UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Head Office: University of Padova

Department of Cardiac, Thoracic and Vascular Sciences

Ph.D. Course Medical Clinical and Experimental Sciences

Curriculum: Cardiovascular Science

XXIX CICLE

CLINICAL AND HEMODYNAMIC RESULTS AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI): EARLY AND LATE (10-YEAR) FOLLOW-UP

Coordinator: Ch.mo Prof. Annalisa Angelini

Supervisor: Ch.mo Prof. Giuseppe Tarantini

Ph.D. Student: Dr. Michela Facchin

Alla mia famiglia

INDEX

ABSTRACT

Backgrounds

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice in patients with severe symptomatic aortic stenosis (AS) considered inoperable or at high surgical risk. More recently, TAVI has been performed also to lower risk patients based on the Heart Team decision. Few studies have studied interaction between surgical risk categories and outcomes.

Aim of the study

To analyze safety and efficacy (VARC-2 defined) TAVI treated patients as function of different preoperative risk. To assess independent predictors of death.

Methods

Four-hundred-eighty-two patients who underwent TAVI in our center between 2007 and 2017 were included in the study. According to Society of Thoracic Surgeons (STS) score and to other parameters, all the patients were retrospectively stratified into 4 groups: prohibitive (contraindications to aortic valve replacement, n = 124), high (STS > 8, n = 131), intermediate (4 ≤ STS ≤ 8, n = 112) and low (STS < 4, n = 115) risk. Early, 1-year and long-term outcomes have been evaluated in those 4 groups according the VARC 2 criteria.

Results

The TAVI procedure resulted to be safe because of low mortality rate throughout all risk groups. The lowest 30-days mortality rate was observed in low and prohibitive-risk patients (p=0.048). In the low risk group, in-hospital mortality was 0%. The results were similar at 1-year of follow-up, with a mortality rate of 6% and 7% in low- and prohibitive-risk patients vs 21% and 19% in intermediate- and high-risk groups, (p<0.008). At 5-year of follow-up the mortality rate was 52% and it appeared to be lower only in low-risk patients at long-term follow-up. Independent predictors of mortality were pre-procedural congestive heart failure (CHF), neoplastic disease, pre-procedural-creatinine, post-procedural major or life threatening bleeding and post-procedural acute kidney injury (AKI). Implanted prosthesis performed well with stable hemodynamic results over time and rare dysfunction (2.1%).

Conclusions

In our study population, TAVI was safe and effective, with low rates of mortality and adverse events regardless of the surgical risk. At longer follow-up mortality rate was significantly lower in low-risk patients. Pre-procedural CHF, neoplastic diseases, pre-procedural creatinine, post-procedural severe bleedings and post-procedural AKI were independent predictors of mortality. Transcatheter heart valves (THV) performance after the procedure was excellent and stable over time with low rate of late prosthesis dysfunction. Further studies should be addressed to confirm the promising long-term results among low-risk patients and the long-term durability of THV.

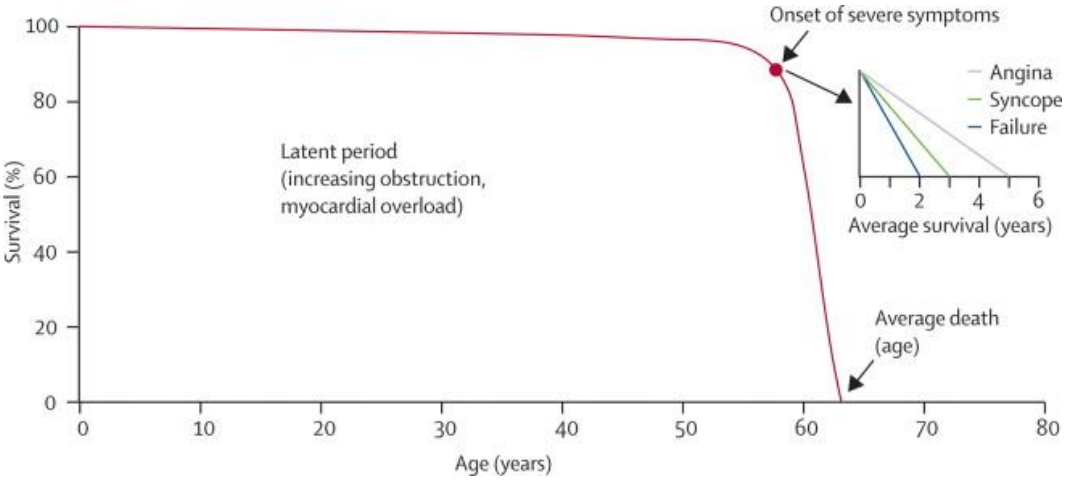
INTRODUCTION

AORTIC VALVE STENOSIS

Aortic valve Stenosis (AS) is usually caused by cups calcifications without commissural fusion. Consequently, valvular motion and effective area decrease and leads to blood flow obstruction, trans-valvular pressure gradient and left ventricular (LV) hypertrophy. The evolution of AS is slow, but when symptoms appear the progression is rapid towards death if left untreated (1,2). AS occurrence increases with age; and 2% of the overall population is affected after 65 years old. Moreover, one third of them shows echocardiographic signs of leaflet calcifications (3,4). AS is the most common primary valve disease leading to surgery or catheter intervention in Europe and North America, with a growing prevalence due to the population ageing (5-7).

Natural History

As reported by Ross and Braunwald (1), patient outcome is similar to overall population until symptoms occur. Clinical manifestations generally develop when the aortic valve area (AVA) decreases to less than 1 cm^2 and are associated with a severe worsening of survival (Figure 1)



Figuere 1. **Natural history of aortic stenosis without treatment** (1)

The three principal symptoms of AS are angina, syncope, and dyspnea (or congestive heart failure (CHF)). (8-11)

Angina is usually the earliest symptom and is associated to a mean survival of 4 to 5 years. Angina is present in around 50-70% of the patients with AS. Because of LV hypertrophy and end-diastolic pressure rise, myocardial perfusion decreases, especially at the level of the sub-endocardium, and this discrepancy causes angina.

When the patient suffers for *syncope*, survival is typically less than 3 years. Syncope is due to the reduced blood flow through the stenotic valve that causes decreased cerebral perfusion. Furthermore, peripheral vasodilatation during exercise may worsen this condition since cardiac output cannot be modified.

Patients with *dyspnea* and *CHF*, in keeping with their associated left ventricular dysfunction, have a mean survival of 1 to 2 years. CHF is the presenting symptom in nearly one third of the patients. Dyspnea is the consequence of the reduced capacity of the heart to increase

the stroke volume in response to an increased metabolic demand. It can be also a consequence of the diastolic dysfunction (12).

Stages of AS

Medical and interventional approaches to the management of patients with AS mainly depend on the disease's cause and staging. The classification of AS stages (13) is reported in Table 1 according to 2014 American College of Cardiology/American Heart Association guidelines (ACC/AHA). The stages of AS range from patients at risk of AS (stage A) or with progressive hemodynamic obstruction (stage B) to severe asymptomatic (stage C) and symptomatic AS (stage D). Each of these stages considers valve anatomy, valve hemodynamics, the consequences of valve obstruction on the left ventricle, as well as by patient symptoms.

Hemodynamic AS severity is best characterized by the transaortic maximum velocity (or mean pressure gradient) when the transaortic volume flow rate is normal. However, some patients have low transaortic volume flow due to LV systolic dysfunction with reduced stroke volume. This low-flow AS subgroups requires a distinct approach compared to the majority of AS with high gradient and normal flow (14).

The definition of severe AS is based on natural history studies of medically treated patients, in which prognosis is poor when peak aortic valve velocity is >4.0 m/sec, or mean aortic valve gradient is >40 mmHg.

Table 1. Stages of AS (Nishimura, RA et al. 2014 AHA/ACC Valvular Heart Disease Guideline)

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk of AS**	. Bicuspid aortic valve (or other congenital valve anomaly) . Aortic valve sclerosis	Aortic Vmax <2 m/s	None	None
B	**Progressive AS**	.Mild-to-moderate leaflet calcification with some reduction in systolic motion .Rheumatic valve changes with commissural fusion	. Mild AS: Aortic Vmax 2.0–2.9 m/s or mean ΔP <20 mm Hg . Moderate AS: Aortic Vmax 3.0–3.9 m/s or	. Early LV diastolic dysfunction may be present . Normal LVEF	None
C: Asymptomatic severe AS					
C1	**Asymptomatic severe AS**	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	. Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg . AVA typically is ≤1.0 cm2 (or AVAi ≤0.6cm2/m2) . Very severe AS is an aortic Vmax ≥5 m/s or mean ΔP ≥60 mm Hg	. LV diastolic dysfunction . Mild LV hypertrophy . Normal LVEF	None: Exercise testing is reasonable to confirm symptom status
C2	**Asymptomatic severe AS with LV Dysfunction**	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	. Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg . AVA typically ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2)	LVEF <50%	None
D: Symptomatic severe AS					
D1	**Symptomatic severe high-gradient AS**	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	. Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg . AVA typically ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2) but may be larger with mixed AS/AR	. LV diastolic dysfunction . LV hypertrophy . Pulmonary hypertension may be present	.Exertional: dyspnea or decreasedexercise tolerance , or angina or syncope
D2	**Symptomatic severe low-flow/low-gradient AS with reduced LVEF**	Severe leaflet calcification with severely reduced leaflet motion	. Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg . AVA typically ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2) but may be larger with mixed AS/AR	. LV diastolic dysfunction . LV hypertrophy . LVEF <50%	. HF . Angina . Syncope or presyncope
D3	**Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS**	Severe leaflet calcification with severely reduced leaflet motion	. AVA ≤1.0 cm2 with aortic Vmax <4 m/s or mean ΔP <40 mm Hg . Indexed AVA ≤0.6 cm2/m2 . Stroke volume index <35 mL/m2 . Measured when patient is normotensive (systolic BP <140 mmHg)	. Increased LV	. HF

In case of low flow, AS may be severe with lower valve velocities and gradients, and AVA should be calculated. The prognosis of patients with AS is poorer when AVA is <1.0 cm^2. At normal flow rates, AVA <0.8 cm^2 generally correlates with a mean gradient >40 mmHg. However, symptomatic patients with calcification and AVA between 0.8 cm^2 and 1.0 cm^2 should be closely evaluated to determine whether they would benefit from intervention (15).

Meticulous attention to detail is mandatory when assessing aortic valve hemodynamics, either with Doppler echocardiography or cardiac catheterization, and the inherent variability of the measurements and calculations should always be considered in clinical-decision making.

Management

In the past, medical therapy with or without Balloon Aortic Valvuloplasty (BAV) was the only treatment options for inoperable patients with an average survival of 2–3 years after the symptoms onset (16). Over the last decade, transcatheter aortic valve implantation (TAVI) become the treatment of choice for inoperable patients and the preferred alternative for high-risk patients with severe AS.

From Cribier's first implantation in 2002 (17), more then 100 000 TAVI procedures have been performed worldwide. Nevertheless, surgical aortic valve replacement (SAVR), first reported in 1960 by Harken, remains the gold standard for patients at low operative risk because of excellent long-term outcomes and low perioperative risk. (18-20).

The technical advances in new transcatheter heart valves (THV) significantly improved TAVI safety and efficacy. The excellent TAVI results observed in recently published randomized controlled trials and multiple international prospective registries (21-24) have broadened the indications for TAVI to intermediate-risk patients as an alternative (class I, LoE B) to SAVR (19). This suggest that TAVI might become a valuable treatment option also for a large number of lower (intermediate- to low-) risk patients, representing over 80% of the subjects currently undergoing SAVR (25).

In clinical practice and in randomized trials, the risk scores used to judge patient's indication to TAVI have been inherited from surgery. The Society of Thoracic Surgeons predicted risk for mortality (STS) (26) and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I and II (27, 28) are the most widely used scores in North America and Europe, respectively. Patients are usually considered at high-risk when STS score >8 or logistic EuroSCORE >20, at intermediate-risk when STS score is 4–8% and logistic EuroSCORE is 10–20, at low-risk when STS score is <4 and logistic EuroSCORE is <10. However, while these risk models correctly predicted SAVR outcomes (29, 30), they significantly overestimated TAVI mortality. The difference between predicted and observed mortality of surgical scores applied to TAVI was related to many confounders, including the fact that general anesthesia was often not needed in TAVI, and as a consequence most variables present in the surgical scores had a lesser influence on TAVI outcomes. Of note, several new TAVI risk models (31-36) had been developed, but none was routinely used nor is included in ongoing trials, mostly because of their complexity, poor accuracy and entry bias in regard to patient inclusion, that preclude broad generalization (35). Accordingly, guidelines acknowledge the imperfect nature of surgical risk scores and recommend that the decision

to perform TAVI should be made on the basis of multidisciplinary Heart Team evaluation (13,19). In other words, risk scores should never be a substitute for clinical judgment and the participation of patients and their families in to the decision. It is well documented that age remains one the most important reasons for surgical refusal (37), and referral to TAVI. To this regard, in the STS registry, SAVR patients had a mean age of 67 years and a mean STS of 1.8% (only 6.2% patients had an STS >8%), and there was a clear correlation between STS value and age. On the other hand, the common thread across TAVI trials and registries remained the older age, regardless of risk score. Indeed, despite the absence of an absolute age cut-off in the inclusion criteria for most studies, TAVI patients in all major recent and ongoing trials are still predominantly octogenarians. This implies that 'lower-risk' does not necessarily mean 'younger'. The relative lack of major comorbidities illustrates the common entity of entry bias in previous and ongoing trials comparing SAVR with TAVI, in which patients had to be considered eligible for both procedures in order to be included (for instance, in the PARTNER trial, less than one-third of the screened patients were eventually enrolled) (38). This is illustrated by the demographics of patients in clinical practice at large, in which the indication for TAVI is not simply based on surgical scores, as shown by the fact that almost 2/3 of patients included in contemporary European registries are at intermediate and even low surgical risk. Accordingly, in the STS/ACC Transcatheter Valve Therapy Registry TAVI patients have a mean STS score of 6.7%, and almost 70% of them are ≥ 80 years of age (39).

The recommendations for choice of intervention for AS apply to both surgical AVR and TAVI. The decision should be based on a patient's individual risk–benefit analysis including cardiac

and extracardiac characteristics, risk of surgery assessed by the Heart Team in addition to scores, and TAVI feasibility according to local experience and outcome.

Data on TAVI are still very limited for patients <75 years of age and for surgical low-risk patients, for whom SAVR remains the reference method. It has to be emphasized that younger patients presented more bicuspid valves that worsen TAVI results and were usually excluded from trials. In addition, THV durability is still lacking.

In elderly patients at increased surgical risk, available mortality data from trials and registries showed TAVI was superior to medical therapy in extreme-risk patients (40), non-inferior or superior to surgery in high-risk patients (41-44), and non-inferior to surgery and even superior when transfemoral access is possible in intermediate-risk patients (25,45-48). In the two large studies on intermediate risk, the mean age of patients were 82 and 80 years (46,48), the mean STS scores were 5.8% and 4.5%,(48) and several cases were considered frail. Thus, results are valid only for comparable patient groups. Overall, rates of vascular complications, pacemaker implantation and paravalvular regurgitation were significantly higher for TAVI and depended on the device (47-48). On the other hand, severe bleeding, acute kidney injury (AKI) and new-onset atrial fibrillation were significantly more frequent with surgery, whereas no differences were observed in cerebrovascular events.(47-48) The favorable results of TAVI had been reproduced in multiple large-scale, nationwide registries supporting the generalizability of outcomes observed in randomized controlled trials. This favors the use of TAVI over surgery in elderly patients at increased surgical risk.

However, overall, Heart Team should make the final decision between SAVR and TAVI (including the choice of access route) after careful individual evaluation (19,49).

The 2017 ACC/AHA guidelines flow chartis reported figure 2 (49).

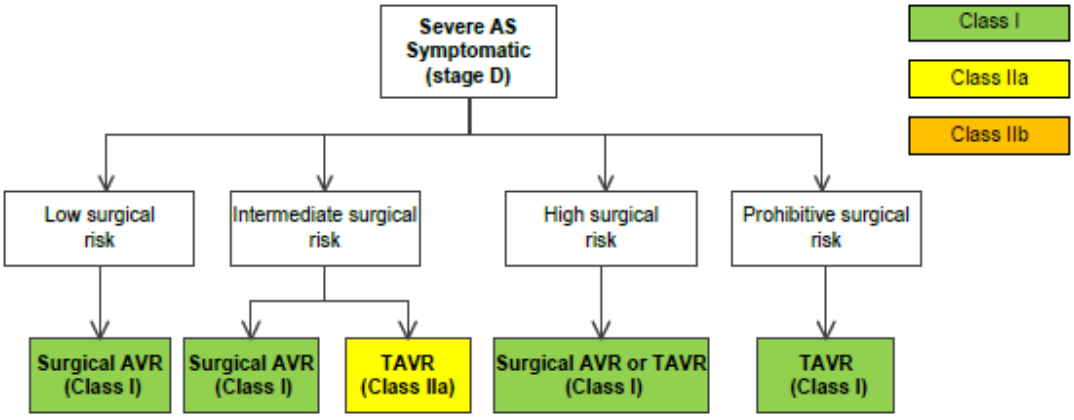


Figure 2. Choice of intervention in severe AS symptomatic patients according to ACC/AHA 2017 guideline.

AIM OF THE STUDY

General assessment:

First, to analyze early, 1-year and long-term outcomes of TAVI procedure in a single monocentric series.

Second, to compare the outcomes of different surgical risk classes.

Third, to assess the independent predictors of mortality.

Fourth, to observed durability of prosthesis with time and type of dysfunction.

METHODS

Study population

Between Jane 2007 and February 2017, all patients affected by severe symptomatic AS or aortic bio-prosthesis dysfunction treated with TAVI at our Institution were collected in a prospective monocentric registry named PUREVALVE (Padua University Revalving Experience).)

All patients underwent complete screening in order to evaluate the eligibility to TAVI and to choose the most appropriate vascular access and device. Blood tests, chest radiography, electrocardiogram, coronary angiography, multislice computed tomography (CT) scan of aortic root, ascending and abdominal aorta, and iliac-femoral axis, doppler ultrasound evaluation of carotid and vertebral arteries and pulmonary function investigation were performed.

Heart Team, composed by a clinical and interventional cardiologist, a cardiac surgeon and an anesthetist, performed the final choice on the best treatment strategy. Furthermore, the patients and their families were informed for the final decision on the best treatment option. Patients without clinical and echocardiographic 30-day follow-up were excluded by the analysis, while patients died during the procedure or hospitalization were considered.

The study population was retrospectively divided in four risk groups (low, intermediate, high and prohibitive) according to STS score and to other main features. Table 2 reported a combination of STS risk, frailty, major organ system dysfunction, and procedure-specific impediments for better risk assessment as reported in 2014 and 2017 AHA/ACC guidelines

(13,49). The prohibitive risk class included patients with almost one of these characteristics: 1-year mortality risk higher than 50%, specific contraindications of surgical intervention or more than three organ system disorders (28). The low-risk class included patients with a STS score inferior to 4%, the patients with intermediate risk class had a STS score between 4-8% and the high-risk group included patients with a STS score of more than 8%.

Table 2. Risk classes stratification according AHA/ACC 2014/2017 guideline.

	Low risk (must meet all criteria in this column)	Intermediate risk (any 1 criterion in this column)	High risk (any 1 criterion in this column)	Prohibitive risk (any 1 criterion in this column)
STS PROM*	<4%	4%-8%	>8%	Predicted risk with surgery of death or major morbidity (all-cause)
	AND	OR	OR	
Frailty†	None	1 Index (mild)	≥2 Indices (moderate to severe)	>50% at 1 y
	AND	OR	OR	OR
Major organ system compromise not to be improved postoperatively‡	None	1 Organ system	No more than 2 organ systems	≥3 Organ systems
	AND	OR	OR	OR
Procedure-specific impediment§	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

The assessment of the patient's frailty evaluating independence in feeding, bathing, dressing, transferring, toileting, and urinary continence and independence in ambulation was used.

Major organ system compromise included:

- *Cardiac*: severe LV systolic or diastolic dysfunction or right ventricular (RV) dysfunction.
- *Chronic Kidney Disease* stage 3 or worse
- *Pulmonary* dysfunction with FEV1 <50% or DLCO2 <50% of predicted
- *Central Neurologic System dysfunction*: dementia, Alzheimer's disease, Parkinson's disease, stroke with persistent physical limitation

- *Gastro-intestinal dysfunction*: Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0
- *Cancer*: active malignancy
- *Liver*: any history of cirrhosis, variceal bleeding, or elevated INR in the absence of anticoagulant therapy.

The procedure's specific impediments were tracheostomy, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage. Table 3 were reported similar characteristics to evaluate in the choice of procedure, in according to 2017 ECC/EACTS guidelines (19)

Table 3. Aspects to be considered by the Heart Team for the decision between SAVR and TAVI in patients at increased surgical risk

	Favours TAVI	Favours SAVR
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable access (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavourable for TAVI		+
Presence of thrombi in aorta or LV		+

TAVI procedure

The procedure was performed in a standard catheterization laboratory. Different approaches were used on the basis of the patients's characteristics. Retrograde *transfemoral access* (TF) usually represented the first choice because less invasive. *Transapical* approach (TA) was usually performed under general anaesthesia and endotracheal intubation. An anterolateral minithoracotomy (usually fifth or sixth intercostal space) was performed. Two circular purse-string sutures were placed on the cardiac apex. The procedure started with an apical puncture. At the end of procedure, the apical puncture site could be safely secured by tying the purse-string sutures (50).

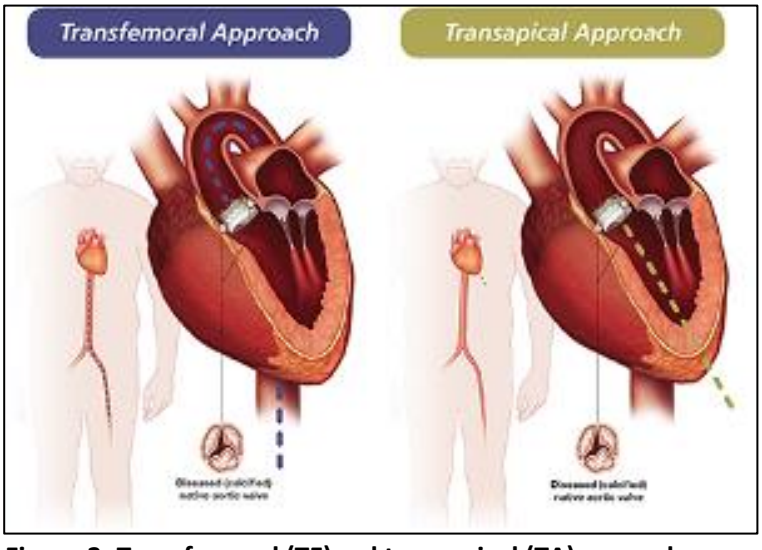


Figure 3. Transfemoral (TF)and transapical (TA) approches

For both approaches, a supra-aortic angiogram was performed to evaluate the presence and degree of aortic regurgitation. A 5-F sheath was placed in the right radial artery and a pigtail advanced (51) in the ascending aorta for hemodynamic monitoring and landmark aortic angiography. Transvenous temporary pacing was placed in the RV. For the TF retrograde approach, the native aortic valve was crossed with a straight 0.035-inch guide wire using an

Amplatz Left-2 coronary catheter advanced to the ascending aorta. The transvalvular gradient was measured and AVA calculated. BAV could be performed before valve implantation. The valve crimped into his catheter, was introduced on the same guide-wire by retrograde approach until the native aortic valve. The supra-aortic angiogram and native valve calcifications were used as anatomical landmarks for valve placement. Hemodynamic improvement was measured immediately afterwards, and a supra-aortic angiogram was performed in absence of renal insufficiency to assess the presence, location, and degree of aortic regurgitation and the patency of coronary arteries, as well as to rule out complications, such as aortic dissection.

Heparin at a dose of 100 IU/kg body weight was administered to yield an activated clotting time of 250-300 seconds throughout the procedure. After the procedure, heparin was neutralized by protamine. Patients were pre-medicated with aspirin and clopidogrel.

TAVI prosthesis

The ideal aortic valve prosthesis should be durable, with optimal hemodynamic performance and able to reduce the current major complications of TAVI procedure, in particular vascular complications (not infrequent with the transfemoral access route), paravalvular leaks, stroke and atrioventricular block requiring a permanent pacemaker. Indeed, TAVI registries and trials showed that major vascular complications are strong predictors of morbidity and early-mortality after TAVI. In addition, moderate and severe paravalvular leak has been associated with increased morbidity and mortality (52-54). Even if inconsistency is present in literature regarding the impact of pacemaker implantation on subsequent outcomes, also this complications seems to have an impact on subsequent outcomes after TAVI (55,56).

In our patients, different devices were used (old and new-generation of valves):

Edwards Lifesciences Sapien, Sapien XT and Sapien 3 THV

The family of Edwards Sapien valve are the balloon expandable prosthesis whose leaflets are made of bovine pericardium mounted on a chrome-cobalt stent. The SAPIEN 3™ (S3) (Edwards Lifesciences, Irvine, CA, USA) is the last of Edwards family's trans-catheter heart valves (THV) (Figura 4A). This device incorporates a number of new and enhanced features intended to reduce the risk of vascular injury and paravalvular regurgitation, and to facilitate rapid and accurate positioning and implantation. The SAPIEN 3 valve incorporates a cobalt chromium stent, bovine pericardial leaflets, and both an inner and new outer polyethylene terephthalate (PET) sealing cuff. The delivery system (Commander; Edwards Lifesciences, Irvine, CA, USA) incorporates an active three-dimensional coaxial positioning (Figura 4B) (53).

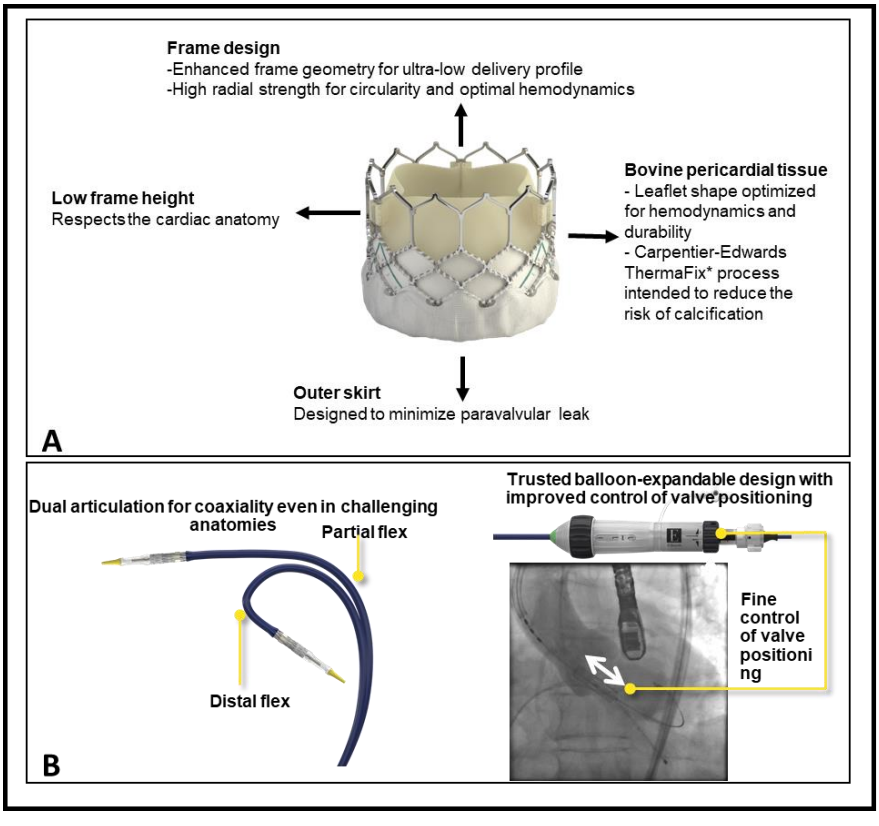
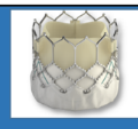


Figure 4. The SAPIEN 3 valve; B: delivery system

The 20-23 and 26 mm S3 THV are compatible with a 14 Fr expandable sheath (eSheath; Edwards Lifesciences), while the 29 mm S3 is compatible with a 16Fr expandable sheath. The low diameter of the sheath reduces the stress on the access vessel by transiently expanding as the crimped THV passes through the sheath and then recoiling to a lower profile (Figure 5). This may reduce the potential for arterial injury during introduction, and may extend the eligibility to TAVI for some patients previously considered unsuitable for the femoral approach due to small vessels.

	 SAPIEN 26 mm	 SAPIEN XT 26 mm	 SAPIEN 3 26 mm
Crimped Profile	8.3 mm	8.3 mm	8.3 mm
Frame height (expanded)	16,1 mm	17,2 mm	20 mm
Frame height (crimped)	18,1 mm	20,1 mm	28 mm
Frame shortening (deployment)	2 mm	2,9 mm	8 mm
Sheat Profile (internal diameter unexpanded)	24 Fr	18 Fr	14Fr
Sheat Profile (outdiameter unexpanded)	-	7,2 mm	6 mm
Sheat Profile (outdiameter expanded)	-	8,9 mm	8 mm
Indicated vessel size	7 mm	6,5 mm	6 mm

Figue 5. Edwards Sapien prosthesis family.

The external “skirt” (outer PET sealing) in the lower portion of the valve and a more accurate positioning of the valve due to the renovated delivery system should ensure a good sealing, thus preventing the occurrence of paravalvular leaks. The increased length of the S3 (20 mm compared to 17 mm of SAPIEN XT) will augment the need of permanent pacemaker due to an increased area of contact with the interventricular septum. Theoretically, a decreased need for oversizing due to the presence of the sealing cuff and a more accurate positioning with a more predictable final valve implantation depth could reduce this risk.

The data on S3 confirmed the advantage of the this valve compared with previous Edwards valves (SAPIEN and SAPIEN XT) in terms of prevention of vascular complications and of moderate-severe paravalvular leaks, but showed an increase in the need of a permanent pacemaker post-TAVI (57). Data on an increased need of permanent pacemakers are not conclusive. In fact, a study conducted in patients treated in Padua with S3 showed that a low final valve implantation depth is the strongest predictor of subsequent AV conduction defects, rather than the valve itself (57, 58).

CoreValve Family

The Medtronic CoreValve (CV), with leaflets made from porcine pericardium sutured into a self-expanding nitinol frame, was the first commercially available self-expanding TAVI system. The US Pivotal Trial showed excellent long-term outcomes after CV implantation in patients classified as high-risk for surgical aortic valve replacement (59). Despite the generally low TAVI complication rates for such high-risk patient collective, several important and prognosis relevant issues including paravalvular leaks (60), access site bleeding (61) or valve dislocation during deployment limited the procedural success of first generation

prosthesis. To tackle these issues, the Evolut R (EVR) with the EnVeo R delivery catheter was introduced in 2014. This second generation prosthesis allows repositioning after implantation, has a lower delivery profile and has an extended sealing skirt to reduce the incidence of paravalvular leaks (Figure 6)

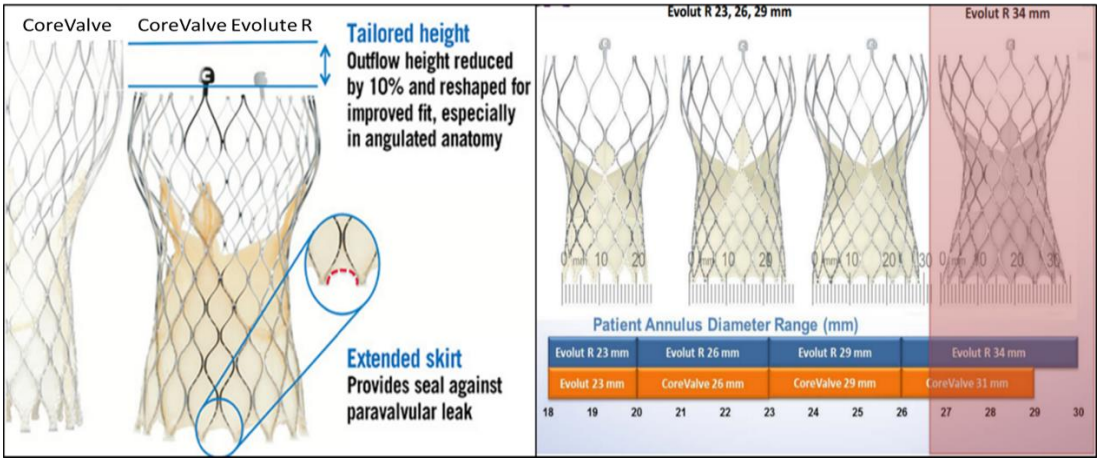


Figure 6. Corevalve prosthesis and size.

Compared to the traditional Medtronic CoreValve prosthesis (left side), new features of the Medtronic Evolut R™ (right side) include a new design of the nitinol frame with a lower height and an extended sealing skirt.

Symetis Acurate Neo Aortic Valve

The ACURATE neo Aortic Valve (Symetis, Lausanne, Switzerland) (Figure 7) with Transfemoral and Transapical Delivery Systems, is a self-expanding, supra-annular valve, offering an intuitive procedure, predictable release, stable positioning, and had demonstrated excellent clinical outcomes.

The most important difference to other self-expanding platforms was the top-down deployment with minimal protrusion of the stent towards the left ventricular outflow tract.

In addition, the supra-annularly placed porcine leaflets provide very low gradients and the pericardial skirt acted very effectively to seal against paravalvular leaks.

The TAVI TF 1000 Registry (62) (Symetis ACURATE neo™ Valve Implantation using TransFemoral Access) was a post-market registry, including 1000 patients trated betwwen October 2014 and April 2016. The results confirmed long-term safety, clinical efficacy and valve performance of the ACURATE neo Transfemoral TAVI System in all-comers, high-risk TAVI Population. Excellent procedural success, survival, and NYHA development.

Figure 7. Symetis Acurate Neo Aortic Valve.

Boston Scientific Lotus

The Lotus™ Aortic Valve Replacement System (Boston Scientific Corporation, Natick, MA, USA) included a bioprosthetic aortic valve implant consisting of three bovine pericardial leaflets attached to a braided nitinol frame with a radiopaque marker and a catheter-based system for introduction and retrograde delivery via the femoral artery (Figure 8). The valve was pre-attached to the delivery system. The Lotus Valve starts working early in deployment, aiding controlled, precise initial positioning, and repositioning or full retrieval at any point prior to definitive release if required. Rapid pacing is not required during the implant

procedure. The valve was designed to expand radially as the valve shortens during deployment. An adaptive seal surrounds the inflow portion of the device and was designed to reduce paravalvular regurgitation. The REPRISE II study (63,64) evaluated results of Lotus valve. All patients were successfully implanted with a Lotus Valve, and 1-year clinical follow-up was available for 99.2%. The mean 1-year transvalvular aortic pressure gradient was 12.6 ± 5.7 mm Hg, and the mean valve area was 1.7 ± 0.5 cm^2. Over 88% patients had no or trivial paravalvular aortic regurgitation at 1 year by independent core lab adjudication, and 97.1% of patients were NYHI class I or II. At 1 year, the all-cause mortality rate was 10.9%, disabling stroke rate was 3.4%, disabling bleeding rate was 5.9%, with no repeat procedures for valve-related dysfunction. A total of 31.9% underwent new permanent pacemaker implantation at 1 year.

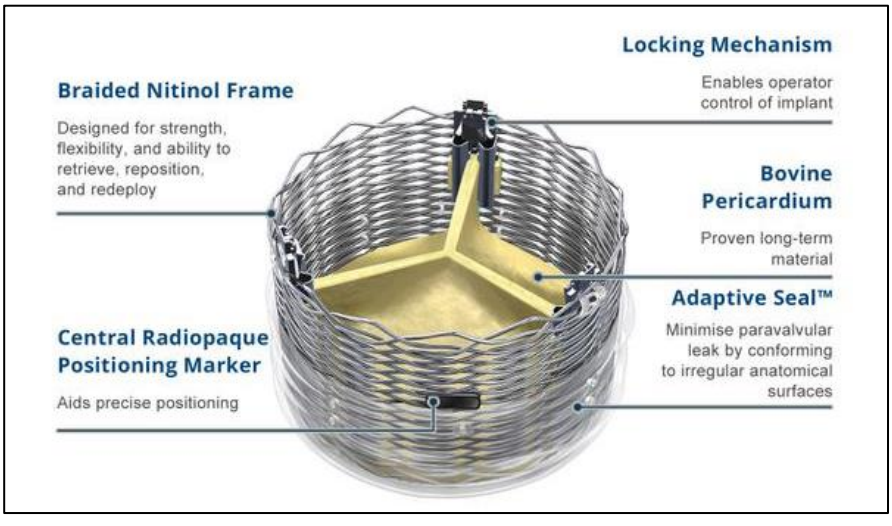


Figure 8. Boston Scientific Lotus trans-catheter heart valve.

Post-TAVI monitoring and management

After TAVI, patients remained in the cardiac intensive care unit for at least 24 hours and were monitored for 48-72 hours with particular attention to hemodynamic balance, vascular access, renal function, infections and eventual onset of cardiac conduction disturbances (especially late atrioventricular block). A transthoracic echocardiography was performed 48 hours after the procedure and pre-discharge. Twelve-lead electrocardiography was performed daily during hospitalization. A chest X-ray was performed during the first 24 hours after TAVI and according to clinical need after then. Blood tests were carried out every 8 hours the first day, then every 12-24 hours. After the procedure, a dual antiplatelet regimen of aspirin 100 mg and clopidogrel 75 mg daily for at least 3 months, and then with single antiplatelet therapy afterwards. When oral anticoagulant was indicated, patients were treated with vitamin K anticoagulant and only one antiplatelet agent.

Follow up and End Points

Clinical and echocardiographic evaluation was performed at hospital admission, before discharge, 1 to 6 months postoperatively, and on a yearly basis thereafter in a TAVI-dedicated outpatient clinic. In this setting, all patients underwent bidimensional and eventually 3-dimensional transthoracic echocardiography using an iE33 echocardiography system (Philips Healthcare, the Netherlands), following the recommendations from the specific guidelines for echocardiography in transcatheter interventions for valvular heart disease (65). If a more detailed evaluation was needed, transesophageal echocardiography was performed. For patients unable to come to our hospital for follow-up evaluation (<10%),

we performed telephone interviews and asked for a copy of the most recent echocardiographic examination.

Preoperative clinical variables were defined according to the European System for Cardiac Operative Risk Evaluation (Euro- SCORE) definitions (27,66).

Postoperative outcomes and clinical end-points were reported following the updated Valve Academic Research Consortium (VARC)-2 definitions (67,68, 69).

Postoperative aortic regurgitation (AR) was graded as no or trivial AR, mild AR, moderate AR, and severe AR. In particular, the presence and severity of AR was based on the evaluation of both central and paravalvular components with a combined measurement of total AR. The assessment of AR was performed according to current guidelines (65,67,68) using quantitative (regurgitant volume, regurgitant fraction, and effective regurgitant orifice area) and semiquantitative (diastolic flow reversal in the descending aorta, circumferential extent of prosthetic valve paravalvular regurgitation) methods.

VARC-2 Definitions: (69)

According to VARC-2, we analyzed the following end-points:

1. <u>All-cause mortality</u>

Cardiovascular mortality: Any of the following criteria: Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure). Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease. All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure. All valve-related deaths including structural or non-

structural valve dysfunction or other valve-related adverse events. Sudden or unwitnessed death and death of unknown cause.

Non-cardiovascular mortality: Any death in which the primary cause of death is clearly related to another condition (e.g. tr auma, cancer, suicide)

2. Myocardial Infarction (MI)

Peri-procedural MI (≤72 h after the index procedure). New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality), and elevated cardiac biomarkers within 72 h after the index procedure (consisting of at least one sample post-procedure with a peak value exceeding 15 times as the upper reference limit for troponin or 5 times for CK-MB. If cardiac biomarkers are increased at baseline, a further increase in at least 50% post-procedure is required and the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure): detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile URL, together with the evidence of myocardial ischaemia. Ischeamia was defined as at least one of the following: Symptoms of ischaemia ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB)); new pathological Q-waves in at least two contiguous leads; imaging evidence of a new loss of viable myocardium or new wall motion abnormality. Also any sudden, unexpected cardiac death, involving cardiac arrest. The evidence of fresh thrombus by coronary angiography and/or at autopsy. Pathological findings of an acute myocardial infarction

3. Stroke

Diagnostic criteria: Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.

Stroke: duration of a focal or global neurological deficit ≥24 h; or 24 h if available neuroimaging documents a new haemorrhage or infarct; or the neurological deficit results in death

TIA (transient ischemic attack): duration of a focal or global neurological deficit < 24 h.

Stroke classification:

- *Ischaemic*: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- *Haemorrhagic*: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
- A stroke may be classified as *undetermined* if there is insufficient information to allow categorization as ischaemic or haemorrhagic

Stroke definitions: disabling or non-disabling stroke

4. Bleeding

Life-threatening or disabling bleeding: Fatal bleeding (BARC type 5) or bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) or bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or

surgery (BARC type 3b) or overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 unitsa (BARC type 3b)

Major bleeding (BARC type 3a): Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery and does not meet criteria of life-threatening or disabling bleeding

Minor bleeding (BARC type 2 or 3a, depending on the severity): any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life threatening, disabling, or major.

5. Acute kidney injury (AKI classification)

Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) or increase of ≥0.3 mg/dL (≥26.4 mmol/L) or urine output 0.5 mL/kg/h for 6-12 hours.

Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) or urine output 0.5 mL/kg/h for 12-24 hours.

Stage 3: Increase in serum creatinine to ≥300% (.3 × increase compared with baseline) or serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR Urine output 0.3 ml/kg/h for ≥24 h or anuria for ≥12 h.

6. Vascular access site and access-related complications

Major vascular complications: Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm. Any access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, compartment syndrome,

percutaneous closure device failure) leading to death. Life-threatening or major bleeding, visceral ischaemia, or neurological impairment. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage. The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment. Any new ipsilateral lower extremity ischaemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram. Surgery for access site-related nerve injury or permanent access site-related nerve injury

Minor vascular complications: Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, haematomas, percutaneous closure device failure) not leading to death. Life-threatening or major bleedinga, visceral ischaemia, or neurological impairment or distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication. Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft).

The cumulative end-points were:

1. Device success: defined as absence of procedural mortality and correct positioning of a single PHV into the proper anatomic location and intended performance of the prosthetic heart valve (no prosthesis/ patient mismatch and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s and no moderate or severe prosthetic valve regurgitation.

2. Early safety (at 30 days): defined as absence of all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, AKI (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

3. Clinical efficacy (at 1 years): defined as absence of all-cause mortality; all-stroke (disabling and non-disabling); requirement of hospitalization for valve-related symptoms; worsening CHF, NYHA class III or IV; valve-related dysfunction (mean aortic valve gradient >20 mm Hg, effective orifice area (EOA) ≤ 0.9–1.1 cm2 or dimensionless valve index <0. 35 (or both), or moderate or severe prosthetic valve regurgitation.

4. Time-related valve safety: Structural valve deterioration: calve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm2c or moderate or severe prosthetic valve regurgitation); requiring repeat procedure (TAVI or SAVR). Prosthetic valve endocarditis; prosthetic valve thrombosis; thrombo-embolic events (e.g. stroke).

5. Late prosthesis failure was defined as mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9–1.1 cm2 and/or Doppler velocity index <0.35 m/s and/or moderate or severe prosthetic valve regurgitation; the presence of leaflets thrombosis or valve endocarditis was excluded by computed tomography (CT) scan or autopsy.

In the table 4 were reported the 2017 ECC/EACTS guideline definitions for the prosthetic valve dysfunction.

Table 4. Classification of prosthesis valve dysfunction (2017 ECC/EACTS guideline).

	Prosthetic aortic valve stenosis[a]		
	Normal	**Mild stenosis**	**Moderate/severe stenosis**
Quantitative Parameters (flow-dependent)[b]			
Peak velocity (m/s)	<3 m/s	3–4 m/s	>4 m/s
Mean gradient (mmHg)	<20 mmHg	20–40 mmHg	>40 mmHg
Quantitative parameters (flow-independent)			
Doppler velocity index[c]	>0.35	0.35–0.25	<0.25
Effective orifice area[d]	>1.1 cm^2	1.1-0.8 cm^2	<0.8 cm^2
Effective orifice area[e]	>0.9 cm^2	0.9–0.6 cm^2	<0.6 cm^2
	Prosthesis–patient mismatch (PPM)		
	Insignificant	**Moderate**	**Severe**
Indexed effective orifice area[f] (cm^2/m^2)	>0.85 cm^2/m^2	0.85–0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area[g] (cm^2/m^2)	>0.70 cm^2/m^2	0.90–0.60 cm^2/m^2	<0.60 cm^2/m^2
	Prosthetic aortic valve regurgitation		
	Mild	**Moderate**	**Severe**
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)[h]	<10%	10–29%	≥30%
Quantitative parameters[c]			
Regurgitant volume (mL/beat)	<30 mL	30–59 mL	≥60 mL
Regurgitant fraction (%)	<30%	30–49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10–0.29 cm^2	≥0.30 cm^2

Statistical analysis

Quantitative variables were analyzed descriptively, reporting mean ± standard deviation (SD) in case of normal distribution, median and 25th to 75th percentile [interquartile range (IQR)] otherwise. The risk-classes groups were compared with Student's t-test or Wilcoxon rank sum test, as appropriate. Categorical variables were reported as numbers and percentages and compared between groups using Chi-square or Fisher's exact tests, as appropriate. Survival analysis was conducted with the Kaplan-Meier method. Cox regression was used to identify univariate predictors of events from the major baseline and procedural characteristics. Variables with $P<0.15$ at the univariate analysis were subsequently considered in a multivariable Cox regression model to identify independent predictors of

death. Results of the Cox regression were reported as hazard ratio (HR), 95% confidence interval (CI) and P values. Statistical analysis was conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

RESULTS

The overall population comprised 482 patients with severe symptomatic AS (95%) or aortic bioprosthesis dysfunction (5%). All of them were retrospectively divided in four risk classes (low, intermediate, high and prohibitive).

Groups were similarly represented; in fact, 115 (23.9%) patients were at low risk with STS score < 4, 112 (23.2%) at intermediate risk with STS score 4-8, 131 (27.2%) at high risk with STS score > 8 and the remaining 124 (25.7%) at prohibitive risk.

Most of the prohibitive cases (91%) had specific anatomic or technical contraindications to surgery as reported in Table 5. Only one (0.8%) patient presented a STS score with a 1-year mortality risk >50% and 15 (12%) suffered of at least three major organ disorders. Some patients present more than one clinical contraindication.

Table 5. Anatomic or technical SAVR contraindication in prohibitive patients

SAVR Contraindications in prohibitive population	n (%)
Porcelain aorta	64 (52%)
Hostile chest	43 (35%)
Connective tissue disease	7 (6%)
Previous chest radiotherapy	21 (17%)

Over time, the group distributions significantly changed with more high and prohibitive risk patients in the first year compared to more low and intermediate ones in the last years (figure 9).

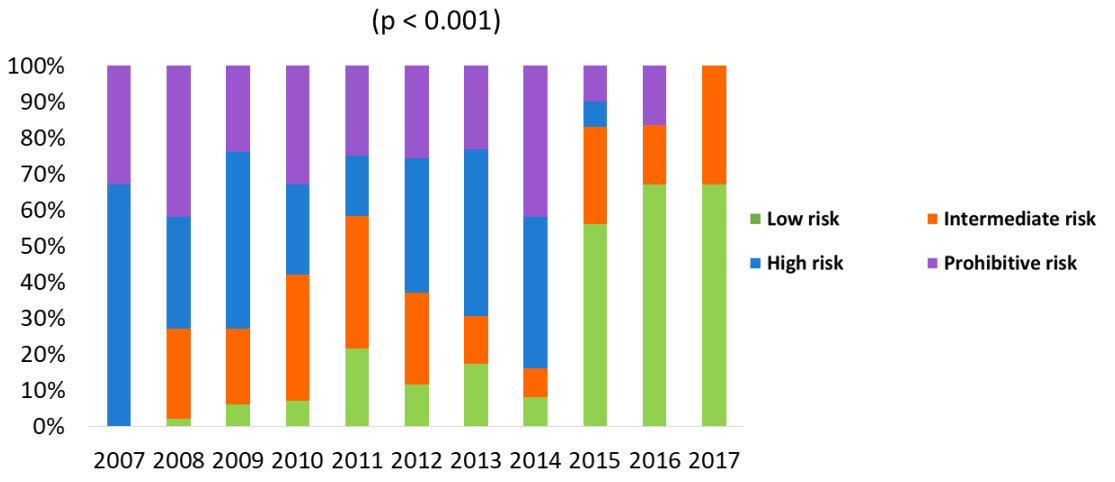


Figure 9. Distribution of patients for risk-classes during years 2007-2017

Table 6 reported baseline clinical characteristics of the populations. Mean age was 80.4±6.6 years old and prohibitive-risk patients were significantly younger ($p<0.001$) than low, intermediate and high risk ones (76.9±7.7, 80.4±4.8, 82.0±6.8 and 82.2±5.2 years old, respectively).

Overall, more than half of the cases (64%) showed New York Heart association (NYHA) functional class III or IV, with a significant lower rate in low-risk patients. One third of the population suffered for angina and syncope occurred in 17%, without differences among groups.

Previous myocardial infarction, kidney and chronic obstructive pulmonary disease were significantly less reported in low-risk group. The rate of neoplasia was significantly higher in prohibitive risk group with respect to other ones, ie 23% vs 15% (high), 11% (intermediate) and 11% (low).

Table 6. Baseline characteristics.

	All patients	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
N° of patients	482	24%(115)	23%(112)	27%(131)	26%(124)	0.456
Age (years)	80.35±6.60	80.41±4.84	82.04±6.93	82.15±5.21	76.86±7.65	**<0.001**
Sex (male)	45% (217)	53% (61)	40% (45)	43% (56)	44% (55)	0.226
BMI (kg/m²)	26.56±6.16	26.90±3.99	25.62±3.85	27.05±9.40	26.59±5.07	0.084
STS score	9.36±8.99	2.82±0.73	5.62±1.15	18.82±9.15	8.81±8.83	**<0.001**
NYHA functional class						**0.002**
I	8% (38)	12% (13)	8% (9)	2% (3)	11% (13)	
II	28% (134)	36% (41)	29% (33)	27% (35)	20% (25)	
III	53% (251)	49% (55)	47% (53)	60% (78)	53% (65)	
IV	11% (53)	4% (4)	15% (17)	10% (13)	16% (19)	
CCS grading of angina pectoris						0.679
0	72%(344)	78% (88)	75%(84)	68% (87)	69% (85)	
1	2% (8)	1% (1)	2% (2)	2% (2)	2% (3)	
2	12% (56)	12%(14)	9% (10)	11% (14)	15% (18)	
3	9% (45)	4% (5)	10% (11)	13% (17)	10% (12)	
4	5% (24)	4% (5)	4% (5)	6%(8)	5% (6)	
Syncope	17% (84)	12% (14)	23% (26)	19% (25)	15% (19)	0.14
Hypertension	90%(435)	89%(102)	90% (101)	92%(121)	90%(111)	0.787
Dyslipidemia	63% (301)	62% (71)	54% (61)	65% (85)	68% (84)	0.182
Smoking history	27% (129)	23% (26)	32% (36)	26% (34)	27% (33)	0.438
Diabetes	28% (133)	23% (27)	25% (28)	34% (44)	27% (34)	0.273
Previous MI	17% (82)	5% (6)	19% (21)	21% (28)	22% (27)	**0.001**
Coronary artery disease	55% (266)	51% (59)	56% (63)	55% (71)	59% (73)	0.654
Previous PCI	31% (148)	26% (30)	28% (31)	37% (48)	31% (39)	0.294
Previous cardiac surgery	18% (88)	7% (8)	17% (19)	18% (23)	31% (38)	**<0.001**
Previous CABG	12% (58)	4% (5)	11% (12)	12% (16)	20% (25)	**0.002**
Previous BAV	4% (17)	3% (3)	5% (6)	3% (4)	3% (4)	0.681
Carotid artery stenosis > 50%	30% (139)	27% (29)	36% (39)	24% (30)	34% (41)	0.144
CHF	43%(209)	28% (32)	50% (56)	51% (67)	44% (54)	**<0.001**
Cerebrovascular accident	12% (56)	8% (9)	15% (17)	9% (12)	15% (18)	0.207
Renal failure eGFR < 60	57%(275)	48% (55)	68% (76)	66% (86)	47% (58)	**<0.001**

Creatinine clearance	57.0±21.6	62.1±17.1	52.9±22.2	53.2 ±22.2	59.9±22.7	**<0.001**
COPD	26%(126)	13% (15)	27% (30)	37% (48)	27% (33)	**<0.001**
Atrial fibrillation	34%(163)	33% (38)	36% (40)	31% (41)	36% (44)	0.857
Pacemaker	9% (41)	9% (10)	10% (11)	7% (8)	10% (12)	0.772
Neoplastic disease	15% (72)	15% (17)	11% (12)	11% (15)	23% (28)	**0.036**
Neurological dysfunction	8% (37)	11% (12)	5% (6)	6% (8)	9% (11)	0.375
Endocarditis	1% (3)	1% (1)	1% (1)	1% (1)	0% (0)	0.786
Liver failure	2% (11)	2% (2)	3% (3)	2% (2)	3% (4)	0.79

The main echocardiographic findings were listed in the table 7.

Table 7. Baseline echocardiographic data.

	All patients	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
AVA (cm^2)	0.79±0.24	0.76±0.21	0.78±0.23	0.82±0.27	0.80±0.21	0.199
iAVA(cm^2/m^2)	0.45±0.13	0.43±0.13	0.45±0.14	0.47±0.14	0.46±0.12	**0.043**
Peak transvalvular gradient (mmHg)	73.3±23.2	76.8±24.0	75.5±25.0	72.1±21.8	69.4±21.5	0.186
Mean transvalvular gradient (mmHg)	44.8±15.1	48.2±15.3	46.5±16.4	42.9±14.2	42.3±14.0	**0.027**
LVEF(%)	54.9±12.2	55.9±10.9	55.1±13.0	53.5±12.1	55.3±12.8	0.409
End diastolic volume (ml/m^2)	66.7±24.2	65.5±23.4	66.2±26.0	65.3±21.4	69.7±25.9	0.556
Pulmonary artery pressure (mmHg)	40.5±13.8	37.7±11.9	41.3±13.1	41.4±14.6	41.2±15.0	0.316
Aortic regurgitation						0.626
None or trivial	33% (153)	41% (44)	34% (37)	31% (40)	26% (32)	
Mild	44% (205)	38% (41)	43% (47)	43% (54)	52% (63)	
Moderate	18% (83)	17% (18)	17% (19)	20% (25)	17% (21)	
Severe	5% (25)	5% (5)	6% (6)	6% (8)	5% (6)	
Mitral regurgitation >2	29% (140)	23% (26)	34%(38)	32% (42)	27% (34)	0.227
Tricuspid regurgitation >2	22% (108)	18% (21)	26% (29)	22% (29)	23% (29)	0.574

Echocardiographic data showed few significant differences in terms of index AVA (mean 0.46±0.12 cm^2/m^2) and mean transvalvular gradient (mean 44.8±15.1 mmHg) among groups, whereas LVEF (mean 54.9±12.2%) and end diastolic volume (mean 66.7±24.2 ml/m^2).

Procedural and in-hospital data.

TAVI procedure details were showed in Table 8. In 74% of cases, TF access was used without significant differences among groups (Figure 10).

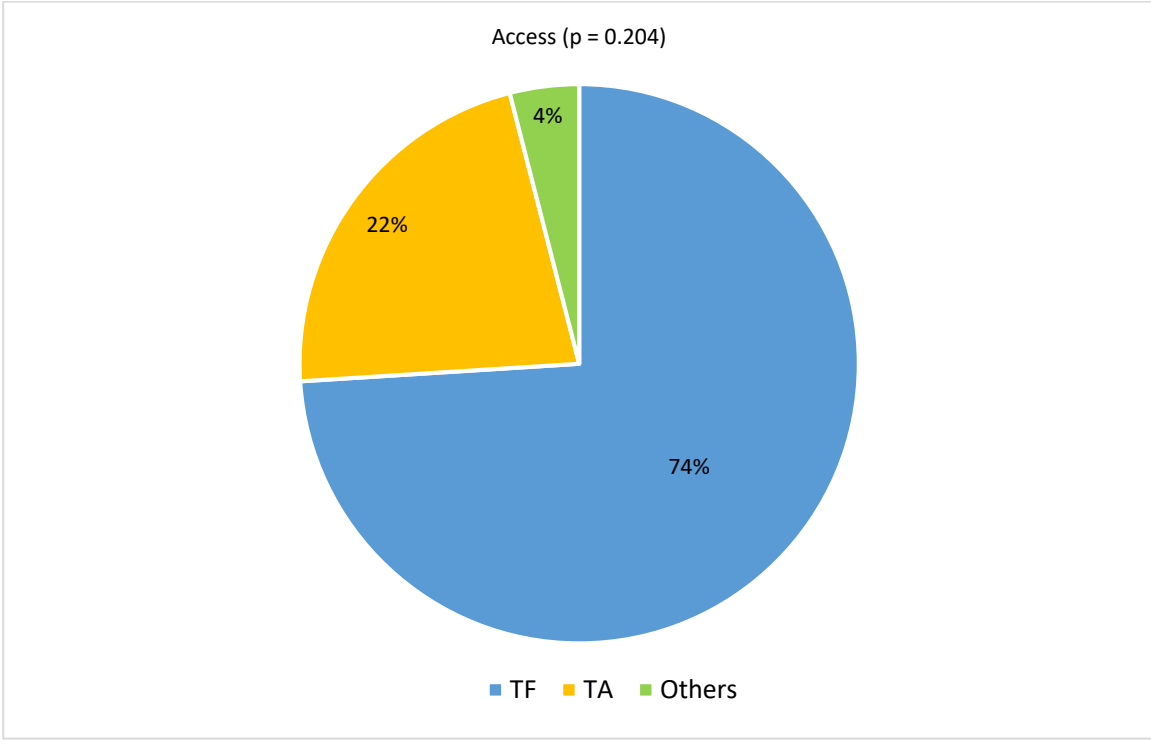


Figure 10. Access type.

Table 8. Procedural Data.

	All patients	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
Access						0.204
TF	74% (356)	81% (93)	79% (88)	73% (95)	65% (80)	
TA	19% (93)	18% (21)	16% (18)	16% (21)	27% (33)	
Device						**<0.001**
CoreValve	18% (88)	3% (4)	21% (23)	22% (29)	26% (32)	
Sapien/Sapien XT	51% (245)	30% (35)	56% (63)	60% (79)	55% (68)	
Sapien 3	17% (82)	26% (30)	15% (17)	17% (22)	10% (13)	
Lotus	11% (55)	31% (35)	8% (9)	1% (1)	8% (10)	
Symetis Acurate	2% (9)	8% (9)	0% (0)	0% (0)	0% (0)	
CoreValve Evolut R	1% (3)	2% (2)	0% (0)	0% (0)	1% (1)	
Valve in valve	5% (23)	3% (4)	4% (5)	5% (6)	6% (8)	0.746
Valve pre-dilatation	74% (353)	49% (56)	75% (82)	93% (120)	78% (95)	**<0.001**
Prosthesis post-dilatation	12% (59)	14% (16)	11% (12)	11% (15)	13% (16)	0.88

Most of the patients received an Edwards Sapien models (Figura 11). CoreValve, Sapien and Sapien XT were more frequently implanted in prohibitive, high and intermediate risk classes. In contrast, second generation devices, such as Lotus and Sapien 3 valves, were more used in low-risk group ($p<0.001$) (Figure 12). Only 9 Symetis Acurate and 3 CoreValve Evolut R were implanted, 10 of them in low risk patients. Overall, 68% of prosthesis were balloon-expandable and the remaining self-expandable.

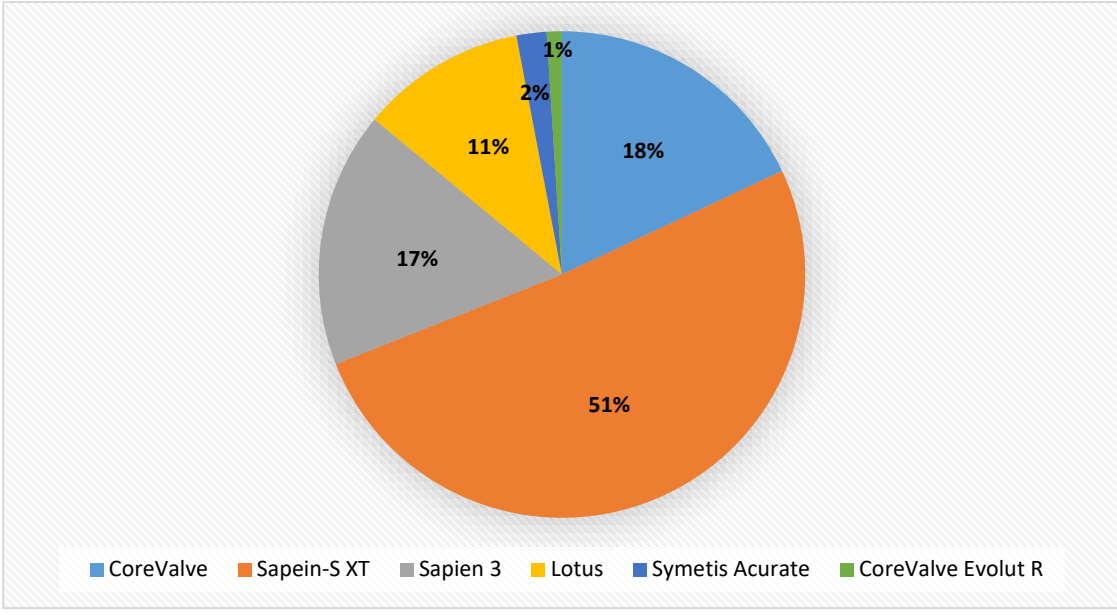


Figure 11. THV type in overall population.

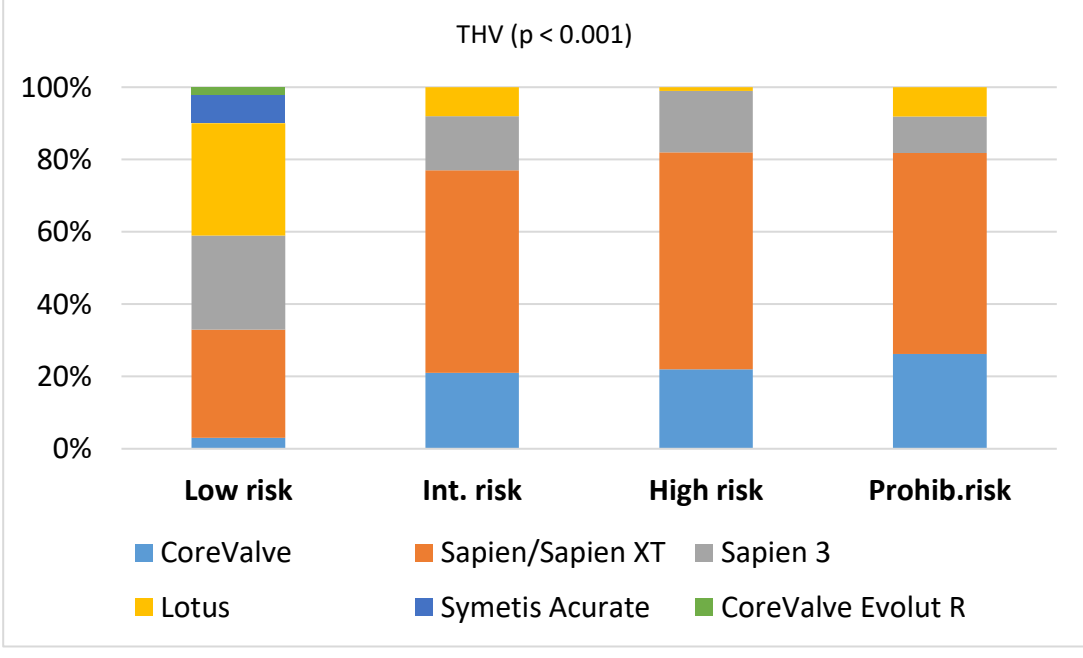


Figure 12. THV types according risk-classes.

Pre-dilatation of aortic valve was performed in 74% of patients, ranging from 49% of low risk to 93% of high risk ones (p <0.001). Pre-dilatation use decreased over time from >90% in the first years to <20% in the last ones (p<0.001 (Figure 13). No differences in the prosthetic post-dilatation were present.

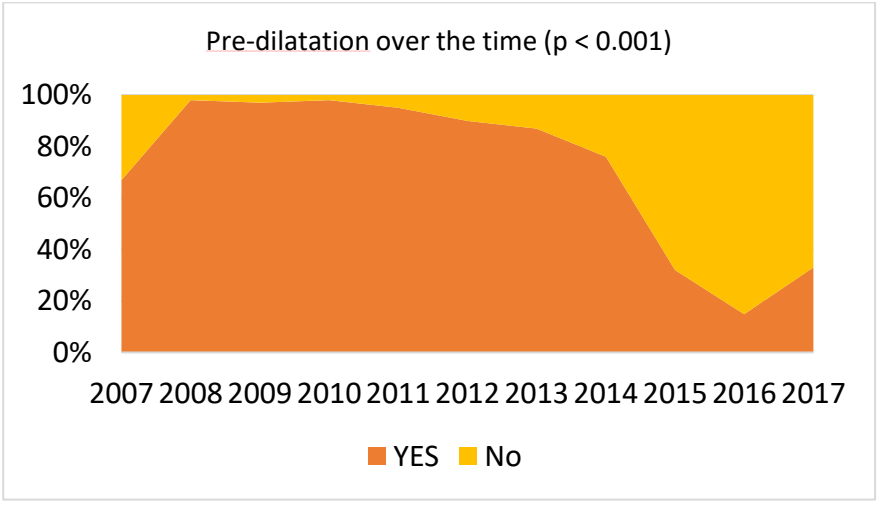


Figure 13. Aortic valve pre-dilatation over the time.

Procedural and in-Hospital outcomes are shown in Table 9.

Procedural success was high (95%) even in high-risk patients and intraoperative mortality was low (<1%). Complications did not differ among groups, with the only exception for bleeding. In fact, severe bleeding (major and life-threatening) occurred more frequently in high-risk patients (29% vs, p=0.015). Hospitalization was shorter in low-risk patients (12.7 ± 8.8) compared to intermediate (17.2 ± 13.4), high (16.8 ± 12.6) and prohibitive (16.6 ± 12.4) ones (days, p=0.001). The rate of permanent pacemaker implantation was 17%, without differences among groups.

Table 9. Procedural and in-hospital outcome.

	All pts	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
Procedural mortality	1% (4)	0% (0)	0% (0)	2% (3)	1% (1)	0.153
Device success	95% (458)	95%(109)	95%(106)	94%(123)	97% (120)	0.746
Stroke	1% (3)	0% (0)	1% (1)	1% (1)	1% (1)	0.806
TIA	1% (7)	1% (1)	2% (2)	2% (3)	1% (1)	0.717
MI	1% (4)	1% (1)	2% (2)	0% (0)	1% (1)	0.5
Major vascular complications	11% (54)	10% (11)	11% (12)	17% (22)	7% (9)	0.1
Bleeding						**0.015**
Minor	17% (82)	19%(22)	15%(17)	17%(22)	17% (21)	
Major	17% (79)	12% (14)	13% (14)	23% (30)	17% (21)	
Life-threatening	3% (15)	0% (0)	5% (6)	6% (8)	1% (1)	
AKI Stage						0.162
1	7% (34)	6% (7)	8% (9)	5% (7)	9% (11)	
2	4% (21)	1% (1)	5% (6)	7% (9)	4% (5)	
3	3% (14)	0% (0)	3% (3)	5% (6)	4% (5)	
III - AV block	13% (60)	12% (14)	16% (18)	11% (14)	11% (14)	0.589
Ventricular fibrillation	3% (12)	2% (2)	1% (1)	3% (4)	4% (5)	0.416
Pacemaker implantation	17% (81)	17% (19)	20% (22)	15% (19)	17% (21)	0.742
Conversion to surgery	1% (7)	0% (0)	1% (1)	3% (4)	2% (2)	0.232
Ventricular septal perforation	1% (3)	0% (0)	0% (0)	2% (2)	1% (1)	0.362
Cardiac tamponade	2% (11)	0% (0)	2% (2)	5% (6)	2% (3)	0.117
Aortic dissection	1% (4)	0% (0)	2% (2)	2% (2)	0% (0)	0.259
Device embolization	1% (7)	0% (0)	2% (2)	2% (3)	2% (2)	0.485
TAVI in TAVI	2% (9)	1% (1)	3% (3)	2% (3)	2% (2)	0.745
Coronary obstruction	1% (4)	1% (1)	2% (2)	0% (0)	1% (1)	0.5
Length of hospital stay (days)	15.9±12.1	12.7±8.8	17.2±13.4	16.8±12.6	16.6±12.4	**0.001**

Echocardiographic data at 48 hours after TAVI procedure are reported in Table 10. Transvalvular aortic mean gradient (11.2±5.2 mmHg) significantly decreased with corresponding improvement of effective orifice area (2.1±1.3 cm^2) without differences among groups. Significant paravalvular leak (PVL), defined as a regurgitation more than moderate, occurred in 49 (10%) of patients and in 60% of cases in the first three years of TAVI program (2007-2009).

Table 10. Echocardiographic data at 48 hours after TAVI procedure.

	All pts	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
End diastolic volume (ml/m^2)	65.3±22.2	63.5±20.3	64.9±25.7	65.1±20.3	67.6±22.7	0.437
LVEF (%)	55.7±11.7	56.9±10.3	56.2±11.7	54.7±12.9	55.0±11.5	0.487
AVA (cm^2)	2.06±0.7	2.01±0.6	2.09±0.6	2.1±0.8	1.98±0.6	0.21
iAVA (cm^2/m^2)	1.20±1.1	1.13±0.3	1.22±0.3	1.33±2.1	1.13±0.3	0.165
Peak gradient (mmHg)	20.42±8.9	20.33±9.3	20.84±9.1	21.08±9.3	19.46±7.7	0.619
Mean gradient (mmHg)	11.22±5.2	11.68±5.3	11.51±5.2	11.14±5.6	10.63±4.7	0.24
PVL						0.792
1	19% (87)	14% (16)	21% (21)	21% (25)	21% (25)	
2	28% (126)	28% (32)	28% (28)	31% (37)	24% (29)	
3	9% (42)	9% (10)	8% (8)	10% (12)	10% (12)	
4	1% (5)	1% (1)	0% (0)	1% (1)	3% (3)	
Mitral valve regurgitation > 2	23% (101)	20% (21)	26% (25)	26% (31)	21% (24)	0.62
Tricuspid valve regurgitation > 2	23% (98)	17% (18)	28% (27)	26% (30)	21% (23)	0.181

Early and 1-year clinical and hemodynamic outcomes.

Thirty-day clinical and hemodynamic results are reported in Table 11. Overall mortality was 3% with a significantly (p= 0.048) lower rates in low (any patients) and prohibitive risk groups (2%) compared to intermediate (4%) and high (6%) risk ones. Others adverse events were infrequent (stroke 2%, MI 2%, CHF 4%) and did not differ among groups. Overall MACE were

10% and resulted significantly lower in the low risk group compared to the others. Early-safety at 30 days was 82% and resulted significantly higher (p=0.049) in low and prohibitive risk groups (88% and 86%, respectively) versus intermediate (80%) and high (76%) risk ones. In addition, low-risk class predicted early-safety with respect to other groups (HR 2.4, CI 1.19-4.87, p= 0.05).

Echocardiography data confirmed the efficacy of TAVI to reduce mean transvalvular aortic gradient (10.4±4.7 mmHg) with an improvement in effective orifice area (1.9±0.4 cm^2) in absence of differences among groups. Significant PVL was observed in 13% of the patients, without differences among groups.

Table 11. Clinical and hemodynamic outcome at 30 days

	All pts	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
Mortality	3% (16)	0% (0)	4% (5)	6% (8)	2% (3)	**0.048**
All stroke	2% (11)	0% (0)	2% (2)	4% (5)	3% (4)	0.191
MI	2% (9)	1% (1)	3% (3)	2% (3)	2% (2)	0.75
CHF	4% (17)	2% (2)	5% (6)	2% (3)	5% (6)	0.344
MACE	10% (50)	3% (4)	12% (13)	15% (19)	11% (14)	**0.034**
Early safety	82% (389)	88% (100)	80% (87)	76% (99)	86% (103)	**0.049**
AVA (cm^2)	1.85±0.43	1.87±0.43	1.77±0.44	1.88±0.39	1.86±0.45	0.15
iAVA (cm^2/m^2)	1.05±0.27	1.06±0.25	1.02±0.30	1.07±0.28	1.05±0.27	0.498
Mean gradient (mmHg)	10.4±4.7	10.9±4.6	10.5±5.2	9.9±4.8	10.3±4.1	0.381
PVL						0.205
1	21% (82)	15% (15)	26% (24)	23% (23)	20% (20)	
2	27% (106)	26% (26)	26% (24)	28% (28)	28% (28)	
3	13% (50)	8% (8)	11% (10)	14% (14)	18% (18)	
4	0% (1)	0% (0)	0% (0)	1% (1)	0% (0)	

Table 12 shows clinical and hemodynamic results at 1 years and the number of patients at risk at 1 year was 331. Overall mortality was 14% with significant (p=0.008) higher rates in

high (19%) and intermediate (21%) risk groups compared to low (6%) and prohibitive (7%) risk ones. Cardiovascular death was 7% with statistical trend in favor of low (1%) and prohibitive (5%) risk patients when compared to intermediate and high risk ones (13%). One-year clinical efficacy was 73% without differences among groups. Others clinical and hemodynamic features did not differed.

Table 12. Clinical and hemodynamic outcome at 1 year

	All pts	Low risk	Intermediate risk	High risk	Prohibitive risk	p-value
Mortality	14% (50)	6% (3)	21% (19)	19% (21)	7% (7)	**0.008**
Cardiovascular mortality	7% (33)	1%(2)	13% (12)	13% (14)	5% (5)	0.068
All stroke	4% (14)	0% (0)	2% (2)	6% (6)	6% (6)	0.283
MI	4% (13)	5% (2)	4% (3)	6% (6)	2% (2)	0.555
CHF	18% (62)	17% (8)	16% (14)	14% (15)	25% (25)	0.23
MACE	32% (114)	29% (15)	32% (29)	36% (40)	29% (30)	0.758
Clinical efficacy	73% (277)	68% (40)	73% (65)	77% (95)	72% (77)	0.575
Prosthesis dysfunction	9% (31)	9% (10)	7% (7)	11% (13)	9% (11)	0.76
AVA (cm^2)	1.75±0.34	1.83±0.35	1.72±0.30	1.74±0.29	1.74±0.39	0.619
iAVA (cm^2/m^2)	1.03±0.61	1.04±0.25	1.05±0.34	1.02±0.20	1.03±0.25	0.835
Mean gradient (mmHg)	10.7±5.3	11.5±5.2	9.8±4.1	10.2±4.2	11.6±6.7	0.14
PVL						0.269
1	31% (66)	14% (4)	38% (20)	36% (22)	30% (20)	
2	28% (59)	24% (7)	30% (16)	28% (17)	28% (19)	
3	10% (21)	10% (3)	8% (4)	10% (6)	12% (8)	
4	1% (2)	3% (1)	2% (1)	0% (0)	0% (0)	

Kaplan Meier (KM) survival curves are reported in figure 14.

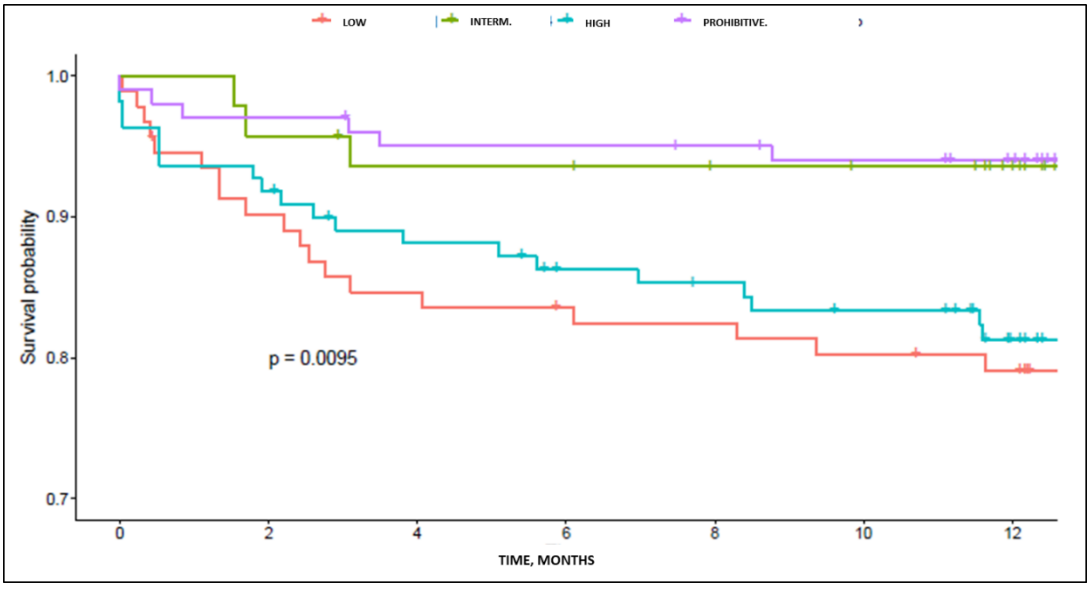


Figure 14. Kaplan-Meier survival curves at 1 year.

Long-term clinical outcome

Median follow-up in the overall population was 3.1 years (13 days-9 years), with a 94% of completeness. The duration was significantly shorter in low risk patients (2.0±1.9 years) compared to overall population (3.2±2.9 years). Overall, clinical outcome at 5-years is showed in table 13.

Table 13. Long-term clinical outcome.

	All patients
Mortality	52% (131)
Cardiovascular mortality	17% (42)
All stroke	7% (18)
MI	6% (15)
CHF	33% (83)
MACE	53% (133)

Overall death occurred in 131 (52%) patients at 5 years and the KM curves (Figure 15) showed a significantly improved survival only in low risk patients.

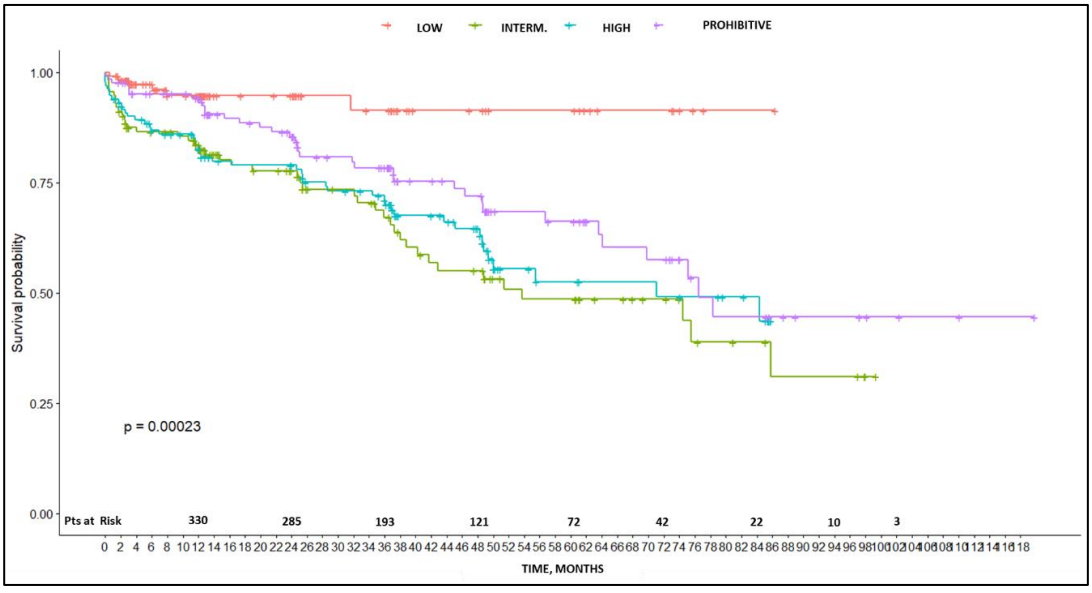


Figure 15.Long term KM survival curves free from overall death.

With regard to cardiovascular death, low and prohibitive risk groups showed better survival than intermediate and high risk ones (Figure 16).

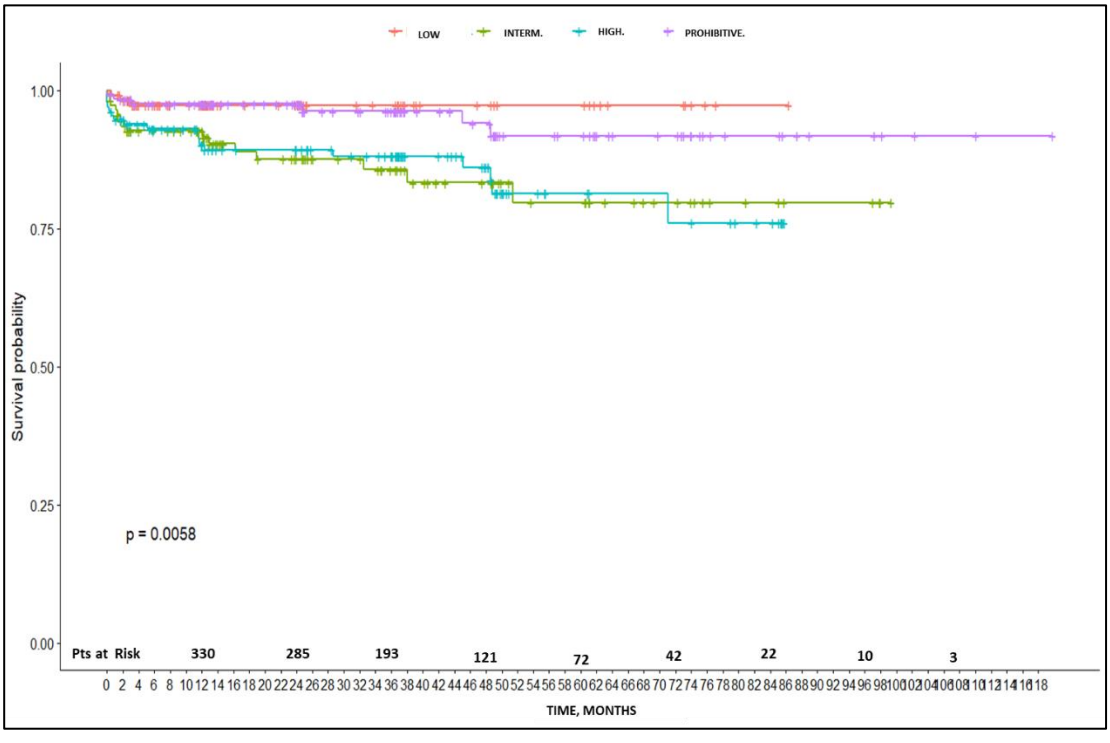


Figure 16. Long term KM survival curves free from cardiovascular death.

A significant and sustained improvement in NYHA functional class was observed in all risk groups (Figure 17).

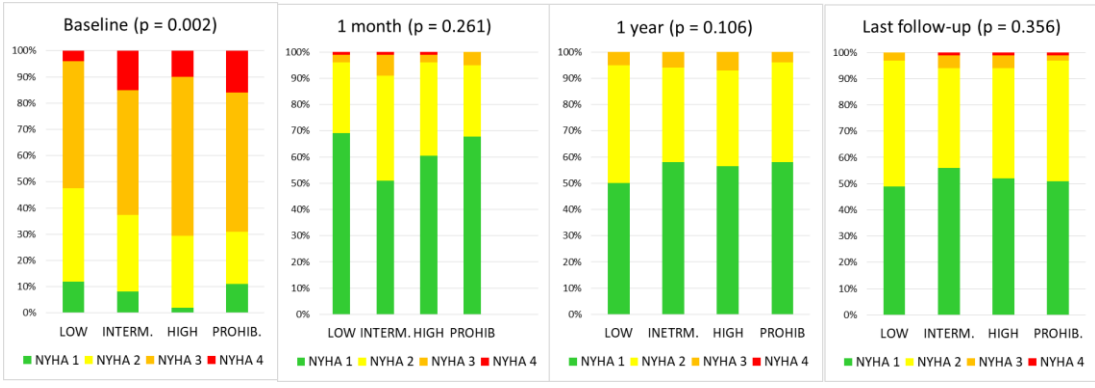


Figure 17. NYHA functional status. Longitudinal trend in NYHA functional status before and after TAVI, according to risk-classes.

The significant results of multivariate analysis to predict death are showed in table 14. CHF (HR 1.7, p=0.01), neoplastic disease (HR 1.67, p =0.05) and creatinine values in mg/dl (HR 1.13, p=0.001) were pre-procedural independent predictor of death. Severe bleeding (major or life tethering) (HR 4.57, 95% CI 1.48-14.06, p=0.05) and any AKI stage (HR 2.46, p=0.001) were post-procedural independent predictor of death. The risk class did not result to significantly predict death at multivariate analysis (low HR 0.49, 95% CI 0.18-1.33, intermediate HR 0.50, 95%CI 0.68-1.82, high HR 0.90, 95%CI 0.68-1.82 and prohibitive HR 0.90, 95%CI 0.53-1.52).

Table 14. Independent predictor of death at multivariate analysis.

	HR	ICs.		P
CHF	1.7755	1.1543	2.7309	0.01
Neoplastic disease	1.6664	0.99589	2.7885	0.05
Severe bleeding	4.5675	1.4834	14.064	0.05
Creatinine pre-procedure (mg/d).	1.1259	1.0261	1.2353	0.01
AKI	2.5498	2.4588	1.2944	4.6705

Long-term hemodynamic outcome and prosthesis dysfunction.

Prosthetic hemodynamic performances at last follow-up was reported in Table 15 and Figure 18.

Table 15. Prosthesis hemodynamic performance at long term follow-up

	All patients
Prosthesis dysfunction	11.4% (38)
Aortic valve area (cm^2)	1.72±0.41
Indexed valve area (cm^2/m^2)	1.03±0.61
Mean gradient (mmHg)	10.9±5.1
PVL > 2	11% (24)

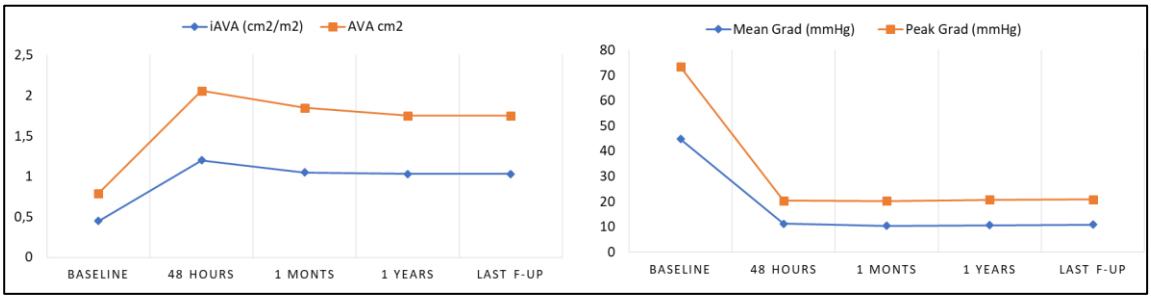


Figure 18. Variation of transaortic gradient (peak and mean) and effective orifice area of patient undergoing TAVI procedure

Trans-prosthetic gradient and effective orifice area remained stable over time in all the groups. Post-procedural PVL was significant (>2) in 11% of patients. Among patients with trivial or mild PVL, no changes in leak severity were observed over time. Considering patient at risk at 1 year, 31 patients (9%) had a prosthetic dysfunction that appeared in the first year after procedure. All these patients had a high transvalvular mean gradient (mean 15 mmHg) or almost a mild PVL after procedure. Overall prosthesis dysfunction at long-term was 11.4% (Figure 19) and late prosthesis failure occurred in 7 patients (2.1%). CT scan or autopsy, whenever possible, confirmed structural valve deterioration. Two patient developed both

increased trans-prosthetic gradients and severe intra-prosthetic regurgitation at 3 and 4 years. One case underwent a valve-valve procedure. Three patients had valve restenosis (mean gradients 38 and 43 mmHg, 25 mmHg, respectively) after 4 years. Two patients developed a severe intra-prosthetic regurgitation at 3 and 7 years. All these patients were treated conservatively because of their high frailty status.

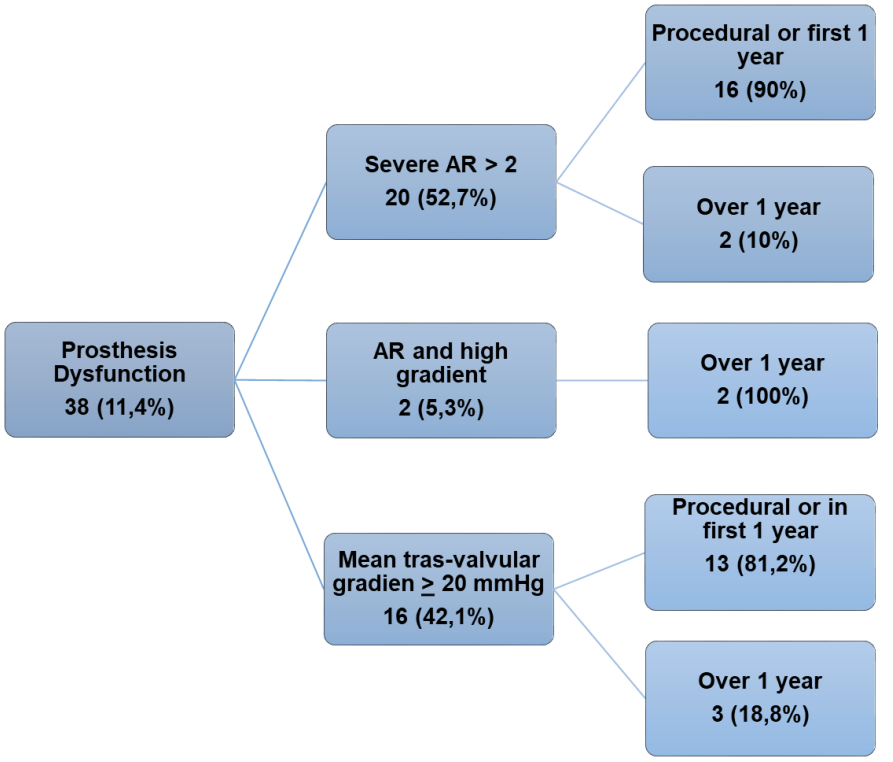


Figure 19. Prosthesis dysfunction

DISCUSSION

The main results of the following single center study analyzing safety and efficacy of 482 real world patients treated by TAVI for symptomatic AS or aortic bio-prosthesis dysfunction as function of different surgical risk scores are:

I) The distribution of the population according to surgical risk score was similarly represented (23.9% low-risk, 23.2% intermediate-risk, 27.2% high-risk and 25.7% prohibitive-risk), but over the time the group distributions significantly changed with more low- and intermediate-risk patients in the last years.

II) TAVI was safe and effective at 1-year, with low rates of mortality and adverse events regardless of the surgical risk.

III) At longer follow-up mortality rate was significantly lower in low-risk patients.

IV) Pre-procedural CHF, neoplastic diseases, pre-procedural creatinine, post-procedural severe bleedings and post-procedural AKI were independent predictors of mortality.

V) THV performance after the procedure was excellent and stable over time with low rate of late prosthesis dysfunction (<2.5%).

The device success in our analysis resulted to be satisfactory (95%) as also reported by other registries as SOURCE (93.8%), SOURCE XT (94.5%), SOURCE 3 (98.3%) and French registry (FRANCE-2 96.9%) (70,71,72). These data confirm the feasibly of TAVI in almost all cases, despite the apparent complexity of the procedure. The risk class did not influence the occurrence of procedural mortality (1%) or others complications, with the only exception of severe bleeding that was higher in high-risk patients (p=0.015) as showed by other studies

(73-74). The significant reduction of the hospitalization time in low-risk patients (12.7±8.8 days vs 15.9±12.1 days on average, p=0.001) is not surprising and may be explained by the younger age and the lower rate of previous MI (p< 0.001), CHF (p<0.001), chronic kidney disease (p<0.001) and COPD (p<0.001) in this group compared to other ones.

As in previous studies (38,45,71), early safety was achieved in most of patients and significantly differed among groups (low-risk 88%, prohibitive-risk 86%, intermediate-risk 80%, high-risk 76%, p = 0.049). This dissimilarity may be explained by the fact that early mortality and bleeding differed as well.

In our study, the 30-day mortality was 3% similarly to other trials and registries in which it ranged from 1% (SOURCE-3 1.1%, NOTION registry 2.1%, SURTAVI 2.2%, PIVOTAL trial with CoreValve 3.3%, PARTNER TAVI arm 3.4%) to nearly 10% in multicentric FRANCE-2 registry, 8.4% in CoreValve ER (38,45,48,59,71,72). Similar data were observed in high-risk patients undergoing traditional surgery (PARTNER SAVR arm 6.5%) (38). Moreover, the mortality risk estimated by STS score looked to be higher than our results in all risk groups, confirming poor calibration for mortality estimation in TAVI patients (75,76).

The low-risk group showed no death at 30 days and a 1-year mortality rate of 6%. This observation was comparable with data available from other studies in which low risk patients' mortality ranged from 2-3% at 30 days to 5-10% at one year. (73-77). Even the prohibitive-risk group showed low mortality rates, 2% at 30 days and 7% to 1 year. This result could be explained by the fact that most of these patients underwent TAVI because of technical contraindications to SAVR more than increased comorbidities. A similar effect emerged also in other studies (69,77) in which technically inoperable patients had better outcomes than clinically inoperable ones. Thus, for example, our prohibitive-risk group was

composed of younger patients with a higher rate of neoplastic disease and life expectancy >1 year, instead they should have been excluded from the program.

In high-risk cases, the mortality at 30-days was 6% and at one year 19%. Data Literature reported discordant data in this group of patients. In fact, some studies showed similar rates of death (73,74) but in other ones the mortality rate was higher, up to 34% at 1-year (77-79). In our study, the intermediate-risk group's mortality was comparable to the high-risk one. However, in other studies survival was improved (74,77,80) and this dissimilarity could be due to different characteristics of the population and nonhomogeneous criteria for risk classes stratification. Finally, the worse prognosis of intermediate- and high-risk classes could be associated to the older age and the higher rate of CHF, kidney failure and chronic lung disease that were independent predictors of mortality (81-85).

Survival free from MACE at 30 days was more favorable in the low-risk group (3%) than other ones (intermediate 12%, high 15%, prohibitive 11%, p = 0.034). This effect was mainly caused by the higher rate of mortality and severe bleeding in the former group with respect to the latter ones. Subsequently, after 1 year the statistical significance (p=0.758) was lost. The increased mortality of intermediate- and high-risk patients could be explained by advanced age and multiple comorbidities, as previously described (86). Overall stroke rate at 1 year was 4%, as shown in earlier studies (45,80), and no cerebrovascular events occurred in the low-risk group (p = 0.283).

At one year, 90% of patients were asymptomatic for dyspnea with NYHA 1-2 class (p = 0.106). Less than 20% of cases were re-hospitalized for CHF and nearly half of these patients presented severe mitral regurgitation consistently with previous data (85).

The global mortality at 5 years was 52% (131 patients) according to Chakos systematic review (86) that analyzed 13857 patients with 5-years mortality rate of 48%. The KM survival curves showed a significantly improved survival only in low-risk group. However, multivariate analysis did not confirm low-risk class as significant predictor of survival (HR 0.49 for mortality, p= 0.49). The different duration of follow-up and the small number of patients at risk after 2 years in low-risk group could justify this result. In fact, the median follow-up in the overall population was 3.1 years (30 days-9 years) and the follow-up duration differed among the groups, being significantly shorter in low-risk patients compared to other ones (mean 2.0±1.9 years vs 3.2±2.9 years overall).

After 1 year, the survival of the prohibitive-risk group decreased progressively and tended to match high- and intermediate-risk outcomes. This result could be explained by the higher rate of associated diseases that affected these patients. In particular, neoplastic diseases were frequent and resulted to be an independent predictor of mortality. As shown in Figure 13, also the KM curve outlined that most of death in the prohibitive-risk group were non-cardiovascular related. Similar results were observed also in the 5-year analysis of PARTNER 1 trial, in which over 2/3 of the deaths were non-cardiovascular (43).

The independent predictor of long-term mortality at multivariate analysis were few pre-procedural features and post-procedural complications. Chronic kidney disease (creatinine clearance < 60ml/min/1.73m”) was one of the more frequent comorbidities in high- and intermediate-risk patients compared to low- and prohibitive-risk ones (respectively, 66% and 68% vs 48% and 47%, p < 0.001) . The multivariate analysis individuated pre-procedural creatinine value as predictor of death with HR of 1.13 (p<0.01) as reported in PARTNER trial and registries (38, 88). In our study, we observed that the rate of post-procedural AKI was

14% and that any AKI stage resulted to be an independent predictor of mortality with HR of 2.46 (p=0.001). Also in this case, several trials and registries reported similar results and the significant impact of kidney dysfunction on early and long-term survival (82-93).

In our center, active cancer with life expectancy <1 year represented a contraindication to TAVI and patients with a previous cancer were enrolled only after a complete oncologic evaluation. The rate of preprocedural neoplastic disease in the study population was 15% with significant higher rate in the prohibitive group (23%, p= 0.036). Cancer was the third cause of death in our study and independently predicted mortality (HR 1.67, p = 0.05). Several reports confirmed this observation and the influence of neoplastic disease in this setting (93-95).

At least one pre-procedural CHF event requiring hospitalization occurred in 43% of the study population and it was less frequent in low-risk patients (28%, p < 0.001). To note, pre-procedural CHF was also an independent predictor of mortality, HR 1.7 (p=0.01).

Many studies and registries reported that severe bleeding after TAVI procedure increased hospitalization time and impacted on early mortality (90,91,93,96). In fact, also in our study major and life threatening bleeding represented a strong independent predictor of mortality (HR 4.7, p = 0.05).

TAVI procedure allowed a significant reduction in transvalvular aortic gradient, which was stable over time. Consequently, the effective orifice area improved immediately after TAVI, achieving values that were even better than those obtained with conventional surgery, both for stented and stentless prosthesis (97). This excellent hemodynamic performance decreased the prosthesis-patient mismatch phenomenon (4.98%) with even improved

results in case of small aortic annulus (97). While the transprosthetic gradient was stable over time, the effective orifice area showed a slight decrease at long-term follow-up. This event may be justified by the fact that the effective orifice area estimation was not well defined and so there could have been an intra- and inter-observer variability during time (98). However, this result was comparable to 5-year echocardiographic data of the PARTNER 1 trial that showed that the mean THV gradient does not change throughout 5 years, with very few (<2%) hemodynamic outliers needing re-operation (99).

In our study the cumulative rate of prosthesis dysfunction was 11.4% and occurred during the first year after TAVI in most cases (7.9%). Thereafter, late prosthesis dysfunction decreased to 2.1%. Similarly, PARTNER 1 (99) and Barbanti and colleagues study (88) reported late prosthesic valve failure at 5 year in 1.4% of the cases. SAVR with pericardial bioprosthesis showed that freedom from prothestic deterioration at 15 and 20 years was 78.6% and 48.5%, respectively (100). However, at present, the strongest argument against broadening TAVI indication to younger patients remains undoubtedly valve durability. In fact, the low survival rate of current TAVI patients is attributable to the advanced age and the multiple comorbidities more than to valve failure. On average, 5-year THV hemodynamic data are favorable and comparable to surgical bioprosthesis (43,100,101), and certainly sufficient for the currently treated AS patients, considering the mean life expectancy of the eighty years old patients (i.e. <4–5 years after TAVI) in most Western countries. After that, surgical bioprosthesis are known to degenerate within 10 to 20 years and this phenomenon was highly associated to age (101). Notably, it has been hypothesized that THV durability might be shorter than surgical bioprostheses because of leaflet crimping, torsion during delivery, balloon dilation, possible incomplete, non-circular THV expansion with subsequent

asymmetric leaflet opening and increased sheer stress (102-104). Finally, prosthesis dysfunction was similarly observed in the different risk groups.

Study limitations

This is a single-center, observational study with a fairly limited number of patients. Although at our institution all TAVI patients data are prospectively collected in a dedicate database and follow-up is continuously updated, classification of risk groups has been retrospective and clinical end points were self-adjudicated. Echocardiographic core laboratory was not available and, as in several retrospective studies on heart valve prostheses, the risk of underestimation of prosthesis dysfunction should be acknowledged. Another main limit of the study was the different follow-up duration among risk groups. In fact, the low risk group had a smaller number of patients at long-term follow-up when compared to the other ones, and this difference could have influenced the outcomes.

CONCLUSIONS

In our study population including patients undergoing TAVI for AS or aortic bioprosthesis failure, TAVI was safe and effective, with low rates of mortality and adverse events regardless of the surgical risk. At longer follow-up mortality rate was significantly lower in low-risk patients. Pre-procedural CHF, neoplastic diseases, pre-procedural creatinine, post-procedural severe bleedings and post-procedural AKI were predictors of late adverse events. THV performance after the procedure was excellent and stable over time with low rate of late prosthesis dysfunction. Further studies should be addressed to confirm the promising long-term results among low-risk patients and the long-term durability of THV.

REFERENCES

1. Ross J, Braunwald E. Aortic stenosis. Circulation. 1968;38:61-67

2. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older that 20 years of age with valvular aortic stenosis. Am J Cardiol. 1988;61:123-130

3. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol. 1993;21:1220-1225.

4. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med. 1999; 341:142-147

5. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. The Lancet 2006 September 16,;368(9540):1005-1011.

6. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic Stenosis in the Elderly. Journal of the American College of Cardiology 2013 September 10,;62(11):1002-1012.

7. Thaden JJ, Nkomo VT, Enriquez-Sarano M. The Global Burden of Aortic Stenosis. Progress in Cardiovascular Diseases 2014 May 1,;56(6):565-571.

8. Mann DL, Zipes DP, Libby P, Bonow RO. Malattie del cuore di Braunwald . 10th ed.; 2016.

9. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation 2010 Jan 5;121(1):151-156.

10. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. Eur Heart J 1987 May;8(5):471-483.

11. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J 1988 Apr;9 Suppl E:57-64.

12. Dahl JS, Christensen NL, Videbæk L, Poulsen MK, Carter-Storch R, Hey TM, Pellikka PA, Steffensen FH, Møller JE. Left Ventricular Diastolic Function Is Associated with Symptom Status in Severe Aortic Valve Stenosis. Circ Imaging. 2013;10:1161

13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 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. Circulation. 2014 Jun 10;129(23):e521-643

14. Di Pasquale G, Coutsoumbas GV, Zagnoni S. Severe low-gradient aortic stenosis, with preserved ventricular function: should it be treated? J Cardiovasc Med (Hagerstown). 2017 Jan;18 Suppl 1

15. Rosenhek R, Maurer G, Baumgartner H. Should early elective surgery be performed in patients with severe but asymptomatic aortic stenosis? Eur Heart J 2002;23:1417–1421.

16. Pendyala LK, Ben-Dor I, Waksman R. Evolution of percutaneous balloon aortic valvuloplasty in the treatment of patients with aortic stenosis. Minerva Med 2012;103:415–429

17. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–3008.

18. Harken DE, Soroff HS, Taylor WJ, Lefemine AA, Gupta SK, Lunzer S. Partial and complete prostheses in aortic insufficiency. J Thorac Cardiovasc Surg 1960;40: 744–762.

19. Helmut Baumgartner Volkmar Falk Jeroen J. Bax Michele De Bonis Christian Hamm Per Johan Holm Bernard Iung Patrizio Lancellotti Emmanuel Lansac Daniel Rodriguez Muñoz Raphael Rosenhek Johan Sjögren Pilar Tornos Mas Alec Vahanian Thomas Walther Olaf Wendler Stephan Windecker Jose Luis Zamorano ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal, Volume 38, Issue 36, 21 September 2017, Pages 2739–2791.

20. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. Ann Thorac Surg 2009 Jul;88(1 Suppl):23.

21. Schymik G, Heimeshoff M, Bramlage P, Herbinger T, Wu¨rth A, Pilz L, Schymik JS, Wondraschek R, Su¨selbeck T, Gerhardus J, Luik A, Gonska BD, Tzamalis P, Posival H, Schmitt C, Schro¨ fel H. A comparison of transcatheter aortic valve implantation and surgical aortic valve replacement in 1, 141 patients with severe symptomatic aortic stenosis and less than high risk. Cathet Cardiovasc Interv 2015; 86:738–744.

22. Tokarek T, Sobczynski R, Dziewierz A, Siudak Z, Zasada W, Sorysz D, Pfitzner R, Sadowski J, De¸bski G, Dziewie¸cka E, Gruszka K, Dudek D. Clinical outcomes in patients after surgical and transcatheter aortic valve replacement. Pol Arch Med Wewn 2015;125:755–764.

23. Tamburino C, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, SantiniF, Rosato S, Santoro G, Fusco D, Grossi C, Seccareccia F; OBSERVANT Research Group. 1-year outcomes after transfemoral transcatheter or surgical aortic valve replacement: results from the Italian OBSERVANT Study. J Am CollCardiol 2015;66:804–812.

24. Fraccaro C, Tarantini G, Rosato S, Tellaroli P, D'Errigo P, Tamburino C, OnoratiF, Ranucci M, Barbanti M, Grossi C, Santoro G, Santini F, Covello RD, Fusco D, Seccareccia F; OBSERVANT Research Group. Early and midterm outcome of propensity-matched intermediate-risk patients aged >_80 years with aortic stenosis undergoing surgical or transcatheter aortic valve replacement (from the Italian Multicenter OBSERVANT Study). Am J Cardiol 2016;117:1494–1501.

25. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P,Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC, Smith CR, Alu MC, Parvataneni R, D'Agostino RB, Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016; 387:2218–2225.

26. Ferguson TB Jr, Dziuban SW Jr, Edwards FH, Eiken MC, Shroyer AL, Pairolero PC, Anderson RP, Grover FL. The STS National Database: current changes and challenges for the new millennium. Committee to Establish a National Database in

Cardiothoracic Surgery, the Society of Thoracic Surgeons. Ann Thorac Surg 2000;69:680–691.

27. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.

28. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734–744; discussion 744–5.

29. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, Szeto WY, Dewey TM, Guyton RA, Bavaria JE, Babaliaros V, Gammie JS, Svensson L, Williams M, Badhwar V, Mack MJ. Contemporary real-world outcomes of surgical aortic valve replacement in 141, 905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg 2015;99:55–61.

30. Tran HA, Roy SK, Hebsur S, Barnett SD, Schlauch KA, Hunt SL, Holmes SD, Ad N. Performance of four risk algorithms in predicting intermediate survival in patients undergoing aortic valve replacement. Innovations (Phila) 2010;5:407–412.

31. Seiffert M, Sinning JM, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M, Ghanem A, Kempfert J, Hammerstingl C, Ojeda FM, Kim WK, Koschyk DH, Schirmer J, Baldus S, Grube E, Mo¨llmann H, Reichenspurner H, Nickenig G, Blankenberg S, Diemert P, Treede H, Walther T, Werner N, Schnabel RB. Development of a risk score for outcome after transcatheter aortic valve implantation. Clin Res Cardiol 2014;103:631–640.

32. Edwards FH, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, Grover FL, Tuzcu EM, Thourani VH, Carroll J, Brennan JM, Brindis RG, Rumsfeld J, Holmes DR, Steering Committee of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. JAMA Cardiol 2016;1:46–52.

33. D'Ascenzo F, Capodanno D, Tarantini G, Nijhoff F, Ciuca C, Rossi ML, Brambilla N, Barbanti M, Napodano M, Stella P, Saia F, Ferrante G, Tamburino C, Gasparetto V, Agostoni P, Marzocchi A, Presbitero P, Bedogni F, Cerrato E, Omede` P, Conrotto F, Salizzoni S, Biondi Zoccai G, Marra S, Rinaldi M, Gaita F, D'Amico M, Moretti C. Usefulness and validation of the survival posT TAVI score for survival after

transcatheter aortic valve implantation for aortic stenosis. Am J Cardiol 2014;114:1867–1874.

34. Debonnaire P, Fusini L, Wolterbeek R, Kamperidis V, van Rosendael P, van der Kley F, Katsanos S, Joyce E, Tamborini G, Muratori M, Gripari P, Bax JJ, Marsan NA, Pepi M, Delgado V. Value of the " TAVI2-SCORe" versus surgical risk scores for prediction of one year mortality in 511 patients who underwent transcatheter aortic valve implantation. Am J Cardiol 2015;115:234–242.

35. Hermiller JB, Yakubov SJ, Reardon MJ, Deeb GM, Adams DH, Afilalo J, Huang J, Popma JJ; CoreValve United States Clinical Investigators. Predicting early and late mortality after transcatheter aortic valve replacement. J Am Coll Cardiol 2016;68: 343–352.

36. Kotting J, Schiller W, Beckmann A, Schafer E, Dobler K, Hamm C, Veit C, Welz A. German Aortic Valve Score: a new scoring system for prediction of mortality related to aortic valve procedures in adults. Eur J Cardiothorac Sur 2013;43: 971–977.

37. Agarwal S, Garg A, Parashar A, Svensson LG, Tuzcu EM, Navia JL, Mick S, Kapadia SR. In-hospital mortality and stroke after surgical aortic valve replacement: a nationwide perspective. J Thorac Cardiovasc Surg 2015;150:571–578.e8.

38. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S,Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–1695.

39. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jime´nez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146–e603.

40. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–1607.

41. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, Kleiman NS, Coselli JS, Gleason TG, Lee JS, Hermiller JB Jr, Heiser J, Merhi W, Zorn GL 3rd, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J, Resar J, Aharonian V, Pfeffer T, Oh JK, Qiao H, c DH, Popma JJ, CoreValve US Clinical Investigators. 3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2565–2574.

42. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–2198.

43. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG, PARTNER 1 Trial Investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477–2484.

44. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–1798.

45. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Sondergaard L. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 2015;65:2184–2194.

46. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–1620.

47. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, Sondergaard L, Juni P, Windecker S. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J 2016;37:3503–3512.

48. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321–1331.

49. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 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 Clinical Practice Guidelines. Circulation. 2017 Jun 20;135(25):e1159-e1195

50. Walther T,DeweyT,Borger MA, Kempfert J, Linke A, becht R, FalkV, Schuler G, Mohr FW, Mack M,. Transapical aortic valve implantation: step by ptep. Ann Thorac Surg. 2009;87:276-283.

51. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv. 2008;1:167-175.

52. Willson AB, Webb JG, Labounty TM, Achenbach S, Moss R, Wheeler M 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.

53. Binder RK, Rodés-Cabau J, Wood RA, Mok M, Leipsic J, De Larochellière R et al. Transcatheter aortic valve replacement with the SAPIEN 3. A new balloon-expandable transcatheter heart valve. JACC Cardiovascular Intervention 2013;6:293-300.

54. Tarantini G, Gasparetto V, Napodano M, Fraccaro C, Gerosa G, Isabella G. Valvular leak after transcatheter aortic valve implantation: a clinician update on epidemiology, pathophysiology and clinical implications. Am J Cardiovasc Dis 2011;1:312-20.

55. Fraccaro C, Napodano M, Tarantini G. Conduction disorders in the setting of transcatheter aortic valve implantation: a clinical perspective. Catheter Cardiovasc Interv 2013;81:1217-23.

56. Fraccaro C, Buja G, Tarantini G, Gasparetto V, Leoni L, Razzolini R et al. Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation. Am J Cardiol 2011;107:747-54.

57. Facchin M, Mojoli M, Covolo E, Tarantini G. The SAPIEN 3 valve: lights and shadows. Minerva Med. 2014 Dec;105(6):497-500.

58. Tarantini G, Mojoli M, Purita P, Napodano M, D'Onofrio A, Frigo A, Covolo E, Facchin M, Isabella G, Gerosa G, Iliceto S. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. EuroIntervention. 2015 Jul;11(3):343-50.

59. Popma JJ, D.H. Adams, M.J. Reardon, S.J. Yakubov, N.S. Kleiman, D. Heimansohn, J. Hermiller Jr., G.C. Hughes, J.K. Harrison, J. Coselli, J. Diez, A. Kafi, T. Schreiber, T.G. Gleason, J. Conte, M. Buchbinder, G.M. Deeb, B. Carabello, P.W. Serruys, S. Chenoweth, J.K. Oh, Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J. Am. Coll. Cardiol. 63 (2014) 1972–1981.

60. Sinning JM, Hammerstingl C, Vasa-Nicotera M, Adenauer V, Lema Cachiguango SJ, Scheer AC, Hausen S, Sedaghat A, Ghanem A, Müller C, Grube E, Nickenig G, Werner N. Aortic regurgitation index defines severity of periprosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol. 2012 Mar 27;59(13):1134-41.

61. Hayashida K, T. Lefevre, B. Chevalier, T. Hovasse, M. Romano, P. Garot, D. Mylotte, J. Uribe, A. Farge, P. Donzeau-Gouge, E. Bouvier, B. Cormier, M.C. Morice, Transfemoral aortic valve implantation new criteria to predict vascular complications, JACC Cardiovasc. Interv. 4 (2011) 851–858.

62. .Moellmann H. Real-world experience using a 2nd generation self-expanding prosthesis: 1-year outcomes of 1000 patients enrolled in the SAVI-TF registry.presented EuroPCR 2017.

63. Meredith Am IT, Walters DL, Dumonteil N, Worthley SG, Tchétché D, Manoharan G, Blackman DJ, Rioufol G, Hildick-Smith D, Whitbourn RJ, Lefèvre T, Lange R, Müller R, Redwood S, Allocco DJ, Dawkins KD. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. J Am Coll Cardiol. 2014 Sep 30;64(13):1339-48.

64. Meredith IT, Walters DL, Dumonteil N, Worthley SG, Tchétché D, Manoharan G, Blackman DJ, Rioufol G, Hildick-Smith D, Whitbourn RJ, Lefèvre T, Lange R, Müller R, Redwood S, Feldman TE, Allocco DJ, Dawkins KD. 1-Year Outcomes With the Fully Repositionable and Retrievable Lotus Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results of the REPRISE II Study. JACC Cardiovasc Interv. 2016 Feb 22;9(4):376-384.

65. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. Eur Heart J 2011;32:2189–214.

66. Nashef SAM, Roques F, Michel P, et al. European System for Cardiac Operative Risk Evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.

67. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–17.

68. Kappetein AP, Head SJ, Gènèreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33:2403–18.

69. Kappetein P, Head SJ, GénéreuxP, Piazza N, van Mieghem N, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rode´ s-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. European Heart Journal (2012) 33, 2403–2418

70. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O: Thirty-Day Results of the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry. A European Registry of Transcatheter Aortic Valve Implantation Using the Edwards SAPIEN Valve. Circulation.2010;122:62-69.

71. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Ihlberg L, Neumann FJ, Tarantini G, Zamarano JL, Vahanian A. SOURCE 3 Registry: Design and 30-Day Results of the European Postapproval Registry of the Latest Generation of the SAPIEN 3 Transcatheter Heart Valve. Circulation. 2017 Mar 21;135(12):1123-1132

72. Iung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, Fajadet J, Leprince P, Leguerrier A, Lièvre M, Prat A, Teiger E, Laskar M, Vahanian A, Gilard M; FRANCE 2 Investigators. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. Heart. 2014 Jul;100(13):1016-23. doi: 10.1136/heartjnl-2013-305314. Epub 2014 Apr 16

73. Barbash IM, Finkelstein A, Barsheshet A, Segev A, Steinvil A, Assali A, et al. Outcomes of Patients at Estimated Low, Intermediate, and High Risk Undergoing Transcatheter Aortic Valve Implantation for Aortic Stenosis. The American Journal of Cardiology 2015 December 15,;116(12):1916-1922.

74. Jabbour RJ, Pagnesi M, Kawamoto H, Tanaka A, Regazzoli D, Mangieri A, et al. Transcatheter aortic valve implantation in intermediate- and low-risk populations: An inevitable progression? International Journal of Cardiology 2016 May 1,;210:35-37.

75. D'Ascenzo F, Ballocca F, Moretti C, Barbanti M, Gasparetto V, Mennuni M, et al. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. J Cardiovasc Med (Hagerstown) 2013 Dec;14(12):894-898.

76. Silaschi M, Conradi L, Seiffert M, Schnabel R, Schon G, Blankenberg S, et al. Predicting Risk in Transcatheter Aortic Valve Implantation: Comparative Analysis of EuroSCORE II and Established Risk Stratification Tools. Thorac Cardiovasc Surg 2015 Sep;63(6):472-478.

77. Wenaweser P, Stortecky S, Schwander S, Heg D, Huber C, Pilgrim T, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. Eur Heart J 2013 Jul;34(25):1894-1905.

78. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. New England Journal of Medicine 2011 June 9,;364(23):2187-2198.

79. Barbanti M, Schiltgen M, Verdoliva S, Bosmans J, Bleiziffer S, Gerckens U, et al. Three-Year Outcomes of Transcatheter Aortic Valve Implantation in Patients With Varying Levels of Surgical Risk (from the CoreValve ADVANCE Study). The American Journal of Cardiology 2016 March 1,;117(5):820-827.

80. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. The New England journal of medicine 2016 Apr 28,;374(17):1609.

81. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010 Mar 16;55(11):1080-1090.

82. Zahn R, Gerckens U, Linke A, Sievert H, Kahlert P, Hambrecht R, et al. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. Am J Cardiol 2013 Jul 15;112(2):272-279.

83. Giordana F, D'Ascenzo F, Nijhoff F, Moretti C, D'Amico M, Biondi Zoccai G, et al. Meta-analysis of predictors of all-cause mortality after transcatheter aortic valve implantation. Am J Cardiol 2014 Nov 1;114(9):1447-1455.

84. Gargiulo G, Capodanno D, Sannino A, Perrino C, Capranzano P, Stabile E, Trimarco B, Tamburino C, Esposito G. Impact of moderate preoperative chronic kidney disease on mortality after transcatheter aortic valve implantation. Int J Cardiol. 2015;189:77-8.

85. Thourani VH, Forcillo J, Beohar N, Doshi D, Parvataneni R, Ayele GM, et al. Impact of Preoperative Chronic Kidney Disease in 2,531 High-Risk and Inoperable Patients Undergoing Transcatheter Aortic Valve Replacement in the PARTNER Trial. Ann Thorac Surg 2016 Oct;102(4):1172-1180.

86. Chakos A, Wilson-Smith A, Arora S, Nguyen TC, Dhoble A, Tarantini G, Thielmann M, Vavalle JP, Wendt D, Yan TD, Tian DH. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. Ann Cardiothorac Surg. 2017 Sep;6(5):432-443.

87. Gargiulo G, Sannino A, Capodanno D, Perrino C, Capranzano P, Barbanti M, Stabile E, Trimarco B, Tamburino C, Esposito G. Impact of postoperative acute kidney injury on clinical outcomes after transcatheter aortic valve implantation: A meta-analysis of 5,971 patients. Catheter Cardiovasc Interv. 2015 Sep;86(3):518-27

88. Barbanti M, Petronio AS, Ettori F, Latib A, Bedogni F, De Marco F, Poli A, Boschetti C, De Carlo M, Fiorina C, Colombo A, Brambilla N, Bruschi G, Martina P, Pandolfi C, Giannini C, Curello S, Sgroi C, Gulino S, Patane` M, Ohno Y, Tamburino C, Attizzani GF, Imme` S, Gentili A, Tamburino C. 5-year outcomes after transcatheter aortic valve implantation with corevalve prosthesis. JACC Cardiovasc Interv 2015;8:1084–1091.

89. Gargiulo G, Sannino A, Capodanno D, et al. Impact of postoperative acute kidney injury on clinical outcomes after transcatheter aortic valve implantation: a meta-analysis of 5,971 patients. Catheter Cardiovasc Interv 2015;86:518–27.

90. Xiong TY, Liao YB, Zhao ZG, Xu YN, Wei X, Zuo ZL, et al. Causes of Death Following Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2015 Sep 21;4(9):e002096

91. Gargiulo G, Capodanno D, Sannino A, Perrino C, Capranzano P, Stabile E, Trimarco B, Tamburino C, Esposito G.. Impact of postoperative acute kidney injury on clinical outcomes after transcatheter aortic valve implantation: a meta-analysis of 5,971 patients. Catheter Cardiovasc Interv 2015;86: 518–27.

92. Franzone A, Stortecky S, Pilgrim T, Asami M, Lanz J, Heg D, Langhammer B, Piccolo R, Lee JKT, Praz F, Räber L, Valgimigli M, Roost E, Windecker S. Incidence and impact of renal dysfunction on clinical outcomes after transcatheter aortic valve implantation. Int J Cardiol. 2017 Oct 3. pii: S0167-5273(17)33885-8.

93. Van Mieghem NM, van der Boon RM, Nuis RJ, et al. Cause of death after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2014;83:E277-82.

94. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome(SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011;124:425-33

95. Saia F, Latib A, Ciuca C, Gasparetto V, Napodano M, Sticchi A, Anderlucci L, Marrozzini C, Naganuma T, Alfieri O, Facchin M, Hoxha B, Moretti C, Marzocchi A, Colombo A, Tarantini G. Causes and timing of death during long-term follow-up after transcatheter aortic valve replacement. Am Heart J. 2014 Nov;168(5):798-806.

96. Tarantini G, Gasparetto V, Napodano M, Frigo AC, Fraccaro C, Buja P, D'Onofrio A, D'Amico G, Barioli A, Baritussio A, Facchin M, Dariol G, Isabella G, Gerosa G, Iliceto S. Transcatheter aortic valve implantation and bleeding: Focus on Valve Academic Research Consortium-2. Int J Cardiol. 2013 Oct 12;168(5):5001-3.

97. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De Larochelliere R, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodes-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 2009;53:1883-1891.

98. Clavel MA, Rodes-Cabau J, Dumont E, Bagur R, Bergeron S, De Larochelliere R, Doyle D, Larose E, Dumesnil JG, Pibarot P. Validation and characterization of transcatheter aortic valve effective orifice area measured by Doppler echocardiography. JACC Cardiovasc Imaging. 2011;4:1053-1062.

99. Daubert MA, Weissman NJ, Hahn RT, Pibarot P, Parvataneni R, Mack MJ, Svensson LG, Gopal D, Kapadia S, Siegel RJ, Kodali SK, Szeto WY, Makkar R, Leon MB, Douglas PS. Long-term valve performance of TAVR and SAVR: a report from the PARTNER I trial. JACC Cardiovasc Imaging 2016; doi: 10.1016/j.jcmg.2016.11.004.

100. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards Perimount Valve in aortic position. Ann Thorac Surg 2015;99:831–7.

101. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, Kleiman NS, Coselli JS, Gleason TG, Lee JS, Hermiller JB, Heiser J, Merhi W, Zorn GL, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J, Resar J, Aharonian V, Pfeffer T, Oh JK, Qiao H, Adams DH, Popma JJ: CoreValve US Clinical Investigators. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2565–2574.

102. Rahimtoola SH. Choice of prosthetic heart valve in adults an update. J Am Coll Cardiol 2010;55:2413–2426.

103. Mylotte D, Andalib A, The´riault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N. Transcatheter heart valve failure: a systematic review. Eur Heart J 2015;36:1306–1327.

104. Webb JG, Dvir D. Is transcatheter aortic valve replacement a durable therapeutic strategy? JACC Cardiovasc Interv 2015;8:1092–1094.