardiovascular Interventions. 2021 Feb 15;97(3):477–85.

46. Koch R, Inci E, Grubb K, Leshnower B, Paone G, Ueyama H, et al. A Comparison of Thirty-Day Clinical and Echocardiographic Outcomes of Patients Undergoing Transcatheter vs. Surgical Aortic Valve Replacement for Native Aortic Insufficiency. Cardiovascular Revascularization Medicine. 2023 Jan 1;46:85–9.

47. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 Oct 21;363(17):1597–607.

48. Stachon P, Kaier K, Heidt T, Bothe W, Zirlik A, Zehender M, et al. Nationwide outcomes of aortic valve replacement for pure aortic regurgitation in Germany 2008–2015. Catheterization and Cardiovascular Interventions. 2020 Mar 1;95(4):810–6.