# Transcatheter aortic valve replacement in bicuspid aortic valve disease

**Reference:**

Mylotte Darren, Lefevre Thierry, Søndergaard Lars, Bosmans Johan, e.a..- *Transcatheter aortic valve replacement in bicuspid aortic valve disease*

**Journal of the American College of Cardiology** / **American College of Cardiology** - ISSN 0735-1097 - 64:22(2014), p. 2330-2339

DOI: http://dx.doi.org/doi:10.1016/j.jacc.2014.09.039

# Transcatheter Aortic Valve Replacement in Bicuspid Aortic Valve Disease

Darren Mylotte, Thierry Lefevre, Lars Søndergaard, Yusuke Watanabe, Thomas Modine, Danny Dvir, Johan Bosmans, Didier Tchetche, Ran Kornowski, Jan-Malte Sinning, Crochan O'Sullivan, Marco Barbanti, Jean Buithieu, Pablo Codner, Magdalena Dorfmeister, Giuseppe Martucci, Peter Wenaweser, Corrado Tamburino, Eberhard Grube, John G Webb, Stephan Windecker, Ruediger Lange, Nicolo Piazza.

**Institutions**

University Hospital Galway, Ireland; McGill University Health Centre, Montreal; Hopital Jacques Cartier, Massy, France; Rigshospitalet, Copenhagen, Denmark; Hôpital Cardiologique, Lille, France; St. Paul's Hospital, Vancouver, British Columbia, Canada; University Hospital Antwerp, Wilrijk, Belgium; Clinique Pasteur, Toulouse, France; Rabin Medical Center and Tel-Aviv University, Tel-Aviv, Israel; Universitätsklinikum Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn, Germany; Bern University Hospital, Bern, Switzerland; German Heart Center, Munich, Germany; Ferrarotto Hospital, University of Catania, Catania, Italy.

**Corresponding Author**

Nicolo Piazza, Department of Interventional Cardiology, McGill University Health Centre, 687, Pine Ave West, Montreal H3A-1A1, Quebec, Canada. Phone: +1 514 778 0530; Fax: +1 514 934 1934; Email nicolopiazza@mac.com

**Word count: 3968**

**Relationships with Industry**

## Abstract

### Objectives

To evaluate the results of transcatheter aortic valve (TAV) implantation in bicuspid aortic valve (BAV) disease.

### Background

Experience with TAV-in-BAV procedures is limited.

### Methods

Baseline characteristics, procedural data, and clinical follow-up were collected retrospectively from 12 centers that have performed TAV-in-BAV.

### Results

A total of 143 patients underwent TAV-in-BAV with the Edwards SAPIEN (n=52), Medtronic CoreValve (n=91), or Sadra Lotus (n=1) prostheses. The mean age was 77.7±9.1 years and the mean STS score was 4.9±3.4%. BAV stenosis occurred in 65.0%, regurgitation in 0.7%, and mixed disease in 34.7%. BAV types were: 25.8% Type 0; 69.3% Type 1; and 4.9% Type 2. TAV malposition and embolization occurred in 6.4% and 2.1%, respectively. A second TAV was implanted in 3.5% and 2.1% converted to surgery. Procedural mortality occurred in 3.5%. The mean aortic valve gradient decreased from 48.6±16.4 to 11.5±9.8 mmHg (P<0.0001). Post-implantation aortic regurgitation (AR) ≥grade 2 was present in 27.6%. On multivariable analysis, male sex (odds ratio [OR] 4.0, 95% confidence intervals [CI]: 1.6-10.4, P=0.0004) predicted AR ≥grade 2. CT-based TAV-sizing was associated with a reduction AR (OR 0.1, 95% CI 0.1-0.4, P=0.001). The BAV type or prosthesis

implanted did not influence post-implantation AR. 30-day VARC-defined device safety, success, and efficacy was determined in 79.7%, 90.2%, and 85.3%, respectively. One-year mortality was 15.9% and 91.3% were in NYHA class I/II.

**Conclusions**

In high-risk patients, TAV-in-BAV appears to be safe and effective. Short- and intermediate-term clinical outcomes are encouraging, though a high incidence of post-implantation AR is observed.

## Introduction

Bicuspid aortic valve (BAV) is a heritable disease affecting 0.5 to 2% of the general population, with a strong male predilection (1-3). BAV stenosis and/or regurgitation is the most common indication for surgical aortic valve replacement (SAVR) in patients <70 years of age. Nonetheless, a recent study that examined operatively excised aortic valves observed that one-fifth of patients over the age of 80 years had underlying bicuspid pathology; echocardiography identified only in two thirds of these patients (4). BAV has been excluded from the landmark clinical trials involving transcatheter aortic valves (TAV) (5,6). Theoretically, abnormal cusp fusion, heavily calcified and fibrotic leaflets, and calcified raphe could have adverse effects on the expansion of TAVs ultimately leading to paravalvular aortic regurgitation and poor hemodynamic function (7-9). The small number of published case reports and series describing the feasibility of TAV implantation in BAV stenosis (TAV-in-BAV), have been limited in their demonstration of safety and efficacy (10-16). Given the number of elderly patients undergoing TAV replacement and its shift towards treating younger patients, the clinical outcomes of patients subjected to TAV-in-BAV needs to be better understood (17,18).

The objective of the current multicenter study was to describe the efficacy and safety of TAV-in-BAV in a large group of patients. More specifically, we sought to assess the hemodynamic, echocardiographic and clinical outcomes, and the association between BAV morphology or TAV prosthesis type to these aforementioned outcomes.

## Methods

### Participating Centers and Patients

The TAV-in-BAV registry is a multinational collaboration of interventional cardiologists and cardiac surgeons from high-volume TAVR centers. Data from TAV-in-BAV patients were retrospectively collected from twelve participating centers in Europe and Canada (online data supplement). More recently, prospective data collection has been undertaken. In each case, centers submitted a dedicated case report form detailing patient baseline characteristics, echocardiographic and/or multislice computed tomographic data, procedural information and scheduled clinical follow-up.

**Bicuspid Aortic Valve**

BAV was defined as a spectrum of abnormal aortic valve morphology, consisting of two functional cusps with less than three zones of parallel apposition between cusps (19). BAV classification was assigned according to the number and spatial orientation of the raphe (**Figure 1**): type 0, commonly referred to as "pure BAV", has two normally developed cusps, sinuses, and commissures, and no raphe; type 1 has three anlagen, two under- and one fully-developed cusps, one under- and two fully developed commissures, and a single raphe whose orientation in relation to the sinuses defined sub-categorization (left-right; right-non; and left-non); and type 2 with three anlagen, two under- and one fully-developed cusps, two under- and one fully developed commissures, and two raphe (19). Consistent with prior publications, cases of commissural fusion with a raphe <3mm long were not considered to represent BAV (20). All participating sites retrospectively confirmed the diagnosis and classification of BAV using multimodal imaging: transthoracic and transesophageal echocardiography (TEE) and multislice computed tomography (MSCT). When both echocardiography and MSCT were performed, cases were excluded if the diagnosis of BAV was not consistent or remained speculative.

## Endpoints and Definitions

Procedural and 30-day mortality, and other major clinical endpoints were defined according to the updated Valve Academic Research Consortium (VARC) criteria (21). Of particular interest were the composite clinical endpoints of valve efficacy, safety, and success (21). Post-implant aortic regurgitation represented an important non-clinical endpoint (22). Regurgitation was defined as the sum of trans- and paravalvular regurgitation following prosthesis implantation and removal of the stiff guide wire. At each institution, the severity of regurgitation was qualitatively assessed and graded using TEE according to established guidelines (23,24). Regurgitation was categorized as paravalvular, transvalvular, or mixed, and classified as none (0), trace (I), mild (II), moderate (III), and severe (IV) (23,24).

The dimensions of the aortic valve annulus were measured using TEE or MSCT. TAV sizing was thus defined as either TEE- or MSCT-based.

## Statistics

Continuous variables are presented as mean ± standard deviation median and range, and were compared using the Student t-test, Mann-Whitney test, or paired t-test for repeated measures. Categorical variables are presented as frequencies and percentages and were compared using the Chi-square or Fisher exact test. The rates of 1-year mortality were depicted using Kaplan–Meier curves and between group differences were analyzed with the log-rank test. Logistic regression was performed to identify possible predictors of 1-year survival and post-implantation aortic regurgitation. All variables that could plausibly be associated with these outcomes were evaluated in a univariate approach and then factors with a *P* value <0.1 in the univariate analysis were combined in a multivariate logistic regression model. A p value <0.05 was

considered significant. Analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, NY).

## Results

### Patients

A total of 143 high-risk elderly patients underwent TAV-in-BAV in the 12 participating centers between April 2005 and January 2014. Isolated BAV stenosis occurred in 93 (65.0%) patients, isolated regurgitation in 1 (0.7%), and mixed disease in 49 (34.7%). The baseline demographics of the study patients are outlined in **Table 1**. The mean age was 77.7 ± 9.1 years and the mean STS risk of mortality score was 4.9 ± 3.4%.

### Bicuspid Morphology

Evaluation of the morphology of the aortic valve was performed using transesophageal echocardiography in all patients. MSCT was performed for the purposes of TAV-sizing in 92 (64.3%) cases. The BAV type was definitively established in 124 (86.7%) patients and remained uncertain in 19 (13.3%) cases, despite multimodal imaging. Among patients with a confirmed BAV type **(Table 2)**, 32 (25.8%) were Type 0, 86 (69.3%) Type 1 (Left-Right: 62; Right-Non: 17; and Left-Non: 7), and 6 (4.9%) Type 2.

### Procedures

**Table 3** outlines the procedural characteristics and early results of TAV-in-BAV in the total cohort and is further separated into Edwards SAPIEN (Figure 2) and Medtronic CoreValve (Figure 3) groups. Most patients underwent transfemoral TAV implantation (79.0%) with the Edwards SAPIEN (n = 51, 35.7%) (Edwards

Lifesciences Inc., Irvine, CA, USA) or Medtronic CoreValve (n = 91, 63.6%) (Medtronic Inc., Minneapolis, MN, USA). One patient (0.7%) received the Sadra Medical Lotus valve (Boston Scientific, Natick, Massachusetts). Initial balloon aortic valvuloplasty was performed in all but 2 patients and a TAV was subsequently implanted in 141 (98.6%) cases. Two patients did not receive a TAV: one case of severe aortic incompetence and fatal cardiogenic shock following balloon valvuloplasty, and one case where the Edwards SAPIEN valve failed to cross the native aortic valve. Post-implantation balloon valvuloplasty was performed in 25 (17.7%) cases, and TAV malposition and embolization occurred in 9 (6.4%) and 3 (2.1%) cases, respectively. A second TAV was implanted in 5 (3.5%) patient and 3 cases converted to surgical aortic valve replacement (2.1%). Procedural mortality occurred in 5 (3.5%), and was attributed to cardiac tamponade as a result of guide wire perforation of the left ventricle (n = 2), major vascular complication, annular rupture, and the previously described case of severe aortic regurgitation following balloon aortic valvuloplasty.

**Clinical Outcomes**

The median duration of hospital stay was 8 (5, 11) days (**Table 4**). The 30-day rates of death, myocardial infarction and stroke were 4.9%, 3.5%, and 3.5%, respectively. Bleeding occurred in 35.9%, life-threatening bleeding in 10 (7%) patients, and major vascular complications in 9 (6.3%). Overall, 114 (79.7%) patients met the combined safety endpoint and device success was observed in 129 (90.2%). At 30-days, the combined efficacy endpoint was achieved in 122 (85.3%) patients.

Follow-up was available for all patients. At the time of data lock, 140 (97.9%) and 132 (92.3%) patients had reached 6- and 12-month follow-up, respectively. The

Kaplan-Meier survival curve is presented in **Figure 4**. There were 13 deaths (9.3%) at 6 months and 21 (15.9%) deaths at 12 months. Cardiovascular death accounted for 66.6% of deaths at 12 months. On multivariable analysis (**Table 5**), THV malposition was associated with reduced survival at 1-year (odds ratio [OR] 5.70, 95% confidence intervals [CI]: 0.99 to 32.72, P=0.05). The use of the CoreValve was associated with a borderline increase in 1-year survival (OR 0.35, 95% CI: 0.16-0.99, P=0.05). Among survivors, 60.2%, 31.1%, and 8.7% were NHYA functional class I, II, or III, at 1-year follow-up, respectively.

**Postprocedural Echocardiography**

Among the 141 patients that received a TAV, the mean aortic valve gradient decreased from 48.6 ± 16.4 mmHg at baseline to 11.5 ± 9.8 mmHg at 30-days (P <0.0001), while the mean aortic valve area increased from 0.6 ± 0.2 $cm^2$ at baseline to 1.7 ± 0.5 $cm^2$ at 30-days (P <0.0001). Post-implantation aortic regurgitation ≥grade 2 (paravalvular in 92% of cases) was present in 39 (27.6%) patients at 30-days. On multivariable analysis, male sex (OR 4.27, 95% CI: 1.61 to 11.37, P=0.0004) was the only independent predictor of aortic regurgitation ≥grade 2 (**Table 6**). CT-based TAV sizing was independently associated with a reduction in the incidence of post-implantation aortic regurgitation ≥grade 2 (OR 0.17, 95% CI: 0.05 to 0.55, P=0.003). Aortic regurgitation ≥grade 2 occurred in 13.3% of BAV Type 0 patients, 32.2% of Type 1, and 20% of Type 2 (P=0.07). BAV type 1 was not associated with a significant increase in aortic regurgitation ≥grade 2 after adjustment for other variables (OR 2.37, 95% CI: 0.95-5.94, P=0.06).

**Prosthesis Choice**

Baseline characteristics among patients treated with the Edwards SAPIEN or Medtronic CoreValve were similar, though functional class 3 or 4 was more common in the Edwards SAPIEN cohort (P=0.02). There was a trend towards a higher incidence of Type 0 BAV morphology in CoreValve-treated patients (18.6% vs. 30.0%, P=0.09). MSCT-based THV sizing was performed more frequently in the Edwards SAPIEN cohort (78.8% vs. 56.0%, P=0.01), and the transfemoral approach was more common among CoreValve patients (64.7% vs. 86.8%, P=0.003). There was a trend towards an increased incidence of post-implantation regurgitation ≥grade 2 among CoreValve-treated patients (18.0% vs. 32.2%, P=0.08). When patients that underwent only MSCT-based TAV sizing were considered, the incidence of aortic regurgitation ≥grade 2 was similar between the two prostheses (6 of 40 [15.0%] vs. 9 of 50 [17.6%], P=0.78). The choice of TAV was not with post-implantation aortic regurgitation in the multivariable analysis. There were no significant differences in procedural outcomes between patients receiving the two types of valves, except for an increase in the rate of minor vascular complications among CoreValve patients (4.0% vs. 20.9%, P=0.006). At 12 months, death occurred in 10 (23.3%) Edwards SAPIEN cases and 11 (12.5%) CoreValve recipients (log-rank P=0.26) **(Figure 3)**.

## Discussion

The current study is the first large multicenter analysis of TAV implantation in patients with significant BAV stenosis or regurgitation. The results demonstrate that, TAV-in-BAV in high surgical risk patients with aortic stenosis is feasible; device success and 30-day mortality rates were 90% and 5%, respectively. Furthermore, 1-year mortality was low at 16% and the majority of patients were NYHA class I or II.

The current analysis, however, suggests that the incidence of post-implantation aortic regurgitation ≥grade 2 is higher than expected.

**Procedural Safety and Efficacy**

Treating BAV disease with TAV technology is considered an off-label indication. Surgically excised bicuspid valves typically demonstrate leaflet fusion (raphe) and extensive and nodular calcification. The histoarchitectural distribution of calcific deposits in BAV leaflets is different than that of stenotic tricuspid valves (25), and the more diffuse calcium deposition in the body of bicuspid aortic valve leaflets could impair TAVR outcomes (19,26). The experience of registry participants was that crossing the stenotic BAV with the guide wire and/or transcatheter valve, and positioning the prosthesis was more difficult than with tricuspid aortic valve stenosis. Nevertheless, the rate of acute TAV malposition was acceptable (6.4%) and the rate of prosthesis embolization (2.1%) lower than previously reported (27,28). The 30-day rates of VARC-defined device success (90.2%), safety (79.9%) and efficacy (85.3%) were also satisfactory and comparable to other TAV cohorts (5,6,29,30).

**Post-implantation aortic regurgitation**

Clinically significant post-implantation aortic regurgitation (principally paravalvular) occurs relatively frequently after TAV-in-BAV. In the current analysis, aortic regurgitation ≥grade II occurred in more than one in four (27.6%) patients. This rate is consistent with that reported in smaller TAV-in-BAV series (13-15), and compares poorly with reported rates (<20%) of aortic regurgitation following TAV for tricuspid aortic stenosis (28,31,32). The high rate of paravalvular regurgitation is likely explained by the inability of the TAV frame to expand completely and oppose to the native annulus in the presence of heavy calcification and in particular, a calcified

raphe. Aortic root dilatation and/or angulation, and concomitant native aortic valve incompetence may further impede accurate TAV positioning and contribute to the risk of paravalvular regurgitation. In the multivariable analysis, CT-based TAV sizing was associated with a significant reduction in paravalvular regurgitation. This information is consistent with several prior analyses demonstrating the utility of CT-based sizing in reducing post-implantation regurgitation (33,34). Male sex was also associated with an increased risk of paravalvular regurgitation. This association has previously been noted in TAV cohorts of tricuspid aortic stenosis and may be explained by the increasing annulus size and larger TAV sizes required in males (35,36).

Given the strong association between post-procedural aortic regurgitation and both short- and long-term mortality (22,31), the increased incidence of aortic regurgitation observed in BAV patients is concerning. Indeed, while 1-year outcomes were favorable (15.9% death; 91.3% NYHA I-II), further follow-up is required to ascertain the impact of aortic incompetence in BAV cohorts. Certainly, these findings certainly have implications when considering TAV-in-BAV for patients that may be candidates for surgical aortic valve replacement. In such cases, surgical valve replacement should remain the treatment of choice unless deemed to be of excessive risk by the Heart Team. Currently unproven, emerging TAV technology with dedicated sealing cuffs (SAPIEN 3, [Edwards Lifesciences Inc., Irvine, CA, USA]) or repositionable systems (CoreValve Evolut R [Medtronic, Minneapolis, MN, USA]) have the potential to reduce post-implantation aortic regurgitation (37,38).

**Choice of Prosthesis**

BAV morphology presents potential advantages and disadvantages for balloon- and self-expanding TAV systems. The balloon-expandable Edwards SAPIEN TAV exerts

greater radial force and may circularize the native annulus, obliterating potential sites of paravalvular aortic regurgitation. Calcified nodules or raphe may however prevent complete prosthesis expansion and cause residual paravalvular leak or longer-term leaflet dysfunction. In contrast, the greater compliance of the self-expanding CoreValve, and supra-annular position of the leaflets, has the potential to mitigate against the unequal circular stress on the TAV at the level of the annulus and potentially improve long-term hemodynamic outcomes. In the current study, we observed no significant difference in clinical outcomes in patients treated with the Edwards SAPIEN or Medtronic CoreValve. Use of the CoreValve was however associated with a marginal reduction in 1-year mortality. This observation may relate to the lower risk profile of the patients treated with this prosthesis. We also observed a trend towards increased rates of post-implantation aortic regurgitation ≥grade 2 with the CoreValve (18.0% vs. 32.2%, P=0.08). The relatively low use of CT-based THV sizing in the CoreValve group (78.8% vs. 56.0%, P=0.01) probably accounts for this observation (39). Indeed, CoreValve use was not independently associated with post-implantation aortic regurgitation in the multivariable analysis. Longer-term follow-up of a larger cohort of patients is required to more completely assess THV durability in patients with BAV disease.

**Limitations**

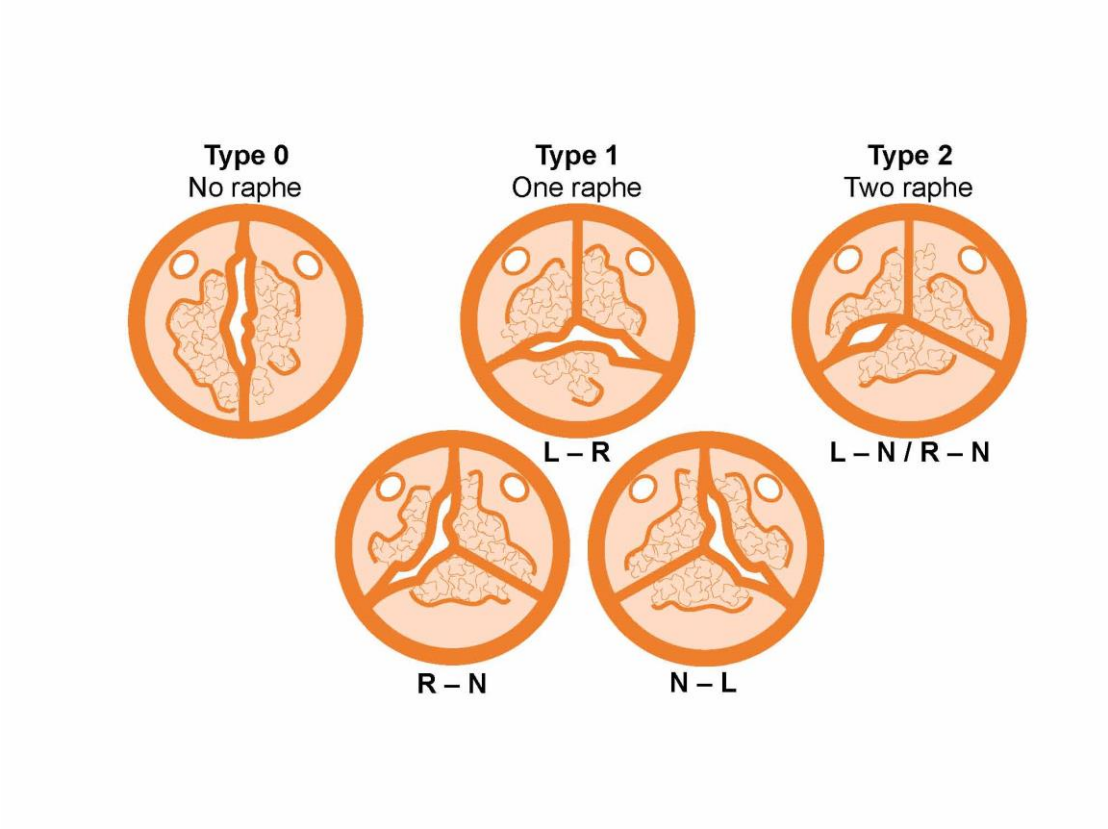
The study findings should be interpreted in light of the study design. This predominantly retrospective voluntary registry of TAV-in-BAV cases necessitates cautious interpretation and definitive conclusions should be avoided. Adverse events and post-implantation aortic regurgitation, which may be operator and laboratory dependent, were adjudicated by the participating centers rather than by a core-laboratory.

## Conclusions

In high-risk patients with significant BAV disease, TAV-in-BAV appears to be both safe and effective. Short- and intermediate-term clinical outcomes are encouraging though a higher incidence of post-implantation aortic regurgitation is observed.

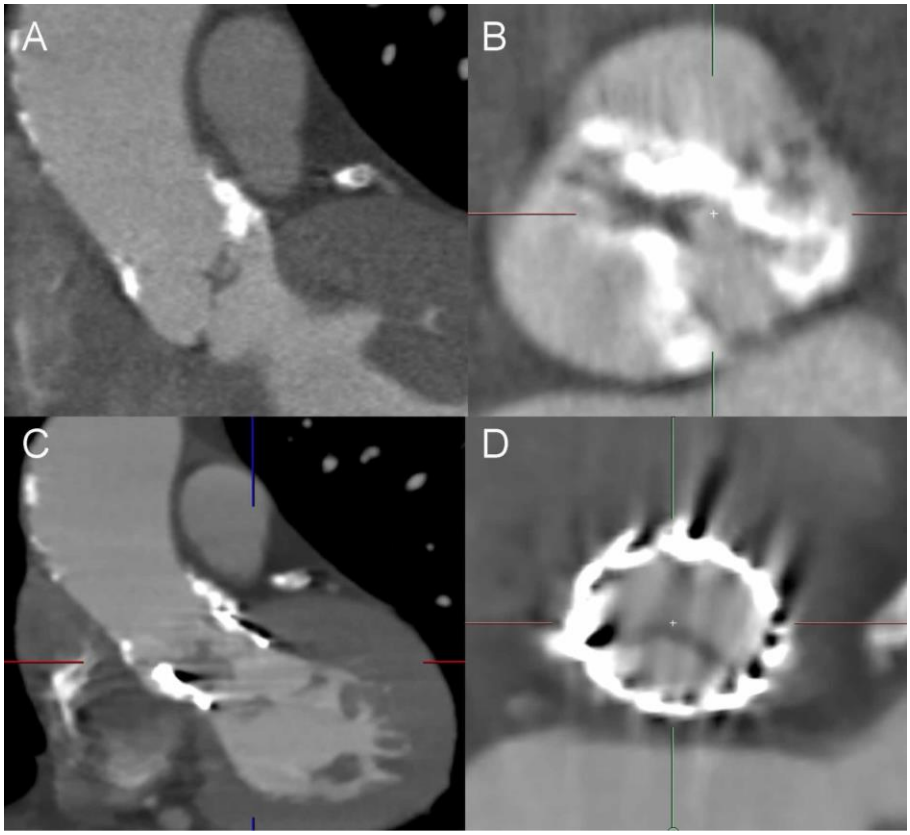
## Figures

**Figure 1. Classification of BAV**



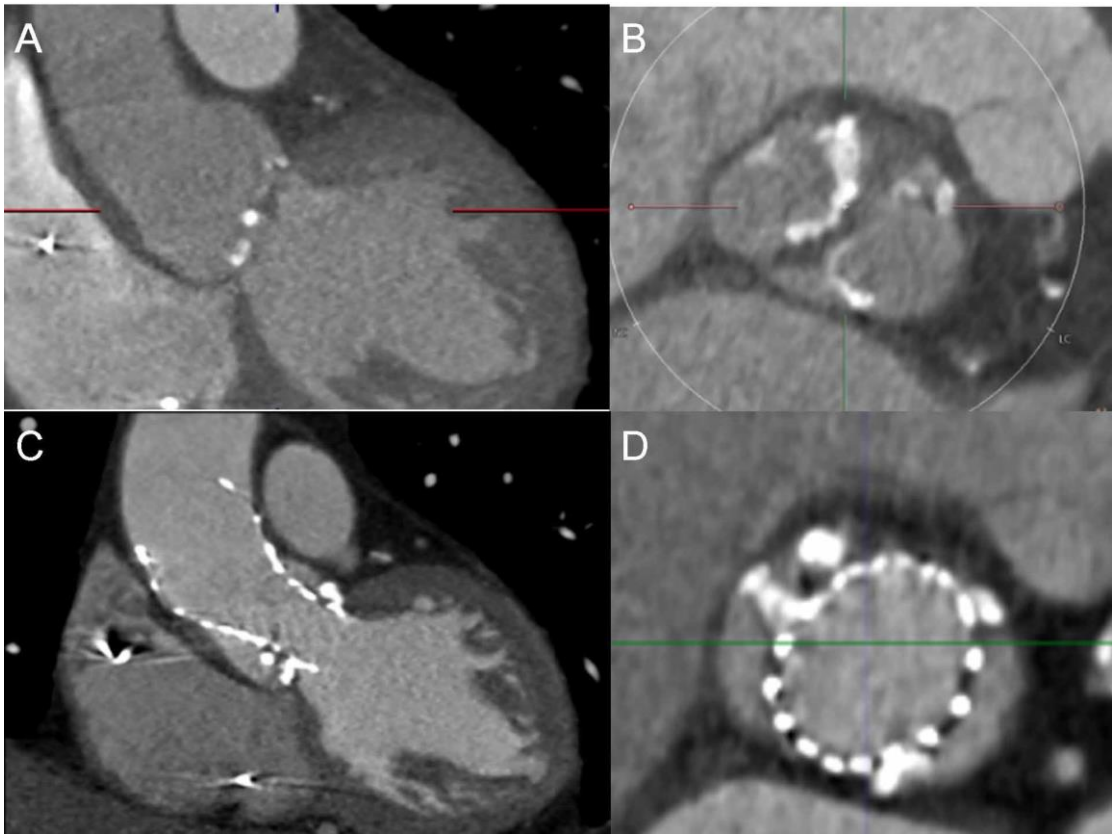

**Legend.** Classification of BAV according to the description of Sievers et al (19).

**Figure 2. Edwards SAPIEN TAV-in-SAV**



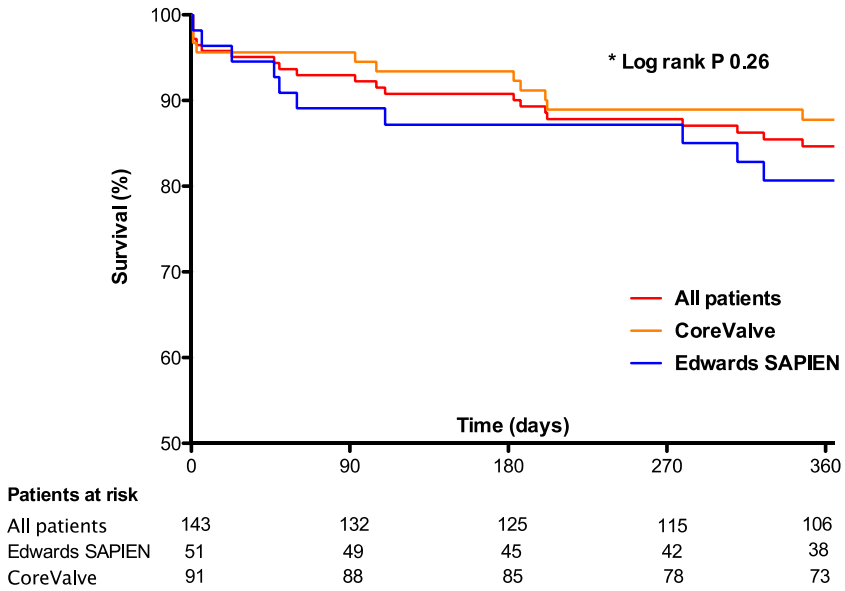

**Legend.** TAV-in-BAV with an Edwards SAPIEN XT. (A and B) Multislice computed tomography of bicuspid aortic valve stenosis (Type 1, NR). (C and D) Same patient following implantation of a XX mm SAPIEN XT.

**Figure 3. Medtronic CoreValve TAV-in-SAV**




**Legend.** TAV-in-BAV with Medtronic CoreValve. (A and B) Multislice computed tomography of bicuspid aortic valve stenosis (Type 1, NL). (C and D) Same patient following implantation of a XX mm CoreValve.

**Figure 4. 1-Year Survival.**




| Patients at risk | | | | | |
|---|---|---|---|---|---|
| All patients | 143 | 132 | 125 | 115 | 106 |
| Edwards SAPIEN | 51 | 49 | 45 | 42 | 38 |
| CoreValve | 91 | 88 | 85 | 78 | 73 |

**Legend.** Kaplan–Meier survival curve of patients undergoing TAV-in-SAV with the Edwards SAPIEN (blue line) or Medtronic CoreValve (orange line) prostheses. P value is log-rank comparison between Edwards SAPIEN and Medtronic CoreValve.

## Tables

**Table 1. Baseline characteristics**

| Characteristic | All patients (n=143) | SAPIEN (n=51) | CoreValve (n=91) | P value |
|---|---|---|---|---|
| Age, years | 77.7±9.1 | 76.7±10.3 | 78.2±8.4 | 0.34 |
| Male sex | 82 (57.3) | 33 (64.7) | 48 (52.7) | 0.22 |
| BMI, Kg/m$^2$ | 25.8±5.8 | 26.8±6.8 | 25.3±5.2 | 0.13 |
| Diabetes mellitus | 36 (25.2) | 16 (31.4) | 20 (22.0) | 0.23 |
| NYHA class | 3.0±0.6 | 3.1±0.5 | 2.9±0.6 | 0.14 |
| NYHA class 3/4 | 118 (82.5) | 47 (92.2) | 70 (76.9) | 0.02 |
| Previous MI | 28 (19.6) | 10 (19.6) | 17 (18.7) | 0.99 |
| Previous PCI | 31 (21.7) | 9 (17.6) | 21 (23.1) | 0.52 |
| Previous CABG | 15 (10.5) | 6 (11.8) | 9 (9.9) | 0.78 |
| Peripheral vascular disease | 18 (12.6) | 7 (13.7) | 11 (12.1) | 0.80 |
| Previous stroke | 9 (6.3) | 5 (9.8) | 4 (4.4) | 0.28 |
| Atrial fibrillation | 34 (23.8) | 7 (13.7) | 27 (29.7) | 0.40 |
| Pulmonary hypertension* | 36 (25.2) | 12 (23.5) | 24 (26.4) | 0.84 |
| eGFR, mL/min | 61.2±25.4 | 62.0±22.4 | 60.9±27.2 | 0.80 |
| eGFR, ≤60 mL/min | 72 (50.3) | 24 (47.1) | 47 (51.6) | 0.73 |
| STS risk of mortality | 4.9±3.4 | 4.9±3.9 | 4.8±3.1 | 0.96 |
| Logistic EuroSCORE | 14.6±10.6 | 14.7±10.6 | 14.5±10.7 | 0.89 |
| EuroSCORE II | 4.6±3.6 | 5.7±4.1 | 4.3±3.4 | 0.25 |
| Aortic valve mean gradient, mmHg | 48.6±16.4 | 49.6±15.5 | 48.1±17.1 | 0.60 |
| Aortic valve area, cm$^2$ | 0.6±0.2 | 0.7±0.2 | 0.6±0.2 | 0.26 |
| Estimated annulus diameter, mm | 23.6±3.3 | 24.2±2.4 | 23.2±3.7 | 0.12 |
| LV ejection fraction, % | 50.3±14.7 | 50.7±14.5 | 50.1±14.9 | 0.83 |
| LV ejection fraction, ≤40% | 42 (29.4) | 14 (27.5) | 28 (30.8) | 0.71 |

**Legend.** Data are number and percentage or mean ± standard deviation. P values represent comparisons between the Edwards SAPIEN or Medtronic CoreValve prostheses. * pulmonary artery systolic pressure ≥ 60 mmHg. BMI = body mass index; NYHA = New York Heart Association; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; STS = Society of Thoracic Surgeons; LV = left ventricle.

**Table 2. Bicuspid Aortic Valve Type**

| | All patients (n=124) | SAPIEN (n=43) | CoreValve (n=80) | P value |
|---|---|---|---|---|
| **Type 0** | 32 (25.8) | 8 (18.6) | 24 (30.0) | 0.09 |
| **Type 1** | 86 (69.3) | 34 (79.1) | 51 (63.8) | 0.71 |
| LR | 62 (50.0) | 28 (65.1) | 34 (42.5) | |
| RN | 17 (13.7) | 3 (7.0) | 13 (16.3) | |
| LN | 7 (5.6) | 3 (7.0) | 4 (5.0) | |
| **Type 2** | | | | |
| LR/RN | 6 (4.9) | 1 (2.3) | 5 (6.2) | 0.41 |

**Legend.** Classification of bicuspid aortic valve morphology according to Sievers et al (19).

**Table 3. Procedures**

| Characteristic | All patients (n=143) | SAPIEN (n=51) | CoreValve (n=91) | P value |
|---|---|---|---|---|
| THV Size (mm) | | | | |
| Mean | 27.8±2.2 | 26.4±2.2 | 28.5±1.8 | <0.0001 |
| 23 | 10 (7.0) | 10 (19.6) | | |
| 26 | 52 (36.4) | 24 (47.1) | 27 (29.7) | 0.05 |
| 29 | 61 (42.7) | 17 (33.3) | 44 (48.4) | 0.11 |
| 31 | 20 (14.0) | | 20 (22.0) | |
| CT-based THV sizing | 92 (64.3) | 40 (78.8) | 51 (56.0) | 0.01 |
| Vascular access | | | | |
| Femoral | 113 (79.0) | 33 (64.7) | 79 (86.8) | 0.003 |
| Subclavian | 5 (3.5) | | 5 (5.5) | |
| Apical | 12 (8.4) | 12 (23.5) | | |
| Aortic | 12 (8.4) | 6 (11.8) | 6 (6.6) | 0.35 |
| Carotid | 1 (0.7) | | 1 (1.1) | |
| General anesthesia | 88 (61.5) | 36 (70.6) | 52 (57.1) | 0.15 |
| Balloon predilatation | 141 (98.6) | 51 (100.0) | 89 (97.8) | 0.54 |
| Predilatation balloon size, mm | 22.6±2.1 | 22.0±2.2 | 22.9±2.0 | 0.04 |
| Balloon postdilatation* | 25 (17.7) | 5 (10.0) | 20 (22.2) | 0.11 |
| Postdilatation balloon size, mm* | 26.5±2.3 | 24.7±2.5 | 26.8±2.1 | 0.36 |
| THV malposition* | 9 (6.4) | 2 (4.0) | 7 (7.8) | 0.50 |
| THV embolization* | 3 (2.1) | 2 (4.0) | 1 (1.1) | 0.29 |
| Requirement for $2^{nd}$ / $3^{rd}$ THV* | 5 (3.5) | 1 (2.0) | 4 (4.4) | 0.66 |
| Tamponade | 5 (3.5) | 0 | 5 (5.7) | 0.16 |
| Aortic root rupture | 1 (0.7) | 1 (2.0) | 0 | |
| Conversion to SAVR | 3 (2.1) | 2 (3.9) | 1 (1.1) | 0.29 |
| Echocardiography | | | | |
| Aortic regurgitation, grade (1-4)* | 1.1±0.9 | 0.9±0.9 | 1.1±0.9 | 0.25 |
| ≥ grade 2 | 39 (27.6) | 9 (18.0) | 29 (32.2) | 0.08 |
| ≥ grade 3 | 8 (5.7) | 3 (6.0) | 5 (5.5) | 0.99 |
| Aortic valve mean gradient, mmHg* | 11.5±9.8 | 12.0±8.6 | 11.3±10.4 | 0.76 |
| Aortic valve area, $cm^2$ * | 1.7±0.5 | 1.7±0.5 | 1.6±0.4 | 0.72 |
| Contrast media, ml | 174±88 | 176±118 | 172±81.5 | 0.17 |
| Fluoroscopy duration, minutes | 20 (14, 28) | 14 (9, 25) | 20 (15, 29) | 0.004 |

**Legend.** Data are number and percentage, mean ± standard deviation, or median and interquartile range. P values represent comparisons between the Edwards SAPIEN or Medtronic CoreValve prostheses. THV = transcatheter heart valve; * Refers to 141 patients that received a THV.

**Table 4. Clinical Outcomes**

| Characteristic | All patients (n=143) | SAPIEN (n=51) | CoreValve (n=91) | P value |
|---|---|---|---|---|
| Hospital stay, days | 8 (5, 11) | 7 (4, 12) | 8 (6, 11) | 0.38 |
| Mortality | | | | |
| Procedural | 5 (3.5) | 1 (2.0) | 4 (4.9) | 0.65 |
| 30-day | 7 (4.9) | 3 (5.9) | 4 (4.9) | 0.70 |
| 6-month* | 13 (9.3) | 7 (14.6) | 6 (6.6) | 0.14 |
| 1-year† | 21 (15.9) | 10 (23.3) | 11 (12.5) | 0.13 |
| Myocardial infarction | 3 (2.1) | 0 | 3 (3.3) | 0.55 |
| Periprocedural | 3 (2.1) | 0 | 3 (3.3) | 0.55 |
| Spontaneous | 0 | | | |
| Stroke | 3 (2.1) | 1 (2.0) | 2 (2.2) | 0.99 |
| Disabling | 2 (1.4) | 1 (2.0) | 1 (1.1) | |
| Non-disabling | 1 (0.7) | 0 | 1 (1.1) | |
| Bleeding | 37 (35.9) | 8 (15.7) | 29 (31.9) | 0.05 |
| Minor | 18 (12.6) | 2 (2.0) | 16 (17.6) | 0.02 |
| Major | 9 (6.3) | 4 (4.0) | 5 (5.5) | 0.72 |
| Life-threatening | 10 (7.0) | 2 (2.0) | 8 (8.8) | 0.33 |
| Acute kidney injury (Stage 3) | 3 (2.1) | 1 (2.0) | 2 (2.0) | 0.99 |
| Vascular complications | 30 (21.0) | 6 (11.8) | 24 (26.4) | 0.05 |
| Minor | 21 (14.7) | 2 (4.0) | 19 (20.9) | 0.006 |
| Major | 9 (6.3) | 4 (4.0) | 5 (5.5) | 0.72 |
| New pacemaker | 32 (22.5) | 8 (15.7) | 24 (26.7) | 0.15 |
| Device success | 129 (90.2) | 46 (90.2) | 82 (90.1) | 0.99 |
| Combined safety endpoint | 114 (79.7) | 42 (82.4) | 71 (78.0) | 0.67 |
| Combined efficacy endpoint | 122 (85.3) | 45 (88.2) | 76 (84.5) | 0.62 |

**Legend.** Data are number and percentage. SAVR = surgical aortic valve replacement.
* 140 and † 132 patients that have reached 6-month or 1-year follow-up, respectively.

**Table 5. Predictors of 1-Year Survival**

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Odds ratio** | **95% CI** | **P value** | **Odds ratio** | **95% CI** | **P value** |
| Age | 1.06 | 0.99-1.13 | 0.09 | 1.06 | 0.99-1.14 | 0.10 |
| Male sex | 1.09 | 0.43-2.80 | 0.85 | | | |
| STS risk of mortality | 1.06 | 0.94-1.20 | 0.38 | | | |
| Mean aortic gradient | 1.00 | 0.97-1.03 | 0.95 | | | |
| Aortic valve area | 0.08 | 0.01-1.44 | 0.09 | 0.84 | 0.01-1.87 | 0.12 |
| LV ejection fraction <40% | 1.18 | 0.44-3.20 | 0.74 | | | |
| Annulus size | 1.02 | 0.88-1.18 | 0.82 | | | |
| THV size | 0.95 | 0.77-1.16 | 0.61 | | | |
| CT-based THV sizing | 0.79 | 0.30-2.11 | 0.64 | | | |
| Bicuspid type 1 | 0.86 | 0.33-2.23 | 0.75 | | | |
| CoreValve | 0.46 | 0.18-1.18 | 0.09 | 0.35 | 0.16-0.99 | 0.05 |
| Year of procedure | 0.89 | 0.66-1.20 | 0.44 | | | |
| Diabetes | 2.02 | 0.55-7.40 | 0.29 | | | |
| NYHA Class II/III | 1.09 | 0.50-2.41 | 0.10 | 1.99 | 0.40-9.89 | 0.40 |
| Pulmonary hypertension | 1.81 | 0.65-5.00 | 0.25 | | | |
| eGFR<60 | 1.50 | 0.57-3.74 | 0.43 | | | |
| THV malposition | 4.42 | 0.91-21.40 | 0.07 | 5.70 | 0.99-32.72 | 0.05 |
| THV embolization | 5.45 | 0.33-90.75 | 0.24 | | | |
| Requirement for 2nd THV | 2.70 | 0.23-31.21 | 0.43 | | | |
| Vascular complication | 1.53 | 0.53-4.38 | 0.43 | | | |
| New pacemaker | 0.76 | 0.24-2.46 | 0.65 | | | |
| AR ≥grade2 | 1.54 | 0.55-4.27 | 0.41 | | | |

**Legend.** eGFR = estimated glomerular filtration rate; AR = aortic regurgitation.

**Table 6. Predictors of Aortic Regurgitation ≥Grade 2**

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Odds ratio** | **95% CI** | **P value** | **Odds ratio** | **95% CI** | **P value** |
| Age | 0.99 | 0.96-1.04 | 0.85 | | | |
| Male sex | 3.28 | 1.41-7.65 | 0.006 | 4.27 | 1.61-11.37 | 0.004 |
| STS risk of mortality | 1.16 | 0.99-1.47 | 0.06 | 1.14 | 0.97-1.35 | 0.12 |
| Mean aortic gradient | 1.00 | 0.98-1.03 | 0.65 | | | |
| Aortic valve area | 0.34 | 0.04-3.14 | 0.34 | | | |
| LV ejection fraction | 1.02 | 0.99-1.05 | 0.16 | | | |
| Annulus size | 1.08 | 0.97-1.21 | 0.15 | | | |
| THV size | 0.91 | 0.77-1.11 | 0.32 | | | |
| CT-based THV sizing | 0.22 | 0.10-0.49 | <0.0001 | 0.17 | 0.05-0.55 | 0.003 |
| Bicuspid type 1 | 1.96 | 0.88-4.39 | 0.10 | 2.37 | 0.95-5.94 | 0.06 |
| CoreValve | 2.09 | 0.90-4.90 | 0.08 | 1.77 | 0.66-4.79 | 0.26 |
| Year of procedure | 1.30 | 0.99-1.70 | 0.06 | 0.91 | 0.62-1.33 | 0.63 |

**Legend.** CI = confidence intervals; LV = left ventricular.

## Appendix 1. Participating Institutions and Physicians

| Institution | Enrolling physicians | Number of cases |
|---|---|---|
| Hopital Jacques Cartier, Massy, France | Thierry Lefevre, MD, Yusuke Watanabe, MD | 35 |
| Rigshospitalet, Copenhagen, Denmark | Lars Søndergaard, MD | 23 |
| German Heart Center, Munich, Germany | Magdalena Dorfmeister, MD, Ruediger Lange, MD, PhD, Nicolo Piazza, MD, PhD | 19 |
| St. Paul's Hospital, Vancouver, British Columbia, Canada | Danny Dvir, MD, John G Webb, MD. | 19 |
| Bern University Hospital, Bern, Switzerland | Crochan O'Sullivan MD, Peter Wenaweser, MD, PhD, Stephan Windecker, MD. | 10 |
| Hôpital Cardiologique, Lille, France | Thomas Modine, MD, PhD | 9 |
| Rabin Medical Center and Tel-Aviv University, Tel-Aviv, Israel | Pablo Codner, MD, Ran Kornowski, MD | 6 |
| Ferrarotto Hospital, University of Catania, Catania, Italy | Marco Barbanti, MD, Corrado Tamburino, MD, PhD | 6 |
| Clinique Pasteur, Toulouse, France | Didier Tchetche, MD | 5 |
| Universitätsklinikum Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn, Germany | Jan-Malte Sinning, MD, Eberhard Grube, MD | 4 |
| McGill University Health Centre, Montreal | Darren Mylotte, MD, Giuseppe Martucci, MD, Pascal Thériault-Lauzier, Jean Buithieu, MD, PhD, Nicolo Piazza, MD, PhD. | 4 |
| University Hospital Antwerp, Wilrijk, Belgium | Johan Bosmans, MD, PhD | 3 |

**References**

1. Steinberger J, Moller JH, Berry JM, Sinaiko AR. Echocardiographic diagnosis of heart disease in apparently healthy adolescents. Pediatrics 2000;105:815-8.
2. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. Mayo Clinic proceedings Mayo Clinic 1999;74:14-26.
3. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789-800.
4. Roberts WC, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients >/=80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. The American journal of cardiology 2012;109:1632-6.
5. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
6. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
7. Zegdi R, Blanchard D, Azarine A, Folliguet T, Fabiani JN. Elliptical shape of a SAPIEN XT prosthesis deployed in a patient with bicuspid aortic valve stenosis. J Heart Valve Dis 2012;21:764-6.
8. Zegdi R, Ciobotaru V, Noghin M et al. Is it reasonable to treat all calcified stenotic aortic valves with a valved stent? Results from a human anatomic study in adults. J Am Coll Cardiol 2008;51:579-84.
9. Mahadevia R, Barker AJ, Schnell S et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. Circulation 2014;129:673-82.
10. Delgado V, Tops LF, Schuijf JD et al. Successful deployment of a transcatheter aortic valve in bicuspid aortic stenosis: role of imaging with multislice computed tomography. Circulation Cardiovascular imaging 2009;2:e12-3.
11. Chiam PT, Chao VT, Tan SY et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. JACC Cardiovascular interventions 2010;3:559-61.
12. Wijesinghe N, Ye J, Rodes-Cabau J et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. JACC Cardiovascular interventions 2010;3:1122-5.
13. Hayashida K, Bouvier E, Lefevre T et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. Circulation Cardiovascular interventions 2013;6:284-91.
14. Bauer T, Linke A, Sievert H et al. Comparison of the effectiveness of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valves (from the German TAVI Registry). The American journal of cardiology 2014;113:518-21.
15. Costopoulos C, Latib A, Maisano F et al. Comparison of Results of Transcatheter Aortic Valve Implantation in Patients With Severely Stenotic Bicuspid Versus Tricuspid or Nonbicuspid Valves. The American journal of cardiology 2014.

16. Himbert D, Pontnau F, Messika-Zeitoun D et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. The American journal of cardiology 2012;110:877-83.
17. Lange R, Bleiziffer S, Mazzitelli D et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. J Am Coll Cardiol 2011;59:280-7.
18. Mylotte D, Osnabrugge RL, Windecker S et al. Transcatheter aortic valve replacement in europe: adoption trends and factors influencing device utilization. J Am Coll Cardiol 2013;62:210-9.
19. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. The Journal of thoracic and cardiovascular surgery 2007;133:1226-33.
20. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 2005;111:920-5.
21. Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. EuroIntervention 2012;8:782-95.
22. Kodali SK, Williams MR, Smith CR et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686-95.
23. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014.
24. Zoghbi WA, Chambers JB, Dumesnil JG et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2009;22:975-1014; quiz 1082-4.
25. Isner JM, Chokshi SK, DeFranco A, Braimen J, Slovenkai GA. Contrasting histoarchitecture of calcified leaflets from stenotic bicuspid versus stenotic tricuspid aortic valves. J Am Coll Cardiol 1990;15:1104-8.
26. Michelena HI, Khanna AD, Mahoney D et al. Incidence of aortic complications in patients with bicuspid aortic valves. Jama 2011;306:1104-12.
27. Makkar RR, Jilaihawi H, Chakravarty T et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of AoRTic

TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). J Am Coll Cardiol 2013;62:418-30.
28. Gilard M, Eltchaninoff H, Iung B et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
29. Roy DA, Schaefer U, Guetta V et al. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. J Am Coll Cardiol 2013;61:1577-84.
30. Ussia GP, Barbanti M, Petronio AS et al. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969-76.
31. Genereux P, Head SJ, Hahn R et al. Paravalvular leak after transcatheter aortic valve replacement: the new achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol 2013;61:1125-36.
32. Abdel-Wahab M, Mehilli J, Frerker C et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. Jama 2014;311:1503-14.
33. Willson AB, Webb JG, Labounty TM et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. J Am Coll Cardiol 2012;59:1287-94.
34. Jilaihawi H, Kashif M, Fontana G et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol 2012;59:1275-86.
35. Ferrante G, Pagnotta P, Petronio AS et al. Sex differences in postprocedural aortic regurgitation and mid-term mortality after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2014.
36. Onorati F, D'Errigo P, Barbanti M et al. Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: Results of the multicenter Italian OBSERVANT Registry. The Journal of thoracic and cardiovascular surgery 2013.
37. Binder RK, Rodes-Cabau J, Wood DA, Webb JG. Edwards SAPIEN 3 valve. EuroIntervention 2012;8 Suppl Q:Q83-7.
38. Piazza N, Martucci G, Lachapelle K et al. First-in-human experience with the Medtronic CoreValve Evolut R. EuroIntervention 2013.
39. Mylotte D, Dorfmeister M, Elhmidi Y et al. Erroneous Measurement of the Aortic Annular Diameter using 2-Dimensional Echocardiography Resulting in Inappropriate CoreValve Size Selection: A Retrospective Comparison with Multislice Computed Tomography. JACC Cardiovascular interventions 2014;In Press.