Transcatheter aortic valve replacement with novel balloon-expandable transcatheter heart valve device

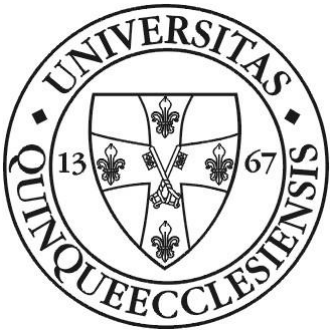
PhD thesis

Balázs Magyari MD

Supervisor: Iván Horváth, Prof, MD, PhD, FESC

Head of the Doctoral School: Prof. Lajos Bogár MD, PhD, DSc

Head of the Doctoral Program: Prof. István Szokodi MD, PhD, DSc



University of Pécs, Medical School

Heart Institute

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1. Introduction

Degenerative aortic stenosis (AS) is the most common valvular disease in adults and is associated with increased mortality. The prevalence is highly age dependent, approximately 4% in patients with the age of 80 or above. The demographic shift resulted in the ageing population may responsible for the growing burden of valvular heart disease. On the other hand, the growing number of less invasive therapeutic opportunities may resulted in more screened patients for TAVI, who were not in the field of vision of healthcare system previously.

The treatment for aortic stenosis included medical therapy, balloon aortic valvuloplasty and the replacement of the native aortic valve. Medical therapy has no real effect on the progression of the AS process and moreover AVR has been proven as superior compare to medical therapy. Since the balloon aortic valvuloplasty has modest effect on patients' hemodynamics, the indication for this procedure is narrowing, especially with the growing number of TAVR centres and the rising availability of this therapy.

Aortic valve replacement is the only definitive therapy for patients with AS, if needed. The indication fort AVR should be made based on the patient's risk profile by the Heart Team decision. Aortic valve replacement is indicated mainly for symptomatic patients with some exception in the asymptomamtic patient group. Management of asymptomatic patients can be challenging. Based on current guidelines, AVR is indicated for asymptomatic patients with severe AS coexisting left ventricular dysfunction with no other cause. As patients with aortic stenosis develope symptoms, the AVR is highly recommended (class I indication in reference to both America and European guidelines) even though if improvement of symptoms after initiating medical therapy occur.

Surgical replacement of the aortic valve (SAVR) was the gold standard treatment for many decades, however due to the aging population, there is a growing number of patients, who are not suitable to open-heart surgery. For these patients, transcatheter aortic-valve replacement (TAVR) provide another possible cure. For transcatheter procedure, mainly two different technical approach were developed: self-expanding heart valve (SEV) and balloon-expandable (BEV) heart valve system. Most recent guidelines are affected by the enormous worldwide experience with mainly two THV system; Edwards SAPIEN as a balloon expendable system (Edwards Lifesciences) and CoreValve (Medtronic) as the self-expandable system, both has its third generation. Both THV systems were analized in different clinical scenarios which result

in its worldwide clinical use. The choice between balloon expandable or self-expandable THV should be made on the individual patient level. In general, using balloon expandable devices can be advised for patients with pre-existing conduction disorders, severe aortic valve calcification, whereas self-expanding devices can be advised for patients with permanent pacemaker, smaller diameter at the access site, small annular dimensions.

However, the safety and efficay of TAVR over SAVR have been well established, even from the early TAVR era, the major limitation of this technique was the higher rate of paravalvular leakage (PVL), need for new permanent pacemaker implantation and the question of the long-term THV durability. This phenomens could even neutralize the advantage come from the survival benefit [1] and may associate with poor long-term prognosis. Therefore, techniques, in order to decrease and/or prevent this phenomen also improved.

The prevalence of bicuspid aortic valve (BAV) anatomy as the most common congenital heart disease ranging between 0.5 and 2 % [2] with male predominancy (3:1) and with the need for undergoing aortic valve replacement before the seventh decade. Patients with stenotic BAV plays a special role, also from the TAVR point of view. Even though the rising number of successful TAVI implantation in BAV patients - due to the fact that most of the landmark trials exclude patients with BAV anatomy - high volume, prospective, randomized studies are missing, and therefore has only class 2b guideline recommendation. Due to the lack randomized studies comparing BEV and SEV systems in this subset of patients, the selection between currently available devices is made mainly upon observational studies, results of meta-analysis and the operator's discretion. Additionally based on the CT scan, high-risk BAV patients should be located and the re-assessment of the Heart Team's decision advised and SAVR in those patient may result in better long-term outcome, if technically feasible.

2. Objectives

The overall purpose of this research was to investigate the results of our TAVR programme including the learning phase, the type of access site preparation and anaesthesia, patient and THV device selection and their effects on clinical outcomes

2.1. The effect of using multiple THV devices for starting a single-centre TAVR program based on early- and mid-term follow-up.

While recommendations for starting a TAVR programme are scarce, and moreover miss proposal for centres regarding which THV system should starting with, we analyzed whether using more than one THV system during the learning curve is safe and effective.

2.2. Experinces with the balloon-expandable Myval transcatheter aortic valve system, based on the 30-day and 1-year follow-up data with the first 100 patients.

Based on the experience in the learning curve, our aim was to analyse the data using the novel, balloon expandable THV device, regarding short and long-term follow up. In addition, the purpose was also to analyse the results of this new THV device in patients underwent TAVR procedure with bicuspid aortic valve anatomy, while conflicting results exist regarding the treatment of these patients with self-expandable THV devices versus balloon expandable THV device.

2.3. Experience with the Balloon-Expandable Myval Transcatheter Aortic Valve System in Patients with Bicuspid Anatomy.

The bicuspid aortic valve (BAV) as the most common congenital defect, plays a special role in the treatment of aortic stenosis. Excluding from pivotal TAVI trials, the comparisons with surgical aortic valve replacement (SAVR) rely on mainly registries and observational studies. Regarding this, the BAV has only a class 2b guideline recommendation for TAVI. Based on our positive experience with the novel balloon expandable THV device, our aim was to analyse the results of this system in patients underwent TAVR procedure with bicuspid aortic

valve anatomy, while conflicting results exist regarding the treatment of these patients with self-expandable THV devices versus balloon expandable THV device.

2.4. Statistical analysis

GraphPad Prism (version 9.0, GraphPad Software Inc, CA, USA), and SPSS Statistics (version 28.0, IBM, Armonk, NY, USA) were used for statistical analysis. Continuous variables are expressed as a mean ±standard deviation (SD), and categorical variables are expressed as numbers and percentages. Data distribution was assessed by D'Agostino-Pearson omnibus K2 normality test. Continuous variables were compared using two-tailed unpaired t-test and paired t-test, as appropriate. The effect of TAVR on hemodynamic parameters in the whole cohort was evaluated using repeated measures one-way ANOVA test with time as a within-subject factor (baseline, discharge, 30-day and 1-year follow-up), Geisser-Greenhouse correction for sphericity, and Tukey's multiple comparisons test. When the effect of TAVR on hemodynamic parameters was compared between patients with BAV and TAV, we used repeated measures of two-way ANOVA test with time as a within-subject factor (baseline, discharge, 30-day and 1-year follow-up) and valve type (BAV or TAV) as a between-subject factor, Geisser-Greenhouse correction for sphericity, and Tukey's multiple comparisons test. For ANOVA tests, the data for each parameter represent only those cases where measurements were available at all time points (baseline, discharge, 30-day and 1-year follow-up). Categorical variables were compared using independent sample z test or McNemar's test, as appropriate. Differences were considered statistically significant at $p < 0.05$.

2.5. Study endpoints and follow-up

Safety and efficacy parameters were collected before discharge, at the 1 month follow-up, and at the 12 month follow-up. As a primary endpoint, safety were evaluated based on periprocedural outcomes, short and long-term hemodynamic performance based on transthoracic echocardiography by independent sonographers. As a secondary endpoint, the 30-day and 1 year combined safety endpoints were defined by Valve Academic Research Consortium-2 (VARC-2). Functional status of the patients was classified based on the NYHA class. All relevant endpoints were defined according to the VARC-2 definitions. Severity of perioperative aortic regurgitation was evaluated by intraoperative echocardiography, angiography, and measurement of the aortic ARI, described previously.

3. The effect of using multiple THV devices for starting a single-centre TAVR program based on early- and mid-term follow-up.

3.1. Study design and Patient Population

This study examined data regarding 122 patients from March 2014 to March 2020, underwent a TAVR procedure at our institution. The learning curve was analysed by comparing outcomes for the first 63 patients (Cohort A, 2014 March to 2019 March) to the last 59 patients (Cohort B, 2019 March to 2020 March). Our TAVR program started in 2014 with the Lotus Valve System (Boston Scientific). After the recall of this THV, we switched to the first-generation Medtronic THV CoreValve system, followed by the second-generation Medtronic THV Evolut R and the latest generation Evolut Pro System (Medtronic). Due to some patients' anatomic difficulties, we introduced three more THV systems: Portico (Abbott Vascular), Accurate Neo (Boston Scientific,), and Myval (Meril Life Sciences). In the first 90 cases we used two THV devices: 10 Lotus cases and 80 cases were performed using the Medtronic-CoreValve system. Transfemoral approach was our standard choice, when feasible. When this access site was not suitable based ont he CT scan, alternative access sites were used: trans-subclavian, trans-axillary or direct aortic approach.

3.2. Results

Between March 2014 and March 2020, 122 consecutive patients underwent TAVR at our institution. Due to a slow accumulation of implantation numbers, we reached the mandatory annual minimum of 50 TAVR procedures only in the last year of this study (Cohort B). There were no significant differences between Cohort A and B in baseline characteristics. The THV systems used were: Medtronic Corevalve Evolute R/Evolute PRO (67.2%); Abbott Portico (10.6%); Boston Scientific Lotus (8.2%); Meril Myval (9%); Boston Scientific Neo Accurate (5%). General anaesthesia was the standard of care (96.7%), and conscious sedation the minority (3.3%). There was a significant decrease in aortic peak (91.8 ± 24.7 mmHg vs. 34.2 ± 9.6 mmHg, p=0.007) and aortic mean gradient (53.01 ± 14.9 mmHg vs. 11.9 ± 6.4 mmHg, p=0.001) after the procedure. There were no procedural deaths and five fatal outcomes

during the hospitalisation period could be detected. Postprocedural outcomes within the first 72 hours are summarised in Table 1.

Postprocedural outcomes < 72 h after the index procedure				
Outcome	**Overall** (n=122)	**Cohort A** (first 63 patients)	**Cohort B** (last 1 year,n=59)	**p value**
	No. (%) of events			
In-hospital mortality	5 (4.1%)	4 (6.3%)	1 (1.7%)	0.195
Device success	119 (97.5 %)	62 (98.4%)	58 (98.3%)	0.963
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	-
Coronary obstruction	0 (0%)	0 (0%)	0 (0%)	-
Stroke or TIA	3 (2.4%)	2 (3.2%)	1 (1.7%)	0.598
Acute kidney injure, stage 2 or 3	3 (2.4%)	3 (4.7%)	0 (0%)	0.09
Major vascular complications	4 (3.3%)	0 (0%)	4 (6.8%)	0.036
Cardiac tamponade	0 (0%)	1 (0%)	1 (0%)	0.963
Annulus rupture	0 (0%)	0 (0%)	0 (0%)	-
Valve malpositioning	2 (1.6%)	1 (1.6%)	1 (1.7%)	0.963
Need for a second valve	2 (1.6%)	1 (1.6%)	1 (1.7%)	0.963
Posptocedural AR grade III or IV	1 (0.9%)	1 (0.9%)	0 (0%)	0.331

Table 1. Detailed data of postprocedural outcomes (< 72 h after the index procedure) of the whole study population and in the Cohort A and Cohort B, based on VARC-2 definition.

3.2.1. Device success

Device success (according to the VARC-2 definition) was achieved in all but three patients (97.5%). There was no periprocedural myocardial infarction from coronary obstruction after valve implantation. In one patient, embolisation caused amaurosis fugax that resolved by the one-year follow-up. Stroke was observed in two patients (1.6%). The first of these patients suffered from severe haemorrhagic stroke leading to death. The second patient had embolisation into the arteria cerebri media. After fibrinolytic therapy, neurological symptoms improved, and the patient completed a successful neurologic rehabilitation program.

Vascular complications were detected in 18 patients; 4 were major, and 14 were minor, according to the VARC-2 criteria (Table 5). Major vascular complications were significantly

higher in Cohort B [A: 0 patients (0%) vs B: 4 (6.8%), p=0.036]. Other than vascular complications, there were no other significant differences between Cohorts A and B for device success. However, there was a remarkable but statistically non-significant decrease in in-hospital mortality [Cohort A: 4 patients (6.3%) vs Cohort B: 1 (1.7%), p=0.195]. All postprocedural outcomes (<72 h after the index procedure) are shown in Table 1.

3.2.2. VARC-2 outcomes at follow-ups

After the five in-hospital deaths (above), there were no subsequent deaths in the first 30 days; thus, 30-day all-cause mortality was 4.1%. There were no new strokes in the 30-day follow-up period after patient discharge. Two patients received a repeat TAVR procedure due to severe valve-related dysfunction.

Between the 30-day and one-year follow-up, four additional deaths occurred: two due to a cardiac event, one due to the progression of ischaemic stroke and one due to an infection that led to multiple organ failure. The mortality rate at one year was 7.4% (9/122) all-cause and 4.9% for cardiac mortality. In addition to the two in-hospital evolving strokes, one other patient had a non-disabling ischaemic stroke, which resulted in a 2.5% (3/122) one-year all-stroke rate. After 30 days, there were no new hospital admissions for heart failure progression. One patient was at NYHA stage III. Five patients had valve-related dysfunction due to an elevated mean gradient on the THV (based on echocardiography) but did not need prosthetic valve re-intervention.

At the three-year follow-up, 17 additional deaths had occurred. Two were due to a cardiac event. Therefore, the three-year mortality rate was 22.9% (28/122), with a 6.5% cardiac mortality rate (8/122). After the one-year follow-up, one non-disabling ischaemic stroke and one transient ischemic attack occurred, leading to a 4.1% (5/122) all-stroke rate at three years.

After the TAVR procedure, the functional status of the patients improved. A minority were NYHA III, and none were NYHA IV. This finding was stable at the one-year follow-up. At the two-year follow-up, the number with NYHA I decreased significantly [113 (89.4 %) vs 105 (74.3%), p=0.003], but the rest were at NYHA II with no significant changes at the three-year follow-up. Between the one-year and three-year follow-ups, four patients required hospitalisations for worsening heart failure. At the two- and three-year follow-ups, no patients

had NYHA stage III or above. Valve-related dysfunction was detected in three additional patients. Two of them had an elevated mean gradient on the THV system without a need for re-intervention of the prosthetic valve. The third patient had THV system endocarditis, leading to their death.

Nine patients already had a permanent pacemaker implantation (PPI), and 14 patients were implanted after the TAVR procedure; therefore, the new PPI rate was 12.4% (14/113). There were no significant differences between patients with or without the need for PPI for implantation depth, age, Euroscore, Euroscore II, STS score, aortic valve calcium score, or presence of calcium in the left ventricular outflow tract. At the one-year follow-up, one patient had implantable cardioverter defibrillator pacemaker implantation. Between the one- and three-year follow-ups, one patient had new PPI. There was a significantly higher rate of PPI during the index procedure in Cohort B [A: 2 patients (3.2%) vs B: 12 (20.3%), p=0.002]. There were no other significant changes between Cohorts A and B in VARC-2 definitions at any time point of the follow-up period except of the major vascular complication (details above). All relevant data from 30 days, one-year, and three-year outcomes of the whole cohort and in the subgroups are summarised in Table 2.

3.2.3. Echocardiographic outcomes and valve durability

The peak and mean aortic gradient decreased significantly after the procedure (88.3 ± 22.9 vs 20.5 ± 9.9 mmHg, $p<0.0001$ and 52.4 ± 14.7 vs 10.2 ± 5.5 mmHg, $p<0.0001$). There were no other significant changes between the time periods. Global ejection fraction was stable during the examined period. There were no significant differences between Cohorts A and B for peak aortic gradient, mean aortic gradient, and global ejection fraction at any point of the follow-up period. An aortic regurgitation grade of two or above was detected in a minority of the patients and did not require THV reintervention based on the patients' clinical condition. Moreover, no relevant paravalvular leak was detected throughout the follow-up period. Details in Figure 1-2.

VARC-2 outcomes at 30-day, 1-year and 3-years follow-up				
Outcome	**Overall** (n=122)	**Cohort A** (first 63 patients)	**Cohort B** (last 1 year,n=59)	**p value**
30 days cumulative clinical outcomes (n=122)				
All-cause mortality	5 (4.1%)	4 (6.3%)	1 (1.7%)	0.195
Cardiac mortality	4 (3.3%)	3 (4.7%)	1 (1.7%)	0.341
All stroke	2 (1.6%)	1 (1.6%)	1 (1.7%)	0.962
Life-threatening bleeding	0 (0%)	0 (0%)	0 (0%)	-
Acute kidney injury, stage 2 or 3	1 (0.8%)	0 (0%)	1 (1.7%)	0.299
Coronary artery obstruction	0 (0%)	0 (0%)	0 (0%)	-
Major vascular complication	4 (3.3%)	0 (0%)	4 (6.8%)	0.035
New pacemaker implantation	14 (12.4%)	2 (3.2%)	12 (20.3%)	0.002
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)	2 (1.6%)	1 (1.6%)	1 (1.7%)	0.962
One-year cumulative clinical outcomes (n=113)				
All-cause mortality	9	6	3	0.348
Cardiac mortality	6	4	2	0.450
All stroke	3	1	2	0.520
Requiring hospitalizations for worsening heart failure	0	0 (0%)	0 (0%)	-
NYHA class III or IV	1	0	1	0.299
Valve-related dysfunction	5	1	4	0.148
Three-year cumulative clinical outcomes (n=94)				
All-cause mortality	28	15	13	0.815
Cardiac mortality	8	5	3	0.524
All stroke	5	3	2	0.702
Requiring hospitalizations for worsening heart failure	4	1	3	0.278
NYHA class III or IV	0	0	0	-
Valve-related dysfunction	3	2	1	0.597

Table 2. Detailed data of postprocedural outcomes at 30-day, 1-year and at 3-years follow-up of the whole study population and in the Cohort A and Cohort B, based on VARC-2 definition.

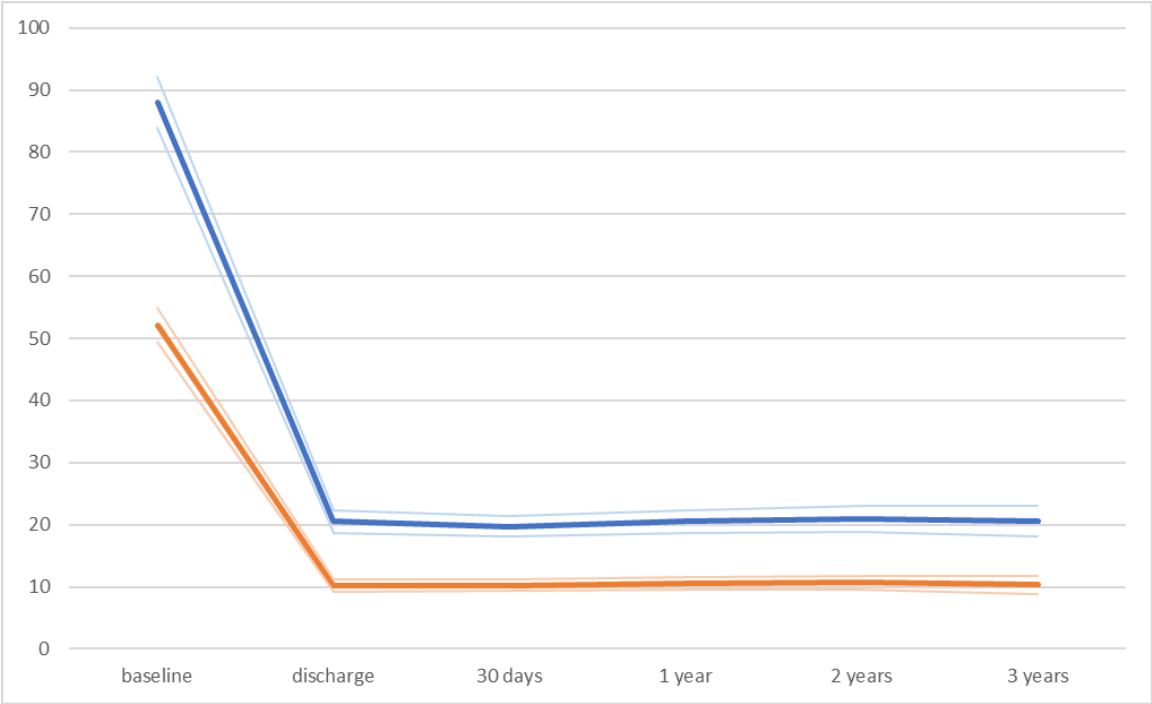

Figure 1. Data regarding aortic peak gradient (blue line) and aortic mean gradient (orange line) in the whole study population.

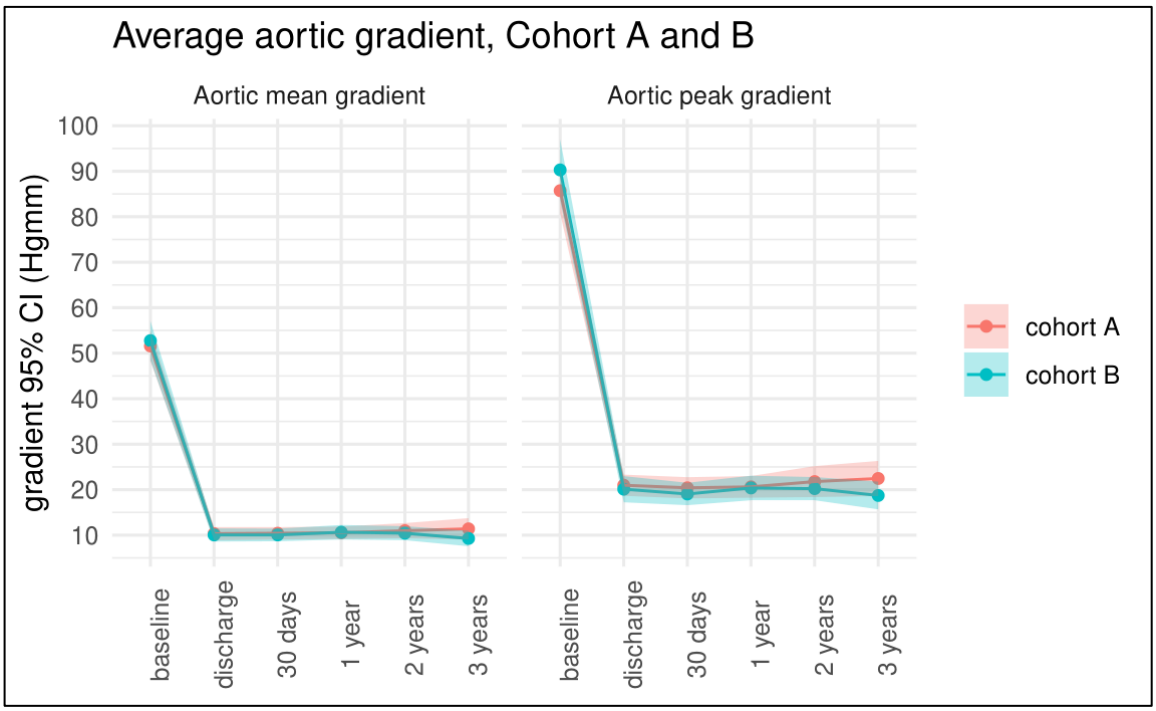

Figure 2. Comparison between Cohort A and Cohort B regarding aortic mean gradient and aortic peak gradient.

3.3. Discussion

The device success rate was high (97.5%), which is outstanding for a learning phase with five different THV systems especially when compared to the learning curve for TAVR in high volume studies. We reached the mandatory annual minimum of 50 TAVR procedures only in the last year of this study (Cohort B). Our mortality rate decreased remarkably this last year, but this difference did not reach statistical significance; this is likely due to the low case numbers. Vascular complication rate is comparable to other studies There was a significantly higher rate of major vascular complications in the last year (Cohort B). This could be explained by more complicated patients in Cohort B than in Cohort A. Finally, there were no significant differences in valve durability between the first 63 patients (Cohort A) and the last 59 patients (Cohort B). This suggests that THV-system training alone may provide stable hemodynamic performance of the prosthetic valve from the beginning.

There were seven patients with a bicuspid aortic valve (5.7%). Using the balloon expandable THV system in BAV anatomy may help to overcome on those difficulties which come from the anatomical differences and therefore may simplify the TAVR procedure in this clinical scenario.

The PPI rate was well within the expected range, a positive outcome for a learning team. Overall, there were no significant differences between patients with or without PPI regarding any known risk factors, so this complication was not procedure-related rather patient-related.

3.4. Conclusions

Our results suggest that learning with multiple THV systems was safe when a well-trained team followed the instruction rigorously. During the learning curve, we found no differences between initial, low-volume TAVR (Cohort A) and later high-volume TAVR (Cohort B) for mortality, although there appeared to be a non-significant decrease in mortality with experience. Using constant roles in the TAVI team, especially in the learning curve, operator-related complication rate is reducible. Overall, well trained interventional team, highly adhering to the instruction for use of the different THV systems with ultrasound guided access site puncture can reach high device success rate with good short and long-term result from the beginning.

4. Experinces with the balloon-expandable Myval transcatheter aortic valve system, based on the 30-day and 1-year follow-up data with the first 100 patients.

4.1. Methods

4.1.1. Study design and Patient Population

One hundred patients diagnosed with significant aortic stenosis and underwent TAVR procedure using MyVal THV device from November 2019 to July 2021 were enrolled for this retrospective study. From them 17 patients had bicuspid aortic valve and one patient had undergone surgical aortic bioprosthesis implantation previously. TAVR were performed using the Myval THV (Meril Life Sciences Pvt. Ltd., Vapi, India). This THV has bovine pericardium leaflet on nickel-cobalt frame with anticalcification treatment, unique cell design resulting in higher radial force, internal and external sealing tissue minimizing PVL. Beyond the standard sizes (20,23,26,29 mm), intermediate (21.5,24.5,27.5 mm) and extra-large valve sizes (30.5,32mm) are available. The transfemoral-first approach was used as the standard of care, therefore transfemoral access was used in the great majority and trans-subclavian access, as femoral alternative access was used only in one patient.

4.2. Results

4.2.1. Procedural outcomes

Transfemoral access was the most frequent (99%) with only a single trans-subclavian implantation (1%). Conscious sedation was the standard of care (97%), general anesthesia was used in minority (3%). In 44 cases (44.5%) standard sizes (23, 26, 29) were implanted and in 55 cases (55.5%) intermediate/extra sizes (21.5, 24.5, 27.5, 30.5, 32) were chosen. In BAV patient group the intermediate/extra sizes THVs were used in a significantly higher proportion compared to standard sizes (76.5% vs. 23.5%, p=0.028), while this ratio was similar in the tricuspid aortic valve (TAV) group (intermediate/extra sizes vs. standard sizes

51.2 % vs. 48.8%). The mean aortic gradient decreased significantly (55.2±17.9 mmHg vs. 5.3±5.7 mmHg, p<0.0001). Procedural parameters did not differ between BAV versus the TAV group, except for longer operation duration in bicuspid patients (75.7±27.1 min. vs. 102.9±44 min., p=0.022). Even ARI was favourable in both groups, slightly better in bicuspid patients (27.3±10.0 vs. 29.1±7.8, p=0.501). No THV malapposition, annular rupture, coronary obstruction or need for second THV occurred. We observed only a single device failure. After the failure of removing the undeployed valve system from the common iliac artery, vascular surgery and direct extraction of the delivery system from the common iliac artery was imperative. The patient died due to the complication of this surgery.

Device success was achieved in all but 1 patient (99%), where the patient died (see above). In one patient with true BAV (Type 0), self-expanding THV implantation was unsuccessful and for safety reason, to avoid fatal complication (aortic rupture, rupture of the free wall etc.) TAVR procedure was terminated and 1 week later the TAVR procedure was successful, where Myval THV system was implanted properly.

However, CEP (cerebral embolic protection) devices are not funded for TAVR procedure, and therefore we were unable to use these systems, the ischaemic stroke was observed only in one patient. After pharmacological therapy neurological symptoms improved and the patient completed a successful neurologic rehabilitation program.

In our study population, 9 patients already had a permanent pacemaker before the TAVR procedure. New PPI was necessary in 28 cases (30.7%). No significant differences occurred in patients with new PPI versus patients without new PPI regarding age, Euroscore II, STS score, calcium score of the aortic valve and the percentage of THV sizing, and implantation depth. The rate of calcium in the LVOT tract tended to be higher in the PPI group (44.8% versus 36.6%), although statistically significant difference could not be detected. However, the presence of calcium in the LVOT tract is a definite risk factor for PPI, the use of intermediate sizes could decrease the chance of this non-disabling complication. PPI was less frequent with intermediate sizes than with standard ones (25.49% vs. 38.46%, p=0.094). The rate of BAV patients tended to be lower in the PPI group comparing with the TAV patients (14.3% vs. 20.9%).

Vascular complications occured in 11 cases. Based on the VARC-2 criterias, major vascular complication (due to the used amount of transfusion) occured in 6 patients, and minor vascular complication were detected in 5 patients. In all cases interventional or surgical procedure could achieve a patent flow at the donor artery.

4.2.2. VARC-2 outcomes at 30-days and 1-year follow-up

At 30 days all-cause mortality was 1%, there were no more cases of death except for the 1 in-hospital death (for details see the above).

Between the 30-day and 1-year period, 6 additional cases of death occurred: 2 patients died due to non-cardiac infections leading to multi-organ failure, 2 patients had endocarditis and 2 patients died due to out-of hospital acquired Covid-19 pneumonia. The all-cause mortality rate at 1 year was 7%, the cardiac mortality was only 2%. In the follow-up period 4 patients had ischaemic stroke, therefore, the 1-year all stroke rate appeared to be 5%. After 30 days, only one patient was admitted due to progression of heart failure, and cardiac resynchronization therapy pacemaker (CRT-PM) was necessary. In addition, one more pacemaker implantation was mandatory due to complete third-degree AV block. The rate of prosthetic valve endocarditis (PVE) at 1 year was 2%, which seems to be higher than expected. At the first, high risk patient (Euroscore: 20,46; STS score: 5,26) the IE occured after 3 months. At the second patient PVE occured after 9 months. The functional capacity of the patient based on NYHA classification improved significantly even till the 30 days control and sustained throughout the follow-up period.All the relevant data from 30-day and 1-year outcomes are summarized in Table 3 and Figure 3.

VARC-2 outcomes at 30-day and one-year follow-up			
Outcome	**Postprocedure outcomes (n=100)**	**30 days follow-up (n=100)**	**1 year follow-up (n=100)**
All-cause mortality	1 (1%)	1 (1%)	7 (7%)
Cardiac mortality	0 (0%)	0 (0%)	2 (2%)
All stroke	1 (1%)	1 (1%)	5 (5%)
Life-threatening bleeding	5 (5%)	5 (5%)	5 (5%)
Acute kidney injury, stage 2 or 3	3 (3%)	3 (3%)	3 (3%)
Coronary artery obstruction	0 (0%)	0 (0%)	0 (0%)
Major vascular complication	6 (6%)	6 (6%)	6 (6%)
New pacemaker implantation	28 (30,7%)	29 (31,8%)	31 (31%)
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)	0 (0%)	0 (0%)	1 (1%)
Requiring hospitalizations for worsening heart failure		0 (0%)	1 (1%)
NYHA class III or IV		0 (0%)	1 (1%)
Valve thrombosis	NA	0 (0%)	0 (0%)
Endocarditis	NA	0 (0%)	2 (2%)

Table 3. Detailed data of outcomes at 30-day and one-year follow-up of the study population based on VARC-2 definition.

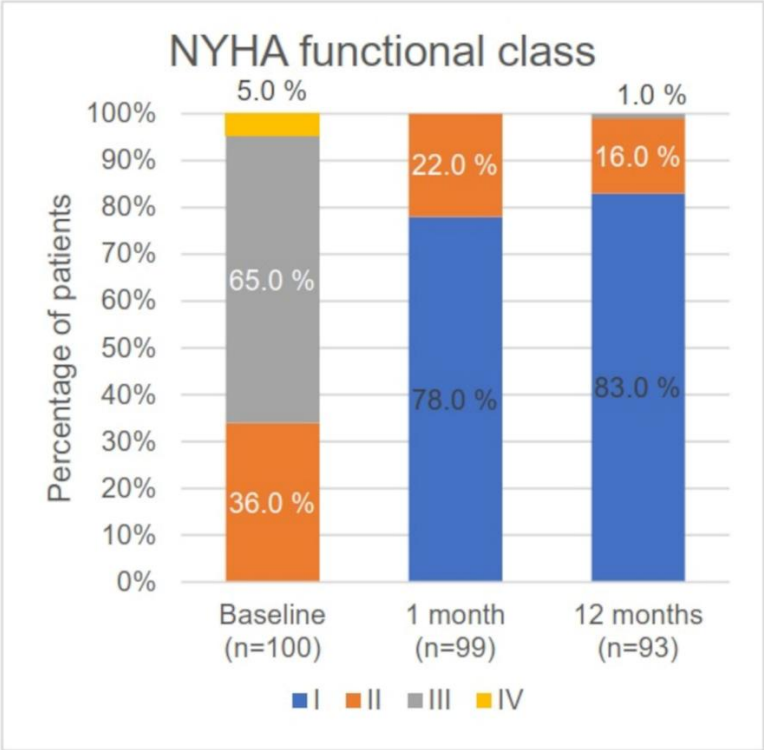

Figure 3. Baseline and follow-up clinical status of the patients based on classification by the New York Heart Association. Values are n (%).

4.2.3. Echocardiographic outcomes

Significant reduction was observed between baseline vs. discharge values of peak aortic gradients (81.4±23.4 vs. 19.1±6.8 mmHg, p<0.0001) and no significant change could be detected from discharge to 30-day follow-up (19.1±6.8 vs. 19.8±7.4 mmHg, p=0.676). There was a substantial decrease between baseline and discharge values (47.9±14.4 vs. 10.0±4.3 mmHg, p<0.0001) and no further significant change in mean aortic gradient was detected at later time points (discharge vs. 30-day follow-up: 10.0±4.3 vs. 9.9±4.3 mmHg, p=0.977; 30-day follow-up vs. 1-year follow-up: 9.9±4.3 vs. 10.7±4.2 mmHg, p=0.105). The type of valve (i.e. BAV vs. TAV) had no effect on changes in the peak and mean aortic valve gradient over time (p=ns for all). Global ejection fraction increased modestly over the follow-up period in the tricuspid group (discharge vs. 1-year follow-up: 55.7±9.8% vs. 59.9±11.4%, p=0.001), but not in the bicuspid group (p=ns).

The percentage of patients with aortic regurgitation grade 2 or above decreased significantly [29 (29.3%) vs. 5 (5.1%), p<0.0001] and no significant change could be seen in the follow-up period: discharge vs. 30-day follow-up [5 (5.1%) vs. 5 (5.1%), p=1.0] and 30-

day vs. 1-year follow-up [4 (4.3%) vs. 4 (4.3%), p= 1.0]. It should emphasized that during the follow-up period there were no aortic regurgitation grade 3 or 4.

4.3. Discussion

In our all-comer patient cohort we found excellent device implantation rate (99%), low in-hospital mortality and stroke rate (only 1-1%) with acceptable vascular complications rate and aortic regurgitation rate. No major mechanical complications such as cardiac tamponade, annular rupture, valve malpositionig and/or need for second THV implantation were seen. Furthermore, mortality and stroke rate were the same at 30 days follow-up.

We found excellent haemodynamic and echocardiographic improvements in overall and beyond in comparison between patients with BAV and TAV. In our study 17 BAV patients were implanted without any mechanical complications, however low case numbers might limit our findings. Overall, intermediate size implantation was more frequent than standard size (55.5 % vs. 44.5%), but this difference was more obvious in the BAV patient group (76.5% vs. 23.5%). However, oversizing was nonsignificantly lower in BAV patients (6.5%±3.5 vs. 7.8±4.0, p=0.221), this represents our effort for oversizing in tricuspid aortic valve patients and for normal sizing in BAV patients, based on CT measurements. Nevertheless, the rising experience with TAVR in bicuspid patients showed favorable results comparing with tricuspid patients [3, 4], randomized, adequately powered studies are still lacking.

The new PPI rate was 30.7% (28 patients from 91) in our cohort, which remained unchanged until 30 days of follow up, and only two patients had PPI after this period.

4.4. Conclusions

Based on our results, excellent safety and efficacy of Myval THV system in patients with significant aortic valve stenosis could be detected, and these results are comparable with studies using other THV systems. Nevertheless, little is known about this new balloon expendable THV systems in patients with BAV disease, which subgroup (with a higher potential complication rate) showed comparable results to patients with tricuspid aortic valve disease thanks to a wide range of intermediate THV sizes. We observed higher new permanent pacemaker implantation rate without any negative consequence on the survival rate. The single-

centre and retrospective collection of data could limit our results. Longer-term follow-up (3, 5 years) with a larger cohort is required to evaluate outcomes and durability of Myval THV in patients with BAV and TAV stenosis.

5. Experience with the Balloon-Expandable Myval Transcatheter Aortic Valve System in Patients with Bicuspid Anatomy.

5.1.1. Study design and Patient Population

We report 52 consecutive Myval cases performed from November 2019 to July 2023 in patients with significant aortic stenosis and BAV anatomy. Propensity score methodology was used to control for differences between BAV and TAV patients in baseline and procedural characteristics. Prior to this study, our centre had no experience with balloon-expandable THV implantation; only self-expandable devices were used. Therefore, our results were influenced by the learning curve with this technique. As the sizing of the THV devices is a crucial part of the TAVI procedure, especially in BAV anatomy, our aim was to optimize PVL/annular rupture rate, using the wide sizing scale of this BEV system and to choose THV size with the annular sizing method.

5.2. Results

5.2.1. Procedural outcomes

Procedural parameters are summarized in Table 4. There were no significant differences between BAV and TAV patients regarding mean pre - and post-procedural aortic gradient in either comparison (unmatched or matched). Procedural parameters did not differ between the BAV and TAV groups, except for the longer operation duration in BAV patients (82.6±28.2 min vs. 95.5±34.2 min, p=0.005 for unmatched and 78.5±24.3 min vs. 95.5±34.2 min, p=0.004 for matched), and significantly higher ARI index in the matched BAV group (25.8±8.5 vs. 30.4±9.2, p=0.014).

		Unmatched (n=269)			Matched (n=52)		
Variable	***Overall (n=269)***	***Tricuspid (n=217)***	***Bicuspid (n=52)***	***p value***	***Tricuspid (n=52)***	***Bicuspid (n=52)***	***p value***
Type of anesthesia							
general	15	11	4	0.459	0	4	***0.041**
local	255	207	48	0.369	52	48	***0.041**
Access site							
femoral (percutaneous)	265	216	49	***0.005**	52	49	0.079
femoral (surgical)	2	0	2	***0.004**	0	2	0.153
subclavia	2	1	1	0.270	0	1	0.315
axillaris	0	0	0	NA	0	0	NA
direct aortic	0	0	0	NA	0	0	NA
Contrast agent	225.3 ± 99.5	224.5 ± 100.2	230 ± 97.4	0.719	218.7 ± 92.1	230 ± 97.4	0.544
Operation duration (min)	85.4 ± 29.5	82.6 ± 28.2	95.5 ± 34.2	***0.005**	78.5 ± 24.3	95.5 ± 34.2	***0.004**
Predilatation	269	217	52	1.000	52	52	1.000
Postdilatation	34	28	6	0.790	6	6	1.000
Preimpl. mean AV gradient	53.6 ± 18.2	53.9 ± 18.5	52.6 ± 17.0	0.658	55.4 ± 19.9	52.6 ± 17	0.452
Postimpl. mean AV gradient	6.4 ± 6.2	6.4 ± 6.3	6.3 ± 5.8	0.942	6.1 ± 5.5	6.3 ± 5.8	0.868
ARI	29 ± 18.7	28.7 ± 20.5	30.4 ± 9.2	0.576	25.8 ± 8.5	30.4 ± 9.2	***0.014**

Table 4. Procedural parameters of the study population of the whole study population and after propensity score matching. ARI: aortic regurgitation index.

There was no in-hospital mortality, device failure, THV malapposition, annular rupture, coronary obstruction, or need for a second THV in the BAV cohort. No significant differences between the BAV and TAV cohorts occurred in postprocedural outcomes, except one transient ischemic attack (TIA) in the BAV group (1.9% vs. 0.0%, p=0.041). Ischemic stroke (non-disabling) was observed in one patient and TIA in another patient; therefore, the stroke and TIA rate was 1.9%.

New PPI was necessary in 17 BAV cases (34%) and 59 TAV cases (30.4%). No significant difference was detected between the two cohorts in the PPI rate for the unmatched (BAV vs. TAV, 34.0% vs. 30.4%, p=0.429) or matched comparisons (BAV vs. TAV, 34.0% vs. 24.0%, p=0.274). The calcium score of the aortic valve was non-significantly higher in the BAV-PPI group (3975±2310 vs. 3112±1568, p=0.087). These differences disappeared after propensity matching. There were no significant differences between BAV-PPI and TAV-PPI patients in implantation depths in the unmatched or matched comparisons. The rate of calcium in the left ventricular outflow tract (LVOT) was similar between BAV-PPI and TAV-PPI patients. On the other hand, in the whole Myval cohort (including BAV and TAV patients), the rate of calcium in the LVOT tract was significantly higher in patients with new PPI after the

TAVI procedure (47.4% vs. 30.5%, p=0.009). In 10 patients (three BAV and seven TAV patients), PPI was performed based on the latest electrophysiological guidelines due to the new onset of borderline conduction disturbances.

Vascular complications occurred in six BAV cases, two cases were major and four cases were minor. Vascular complications occurred in 19 TAV cases, five cases were major and 14 cases were minor.

5.2.2. Distribution of THV sizes according to valve types

In 12 cases (23.1%), standard sizes (23, 26, 29 mm) were implanted. In 40 cases (76.9%), intermediate/extra sizes (21.5, 24.5, 27.5, 30.5, 32 mm) were chosen. The intermediate/extra-size THVs were used in a significantly higher proportion of BAV cases compared to standard sizes (76.9% vs. 23.1%, p<0.0001); this ratio was similar in the TAV group, both in the unmatched (52.5% vs. 47.51%, p=0.337) and matched (55.8% vs. 44.2%, p=0.239) cohorts.. The percentage of oversizing was significantly higher in the TAV patients (6.9±4.4% vs. 4.8±4.7%, p=0.002) compared to BAV patients; this remained after propensity matching (6.4±4.9% vs. 4.8±4.7%, p=0.044). Details are in Tables 5.

THV size	**Unmatched (n=269)**			**Matched (n=52)**		
	Tricuspid (n=217)	*Bicuspid (n=52)*	*p value*	*Tricuspid (n=52)*	*Bicuspid (n=52)*	*p value*
21.5	6	4	0.092	2	4	0.400
23	34	3	0.063	6	3	0.295
24.5	54	11	0.572	10	11	0.807
26	49	4	0.015	12	4	0.030
27.5	45	14	0.333	13	14	0.823
29	20	5	0.929	5	5	1.0
30.5	5	8	<0.0001	4	8	0.220
32	3	3	0.054	0	3	0.079
Oversizing (%)	6.9 ± 4.4	4.8 ± 4.7	0.002	6.4 ± 4.9	4.8 ± 4.7	0.044
Standard size	103 (47.5%)	12 (23.1%)	*0.001*	23 (44.2%)	12 (23.1%)	0.022
Intermediate/extra size	113 (52.5%)	40 (76.9%)	*0.001*	29 (55.8%)	40 (76.9%)	0.022
	0.337 *	<0.0001 **		0.239 *	<0.0001 **	

Table 5. Distribution of different THV sizes regarding the comparison between tricuspid aortic valve and bicuspid aortic valve patients. THV: transcatheter heart valve, Standard size: 23,26,29, Intermediate+extra size: 21.5, 24.5, 27.5, 30.5, 32.

5.2.3. CT measurements

The implantation angulation and the proportion of horizontal aorta were significantly higher in the BAV cohort. Furthermore, aortopathy (defined as the aortic ascendens above 40 mm in diameter[5]) was drastically more frequent in BAV anatomy ($p<0.0001$). Based on CT scans from the 39 raphe-type BAV patients, 9 (23%) patients had no calcified raphe or excessive leaflet calcification, 10 (26%) patients had calcified raphe or excessive leaflet calcification, and 20 (51%) patients had calcified raphe plus excessive leaflet calcification. Taking into consideration these CT-based subcategories based on the report from Sung-Han Yoon *et al*., our BAV patient cohort was at high risk for long-term all-cause mortality.

5.2.4. VARC-2 outcomes at 30-day follow-up

At 30 days, there were no deaths in the matched comparison. In the unmatched TAV group, there were two cases of death (one case due to COVID-19 pneumonia and one case due to life-threatening bleeding); these findings resulted in 2.3% all-cause mortality and 0.5% cardiac mortality. During the 30-day follow-up period after patient discharge, there were no new strokes, no need for new PPI, and no valve-related dysfunction requiring repeat procedures. At 30 days, no bleeding complication, prosthetic valve endocarditis/thrombosis or thrombo-embolic events were detected. Significant improvement in NYHA functional class could be detected and there were no patients at NYHA functional class III in the BAV cohort with only two in the unmatched TAV cohort. Details are listed in Tables 6,7 and in Figure 4.

Postprocedural outcomes (< 72 h after the index procedure) of the study population (*n* = 269)		Unmatched (n=269)			Matched (n=52)		
		Tricuspid (n=217)	Bicuspid (n=52)	p value	Tricuspid (n=52)	Bicuspid (n=52)	p value
Outcome	***No. (%) of events***						
In-hospital mortality	3 (1.1%)	3 (1.4%)	0	0.394	0	0	NA
Device success	267 (99.3%	215 (99.1%)	52 100%)	0.487	52 (100%)	52 (100%)	NA
Myocardial infarction	0	0	0	NA	0	0	NA
Coronary obstruction	0	0	0	NA	0	0	NA
TIA	1 (0.4%)	0	1 (1.9%)	0.041	0	1 (1.9%)	0.315
Stroke	3 (1.2%)	2 (0.9%)	1 (1.9%)	0.537	0	1 (1.9%)	0.315
Acute kidney injure, stage 2 or 3	5 (1.8%)	5 (2.3%)	0	0.269	1 (1.9%)	0	0.315
Minor vascular complications	19 (7.1%)	15 (6.9%)	4 (7.4%)	0.844	3 (5.7%)	4 (7.7%)	0.696
Major vascular complications	7 (2.6%)	5 (2.3%)	2 (3.8%)	0.530	0	2 (3.8%)	0.475
Permanent Pacemaker Implantation	76 (31.1%)	59 (30.4%)	17 (34%)	0.429	12 (24%)	17 (34%)	0.274
Cardiac tamponade	1 (0.4%)	1 (0.5%)	0	0.624	0	0	NA
Annulus rupture	0	0	0	NA	0	0	NA
Valve malpositioning	1 (0.4%)	1 (0.5%)	0	0.624	0	0	NA
Need for a second valve	0	0	0	NA	0	0	NA
Posptocedural AR grade III or IV	0	0	0	NA	0	0	NA

Table 6. Detailed data of postprocedural outcomes (<72 h after the index procedure) of the study population and comparison between patients with tricuspid and bicuspid anatomy regarding unmatched and after propensity score matching. Outcomes based on VARC-2 definition.

VARC-2 outcomes at 30 days follow-up		Unmatched (n=269)			Matched (n=52)		
		Tricuspid (n=217)	Bicuspid (n=52)	p value	Tricuspid (n=52)	Bicuspid (n=52)	p value
30 days cumulative clinical outcomes (n=269)	*No. (%) of events*						
All-cause mortality	5 (1.8%)	5 (2.3%)	0	0.269	0	0	NA
Cardiac mortality	1 (0.4%)	1 (0.5%)	0	0.623	0	0	NA
All stroke	3 (1.2%)	2 (0.9%)	1 (1.9%)	0.537	0	1 (1.9%)	0.315
Life-threatening bleeding	1 (0.4%)	1 (0.5%)	0	0.623	0	0	NA
Acute kidney injury, stage 2 or 3	2 (2.4%)	2 (0.9%)	0	0.486	0	0	NA
Coronary artery obstruction	0	0	0	NA	0	0	NA
Minor vascular complications	19 (7.1%)	15 (6.9%)	4 (7.7%)	0.844	3 (5.7%)	4 (7.7%)	0.696
Major vascular complications	7 (2.6%)	5 (2.3%)	2 (3.8%)	0.530	0	2 (3.8%)	0.475
New pacemaker implantation	76 (31.1%)	59 (30.4%)	17 (34%)	0.429	12 (24%)	17 (34%)	0.274
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)	0	0	0	NA	0	0	NA
NYHA class III or IV	2 (2.4%)	2 (0.9%)	0	0.621	0	0	NA
Prosthetic valve endocarditis	0	0	0	NA	0	0	NA
Prosthetic valve thrombosis	0	0	0	NA	0	0	NA
Thrombo-embolic events	0	0	0	NA	0	0	NA

Table 7. Detailed data of outcomes at 30-day follow-up of the study population and comparison between patients with tricuspid and bicuspid anatomy regarding unmatched and after propensity score matching. Outcomes based on VARC-2 definition.

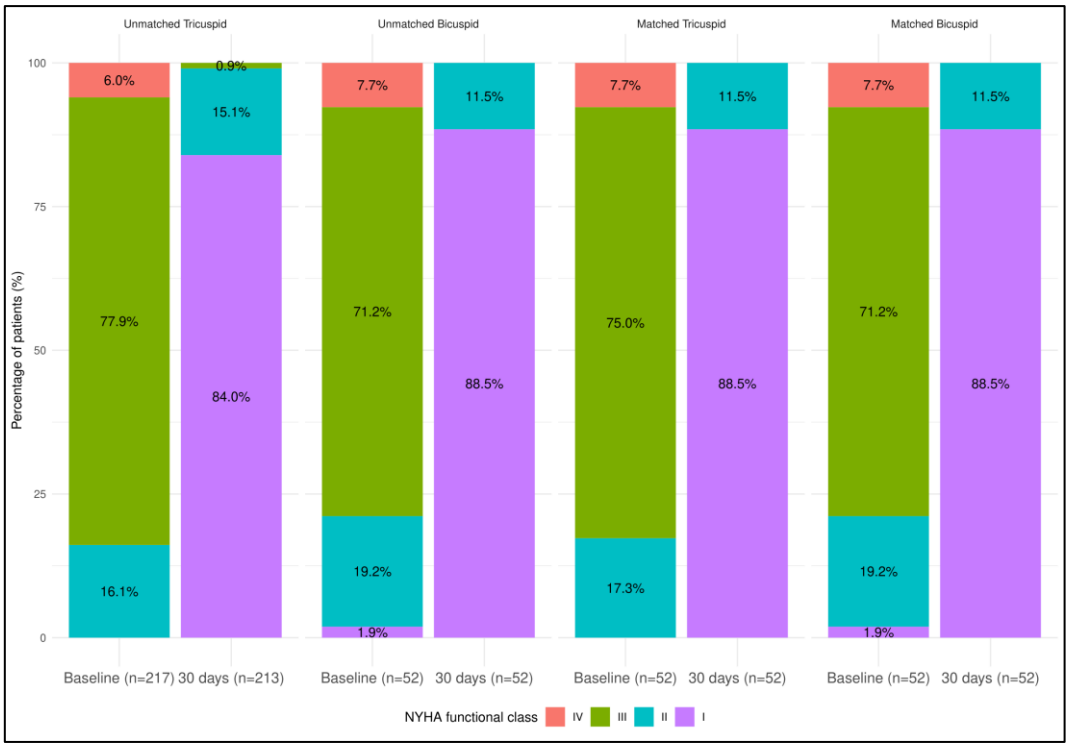

Figure 4. Patient distribution according to NYHA functional class regarding the unmatched tricuspid versus bicuspid comparison and the matched tricuspid versus bicuspid comparison. NYHA functional class improved significantly in every patient cohort from baseline to 30 days follow-up (patient at NYHA III/IV vs. NYHA I/II, $p<0.0001$ for all comparison).

5.2.5. Echocardiographic Outcomes

After the TAVI procedure, no significant difference could be detected between TAV and BAV cohorts in LVEF, pAVG, and mAVG at discharge and 30-day follow-up. Paravalvular leakage (grade moderate or above) was absent in the BAV patients and was present in a minority of TAV patients. These favorable echocardiographic results occurred in both unmatched and matched comparisons. Detailed data are in Figure 5.

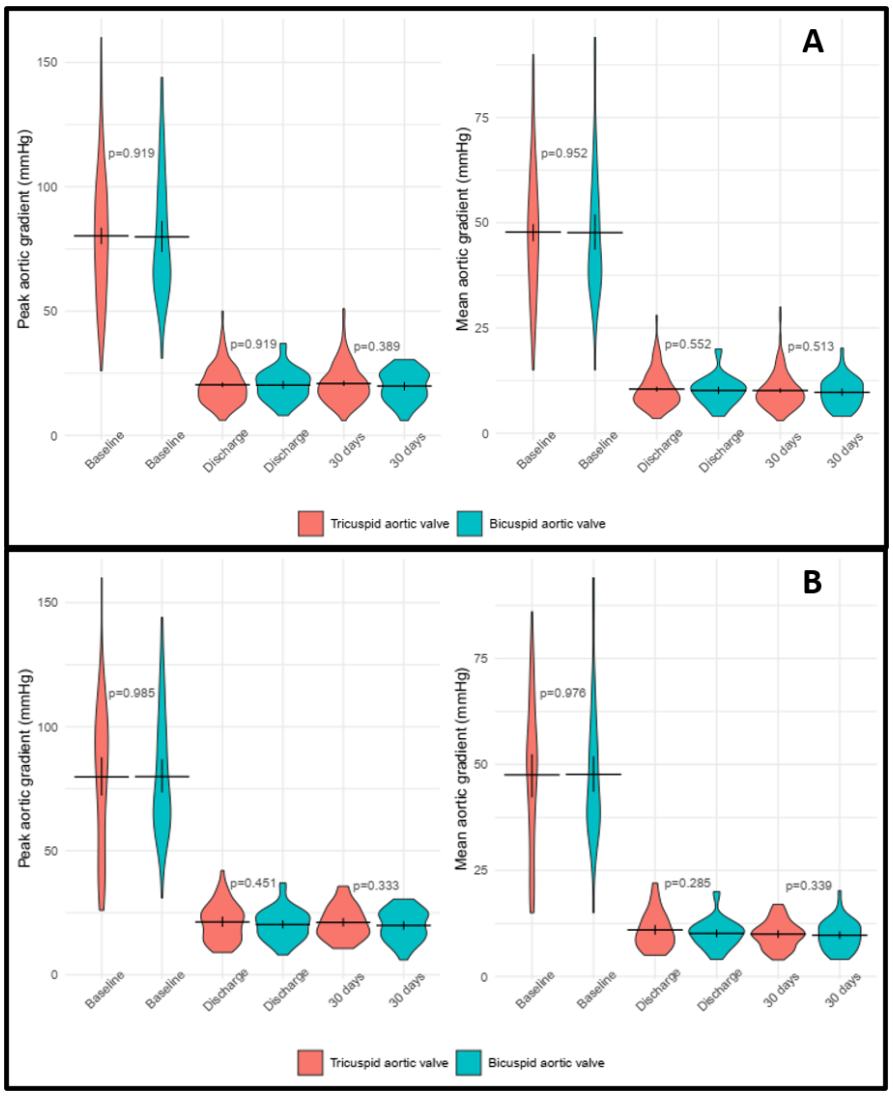

Figure 5. Peak and mean aortic gradients at the different time period regarding the unmatched comparison (panel A) and after propensity score matching (panel B).

5.3. Discussion

The present study was conducted to analyze the safety, efficacy, procedural, and clinical outcomes of the TAVI procedure using the novel balloon-expandable THV device in BAV anatomy and to compare the results to patients with TAV aortic stenosis. The major findings are as follows:

1. The TAVI procedure with the Myval THV system is safe, with no significant differences in VARC-2 outcomes in the unmatched and propensity score matched comparisons.

2. The TAVI procedure with the Myval THV system is effective, with no significant differences in hemodynamic performance between BAV and TAV patients based on invasive and non-invasive measurements. Moreover, ARI was significantly higher after the BAV TAVI procedure.

3. The sizing method used, alongside the wide range of standard and intermediate/extra sizes, allowed all patients to be suitable for the TAVI procedure regardless of their anatomical dimensions. Also, there was a significantly lower rate of oversizing in BAV patients compared to TAV.

4. Beyond the lack of major mechanical complications, the rate of PPI was high in both groups. No significant differences in risk factors were detected between BAV and TAV patients with post- TAVI PPI, except for a tendency for higher aortic valve calcium scores in BAV patients in the unmatched comparison.

5.4. Conclusion

The novel balloon-expandable THV system is safe and effective in BAV patients compared to TAV for procedural outcomes and 30-day follow-up. Beyond standard sizes, the intermediate and extra sizes have additional value in BAV anatomy when considering the lack of annular rupture and the absence of moderate-or-above PVL grade. This technology combines the known positive features of BEV and SEV systems without their negative ones. Based on our results, the high PPI rate was likely due to patient characteristics rather than device-related.

6. Conclusion and novel findings

The main findings of our study that starting a TAVR programme is safe in a well trained centre, if the implanting physician follow the principle steps of the procedure. However, there is no clear recommendation regarding which THV system should starting with and whether using different THV systems in the learning curve is safe and effective, our results support this theory. Taking into consideration that patients have different anatomical parameteres based on the CT scans, pro and cons are exist between the different THV systems on the individual patient level. Therefore, starting TAVR centres, facing with distinct patient anatomy, should not apply the „one system fits all" technique.

After switching from surgical cut-down to percutaneous technique for access site preparation, using the ultrasound guided puncture is mandatory to obtain high success rate without relevant bleeding/vascular complication, as one of the major limitation of this procedure.

The results of our data regarding the first 100 patients treated with balloon expandable THV system, proved that this novel THV system is safe and effective. The unique wide range of this THV sizes gives the opportunity for the operators to chose the most appropriate THV size taking into consideratrion the patients anatomical parameteres. Using this THV system combining the low PVL rate as a consequence of high radial force of the BEV systems and the low rate (or even the absence) of annular rupture, as the advantage of SEV systems is achievable.

Another advantage of this novel BEV system is the uniqe, flexible-steerable delivery system, which allows to manipulate actively even in the aortic arch. With this active manoeuvre, physician can avoid to touch the atherosclerotic plaques of the aorta, which may result in lower incidence of TIA or STROKE. Our low rate of cerebrovascular complication can underpower this theory.

Based on our results, the wide sizing scale of this novel balloon-expandable THV device has an additive value. Comparing the TAVR results regarding patients with BAV anatomy to patients with TAV aortic stenosis, we proved that the TAVI procedure with the Myval THV system is safe, with no significant differences in VARC-2 outcomes in the unmatched and propensity score matched comparisons. Above the safety, efficacy also could be detected, as no

significant differences in hemodynamic performance between BAV and TAV patients based on invasive and non-invasive measurements occured. Moreover, the ARI was significantly higher after the BAV TAVI procedure.The wide range of standard and intermediate/extra sizes, allowed all patients to be suitable for the TAVI procedure regardless of their anatomical dimensions and additionally enable to use a significantly lower rate of oversizing in BAV patients compared to TAV, based on the CT scans. On the other hand, beyond the lack of major mechanical complications, the rate of PPI was high in both groups. Based on our analyzes, this higher PPI rate seems to be related more to patient characteristics than device-related.

7. Publications of the author

7.1. Original research publications related to the thesis

11.1.1. Full papers

1, **Balázs Magyari, MD;** Bálint Kittka, MD; Ilona Goják, MD; Kristóf Schönfeld, MD; László Botond Szapáry, MD; Mihály Simon, MD; Rudolf Kiss MD, Andrea Bertalan MD; Edit Várady MD, Phd, András Gyimesi, MSc; István Szokodi, MD, Phd, DSc; Iván Horváth, MD, Phd. Learning curve for starting a successful single-centre TAVR programme with multiple devices: early and mid-term follow-up. J. Clin. Med. 2024, 13(4), 1088; ***Impact Factor: 3.9***

2, **Balázs Magyari, MD**; Bálint Kittka, MD; Ilona Goják, MD; Gábor Kasza, MD; Kristóf Schönfeld, MD; László Botond Szapáry, MD; Mihály Simon, MD; Rudolf Kiss MD, Andrea Bertalan MD; Edit Várady MD, Phd, András Gyimesi, MSc; István Szokodi, MD, Phd, DSc; Iván Horváth, MD, Phd. Single centre experience with the balloon-expandable Myval transcatheter aortic valve system with the first 100 patients: 30-day and 1-year follow-up. Catheter Cardiovasc Interv. 2023;1–14. ***Impact Factor: 2.585***

3, **Balázs Magyari, MD**; Bálint Kittka, MD; Ilona Goják, MD; Kristóf Schönfeld, MD; László Botond Szapáry, MD; Mihály Simon, MD; Rudolf Kiss MD, Andrea Bertalan MD; Edit Várady MD, Phd, András Gyimesi, MSc; István Szokodi, MD, Phd, DSc; Iván Horváth, MD, Phd. Single-Center Experience with the Balloon-Expandable Myval Transcatheter Aortic Valve System in Patients with Bicuspid Anatomy: Procedural and 30-Day Follow-Up. Journal of Clinical Medicine. 2024 Jan; 13(2): 513. ***Impact Factor: 3.9***

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3, Komocsi A, Pinter T, Faludi R, **Magyari B**, Bozo J, Kumanovics G, Minier T, Radics J, Czirjak L Overlap of coronary disease and pulmonary arterial hypertension in systemic sclerosis ANNALS OF THE RHEUMATIC DISEASES 69 : 1 pp. 202-205. , 4 p. (2010)

4, Pintér T, Faludi R, **Magyari B**, Vorobcsuk A, Kumánovics G, Minier T, Czirják L, Komócsi A Mechanism of coronary flow reserve reduction in systemic sclerosis, insight from intracoronary pressure wire studies RHEUMATOLOGY (UNITED KINGDOM) 50 : 4 pp. 781-788. , 8 p. (2011)

5, Lukács E, **Magyari B**, Tóth L, Petrási Zs, Repa I, Koller Á, Horváth I: Overview of large animal myocardial infarction models Acta Physiol. 2012;99,4, 365-381.

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