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Transcatheter aortic valve implantation for mixed versus pure stenotic aortic valve disease

Running title: ***TAVI for mixed aortic valve disease***

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Competing interests: Rogério Sarmento-Leite, José A. Mangione, and Fabio S. de Brito Jr are proctors for Medtronic and Edwards Lifesciences. Pedro A. Lemos is a proctor for Edwards Lifesciences and Boston Scientific. All other authors have no relevant conflicts of interest to declare.

ABSTRACT:

Aims: In addition to patients with pure/predominant aortic stenosis (PAS), real-world transcatheter aortic valve implantation (TAVI) referrals include patients with mixed aortic valve disease (MAVD; severe stenosis + moderate-severe regurgitation). We sought to compare TAVI outcomes in patients with MAVD vs. PAS.

Methods and results:

Out of 793 consecutive patients undergoing TAVI, 106 (13.4%) had MAVD. Patients with MAVD were younger and had a higher operative risk, a severer adverse cardiac remodeling, and a worse functional status than patients with PAS. Moderate-severe prosthetic valve regurgitation (PVR) was significantly more frequent in patients with MAVD than in patients with PAS, (15.7% vs. 3.6%, p=0.003), even after propensity-score and multivariable adjustments. Moderate-severe PVR was associated with increased one-year mortality in patients with PAS (log-rank p=0.002), but not in patients with MAVD (log-rank p=0.27). Eventually, all-cause and cardiac mortality as well as the functional capacity were similar in the two study groups up to one-year.

Conclusions: A significant proportion of patients referred for TAVI in a real-world registry has MAVD. Moderate-severe AR at baseline can influence the rate and modify the clinical sequelae of post-TAVI PVR. Eventually, clinical outcomes in patients with MAVD are comparable to patients with PAS in the acute and mid-term phases, in spite of a baseline higher risk. MAVD should not be considered a contra-indication for TAVI.

Keywords: Aortic regurgitation; Aortic stenosis; Paravalvular leak; TAVI

CONDENSED ABSTRACT:

We compared TAVI outcomes in patients with mixed aortic stenosis and regurgitation (MAVD) vs. patients with pure/predominant aortic stenosis. Patients with MAVD (13.4%) were younger and more morbid at baseline. Device failure was significantly more frequent in patients with MAVD mainly due to more moderate-severe prosthetic valve regurgitation which did not increase the mortality in this group of patients. All-cause and cardiac mortality and symptomatic status were similar in the two study groups up to one-year.

ABBREVIATIONS:

AR=artic regurgitation

AS=aortic stenosis

CABG=coronary artery bypass grafting

EuroSCORE=European System for Cardiac Operative Risk Evaluation

LVEF=left ventricular ejection fraction

MAVD=mixed aortic valve disease

NYHA=New York Heart Association

PG=pressure gradient

PVR=prosthetic valve regurgitation

SAVR=surgical aortic valve replacement

STS-PROM=Society of Thoracic Surgeons predicted risk of mortality

TAVI=transcatheter aortic valve implantation

VARC=Valve Academic Research Consortium

INTRODUCTION:

In patients with severe symptomatic aortic stenosis (AS), transcatheter aortic valve implantation (TAVI) can improve quality of life and significantly reduce mortality[1-3]. However, the role of TAVI in the management of patients with native aortic valve regurgitation (AR) is less established[4]. Although mixed aortic valve disease (MAVD) is frequently encountered in clinical practice[5], data on its prevalence and natural history are scarce[6]. MAVD (moderately-severe AR co-existing with severe AS) was considered as an exclusion criterion in the landmark PARTNER trial[1-3] as well as in the SURTAVI trial[7]. Likewise, TAVI is not recommended in patients with AS who also have severe AR in some of the practice guidelines[8].

However, post-approval real-world TAVI practice has expanded to groups of patients who were excluded from the pivotal clinical trials, including patients with MAVD[9]. As TAVI is suggested to be increasingly performed in younger patients as well as in patients with bicuspid aortic valve disease, more MAVD will be encountered among TAVI referrals.

The aim of this study was to 1) define the frequency and characteristics of patients with MAVD referred for TAVI in a real-world multicenter registry, and to 2) compare the outcomes of TAVI in patients with MAVD vs. pure/predominant AS, using a propensity score adjusted analysis.

METHODS:

The study included consecutive patients enrolled in a prospective multicenter TAVI registry from January 2008 to January 2015. List of participating centers, details of inclusion and exclusion criteria, and TAVI-procedure technical aspects have been previously described elsewhere[10]. The study protocol was approved by the ethics committee at each of the participating centers and all patients provided written informed consent. Patients were considered eligible for inclusion if they had severe symptomatic AS and were considered by the heart team as inoperable or at high surgical risk.

Aortic regurgitation (AR) severity was graded in accordance with the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging[11, 12]. According to the severity of AR at baseline, the study population was divided into two groups; pure/predominant aortic stenosis (PAS, if AR was mid-or-less), and mixed aortic valve disease (MAVD, if AR was moderate or severe). The cover index was calculated as; 100 x ([prosthesis diameter – computed tomographic annular diameter]/prosthesis diameter.

Outcomes:

An independent committee (including a neurologist) adjudicated all events and all end-points are reported according to the Valve Academic Research Consortium-2 (VARC-2) definitions[13].

The primary endpoint of the present study was device success, defined as absence of procedural mortality, correct positioning of a single device into the proper anatomical location, absence of prosthesis–patient mismatch with a trans-aortic mean pressure gradient (PG) <20 mmHg, and absence of moderate or severe prosthetic valve regurgitation (PVR)[13]. Secondary endpoints

included individual valve performance indices (trans-valvular gradient and PVR), early safety endpoints (at 30 days) and clinical efficacy endpoints at 1 year.

Propensity analysis:

To account for baseline and procedural differences between the two groups, a score for propensity[14] to MAVD has been developed using a multivariable logistic regression analysis to represent the probability of a given patient to have MAVD (range, 0.003-0.986). The model was inclusive and comprised 19 variables (**Table 1**). This model yielded a *c* statistic of 0.784 (95% confidence limits, 0.733-0.834; p<0.001), denoting a substantial ability to predict MAVD (vs. PAS).

Statistical methods:

Quantitative variables are summarized as mean ± standard deviation-SD or median [interquartile range-IQR] and are compared by Student *t* test or Mann-Whitney test, as appropriate. Categorical variables are summarized as frequencies and proportions and are compared by the chi-square test.

The association between MAVD and the study endpoints was tested using uni- and multi-variable logistic regression analyses, and was expressed as odds ratio (OR) and 95% confidence interval (CI). In multivariable analysis, the propensity score for MAVD was entered to the model (the propensity score-adjusted multivariable regression analysis).

Cumulative survival curves for patients with MAVD vs. PAS were constructed using the Kaplan-Meier method and compared with the log-rank test. All analyses were performed with SPSS 23

(IBM, Armonk, NY, USA). All probability values were two-tailed, and a *p* value <0.05 was considered significant.

RESULTS:

Patient characteristics:

Out of 793 consecutive patients undergoing TAVI, 106 (13.4%) had MAVD. Baseline and procedural characteristics of patients with MAVD vs. PAS are summarized in **Table 1**. Compared to patients with PAS, those with MAVD, although younger, were at higher surgical risk and had a higher New York Heart Association (NYHA) class. MAVD patients also had a lower trans-aortic pressure gradient (PG), and a larger left ventricular (LV) diastolic diameter and mass. They were also more likely to have history of coronary artery bypass grafting (CABG) or surgical aortic valve replacement (SAVR) and to have lower creatinine clearance and hemoglobin.

MAVD and procedural outcomes (Table 2):

Device failure (VARC-2 definition) was significantly more frequent in patients with MAVD than in patients with PAS in the overall patient population (26.4% vs. 10.0%, p<0.001) as well as after excluding patients with previous SAVR (22.9% vs. 9.7%, p=0.001). After propensity-score adjustment, the risk of device failure remained significantly higher in MAVD patients (OR: 2.14 [1.07-4.27], p=0.032).

In univariable analysis, the two components of prosthetic valve performance were worse in MAVD than in PAS; moderate-severe PVR (15.7% vs. 3.6%, p=0.003; OR: 2.89 [1.49-5.61], p=0.002) and residual trans-aortic mean PG ≥20 mmHg (15.4% vs. 3.6%, p<0.001; OR: 4.81 [2.22-10.43], p<0.001). After propensity-score adjustment, MAVD was no longer significantly associated with residual PG ≥20 mmHg (OR: 0.48 [0.06-3.97], p=0.49).

On the other hand, MAVD remained significantly associated with moderate-severe PVR after excluding patients with previous SAVR (15.1% vs. 5.8%, p=0.011) as well as after propensity-score adjustment (OR: 2.824 [1.294-6.163], p=0.009) and multivariable adjustment (OR: 3.178 [1.060-9.530], p=0.039) (**Table 3**). In addition to MAVD, cover index (OR: 0.935 [0.902-0.970] per 1% increment in oversizing, p<0.001) and the implantation of a self-expanding device (OR: 8.435 [2.234-31.851], p=0.002) were associated with moderate-severe PVR in multivariable regression analysis (**Table 4**).

The incidence of all other procedural/30-day outcomes were similar between both groups, with the exception of LV ejection fraction (LVEF) which was significantly lower at discharge in MAVD patients than in PAS patients (55.8±13.1% vs. 61.3±13.6, p<0.001). Similarly, impaired LVEF (<50%) at discharge was more common in MAVD patients (28% vs. 19%, p=0.048) with the odds ratio being significant in univariable analysis (OR: 1.68 [1.01-2.78,], p=0.045) but not in propensity-score adjusted analysis (OR: 1.15 [0.58-2.28,], p=0.695).

One-year outcomes:

At one-year, the overall mortality rate was 19.3% and was very much the same in the two study groups (MAVD: 19.8% and PAS: 19.2%, log-rank p=0.99) (**Figure 1**). Cardiac deaths constituted 70.5% of all mortalities, with their incidence being similar in both groups (MAVD: 15.1% and PAS: 13.4%, log-rank p=0.72). At the latest follow-up (median [IQR], 375 [79-742] days post-TAVI), dyspnea resolved completely (NYHA I) in 60% and 66%, was mild (NYHA II) in 30% and 26%, and was moderate-severe (NYHA III-IV) in 10% and 8% of MAVD and PAS patients, respectively (p=0.49). Accordingly, 76.4% of MAVD patients and 75.8% of PAS patients were alive beyond one-year in NYHA functional class I or II.

Impact of PVR on clinical outcomes:

Overall, moderate-severe PVR developed in 49 (6.9%) of patients with available echocardiographic data at discharge (n=707) and was associated with a higher one-year all-cause mortality (28.6%) compared to patients with mid-or-less PVR (13.8%, log-rank p=0.005; HR: 2.20, 95% CI: 1.25-3.86). As a higher mortality was expected to arise from the more severe PVR in the MAVD group, the impact of PVR on outcomes was studied in each of the study groups (MAVD vs. PAS) separately. The increased risk of one-year mortality in patients with moderate-severe PVR vs. mid-or-less PVR was even more pronounced in the PAS group (31.4% vs. 13.8%; log-rank p=0.002; HR: 2.64, 95% CI: 1.40-4.96, p=0.004). On the other hand, in the MAVD group, moderate-severe PVR was not associated with a significant increase in one-year mortality (21.4% vs. 13.8%; log-rank p=0.629) (**Figure 2**).

DISCUSSION:

The main findings of the present study are that: 1) MAVD is common among TAVI referrals in real world practice and is typically associated with more severe symptoms and adverse cardiac remodeling and a higher operative risk, and 2) The incidence of PVR is significantly higher in patients with MAVD but does not impair the long-term outcomes of those patients, possibly due to a protective preconditioning of the LV.

Mixed stenosis and regurgitation is common among patients undergoing isolated SAVR, representing 19.3% of patients in the STS database from 2002 to 2010 (n=141,905)[5]. Among patients undergoing TAVI, MAVD was reported in 11-17% of patients in all-comers multicenter registries[9, 15-17]. In the present real world multicenter registry, 13% of TAVI patients had MAVD.

MAVD as a peculiar disease entity:

Anatomically, a direct association between AR and aortic valve cusp calcification and bicuspidity has been reported by population-based studies[18]. Vianello et al[19] compared the aortic valve histologic structure in patients with degenerative aortic valve disease presenting with pure AS and patients presenting with combined AS and AR. Overall, pure AS was characterized by real 'calcium replacement" of the valvular fibrous tissue, calcification of the lipid component, and bone-endochondral metaplasia, while MAVD was characterized by a higher percentage of tissue fibrosis. The authors suggested the consideration of MAVD as a separate nosological entity within the degenerative aortic valve disease spectrum, rather than considering AR as a comorbidity with AS. Those structural differences might account for a differential interaction

between the device and the landing zone, and for the differential rate of PVR seen in the present study.

Hemodynamically, the combination of volume and pressure overload poses a twofold negative impact on LV mechanics and function[20, 21]. Popescu et al[22] studied 181 patients with severe AS, 71 (39%) of whom also had significant AR (i.e. MAVD). Patients with MAVD were younger, more symptomatic, and had higher LV mass, pulmonary capillary wedge pressure, LV end-diastolic pressure, and pulmonary artery pressure and a lower LVEF than those with isolated AS. There is evidence that severe AS patients managed conservatively who have concomitant significant AR have a significantly lower event-free survival than patients with pure AS[23] and that even those with only moderate AS and AR are exposed to a higher rate of adverse events than those with severe pure AS[24]. Therefore, the combination of severe AS with moderate-severe AR represents a unique anatomical (on the valvular complex level) and functional entity.

In the present study, not only MAVD patients presented with more severe LV hypertrophy and functional impairment at baseline, but also they had higher overall estimates of operative risk (higher EuroSCORE and STS-PROM). Therefore, and also due to the aforementioned studies linking MAVD to worse outcome, an earlier intervention should be considered and, because of the high surgical risk, TAVI can be the preferred option. In our study, and earlier studies[22, 24], patients with MAVD are younger than PAS patients at the time when valve implantation is indicated. Accordingly, MAVD represents a disease entity that will be increasingly encountered as TAVI indications are extended to younger patients.

TAVI outcomes in MAVD:

We found that acute TAVI outcomes in MAVD patients were generally favorable, with the exception of an unequivocally higher risk of PVR which remained significant after accounting for patient-, procedure-, and device-related confounders. A similar association with the risk of PVR and the need for balloon post-dilation was reported in AS patients undergoing TAVI who also had >mild AR[9, 17] or any degree of AR[15]. In the latter study, however, the group of patients with MAVD included a large number of patients with mild AR at baseline, a degree of regurgitation that typically does not bear significant hemodynamic consequences that make it hemodynamically distinct from PAS. Such a relation between baseline AR and the risk of PVR is important to consider in order to understand, at least partially, the marked variability in the incidence of PVR among different TAVI studies, even among those involving the same device[25, 26]. This inconsistency, which can be largely attributed to the limitations of the echocardiographic assessment of PVR[27], can also be partially explained by the inter-study variability in the severity of AR considered acceptable for inclusion.

In the present study, MAVD patients did very much the same in terms of mortality and symptomatic status up to one-year post-TAVI in spite of an increased risk at baseline and an increased rate of PVR after the procedure. It turns out, as has been confirmed in subgroup survival analysis, that the higher risk of PVR is compensated-for; possibly by the LV preconditioning[9, 28]. Maneuvers that can be undertaken to reduce the severity of PVR have their own risks[29]. Therefore, identification of patient subgroups with poor or good tolerance to PVR is clinically-relevant[9].

It has been reported in patients with AR (as compared to AS patients) undergoing SAVR, that the post-operative decline of LV end-diastolic volume occurs faster than the normalization of LV

mass, resulting in concentric remodeling, impaired LV relaxation, and to rise of diastolic filling pressure[30]. This gives another explanation of the well-toleration of PVR in those patients, who seem to "benefit" from some degree of regurgitation that probably prevents this concentric remodeling.

These findings collectively suggest that patients with MAVD gain an equivalent benefit from TAVI as do patients with PAS. Considering the worse symptomatic status and the poorer survival in patients with MAVD if left untreated, it turns out that this equivalent absolute outcome in fact reflects a higher relative benefit.

Limitations:

The assessment of AR severity is challenging in the setting of severe AS. However, the classification of AR into mid-or-less vs. moderate-to-severe is less challenging than more granular classifications.

Propensity score adjustment accounts only for the "observed" covariates included in the propensity score construction. We adopted the following actions to limit such a limitation of the propensity score: 1) the model used for propensity score construction was inclusive of, not only covariates different between the two groups, but also other covariate relevant to the endpoints of interest, 2) the score was tested for its discriminative accuracy (revealed to be good as evidenced by a substantial *c* statistic, and 3) the score was used in conjunction with further model-based adjustment using multivariable regression analysis, after exclusion of significant multicollinearity between the propensity score and its derivative covariates.

Significant AR in conjunction with AS is frequent in bicuspid aortic valve pathology. As data are derived from a real-world registry, the challenges in identifying and confirming a bicuspid pathology on echocardiographic studies existed. Obviously it cannot be excluded that some of the extensively calcified valves have an underlying masked bicuspid etiology[31].

The present study did not include lower risk patients or those treated with the next generation transcatheter aortic valves and extending the findings to those patients should be cautious. However, correlates of MAVD were shown in our analysis to be independent of patient-, procedure-, and device-related characteristics.

CONCLUSION:

A significant proportion of AS patients referred for TAVI in a real-world registry has moderate-severe AR and present with an overall higher cardiac adverse remodeling and operative risk. The incidence of PVR is significantly higher in patients with MAVD than in patients with PAS, but does not significantly impact on mortality. Overall, the outcome of patients with MAVD is comparable to that of patients with PAS in the acute and mid-term phases.

Impact on daily practice:

TAVI is likely as effective in patients with mixed aortic valve disease as in patients with pure aortic stenosis. Mixed aortic valve disease is a potential extended indication for TAVI.

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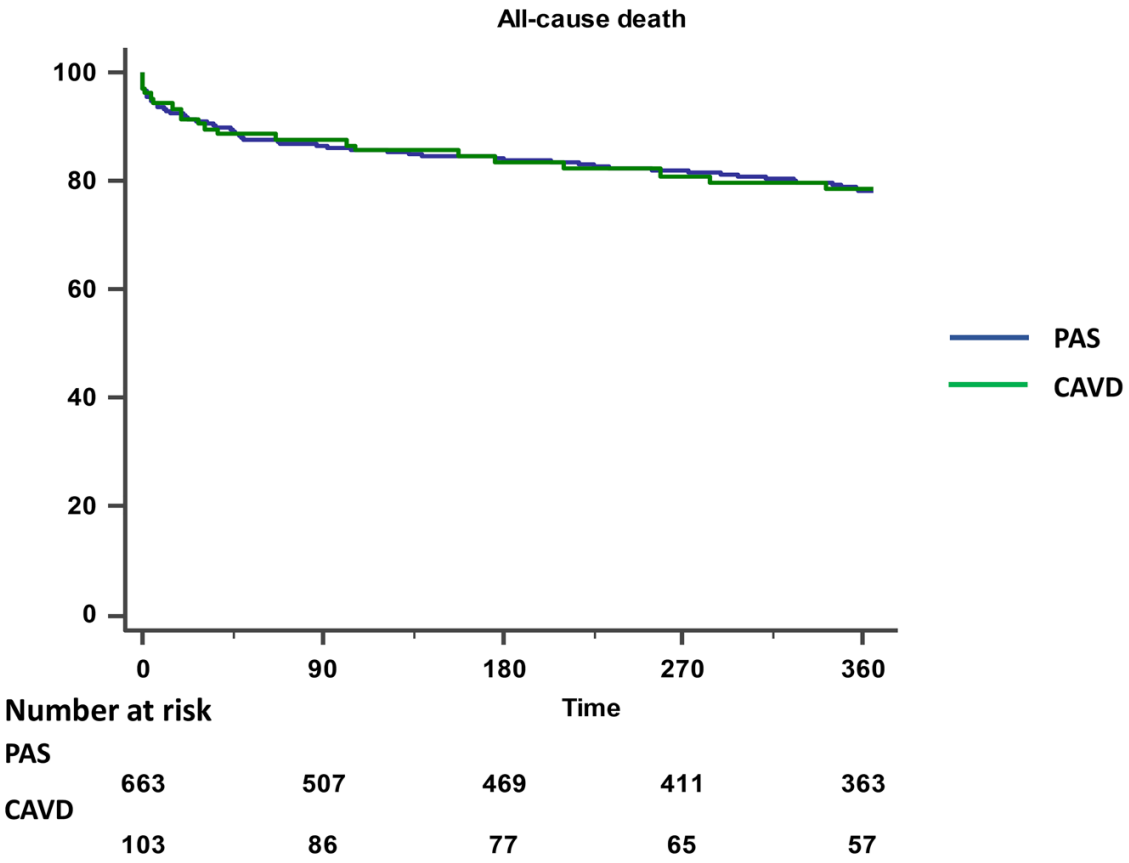
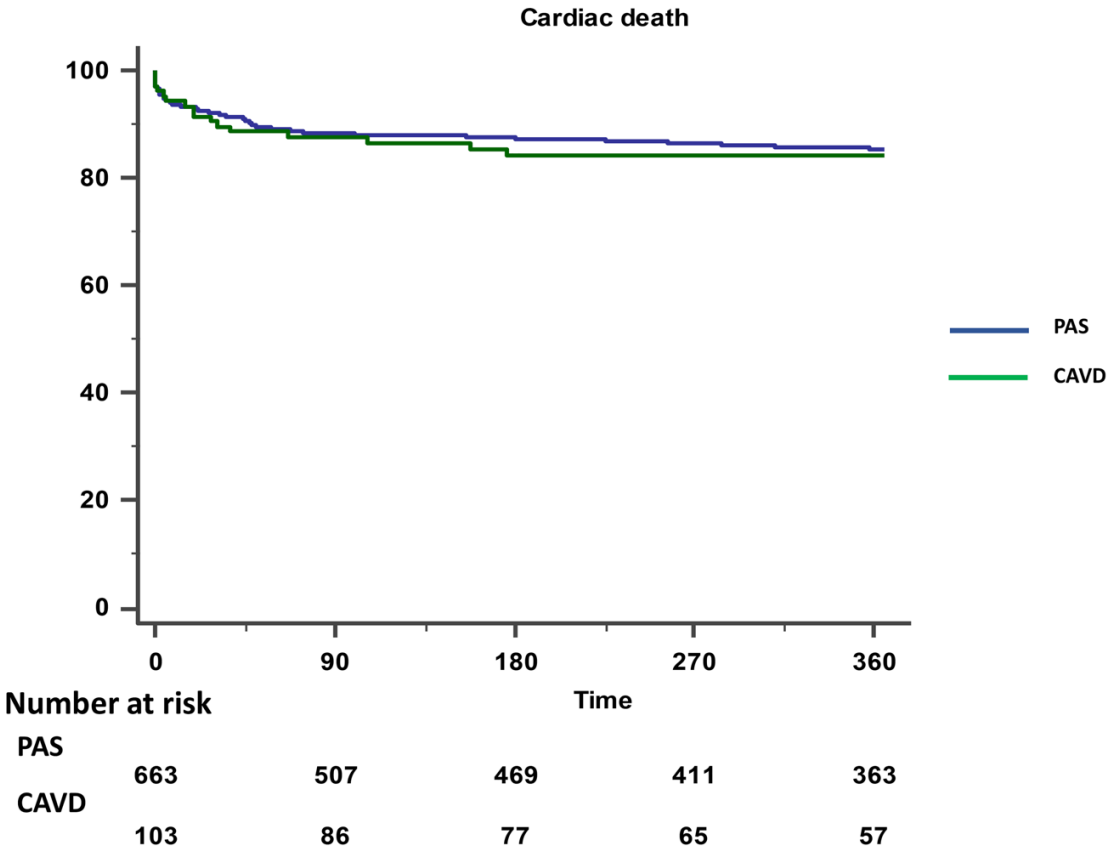
FIGURE LEGENDS:

Figure 1. Kaplan-Meier survival curves for one-year all-cause (A) and cardiac (B) mortality after TAVI according to the type of aortic valve disease (pure/predominant aortic stenosis-PAS vs. mixed aortic valve disease-MAVD).

Figure 2. Kaplan-Meier survival curves for all-cause mortality after TAVI according to the severity of prosthetic valve regurgitation (PVR) in the entire patient population (A), in patients with pure/predominant aortic stenosis-PAS (B), and in patients with mixed aortic valve disease-MAVD (C).





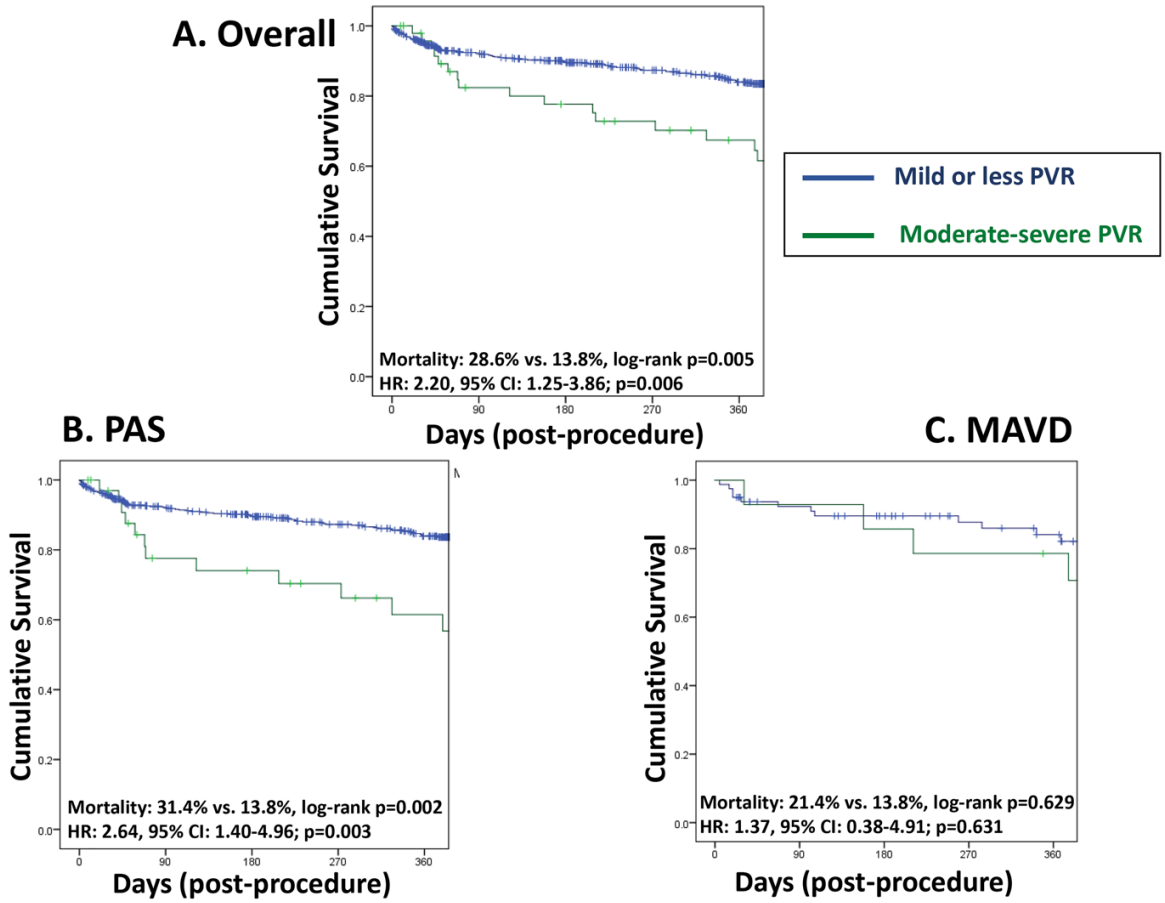


Table 1. Baseline and procedural characteristics according to the type of aortic valve disease:

		Aortic valve disease at baseline		*p*
		Pure/predominant AS (n=687)	Mixed aortic valve disease (n=106)	
Age		81.8±7.1	79.7±8.6	0.019
Male gender		333 (48.5%)	55 (51.9%)	0.532
BMI		26.4±4.7	25.2±4.4	0.005
EuroSCORE		20.0±14.3	23.7±16.3	0.025
STS-PROM		10.0±7.8	12.0±8.7	0.016
Surgical risk category (STS-PROM)	STS<=3.0	81 (11.8%)	14 (13.2%)	0.029
	STS=3.1-8.0	307 (44.7%)	33 (31.1%)	
	STS>8.0	299 (43.5%)	59 (55.7%)	
NYHA class	NYHA 1/2	135 (19.7%)	12 (11.3%)	0.044
	NYHA 3/4	552 (80.3%)	94 (88.7%)	
Aortic valve area (cm^2)		0.66±0.18	0.70±0.27	0.445
Trans-aortic peak PG (mmHg)		82.1±24.3	75.6±26.2	0.046
Trans-aortic mean PG (mmHg)		49.9±15.6	45.5±17.0	0.037
LVEF (%)		59.0±14.9	57.1±15.3	0.117
Impaired LVEF (<50%)		161 (23.7%)	31 (29.5%)	0.222
Low-flow low-gradient AS		74 (12.2%)	5 (7.0%)	0.244
LV diastolic diameter (mm)		50.5±9.1	52.8±11.4	0.004
Interventricular septal thickness (mm)		12.2±2.1	12.1±2.0	0.446
LV posterior wall thickness (mm)		11.6±2.0	11.5±1.7	0.675
Relative wall thickness		0.50±0.34	0.49±0.35	0.021
LV mass index (g/m^2)		139.7±42.5	155.1±46.7	<0.001
Moderate-severe mitral regurgitation		98 (16.3%)	18 (19.6%)	0.454
Pulmonary hypertension		147 (21.4%)	28 (26.4%)	0.258
Atrial fibrillation		92 (14.9%)	12 (12.1%)	0.540
Pervious PPM		63 (9.3%)	5 (4.8%)	0.188
Coronary artery disease		396 (57.6%)	66 (62.3%)	0.398
Previous myocardial infarction		100 (14.6%)	18 (17.0%)	0.557
Previous CABG		122 (17.8%)	29 (27.4%)	0.024
Previous PCI		226 (32.9%)	39 (36.8%)	0.440
Peripheral arterial disease		118 (17.2%)	17 (16.0%)	0.890
Previous carotid artery disease		104 (15.1%)	19 (17.9%)	0.471
Previous stroke		54 (7.9%)	10 (9.4%)	0.566
Porcelain aorta		53 (7.7%)	8 (7.5%)	1.000
Aortic aneurysm		37 (5.4%)	11 (10.4%)	0.076
Diabetes mellitus		221 (32.2%)	31 (29.2%)	0.577
Dyslipidemia		346 (50.4%)	47 (44.3%)	0.253
Systemic hypertension		523 (76.1%)	78 (73.6%)	0.545

Chronic obstructive pulmonary disease		125 (18.2%)	21 (19.8%)	0.687
Creatinine clearance (ml/min)		48.8±21.7	44.5±22.3	0.022
Severe chronic kidney disease*		105 (15.7%)	26 (25.0%)	0.024
Hemoglobin (g %)		11.8±1.8	11.3±1.7	0.002
Previous valvuloplasty		39 (5.7%)	11 (10.4%)	0.082
Previous SAVR		9 (1.3%)	23 (21.7%)	<0.001
MSCT performed		449 (65.4%)	57 (53.8%)	0.023
Valve annulus diameter (mm)		24.7±4.3	24.4±4.3	0.431
Cover index (%)		12.2±13.5	10.1±14.9	0.152
Conscious sedation		63 (9.2%)	10 (9.4%)	0.858
TEE-guided procedure		561 (81.7%)	83 (78.3%)	0.423
Trans-femoral access		635 (92.4%)	102 (96.2%)	0.219
Device type	CoreValve	499 (72.6%)	76 (71.7%)	0.778
	Sapien-XT	168 (24.5%)	28 (26.4%)	
	Inovare	20 (2.9%)	2 (1.9%)	
Device size		27.3±2.3	26.9±2.6	0.119
Predilation		349 (50.8%)	41 (38.7%)	0.022
Postdilation		249 (36.2%)	44 (41.5%)	0.331

Variables in **bold** are included in the generation of the propensity score.

* Defined as a creatinine clearance <30 ml/min.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; EuroSCORE, logistic European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MSCT, multi-slice computed tomography; NYHA, New-York Heart Association; PCI, percutaneous coronary intervention; PG, pressure gradient; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortalit

Table 2. Procedural and 30-day outcomes according to the type of aortic valve disease:

	Aortic valve disease at baseline		*p*
	Pure/predominant AS	***Mixed aortic valve disease***	
Device failure	69 (10.0%)	28 (26.4%)	<0.001
Moderate-severe PVR at discharge	35 (5.7%)	14 (14.9%)	0.003
Trans-aortic mean PG ≥20 mmHg	18 (3.6%)	12 (15.4%)	<0.001
Trans-aortic mean PG at discharge (mmHg)	9.5±5.5	12.9±9.0	<0.001
Periprocedural reduction (%) in mean PG	80.1±12.8%	67.4±40.6%	0.006
Impaired LVEF at discharge	109 (18.7%)	25 (27.8%)	0.048
LVEF at discharge (%)	61.3±13.6	55.8±13.1	<0.001
Moderate-severe MR at discharge	98 (16.3%)	18 (19.6%)	0.454
New-LBBB (within 30 day)	226 (35.6%)	36 (38.3%)	0.646
New-PPM (within 30 day)	128 (18.6%)	14 (13.2%)	0.22
Thirty-day all-cause death	62 (9.0%)	10 (9.4%)	0.857
Thirty-day all-stroke	25 (3.6%)	3 (2.8%)	1.000
Thirty-day major or life-threatening bleeding	101 (14.7%)	14 (13.2%)	0.768
Thirty-day acute kidney injury	122 (17.8%)	15 (14.2%)	0.409
Thirty-day severe acute kidney injury	26 (3.8%)	7 (6.6%)	0.189
Thirty-day major vascular complications	59 (8.6%)	9 (8.5%)	1.000

Abbreviations: LBBB, left bundle branch block; MR, mitral regurgitation; PVR, prosthetic aortic valve regurgitation. Other abbreviations are as in table 1.

Table 3. Regression analysis [odds ratio-OR (95% confidence limits)] of the association between mixed aortic valve disease at baseline and moderate-severe prosthetic aortic valve regurgitation:

Univariable analysis	2.890 (1.490-5.605), p=0.002
Multivariable analysis*	3.178 [1.060-9.530], p=0.039
Propensity-score adjusted analysis	2.824 (1.294-6.163), p=0.009

*Included –in addition to mixed aortic valve disease - previous coronary artery bypass grafting or surgical aortic valve replacement, device type, cover index, access for implantation, transesophageal echocardiographic-guidance, and predilatation as covariates (details displayed in table 4).

Table 4. Multivariable regression analysis [odds ratio-OR (95% confidence limits)] of the predictors of moderate-severe prosthetic aortic valve regurgitation (significant covariates are written in bold.):

	Sig.	OR	95% C.I.	
			Lower	Upper
MAVD (vs. PAS)	**0.039**	**3.178**	1.060	9.530
Previous SAVR	0.709	0.644	0.064	6.479
Previous CABG	0.408	1.559	0.544	4.471
TEE guidance	0.846	0.898	0.305	2.650
Transfemoral access	0.456	2.342	0.249	22.001
Predilatation	0.292	1.632	0.656	4.063
Cover index	**<0.001**	**0.935***	0.902	0.970
Self-expanding THV	**0.002**	**8.435**	2.234	31.851

Abbreviations: CABG, coronary artery bypass grafting; MAVD, mixed aortic valve disease; PAS, pure/predominant aortic stenosis; SAVR, surgical aortic valve replacement; TEE, trans-esophageal echocardiography; THV, transcatheter heart valve.

* OR per 1% increment in oversizing