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Beyond the ten-year horizon: long-term outcome of patients undergoing TAVR with first-generation devices

Sarah Nadja Lochbihler

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Prüfer*innen der Dissertation:

1. Priv.-Doz. Dr. Keti Vitanova
2. Priv.-Doz. Dr. Teresa Trenkwalder

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Affidavit

I, hereby declare that the dissertation titled “Beyond the ten-year horizon: long-term outcome of patients undergoing TAVR with first-generation devices” prepared under the guidance and supervision of PD Dr. med. Keti Vitanova at the German Heart Center Munich and submitted to the responsible department of Medicine of TUM is my own, original work undertaken in partial fulfillment of the requirements for the doctoral degree. I have made no use of sources, materials or assistance other than those specified in § 6 (6) and (7), clause 2.

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Parts of this dissertation (as an original scientific manuscript) was published in the journal Archives of Cardiovascular Diseases.

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For my mother

Abstract

Transcatheter aortic valve replacement (TAVR) is an established treatment for high- or intermediate risk patients with symptomatic aortic valve stenosis. As more low-risk patients are being treated, transcatheter heart valve (THV) durability is gaining importance. Data on structural valve deterioration (SVD) beyond 8 years after TAVR is limited.

The objective of this study was to evaluate longterm outcomes of TAVR in high-risk patients with a follow-up of over 10 years. The focus was on survival, SVD and bioprosthetic valve failure (BVF) according to the 2017 EAPCI/ESC/EACTS definitions.

The study group consisted of patients operated consecutively at the German Heart Center Munich with a follow-up of at least 10 years (n=510). Therefore, echocardiographic data was analyzed for the cumulative incidence for SVD and BVF with ROC-analysis for predictor assessment.

Mean age was 79.6±6.7 years with a mean log EuroScore of 19.8±12.7%. Immediate procedural mortality was 2.9% and 30-day mortality was 7.8%. Kaplan-Meier-estimated survival at 10- and 12-years was 10.3±1.5% and 2.6±1.4%, respectively. At 12 years, the cumulative incidence of SVD and BVF, for the total patient population was 5.1% and 9.8%, respectively. There was a significant difference in SVD and BVF rate depending on the valve type (SVD: Sapien 9.0% vs. CoreValve 2.2% at 11 years, p=0.001; BVF: Sapien 13.9% vs. CoreValve 6.9% at 11 years, p=0.021).

Survival was, as to be expected low. Structural valve deterioration and bioprosthetic valve failure of early THV at 12-years was low. The identified differences between valve types must be validated using current generation devices in younger patients.

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1. Introduction

1.1 Aortic Stenosis

Aortic stenosis (AS) is the most common aquired valvular heart disease in the western world. Higher life expectancy might be the cause for higher prevalence amongst western populations nowadays (1).

AS is a degeneration of the aortic valve provoked by gradual fibrotic scarring and calcification of the leaflets which leads to movement restriction and lastly to valve obstruction. Advanced age, genetic predisposition and clinical risk factors contribute to the deterioration and consequently, dysfunction of the valve. Hyperlipidemia, arterial hypertension, diabetes and smoking are such risk factors that accelerate the stenotic process. Therefore, calcification can be accompanied by an inflammatory process and lipid accumulation. This is the most usual form of AS in the western world and is called calcific aortic stenosis. It is more prevalent in people born with a bicuspid aortic valve because of its anatomical features leading to unphysiological flow and can also be found as a subsequent damage of rheumatic fever (Figure 1) (2,3).

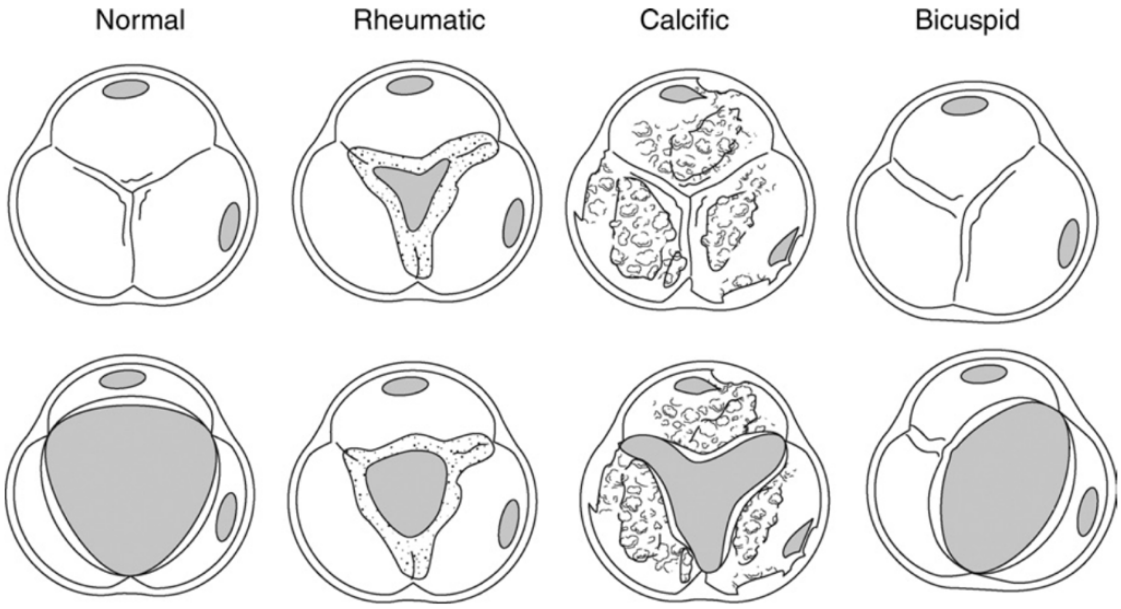


Figure 1 Aortic stenosis aetiology and its morphology of rheumatic, calcific and bicuspid AS (Adapted from C.Otto, Principles of Echhocardiography, 2007) (4)

The pathophysiological process emerges from the tearing stress that the endothelium experiences while opening and closing. Eventually, small damages are caused, which thicken after healing. Inflammatory cells and lipids can be found in the thickened endothelium at this early stenotic stage. Subsequently, a remodeling and fibrotic process will take place by the activation of pro-inflammatory and pro-fibrotic cytokines which predisposes the tissue for calcification. In sever stenotic cases the complete calcification and therefore immobility of the aortic valve leaflets occurs. It is generated by osteoblast and osteoclast activity (5).

Symptoms vary and depend on the severity of AS and the presence of comorbidities. Mild and moderate AS is usually asymptomatic and mostly diagnosed due to other heart conditions. However, also severe forms can be asymptomatic over a long course. Still, predominantly symptoms occur in severe stages and after symptom-onset, patients have a mean survival of 2-3years (6). The chart in Figure 2 was initially presented by Ross and Braunwald in 1968, depicting the survival rate after symptom-onset (gray curve). As the average age of death of the general population has increased since then, current studies have shown this curve to still be relevant, merely displaying a later onset, between the seventh and nineth decade. As a result Bonow and Greenland modified the curve, which can be seen in black (7).

The most common symptoms are: dyspnea on exertion and a rapid commencement of fatigue. Dyspnea is mostly owed to LV hypertrophy and/or systolic dysfunction. Furthermore, angina might appear due to the lack of oxygen as a result of the lower cardiac output. In later stages exercise can lead to syncope and lastly to heart failure (8).

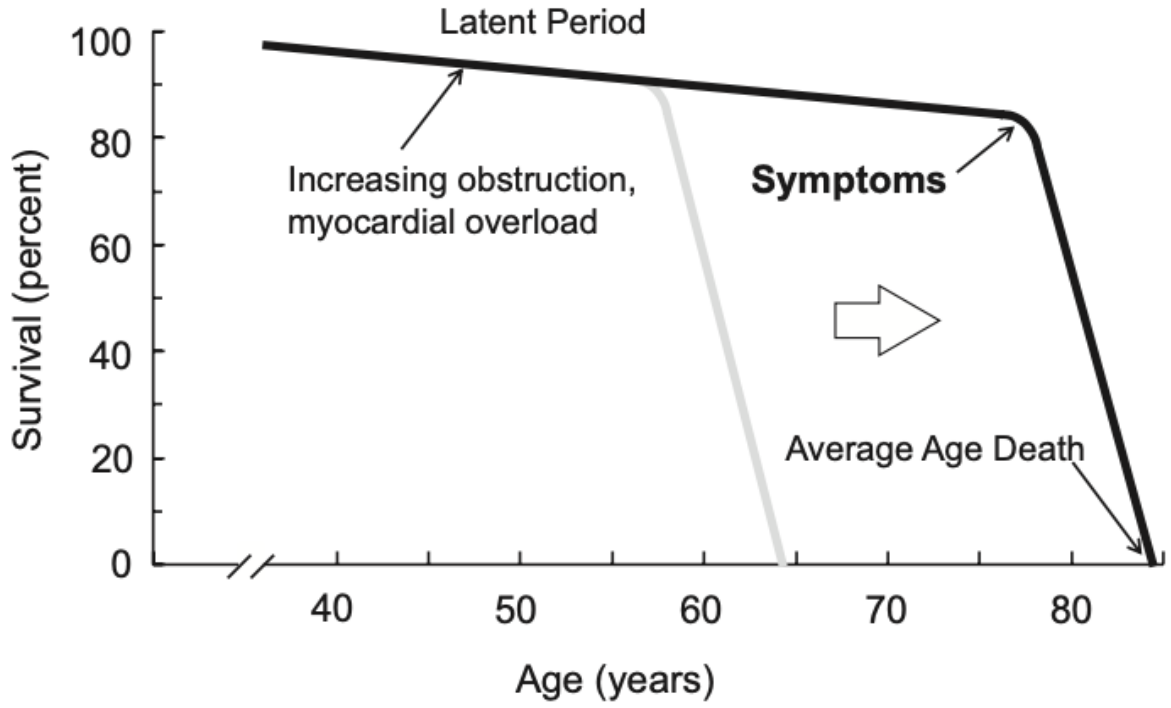


Figure 2 Aortic stenosis symptomatology progression and death in course of lifetime by Ross and Braunwald modified by Bonow and Greenland (7)

1.2 Diagnosis

1.2.1 Clinical criteria

AS patients may present with typical cardiac symptoms such as shortness of breath, cyanosis, angina and oedema accompanied by the typical heart murmur (9). Symptoms can be categorized and classified. Since 1921, the New York Heart Association (NYHA) classification is a worldwide known and applied diagnostic tool for symptom categorization of heart failure (10). It grades the severity of heart insufficiency depending on physical performance abilities and dyspnea of an individual. It ranges from NYHA I to NYHA IV, classifying patients from asymptomatic to severely symptomatic (see Table 1). Thus, NYHA is very subjective, has a low reproductivity and is very dependent on the momentary status of the patient. Nevertheless, it is an important tool in daily practice and it's commonly applied in clinical trials (11).

Class	Definition
NYHA I	Able to carry out all kinds of activities of daily life. No dyspnea, fatigue, palpitation or angina upon physical activity or rest.
NYHA II	Able to carry on slightly to moderately reduced activity. Dyspnea, fatigue, palpitation or angina will appear at stronger physical activity without complaints at rest (e.g. taking the stairs).
NYHA III	Able to carry out only greatly diminished activity. Dyspnea, fatigue, palpitation or angina appear at light physical activity without complaints at rest (e.g. going for a walk).
NYHA IV	Unable to carry out any activity without distress. Symptoms may appear at rest.

Table 1 NYHA classification and definition (10)

1.2.2 Imaging

Echocardiography is the gold-standard for the diagnosis and grading of valvular heart disease. Either transesophageal or transthoracic echocardiography can be used. Doppler techniques are used for the assessment of AS severity (12). Quantitative data such as aortic jet velocity, mean gradient and aortic valve area are the most appropriate measurements for the classification. Values and their classification are listed in Table 2. Additional qualitative information can be obtained, such as left ventricular wall thickness and function, concomitant VHDs and pathologies of the aorta. Nevertheless, single values should be interpreted with caution. The classification and diagnosis of AS should be based on a global assessment of clinical symptoms and imaging data (4,13).

	Mild	**Moderate**	**Severe**
Peak aortic jet velocity (Vmax)	2,6 – 2,9 m/s	3 – 4 m/s	> 4
Mean transvalvular pressure gradient (PG)	< 20 mmHg	20-40 mmHg	> 40 mmHg
Aortic valve area (AVA)	> 1,5 cm^2	1 - 1,5 cm^2	≤ 1cm^2

Table 2 Quantitative data for the grading of AS severity according to the recommendations of the EAC (13,14)

1.3 Treatment options

1.3.1 Medical treatment

Up until now, there is no available medical treatment, that is able to stop or reverse the progression of AS. As mentioned and seen in Figure 2, after onset of symptoms, life-expectancy strongly decreases without an operation. Medical treatment aims at reduction of cardiovascular risk factors and improvement of heart failure symptoms. Applied drugs include statins and antihypertensive drugs. Initially statins were believed to reduce AS or at least reduce its progression due to the similarities to arthrosclerosis. Multiple randomized trials did not support this theory (15–17). Treatment with antihypertensive drugs can have a benefit on hypertensive patients with AS. It has a positive effect on left ventricular hypertrophy, allowing for a degree of remodeling and can lower the risk of cardiac failure after aortic valve replacement (AVR) (18).

1.3.2 Aortic valve replacement (AVR)

Aortic valve replacement (AVR) or surgical aortic replacement (SAVR) was first performed in 1960 by Dwight Harken in annular position by using a mechanical prosthesis called the Harken-Soroff valve (19). Over the next decades, multiple valves, mechanical and biological were developed (see Image 1). Due to good results and contrary to medical treatment alone, prolongation of survival, SAVR quickly established itself as the gold standard for the treatment of aortic valve stenosis. Currently, SAVR is preformed via a minimally-invasive incision or via a median sternotomy. The patient is put on cardio-pulmonary bypass (the heart-lung-machine). The venous cannula is placed in the right atrium in order to drain the blood into the heart-lung-machine, where the blood is oxygenated. The oxygenated blood is then returned to the patient via the arterial cannula, which is placed directly in the aorta. Cannulation can, under certain circumstances also be placed in the respective femoral vessels. Under cardioplegic cardiac arrest, the aorta is opened, and the aortic valve directly excised and replaced. SAVR comes with a certain risk for complications and death in elderly patients as well as those with comorbidities (20). Up until the introduction of TAVR it was the only possibility to replace the aortic valve. As this dissertation focuses in TAVR, AVR will not be discussed in more detail.

Image 1 Evolution of aortic heart valve technology over time (21)

1.3.3 Transcatheter aortic valve replacement (TAVR)

Transcatheter aortic valve replacement (TAVR) is the minimal-invasive alternative to surgical replacement of the aortic valve. Via a vessel or alternative access route, a prosthetic valve, which is folded into a catheter is implanted in aortic valve position, sparing the patient open-heart surgery. In the last years TAVR has become the gold-standard for the treatment of AS in elderly patients with severe symptomatic AS with an intermediate and high risk for surgery. It shows superior outcomes compared to medical treatment and equal or superior results to AVR (22). Apart from lower in-hospital mortality than AVR it has also multiple lower complication rates (23). Overall, TAVR results in lower mortality, lower periprocedural myocardial infarction, less bleeding complications, less renal insufficiency, less atrial fibrillation and less incidence of stroke. However, AVR leads to less paravalvular leakages, less vascular complications and to a lower rate of permanent pacemaker implantations (22). Due to the positive results of various trials, TAVR has become an established therapy for certain patient groups and was incorporated in the guidelines for AS treatment. Details and facts on TAVR will be specified and mentioned later in this dissertation.

1.4 Guidelines

Treatment of symptomatic, and asymptomatic AS is based on qualitative and quantitative diagnostic data, clinical status of the patient and existing comorbidities. An interdisciplinary heart team is recommended for the decision-making process in these patients. The heart team should consist of a cardiologist, a cardiac surgeon and an anesthetist. It should consider age, risk scores (eg. logistic EuroScore, EuroScore II or STS Score), additional anatomical and physiological criteria and the wish of the patient to provide the most adequate treatment option, accomplishing it with few complications and a high success rate (24). The latest guidelines of the 2021 ESC/EACTS list specific indications for interventions and recommendations for the choice of intervention mode as a guide for practitioners in their decision-making (Figure 3).

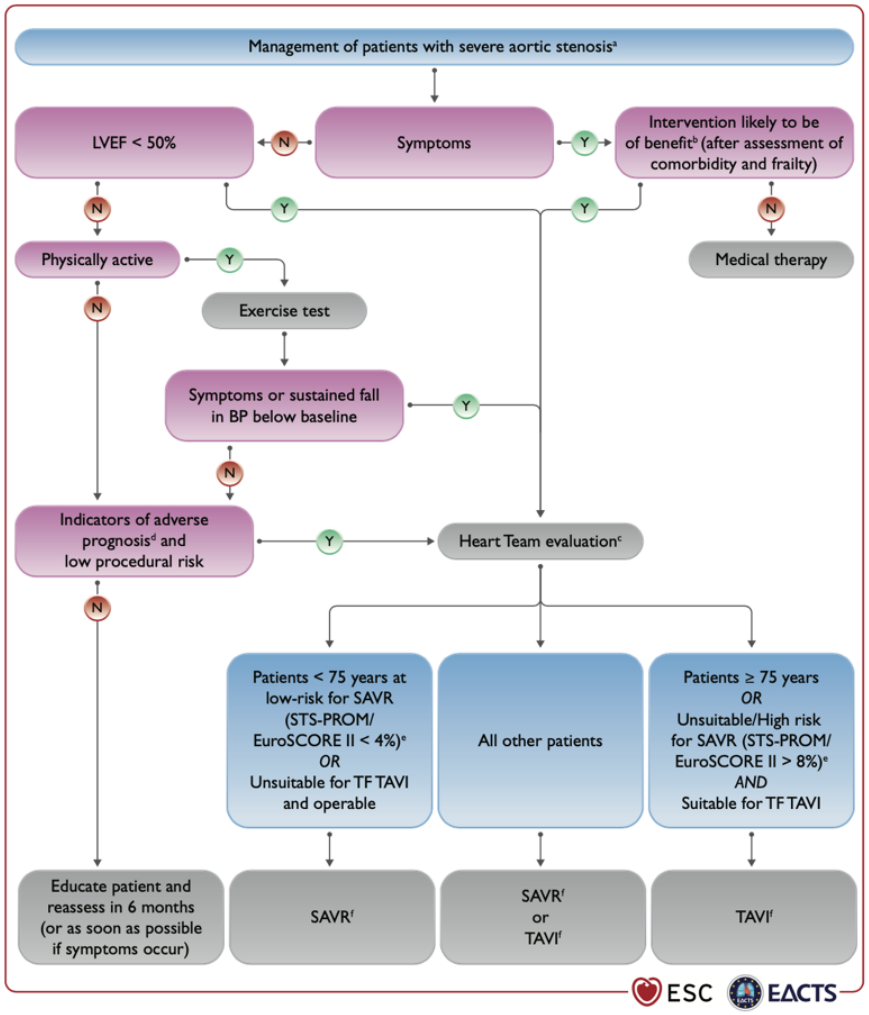


Figure 3 Management of severe aortic stenosis according to the 2021 ESC/EACTS guidelines (12)

1.4.1 Symptomatic aortic stenosis

Surgical treatment is suggested in symptomatic patients with severe, high-gradient and severe low-flow, low-gradient AS with reduced ejection. Symptomatic low-flow, low-gradient AS with normal ejection fraction with positive confirmation of severe aortic stenosis is also taken into account to be an indication for intervention (Figure 4) (12).

A) Symptomatic aortic stenosis	Class[b]	Level[c]
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1.0 cm^2 (or ≤0.6 cm^2/m^2)].[235,236]	I	B
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction (<50%), and evidence of flow (contractile) reserve.[32,237]	I	B
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation that the aortic stenosis is severe[d] (*Figure 3*).	IIa	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient severe aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival >1 year.	III	C

Figure 4 Choice of intervention in symptomatic aortic stenosis patients according to the 2021 ESC/EACTS (12)

1.4.2 Asymptomatic aortic stenosis

Intervention is recommended in patients with severe aortic stenosis and reduced left ventricular function (<50%) or asymptomatic patients with severe stenosis who show symptoms under exercise testing (Figure 5) (12).

B) Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.[9,238,239]	**I**	**B**
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	**I**	**C**
Intervention should be considered in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <55%) without another cause.[9,240,241]	**IIa**	**B**
Intervention should be considered in asymptomatic patients with severe aortic stenosis and a sustained fall in BP (>20 mmHg) during exercise testing.	**IIa**	**C**
Intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe aortic stenosis (mean gradient ≥60 mmHg or V_{max} >5 m/s).[9,242] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[164,189,243] • Markedly elevated BNP levels (>3× age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.[163,171]	**IIa**	**B**

Figure 5 Choice of intervention in asymptomatic aortic stenosis patients according to the 2021 ESC/EACTS (12)

1.4.3 Mode of intervention

Mode of intervention should be selected carefully and by the means of a heart team at a specialized heart center. Currently, AVR is recommended in younger patients (<75years) with a low surgical risk, without contraindications for surgery. TAVR is recommended in older patients(>75years) ineligible for surgery or at a high surgical risk (STS PROM/EuroSCORE II >8%). In patients with an intermediate surgical risk the guidelines recommend a heart-team decision with the preference for TAVR in elderly patients (Figure 6) (12).

C) Mode of intervention		
Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach.	I	C
The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I	C
SAVR is recommended in younger patients who are low risk for surgery (<75 years[e] and STS-PROM/EuroSCORE II <4%)[e,f], or in patients who are operable and unsuitable for transfemoral TAVI.[244]	I	B
TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II[f] >8%) or unsuitable for surgery.[197–206,245]	I	A
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.[202–205,207,209,210,212 f,g]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients and (if feasible) in those with severe aortic stenosis who require urgent high-risk NCS (*Figure 11*).	IIb	C

Figure 6 Mode of intervention in patients with aortic stenosis according to the 2021 ESC/EACTS (12)

1.5 TAVR

1.5.1 Historical background

The first prosthetic aortic valves were implanted in humans in 1952 after establishment of the heart-lung-machine (25). As conventional aortic valve replacement involves a thoracotomy and the use of the heart-lung-machine, the procedure posed a risk, in particular for elderly patients and those with comorbidities. As such, the wish for a less-invasive treatment possibility was great. Percutaneous catheter-based solutions for the replacement of heart valves were first designed and investigated in the 1960's. Image 2 illustrates a prototype of a cone-shaped valve which is mounted on a gauge 5F cardiac catheter (26). In the early 1990's the first animal study was published in which balloon-expandable aortic stent-valves were successfully implanted in pigs via a vascular access. Porcine aortic valves attached to stainless steel wires and a deflated balloon were used (Image 3). It proved the feasibility of the transluminal approach and gave hope for a future implementation in humans (25).

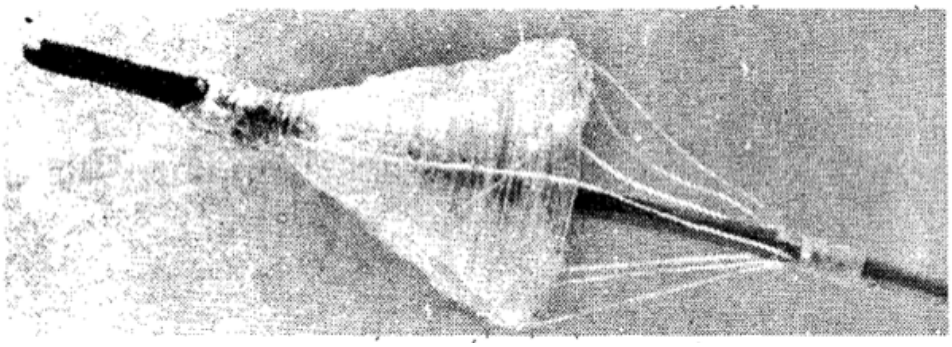


Image 2 Cone-shaped valve mounted on a cardiac catheter by U.S.Catheter Co., Glenns Falls, New York, 1965 (26)

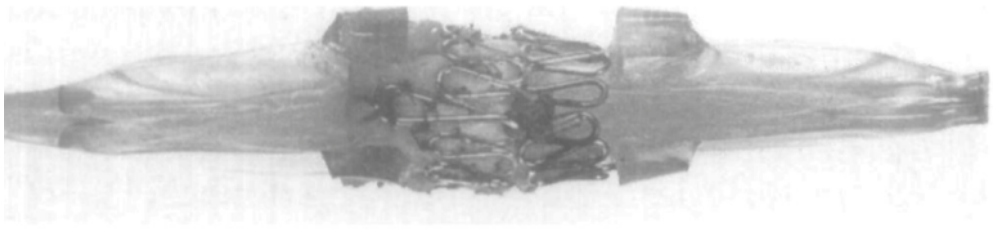


Image 3 Porcine aortic valves and stainless steel wires mounted on a deflated balloon designed for catheter implantation in closed pig chests in 1992 (25)

In 2002 Alan Cribier and his surgical team performed the first TAVR in a human with terminal heart insufficiency due to very severely calcified bicuspid aortic valve, with multiple comorbidities. Cribier implanted a balloon-expandable made of 3 bovine leaflets in a stainless-steel stent. The approach was antegrade via the right femoral vein, crossing the atrial septum and the mitral valve. The intervention was successful, nevertheless the patient died within 17 weeks as result of his comorbidities, not allowing for further follow-up (27). This balloon-expandable model was a precursor model of the Sapien Valve by Edwards (Image 4 (A)) which was subsequently modified as the Edwards XT (Image 4 (B)) changing the stainless steel to a thinner, more flexible and stronger chrome cobalt alloy frame (28).

A few years later, in 2005, the first self-expanding valve prosthesis fabricated by Medtronic (Image 4 (C)) was implanted in a human. Successful implantation and clinical outcome proved the self-expanding deployment to be effective (29).

Serial production and further development of both aortic transcatheter valves enabled a quick spread of transcatheter aortic valve replacement. Starting in 2007, several feasibility trials, larger clinical registries and randomized trials studied and evaluated the outcome of TAVR. At the German Heart Center Munich TAVR was implemented for the treatment of high-risk patients with severe symptomatic AS as early as 2007.

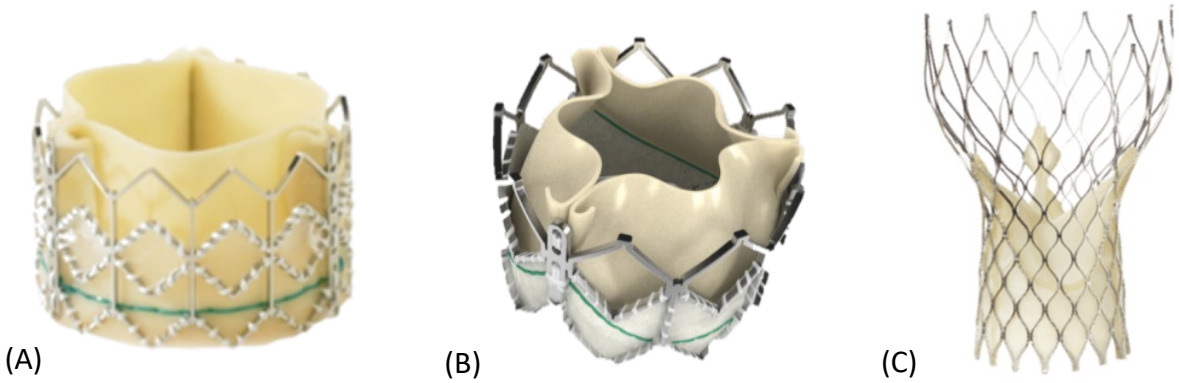


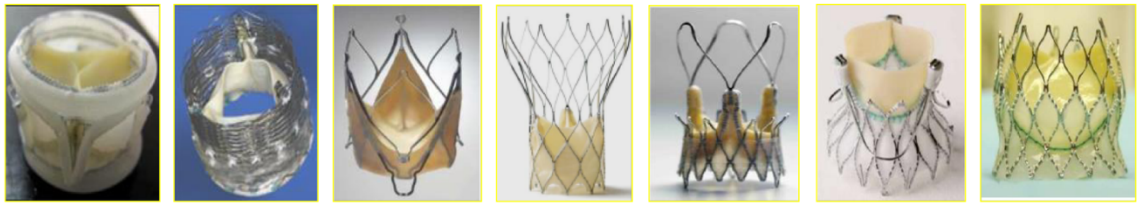
Image 4 Transcatheter heart valve types. Balloon expandable Edwards Sapien (A), Edwards XT Sapien (B), and self-expandable CoreValve (C) (28)

1.5.2 Access routes

The choice of the catheter access route is highly dependent on the patient's given condition and anatomical structures. Four vascular accesses are possible: via the femoral artery (transfemoral, TF), subclavian also axillar artery (transsubclavian, TS), the ascending part of the aorta (transaortic or direct aortic access, DAA) and through the common carotid artery (transcarotid or common carotid access, CCA). Various anatomical specifications can be a contraindication for a transvascular acces route: a vessel diameter less than 5.5mm, partially thrombosed aneurysms, severe kinking of calcified vessels, or status post vascular surgical (such as bypass, stents, vascular prosthesis or dissections). In such cases there is the possibility to implant the valve via a transapical (TA) approach. Careful preoperative assessment of CT images is mandatory to evaluate the possible access routes. Knowing the optimal access route for the patient, a compatible valve system should be chosen (30).

1.5.3 Valve types

Transcatheter heart valves (THV) have experienced a rapid and strong development from the first-in-man models up to the valves used today. These two initially implanted valves differed most prominently in their method of deployment, which, up to date, has not been changed. The Edwards valve is a balloon-expandable valve, meaning the stent frame of the THV is expanded by inflating a balloon. On the other hand, the Medtronic valve is a self-expandable valve, where the properties of the metal frame lead to an expansion of the stent under body temperature. Both companies refined their valves by changing the stent frame or leaflet material, decreasing the sheath size, and offering bigger valve sizes. At the same time, various companies also developed THVs with different valve designs and various deployment techniques (Figure 7). Various valves and their characteristics are mentioned in Table 3. Over time, not all companies were able to prevail (28,31,32).



Direct Flow Direct Flow Medical	**Lotus** Boston Scentific	**Jena Valve** Jena Valve Technologies	**Portico** St. Jude Medical	**Acurate** Symetis	**Engager** Medtronic	**Centera** Edwards Lifesciences

Figure 7 Models of different aortic bioprostheses and manufacturers (31)

	COREVALVE / EVOLUT/ EVOLUT R	SAPIEN / SAPIEN XT/ SAPIEN 3	ENGAGER	LOTUS	DIRECT FLOW	SYMETIS ACURATE NEO 2	JENAVALVE
MANUFACTURER	Medtronic	Edwards	Medtronic	Boston Scientific	Direct Flow Medical	Boston Scientific	Jena Valve Inc.
DEPLOYMENT	Self-Expanding	Balloon-Expanding	Self-Expanding	Mechanical Expansion	Inflatable	Self-Expanding	Self-Expanding
LEAFLETS	Bovine / Porcine Pericardium	Bovine Pericardium	Bovine Pericardium	Bovine Pericardium	Bovine Pericardium	Porcine Pericardium	Porcine Aortic root
SUPPORT STRUCTURE	Nitinol	Stainless steel / Cobalt chromium	Nitinol	Nitinol	Inflatable Polyester	Nitinol	Nitinol
ACCESS ROUTE	All trans-vascular	All trans-vascular + TA	TA	All trans-vascular	TF	TF,TA	TA
AVAILABILITY	Yes	Yes	No	No	No	Yes	Yes

Table 3 Examples of TAVR prosthesis, their manufacturer, characteristics, access routes and availability on the market (28,31–33)

1.6 Previous TAVR outcomes

1.6.1 High risk

High-risk populations were the first being sought most suitable to undergo TAVR and therefore the first study group in randomized clinical trials (RCT). Two large randomized clinical trials were initiated with first-generation devices: The Placement of AoRTic TraNscathethER Valve Trial 1 (The PARTNER Trial) with the Sapien Valve by Edwards and the CoreValve High Risk Trial by Medtronic. High surgical risk is defined by an STS-PROM ≥8. The main objective of both the PARTNER (PARTNER 1A cohort) and the CoreValve High-Risk Study was to compare TAVR to AVR in patients at a high-surgical risk. In a subgroup of the PARTNER Trial, TAVR was compared to conservative medical treatment in patients seen to be inoperable (PARTNER I B). Results showed slight higher mortality after 30 days but lastly better survival rates after 1 and 2 years after TAVR compared to the control (34). These results proved, that TAVR was better than medical treatment alone. The PARTNER 1A (mean age 84 years and STS-Score >8%) trial showed noninferiority of TAVR compared to AVR in regard to mortality at 1 year of follow-up (35). Unvarying, the 5-year outcomes show no significant difference in mortality, stroke, or need for re-hospitalization compared to AVR. Functional outcomes in terms of hemodynamics were similar with no structural deterioration. However, paravalvular regurgitation was associated with higher mortality in patients undergoing TAVR (36). In the CoreValve High Risk Trial (mean age 83years and STS-Score >7%) TAVR reached higher survival rates at 1 year and 2 years compared to AVR (37,38). At 5 years all-cause and cardiovascular mortality did not differ between TAVR and AVR, but aortic valve regurgitation was worse and reinterventions were more common in TAVR patients (39). Both trials demonstrated, that TAVR was a feasible alternative to medical treatment and surgery for the treatment of AS in patients at a high-surgical risk.

1.6.2 Intermediate risk

As non-inferior results to AVR were achieved in high-risk patients, intermediate-risk as well as low-risk populations were the subject of further studies, with newer generation THVs. Intermediate-risk is defined by the STS-PROM between 4-8% (40). The intermediate risk trials PARTNER-2A by Edwards and the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial by Medtronic were initiated. Enrolled patients in the PARTNER-

2A study had a mean age of 81,5 years and a mean STS-score of 5,8%. Comparable results in all-cause mortality and disabling stroke were found after a 5-year follow-up in the PARTNER 2 trial. In the subgroup of patients with a transfemoral approach, superior results were achieved. Patients undergoing transthoracic TAVR had similar or higher complication rates compared to AVR (41). SURTAVI resulted in a mean age of 79,8 years and a mean STS-Score of 4,5%. 2-year follow-up resulted in composite end points of death from any cause or disabling stroke non-inferior compared to AVR. Moreover, no structural valve deterioration was noted and different adverse events were related to either procedure (42). Overall, these two large, randomized trials demonstrated similar or even superior outcomes for transfemoral TAVR compared to AVR in intermediate risk patients.

1.6.3 Low risk

Following the data from the intermediate-risk trials, PARTNER 3 by Edwards and Evolut Low Risk Trial by Medtronic investigated the success of TAVR compared to AVR in patients with a low surgical risk (STS-Score <4% and a mean age of 73years and 74years, respectively). PARTNER 3 showed significantly superior results in regard to the composite endpoint of mortality, stroke and rehospitalization at 1 year for TAVR versus surgical valve replacement (43). Comparable low rates of death and disabling stroke at 30 days, 12 and 24 months between TAVR and AVR was presented in the Evolut Low Risk Trial (44).

The Nordic Aortic Valve Intervention Trial (NOTION), an all-comers trial with a low-risk population enrolling patients > 70 resulting in a mean age of 79 with a mean STS-score of 3,0%. It demonstrated comparable 1-year results regarding death, stroke and MI for both transcatheter aortic valve replacement and aortic valve replacement (45). At 6 years, mortality between both study groups remained similar. Interestingly, structural valve deterioration (SVD) was higher in AVR 24,0% than in TAVR 4,8%, whereas comparable low rates of bioprosthetic valve failure (BVF) were achieved in both (46).

Overall, a risk specific metanalysis concluded a lower risk of all-cause mortality and disabled stroke at 12 months in low-risk TAVR patients compared to AVR (47).

1.6.4 Long-term

Long-term results are of great importance for every kind of intervention in the field of medicine. It can help with the selection and prediction of a treatment and its outcome. Data from TAVR cohorts, such as the PARTNER trial, the CoreValve High Risk trial and smaller studies up to 5 years have shown promising results (39,48–50). Deutsch and Erlebach have published such follow-up data from the German Heart Center in 2018 gathering information beyond the 5 five year horizon (49). Data beyond 8 years is scarce, nevertheless favorable results in terms of SVD and BVF are published. Here the cumulative incidence at 8 years for SVD was less than 4% and BVF less than 5% (51,52). One study reports data with a follow-up up to 10 years after TAVR reporting low rates of SVD and BVF (53). High overall mortality rates due to advanced age and comorbidities in these high-risk study populations makes a follow-up challenging. Nonetheless, SVD and BVF seemed to be low in studies between 5 to 10 years of follow-up based on the new classification of the ESC/EACTS (54). The 6-year NOTION follow-up even resulted in significantly lower SVD in TAVR compared to surgical AVR (46). Up to date, data beyond 10-years is not available for TAVR cohorts.

2. Objectives

As the treated patient population becomes younger, the question of durability becomes more pressing. From surgical aortic valves, it is known, that biological prosthesis start to degenerate after approximately 15 years (55). Data beyond 10 years is currently not available for TAVR patients.

Aim of this study is the determination of long-term durability (beyond a 10-year follow-up) and longevity of TAVR first generation devices in high-risk patients. Primary endpoints are structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) according to the 2017 EAPCI,EAC and EACTS definitions (56). Secondary endpoints are procedural and intra-hospital complications according to Valve Academic Research Consortium-3 (VARC-3) definitions (57), all-cause mortality and specifically cardiovascular mortality.

3. Materials and methods

3.1 Study design and patient population

This is a single-center retrospective evaluation of prospectively collected data of consecutive patients undergoing TAVR from 06/2007 – 12/2010 at the Department of Cardiovascular Surgery of the German Heart Center Munich. Included were those with a minimum follow-up of 10 years. Patients who were planned for TAVR but did not receive TAVR due to procedural complications were excluded. Patients who underwent TAVR but required conversion to AVR during the index procedure were excluded from long-term structural valve deterioration analysis. The study complied with the Declaration of Helsinki and was approved by the local ethics committee of the Technical University of Munich (Number 60/21-S).

3.2 Data and definitions

All baseline demographic data, as well as procedural characteristics and in-hospital complications were collected from the TAVR-database. Baseline data included age, gender, height and weight, NYHA classification, previous medical conditions such as myocardial infarction (MI), atrial fibrillation (AF), stroke, coronary artery bypass graft (CABG), coronary artery disease (CAD), COPD and peripheral artery disease. Surgical risk scores included the logistic European System for Cardiac Operative Risk Evaluation I (log EuroSCORE I) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) which give an estimation for mortality after 30 days for cardiac surgery patients, respecting age, gender and comorbidities such as chronic lung disease, peripheral vascular disease, endocarditis and others (58). Moreover, important cardiovascular risk factors such as diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking and the glomerular filtration rate (GFR) were recorded. Lastly, the preprocedural echocardiographic data: left ventricular ejection fraction (in %), aortic valve area (in cm2), mean aortic gradient and maximal aortic gradient (in mmHg), aortic (AR), mitral (MR) and tricuspid regurgitation (TR) and pulmonary hypertension were documented.

Procedural data and intraoperative data included TAVR date, THV brand and size, access route (transfemoral, transapical and other), intubation, procedural time, pre- and post- dilatation and balloon size. Procedural complications such as annulus rupture, tamponade, coronary

obstruction, reanimation (CPR or ECMO), conversion and immediate procedural mortality were recorded.

In-hospital complications included events that occurred within the first 30 days after the intervention or within the exact duration of hospitalization if the initial hospital stay was longer than 30 days. Complication rates, such as procedural mortality, MI, bleeding and vascular complications and device success were classified according to the VARC-3 criteria (57) Due to the assessment requirements in VARC-3, cerebrovascular insults (CVI) were reported according to VARC-2 criteria (59). Postprocedural echocardiographic data included left ventricular ejection fraction (in %), aortic valve area (in cm2), mean and maximal aortic gradient (in mmHg), AR, MR and TR and 30 days.

Structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) were defined according to the 2017 EAPCI/ESC/EACTS consensus statement on standardized definitions of structural deterioration and valve failure (Figure 8). Severe SVD was defined as a mean transprosthetic gradient ≥40 mmHg, mean transprosthetic gradient ≥20 mmHg change from baseline, or severe intra-prosthetic aortic regurgitation (new or worsening) from baseline. The definition of bioprosthetic valve failure was modified to accommodate for the lack of information about the exact cause of death in this patient series. Thus, it was defined as the aortic valve reintervention rate and severe SVD (56).

Standardized follow-up data was obtained at discharge, six months and from there on yearly. Data was acquired from outpatient visits, referred cardiologists, collected external medical reports, survey sheets and telephone calls. Throughout, echocardiographic and other essential data were collected, including adverse events, valve reinterventions, NYHA class, vitality and in case of death, mortality cause and date. Having the cause of death, we could classify between cardiovascular and non-cardiovascular mortality according to the VARC-3 criteria. In the event of a re-operation of the valve we specified which type of operation (AVR or TAVR), the date of procedure and the reason for the intervention. Follow-up census was October 2020.

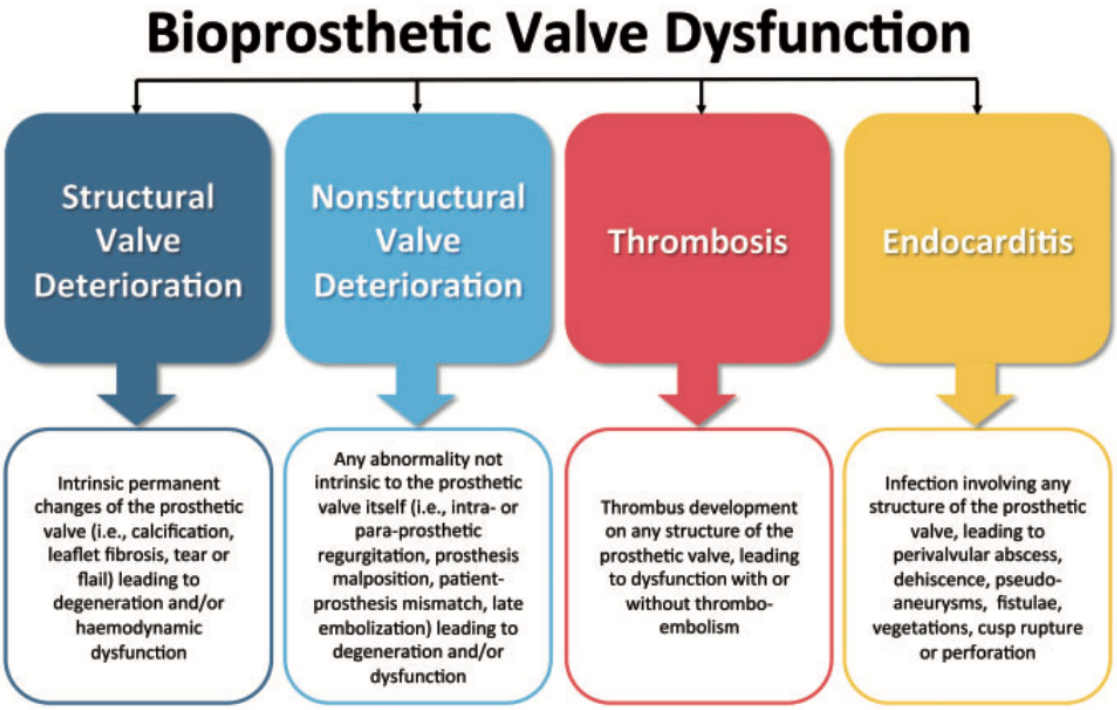


Figure 8 Causes of Bioprosthetic Valve Dysfunction and Structural Valve Deterioration according to the 2017 EAPCI/ESC/EACTS consensus statement on standardized definitions of structural deterioration and valve failure (56)

3.3 Statistical analysis

Continuous variables with normal distribution are presented as mean ± standard deviation (SD). Continuous variables without normal distribution are presented as median values (interquartile range), while categorical values are reported as percentages. Categorical variables were tested applying the $\chi 2$, for continuous variables an independent or paired t-test was used, as appropriate. A p-value of <0.05 was considered statistically significant. Survival was assessed using the Kaplan-Meier estimator, with curves plotted along with the 95% confidence interval (CI). A log-rank test was used for survival comparisons between groups. The cumulative incidence function for competing risk was used to estimate the crude incidence of SVD. The hazard ratio is presented as mean plus 95% CI. A p-value<0.05 was considered to indicate statistical significance. Statistical analysis was done using the SPSS statistical software package, Version 25 (SPSS, Inc., Chicago, Illinois) and R statistics version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

4. Results

4.1 Patient population

4.1.1 Baseline data

A total of 510 people were included into the prospective observational study with a mean age of 79.6 years. Mean operative risk scores were categorized as high with a logEuroScore of 19.8±12.7% and an STS score of 6±4.1%. 63.2 % were female. Cardiac risk factors such as diabetes mellitus was prevalent in 25.7% and arterial hypertension in 79.2%. Previous cardiac events like stroke suffered 14.2%, coronary artery disease 55.1% and previous cardiac surgery 25%. Pacemakers were previously implanted in 7.6% of the patients. Baseline data is listed in Table 4. Preoperative echocardiographic data shows relatively small effective orifice area (0.68±0.21) and elevated mean and maximum aortic valve gradients. Most prevalent AR were mild, followed by none and moderate (see Table 4).

	Total (n=510)
Age, years	79.6±6.7
Female	317 (62.2%)
logES, %	19.8±12.7
STS Score, %	6±4.1
Art. Hypertension	404 (79.2%)
DM	131 (25.7%)
Stroke	72 (14.2%)
Coronary artery disease	281 (55.1%)
Previous cardiac surgery	128 (25%)
Previous PM	39 (7.6%)
COPD	92 (18.1%)
Creatinin mg/dl	1.21±0.6
EOA cm^2	0.68±0.21
Mean AV gradient mmHg	47.3±16.3
Max AV gradient, mmHg	78.1±24.8
Aortic regurgitation	
None	167 (33.1%)
Mild	234 (46.4%)
Moderate	79 (15.7%)
Severe	24 (4.8%)

Table 4 Baseline characteristics and preoperative echocardiographic data

4.1.2 Procedural data

Self-expanding CoreValves were implanted in 68.2% of the patients followed by balloon-expanding Edwards Sapien Valves (31.5%) and others (0.2%) (as seen in Figure 9). Distribution within the size and valve type can be seen in Figure 11. Due to the availability of valve sizes during the study period, no 23mm CoreValve was implanted and merely one 29mm Sapien valve. The principal access route identified was the transfemoral (60.4%) approach, then transapical (31.2%) and lastly, subclavian (7.6%) and transaortic (0.8%) (Figure 10). Patients were operated under general anesthesia in 81% of the cases with a mean procedural time of 91 ±38 minutes. Coronary obstruction occurred in 3 patients (0.6%) and the need for extracorporeal membrane oxygenation (ECMO) and/or cardiopulmonary resuscitation (CPR) developed in 6.2% of the study population. In 3 cases (0.6%) there was the need to convert into open-heart surgery. There was no case of annular rupture. Procedural data is listed in Table 5.

	Total (n=510)
THV Type	
CoreValve	348 (68.2%)
Sapien	147 (28.8%)
Sapien XT	14 (2.7%)
Other	1 (0.2%)
Access	
Transfemoral	308(60.4%)
Transapical	159 (31.2%)
Transaortic	4 (0.8%)
Subclavian	39 (7.6%)
General Anesthesia	413 (81%)
Annulus rupture	0
Pericardial Tamponade	9 (1.8%)
Coronary obstruction	3 (0.6%)
ECMO/CPR	32 (6.2%)
Conversion to conventional surgery	3 (0.6%)
Procedural Time (min)	91±38

Table 5 Procedural data and complications

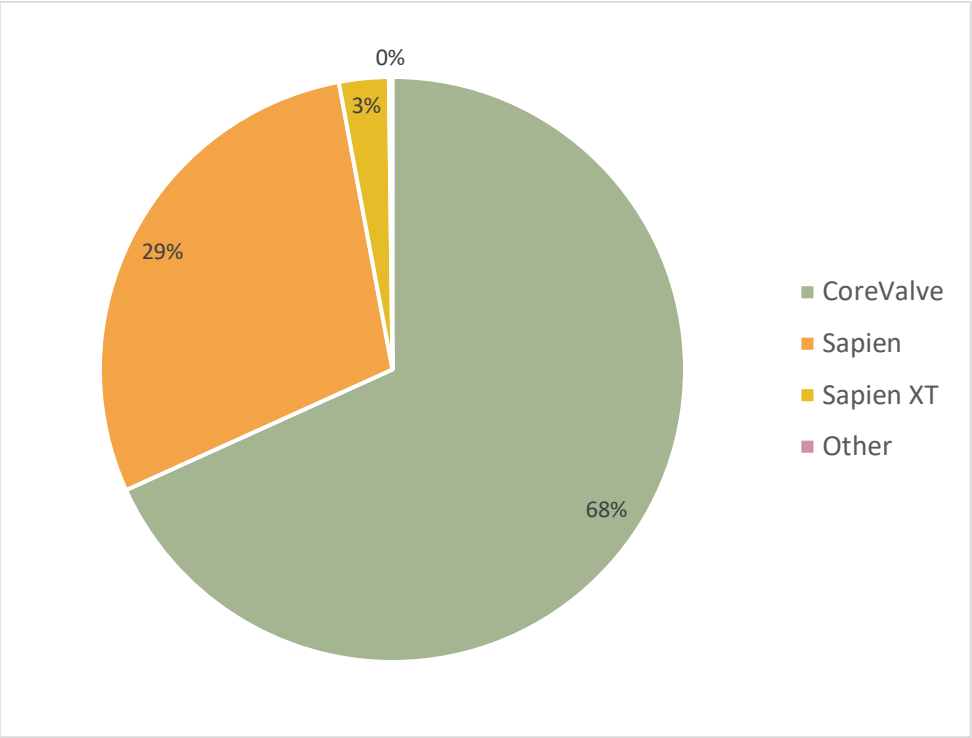


Figure 9 THV Type

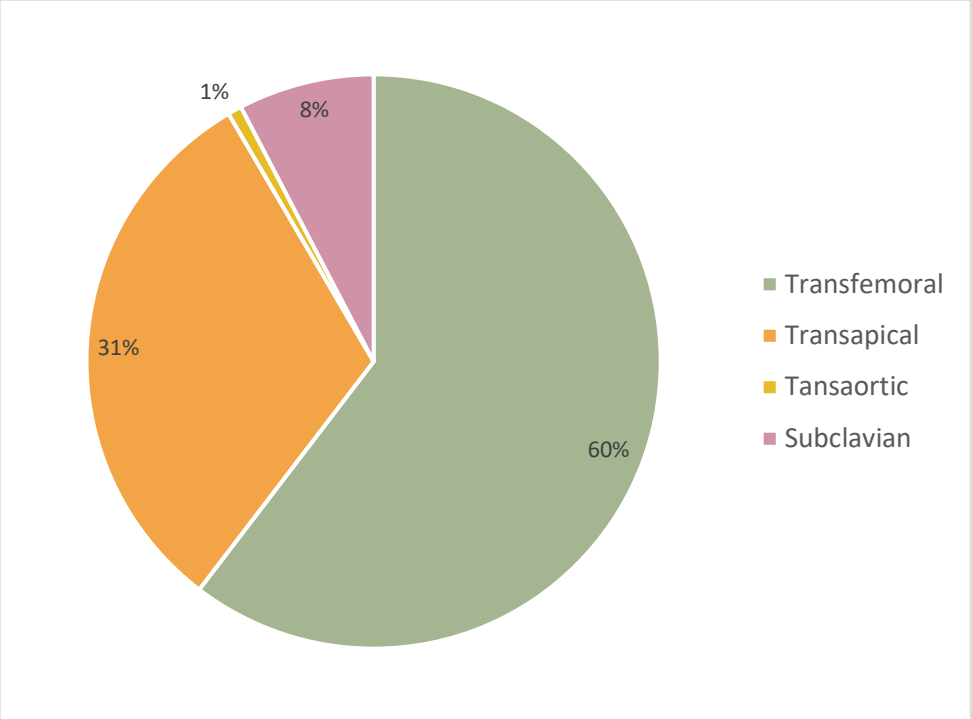


Figure 10 TAVR Access Route

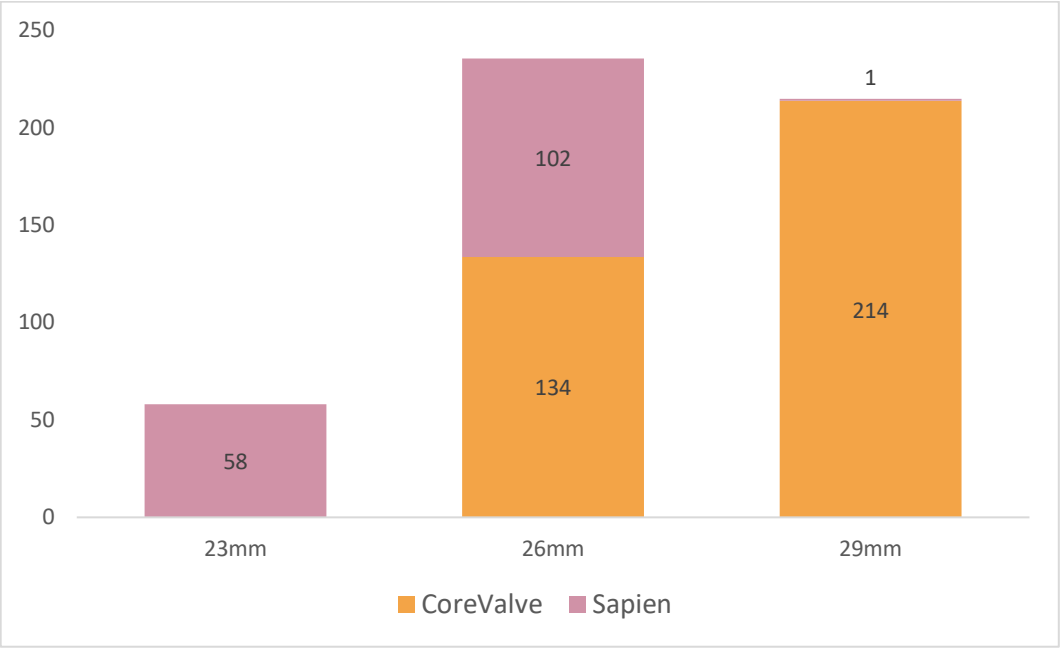


Figure 11 Valve type and size

4.1.3 Postoperative data

Postoperative 30-day events are displayed in Table 6. Immediate procedural mortality within 72 hours post-procedure account for 2.9%, whereas the 30-day mortality lies at 7.8%. Periprocedural neurological events occurred in 4.5%. No myocardial infarction occurred within 30 postoperative days. New pacemakers were implanted in 19.8% and the necessity of initiation of dialysis developed in 9% of the treated patients. Access-related complications occured in 77 (15.1%) patients, of which 27 (5.3%) were major vascular complications. Bleeding complications was 8.2%. Postoperative echocardiographic data shows a significant improvement in valve function. As seen in Figure 12 mean and maximum aortic valve gradients show a considerable reduction. Aortic valve opening area improved from an opening area of 0.68. ±0.21 cm^2 to 1.51 ±0.41 cm^2. Figure 13 demonstrates the steady improvement of AR in severe and mild cases.

	Total (n=510)
30-day all-cause mortality	40 (7.8%)
Immediate procedural mortality	15 (2.9%)
Periprocedural Neurological events	23(4.5%)
TIA	2 (0.4%)
Stroke	21 (4.1%)
Myocardial infarction	0
New onset dialysis	46 (9%)
New PM	101 (19.8%)
Access-related complications	77 (15.1%)
Major vascular	27 (5.3%)
Major non-vascular access-related	6 (1.2%)
Bleeding complication	42 (8.2%)
Type 3	22 (4.3%)
Type 4	9 (1.8%)
EOA cm^2	1.51±0.41
Mean AV gradient mmHg	12.0±5.1
Max AV gradient, mmHg	21.7±8.6
Aortic regurgitation	
None	206 (46%)
Mild	151 (33.7%)
Moderate	81 (18.1%)
Severe	10 (2.2%)

Table 6 Postoperative data and complications within 30 days or hospitalization

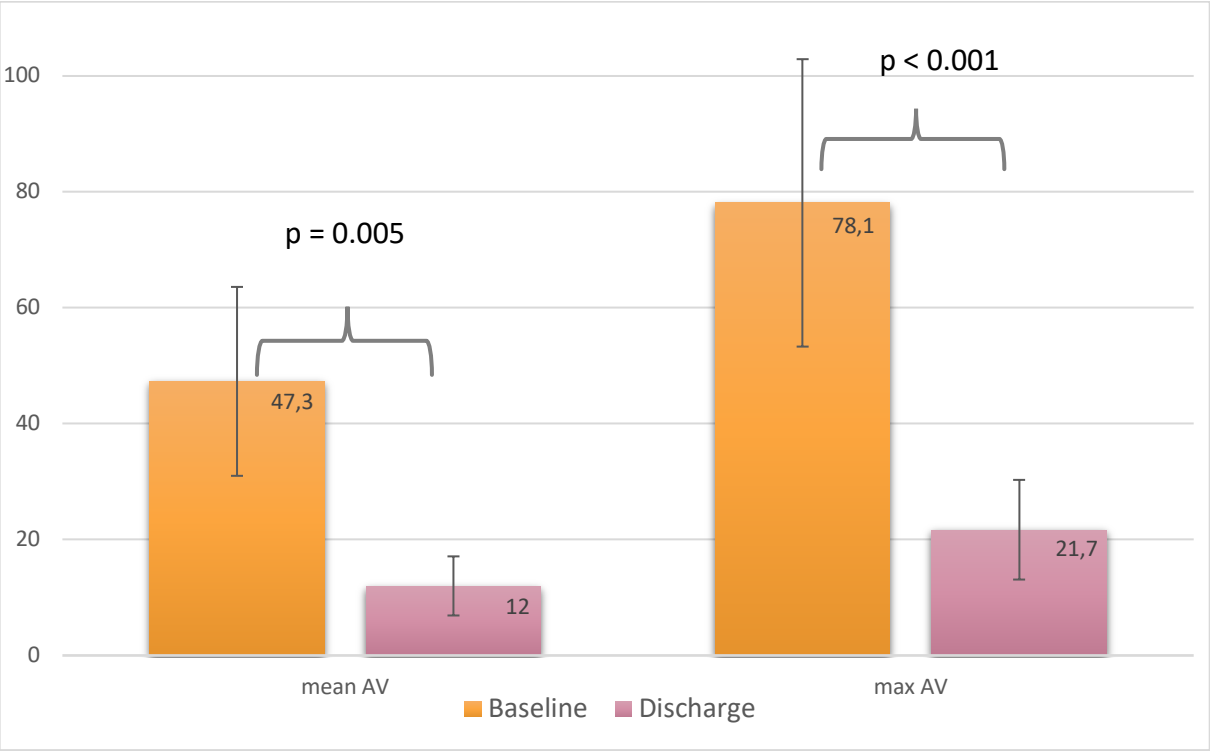


Figure 12 Pre- and post-procedural aortic valve gradients

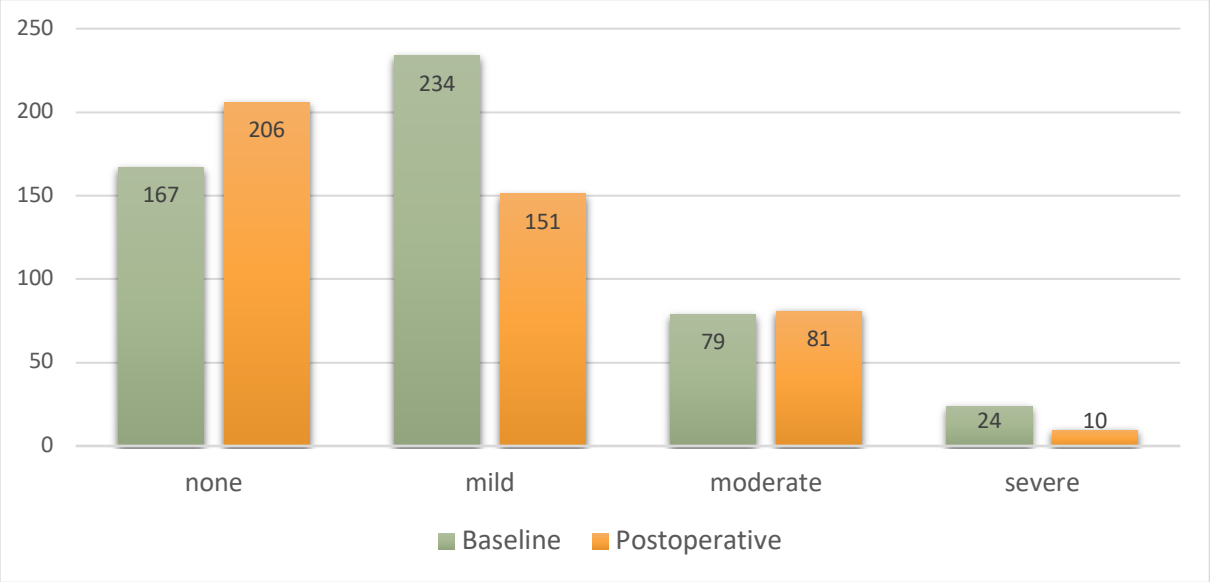


Figure 13 Pre- and postprocedural aortic regurgitation classification

4.2 Follow-up

4.2.1 Survival

In our study survival at 1-, 5- and 10-years was 79.1±1.8%, 44.4±2.2% and 10.3±1.5%, respectively. At 12 years, estimated Kaplan-Meier survival was only 2.6% (Figure 14). There was no significant difference in estimated survival according to the implanted valve type (CoreValve versus Sapien 10-year survival 10.4 ±1.9% versus 9.8±2.7%, respectively, p=0.9).

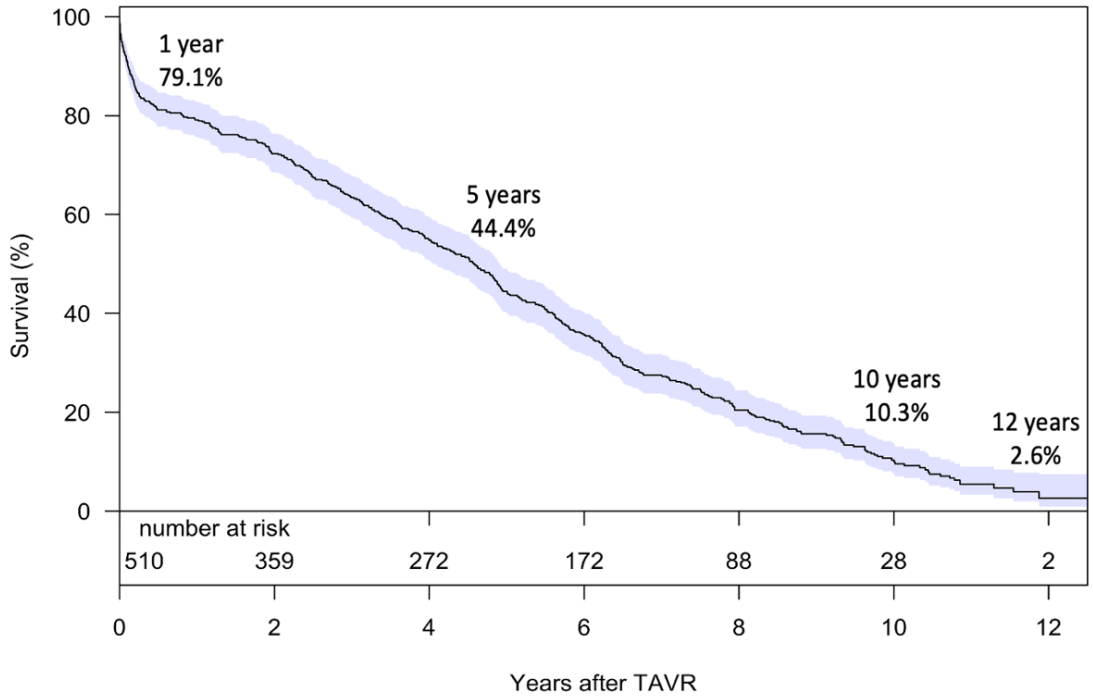


Figure 14 Kaplan-Meier estimated overall survival

4.2.2 Structural Valve Deterioration (SVD)

The SVD rate after TAVR in our study was 5.1% at 12 years after TAVR. The median time to occurrence of SVD was 3.75 (IQR 1.02; 6.90) years. The cumulative incidence (CI) for SVD at 1, 5, 10, and 12 years is 0.8%, 2.6%, 4.3% and 5.1% (seen in Figure 15). A difference in respect to the two different valve types was observed. At 1-, 5-, and 11-years the CI for Edwards Sapien were 1.9%, 5.1%, 9.0% and Medtronic CoreValve 0.3%, 1.5%, 2.2%, respectively, p=0.001 (Figure 16).

Using ROC analysis, CT-derived effective diameter and discharge EOA were not significant predictors for SVD. Mean and maximum aortic gradient at discharge showed a significant result (p=0.002 for both gradients) with an area under the curve (AUC) of 0.713 and 0.711, respectively. According to the Youden-Index, a mean transaortic gradient > 11.8mmHg (Sensitivity 83% and Specificity 53%) and a maximum transaortic gradient >25.75mmHg (Sensitivity 61% and Specificity 75%) predict the occurrence of SVD.

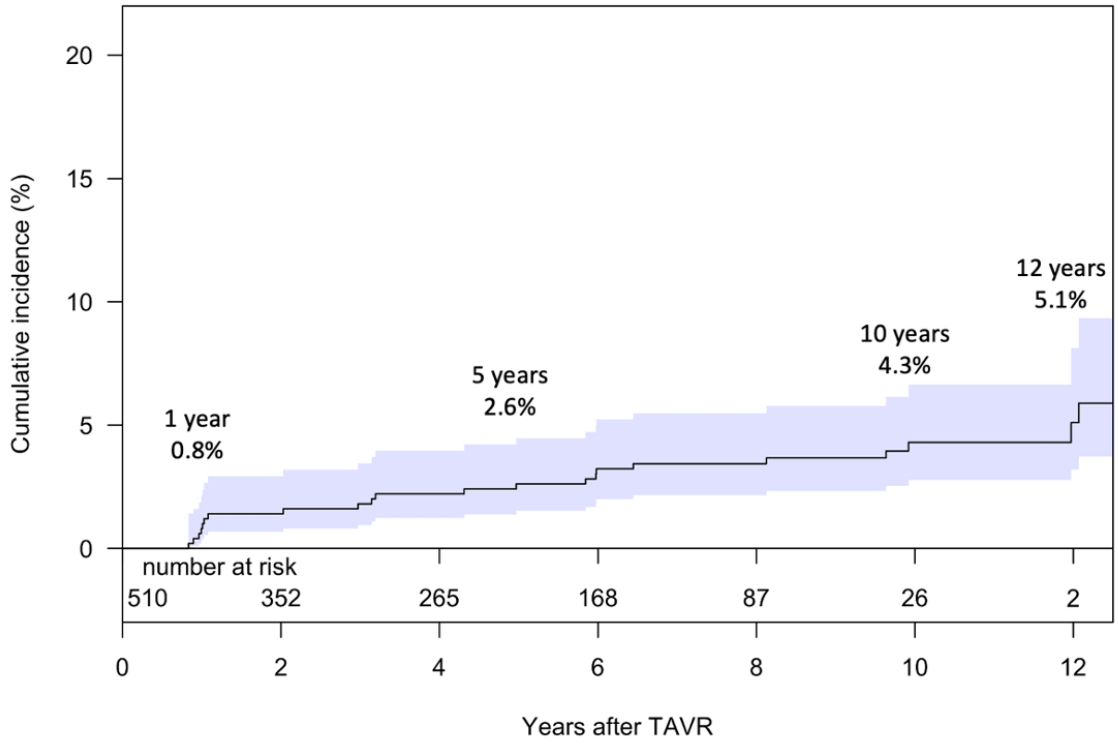


Figure 15 Cumulative Incidence of structural valve deterioration (SVD) for overall patient population

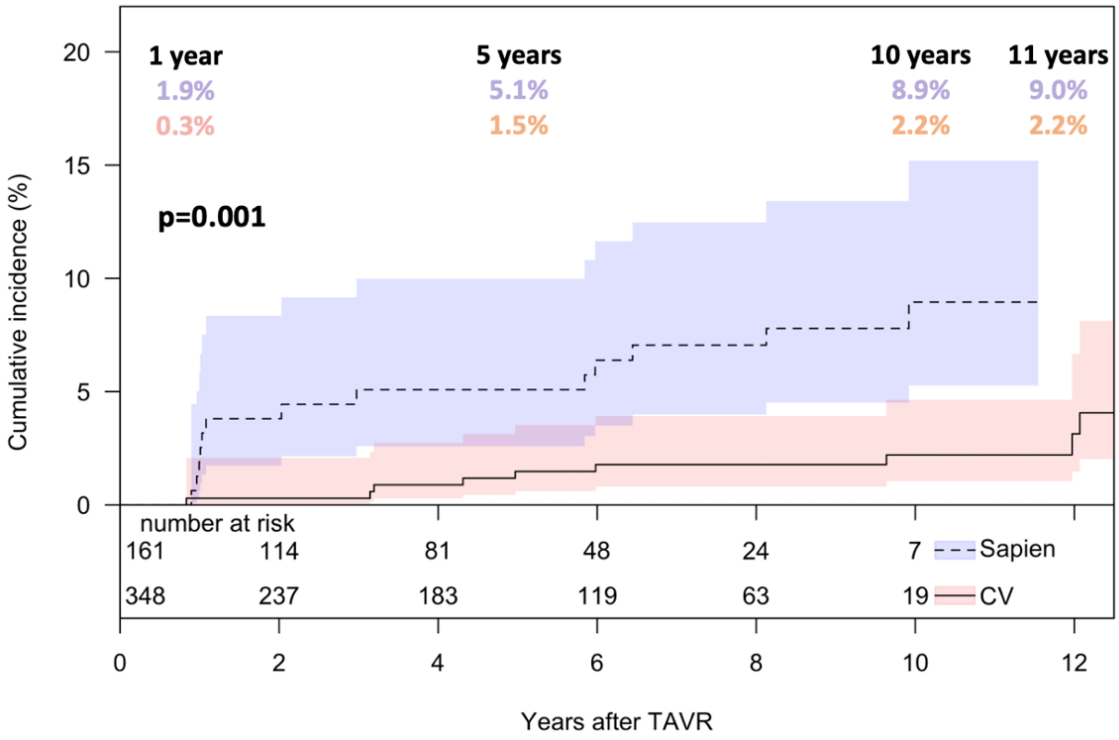


Figure 16 Cumulative Incidence of SVD valve related

4.2.3 Bioprosthetic Valve Failure (BVF)

BVF was found in 46 patients with a median time to BVF of 1.1 (IQR 0.03; 5.71) years. Fourteen cases (30.4%) were early BVF (≤30days), all of which were due to paravalvular leak or malplacement leading to reintervention. Of the late BVF cases (n=32, 69.6%), 16 patients underwent reintervention. Three cases underwent a redo-procedure due to endocarditis, the other cases were due to SVD. Detailed data is shown in Table 7.

The risk to develop BVF at 1 year lies at 4.0%, whereas at 12 years it is 9.8% (Figure 17). BVF showed significantly different cumulative incidences between valve types; CI at 1-, 5-, and 11-years: Sapien 3.8%, 8.2%, 13.9% and CoreValve 4.1%, 5.8%, 6.9%, respectively, p=0.021 (Figure 18).

	Reason	Time until Redo (years)	Age at Redo (years)	Procedure
1	AS	9.5	82.1	TAV-in-TAV
2	AS	6.7	87.6	TAV-in-TAV
3	Central AR	0.3	80.0	TAV-in-TAV
4	Central AR	3.4	90.6	TAV-in-TAV
5	AS	5.6	80.8	TAV-in-TAV
6	AS	10.0	82.2	TAV-in-TAV
7	AS	4.3	48.5	Mech. SAVR
8	Central AR	4.0	81.0	TAV-in-TAV
9	Parav. AR	1.1	72.5	TAV-in-TAV
10	Endocarditis	4.7	74.8	Bio SAVR
11	Endocarditis	0.4	70.5	Bio SAVR
12	AS	6.8	80.5	TAV-in-TAV
13	Parav. AR	1.6	63.7	TAV-in-TAV
14	Parav. AR	5.9	89.2	Bio SAVR
15	AS	5.4	81.2	TAV-in-TAV
16	Endocarditis	1.3	64.4	Bio SAVR

Table 7 Late cases of bioprosthetic valve failure

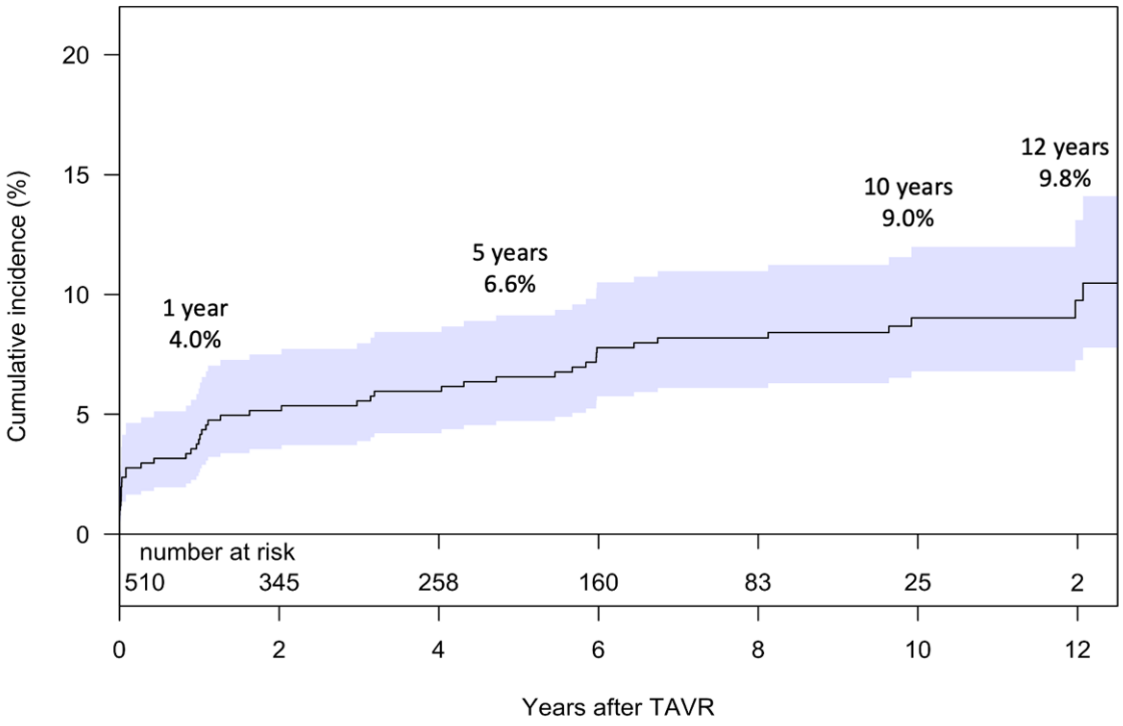


Figure 17 Cumulative Incidence BVF

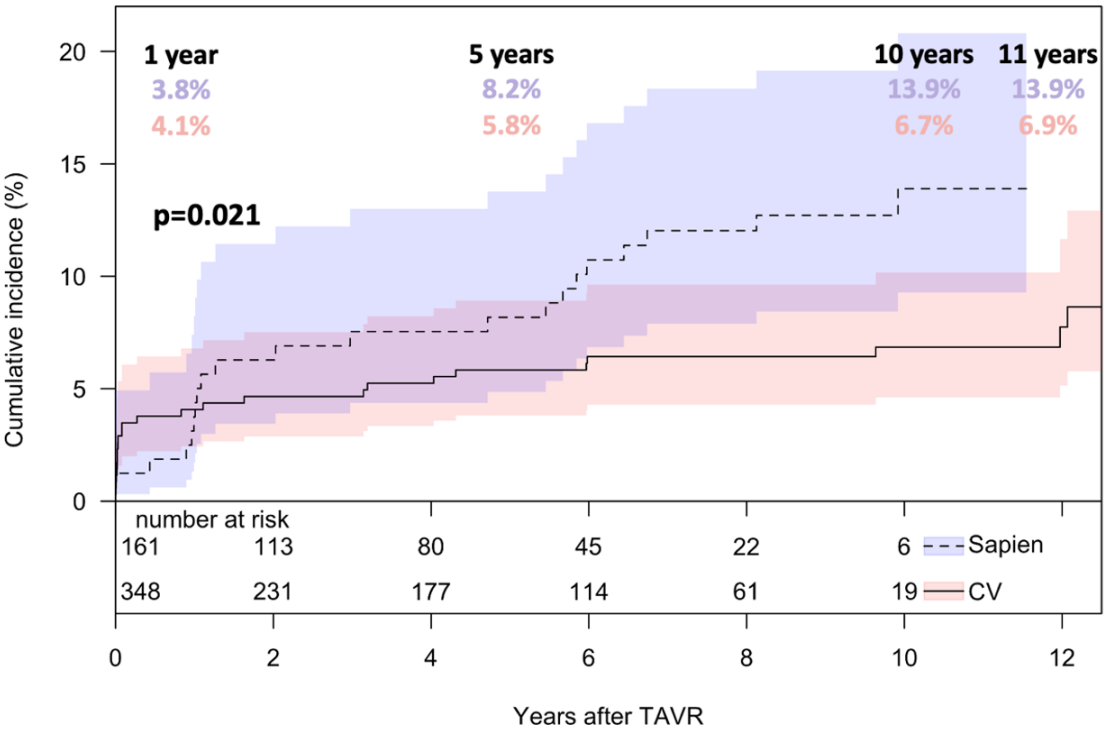


Figure 18 Cumulative Incidence of BVF according to valve type

4.3 Surviving patient cohort

Sixty-six patients were alive follow-up beyond 10 years. These patients were significantly younger with a lower surgical risk-profil at the time of TAVR than patients who died during follow-up. The valve opening area was significantly larger in the surviving patient cohort, perhaps as a sign of less severe/chronic AS. Previous pacemaker implantation, COPD and elevated Creatinin levels was more common in the deceased patient cohort. An overview of all patient data, according to survival status can be seen in Table 8.

	Alive (n=66) 12.9%	**Dead (N=444) 87.1%**	**p-value**
Baseline Characteristics			
Age, years	76.1±7.2	80.1±6.5	<0.0001
Female	38 (57.6%)	279 (62.8%)	0.417
logES, %	14±9.6	20.6±12.8	<0.0001
STS Score, %	3.7±2.1	6.3±4.2	<0.0001
Art. Hypertension	54 (81.8%)	350 (79.4%)	0.744
DM	15 (22.7)	116 (26.3%)	0.651
Stroke	5 (7.6%)	67 (15.2%)	0.129
Coronary artery disease	33 (50%)	248 (55.9%)	0.427
Previous cardiac surgery	20 (30.3%)	174 (24.3%)	0.229
Previous PM	1 (1.5%)	38 (8.6%)	0.056
COPD	5 (7.6%)	87 (19.6%)	0.016
Creatinin mg/dl	1.02±0.33	1.23±0.63	<0.0001
EOA cm^2	0.75±0.22	0.67±0.21	0.006
Mean AV gradient mmHg	47.6±17.6	47.3±16.1	0.879
Max AV gradient, mmHg	78.8±27.3	78±24.4	0.801
Aortic Regurgitation			0.062
None	14 (21.2%)	153 (34.9%)	
Mild	36 (54.5%)	198 (45.2%)	
Moderate	10 (15.2%)	69 (15.8%)	
Severe	6 (9.1%)	18 (4.1%)	
Intraoprocedural Data			
THV Type			0.076
CoreValve	44 (66.7%)	304 (68.5%)	
Sapien	17 (25.8%)	130 (29.3%)	
Sapien XT	5 (7.6%)	9 (2%)	
Other	0	1 (0.2%)	
Access			0.672
Transfemoral	39 (59.1%)	269 (60.6%)	
Transapical	19 (28.8%)	140 (31.5%)	

Transaortic	1 (1.5%)	3 (0.7%)	
Subclavian	7 (10.6%)	32 (7.2%)	
General Anesthesia	45 (68.2%)	368 (82.9%)	0.007
Annulus rupture	0	0	
Pericardial Tamponade	0	9 (2%)	0.613
Coronary obstruction	0	3 (0.7%)	1.000
ECMO/CPR	1 (1.5%)	31 (6.9%)	0.222
Conversion to conventional surgery	1 (1.5%)	2 (0.5%)	0.341
Procedural Time, min	91±35	91±38	0.998
Immediate procedural mortality			
Postoperative Data			
30-day mortality	-	40 (9%)	
Periprocedural neurological event	1 (1.5%)	22 (5.0%)	
TIA		2 (0.5%)	
Stroke	1 (1.5%)	20 (4.5%)	
Myocardial infarction	0	0	
New onset dialysis	4 (6.1%)	42 (9.5%)	0.492
New PM	16 (24.2%)	85 (19.1%)	0.324
Access-related complication	9 (13.6%)	68 (15.3%)	0.854
Major vascular	3 (4.5%)	24 (5.4%)	1.000
Major non-vascular access-related	0	6 (1.4%)	1.000
Bleeding complication	1 (1.5%)	41 (9.2%)	0.03
Type 3	0	22 (4.9%)	0.002
Type 4			
EOA cm^2	1.56±0.42	1.51±0.41	0.416
Mean AV gradient mmHg	13.5±4.4	11.8±5.1	0.024
Max AV gradient, mmHg	24.2±8.5	21.3±8.6	0.020
Aortic regurgitation			0.927
None	28 (46.7%)	178 (45.9%)	
Mild	20 (33.3%)	131 (33.8%)	
Moderate	10 (16.7%)	71 (18.3%)	
Severe	2 (3.3%)	8 (2.1%)	

Table 8 Baseline, Intraprocedural and 30-days complication data for alive and deceased with its p-value

5. Discussion

To our knowledge, this is the first study reporting data on structural valve degeneration beyond a ten-year follow-up for transcatheter aortic valves. This study includes elderly, high surgical risk patients with comorbidities from the beginning of the TAVR program at the Department of Cardiovascular Surgery at the German Heart Center Munich. The main findings are:

1) Peri- und post-procedural complications were considerable but comparable with other studies.
2) Long-term survival was as expected low for this patient cohort.
3) SVD at 12 years was merely 5.1%, with a significantly higher rate for the Edwards Sapien compared to the Medtronic CoreValve.
4) BVF had a cumulative incidence of 9.8% at 12-years, with a significantly higher rate in patients with an Edwards Sapien valve.

5.1 Clinical outcomes

Periprocedural complication rates in this high-risk population were relatively low. Coronary obstruction occurred in 0.6%, these results are in line with the results from the PARTNER 1A study (0%) (35) and the CoreValve HighRisk Study (0.5%) (37). Conversion to conventional surgery in our study was merely 0.6%, also comparable with results from the CoreValve High Risk trial (0.5%) and the PARTNER 1A study (2.6%) (35,37).

Postoperative outcomes and complications show favorable results. Thirty-day postoperative complication rates and postoperative outcomes are comparable with big trials with a similar study population.

Thirty-day all-cause mortality is high, 7.8%, which can easily be explained by the high age and multiple comorbidities of the patients. Data from both the CoreValve High-risk as-treated cohort (3.3 %) as well as outcomes from the Partner 1A intention-to-treat cohort (3.4%) and as-treated cohort (5.2%) were lower (34), but still comparable to our results.

Neurological events such as stroke (minor and major together) were similar in our study 4.1% compared to the As-treated CoreValve high-risk study 4.9% and PARTNER 1A 4.7%.

Vascular related complications were present in 15.1% of the patients, of which 5.2% were classified as major vascular complications. These results are also in line with results from the PARTNER 1A study. Compared to current patient cohorts, this percentage is relatively high. The explanation is clearly to be found in the bigger sheath sizes, stiffness of the delivery systems, lack of closure devices and the learning curve. All these factors influence the occurrence of vascular dissection and ruptures during the first THV implantations (60).

The VARC-3 bleeding complication definition has recategorized bleeding events into 4 categories, ranging from mild bleeding to bleeding leading to death. This new definition makes a comparison to other studies difficult. Nonetheless, the rate of more severe bleeding complication seems to be in line with data from PARTNER and CoreValve High-Risk. New Pacemakers were implanted in 19.8% of our patients, matching the results from the CoreValve High-risk study. These results seem high in comparison to the As-treated new pacemakers 4.4% in the Partner study. This may be due to the high utilization of the Corevalve in our patient cohort.

Echocardiographic data shows a significant hemodynamic improvement after TAVR. Our mean aortic AV gradient, at baseline 47.3±16.3mmHg results in 12.0±5.1mmHg at discharge. These results are in line with both the Partner trial, showing a recovery of the mean gradient to 9.9±4.8mmHg, as well as the CoreValve High Risk results, with the gradient improving to 9.85±4.41mmHg.

In the light of the current TAVR era, these complication rates seem high. Naturally this is influenced by multiple factors, including technological state-of-the-art at the beginning of its development, concerning in particular delivery systems and valve design as well as experience of the surgeons.

5.2 Follow-up

5.2.1 Survival

Patients with aortic stenosis without an aortic valve replacement are estimated to survive two to three years (61). The introduction of TAVR was an innovation and a big step for inoperable patients to extend survival of those patients and elevate their quality of life. This inoperable and high surgical risk population with AS were never to be expected to be studied for valve durability beyond 10 years of follow up. To our knowledge this is the first paper reporting on survival after TAVR beyond 10 years. Previous longterm studies only report up to 5-8 years (36,62,63). At 8 years survival was 17.3% in our cohort. Holy et al. describe a higher survival rate of 27% at 8-years(62). Variations in survival rates can be expected.

Sathananthan et al. reports a 10-year survival rate of 8.4% (53), similar to our rate of 10.3%. Due to the advanced age and comorbidities of the first treated TAVR patients, these low survival rates are not surprising. Survival was, as expected low at 12 years, with 2.6%.

5.2.2 SVD

From long-term data on surgical aortic valve durability it is known, that the majority of valves show signs of valve degeneration 10-15 years after implantation (55,64). An in silico soft tissue model suggested that THV durability would only be approximately 8 years, due to the crimping process, causing microscopic lesions prone to sclerosis and under-/overexpansion or non-circular frame expansion leading to turbulent bloodflow or leaflet folding (65). The available long-term data on TAVR patients does not support this in-vitro model. Previously published studies reporting SVD according to the 2017 EAPCI/ESC/EACTS consensus statement have shown a cumulative incidence of severe SVD in THV at 7-8 years of 2.4-4.2% (51,52,63). Eight-year follow-up data from the NOTION I Trial even showed a lower SVD rate with the Medtronic CoreValve than for surgical valves (14.1% vs 28.5%) (Sondergaard L. “NOTION 8 Years Follow-Up: Long-Term Follow-Up After Medtronic TAVI Versus SAVR In Patients At Lower Surgical Risk“ presented at PCR Valves e-course 2020). Beyond 8-year follow-up data THV durability is scarce. Sathananthan et al. report a cumulative incidence of structural valve deterioration/bioprosthetic valve failure at 10-years of 6.5% in a cohort with a high rate of Sapien prostheses (53). Not only did we see slightly lower rates, but we also found the valve

type to have a significant influence on the occurrence of SVD. The balloon-expandable Edwards Sapien valve had significantly higher rates of SVD and BVF in our study. These results support data shown in a previous study from our center on mid-term follow-up after TAVR with a higher rate of moderate and severe SVD at 7 years in patients with a Sapien valve versus a CoreValve (22.6% vs 11.8%, respectively, p=0.01)(49). Dvir et al. showed in a patient cohort of 378 patients, who received a balloon-expandable Edwards device, freedom from SVD in 82% of patients at six years and 50% at eight years (Dvir D. First look at long-term durability of transcatheter heart valves: assessment of valve function up to 10 years after implantation. Presented at: EuroPCR 2016, Paris, France). One reason for the results in our cohort could perhaps be seen in the availability of valve sizes at the time of the study, leading to a more common implantation of the Sapien valve in smaller annuli. This could have an influence on hemodynamic performance and thus on the stress the valve is exposed to, leading to a higher rate of degeneration. A ROC-analysis was not able to show an influence of annulus diameter on the occurrence of SVD in our study. Further analysis did show, that mean and maximum gradient had a significant AUC, but cut-off values displayed a low sensitivity and a high specificity, relativizing the clinical application. The low survival rate in our cohort and the subsequently low rate of patients at risk most likely reduces the statistical power for these analyses.

5.2.3 BVF and reoperation

The cumulative incidence of BVF range from 0.58%-7.9% in previously published data, with varying timeframes (5-8years) (51,52,62). In the present investigation the cumulative incidence was found to be considerably higher, most likely due to differing definitions and different time ranges. Therefore, aortic valve reintervention rate is also higher compared to those other studies. A large portion of our BVF cases occurred in the first 30 days after the index procedure, due to malplacement or paravalvular leak caused by malpositioning. In our opinion the inclusion of these cases to BVF, as the definition specifies, is misleading. The early generation devices were not repositionable, sealing technologies were not advanced, precise steering was difficult and advanced sizing technologies and techniques, as we know them today were still at the beginning.

6. Limitation

Introduced as a new operation technique in 2007 at the German Heart Center Munich, it is expected for all surgeons to get through a learning curve which might have altered long-term results of first TAVR operations. Furthermore, as first generation devices were implanted, these results cannot be automatically transferred to a current TAVR cohort.

This study is a non-randomized single center retrospective observational study, with all associated disadvantages.

Follow-up data is partially collected from different cardiologists, a corelab assessment was not available. NYHA classification was either classified by the cardiologist or by the patient himself with the help of a questionnaire. Variations may occur in our elderly patients depending on their daily condition and ability.

The current pandemic situation of covid-19 hindered us to obtain follow-up data of some patients that were not able to go to their cardiologist because of their medical state or were not willing to expose themselves to the risk to get a covid-19 infection.

7. Conclusion

Structural valve deterioration and bioprosthetic valve failure of early THV at 12-years was low, exceeding predictions from in-vitro models and meeting data from surgical cohorts. The identified differences between valve types must be validated using current generation devices in younger patients.

8. Appendices

8.1 Abbreviations

AR	aortic regurgitation
AS	aortic stenosis
AUC	area under the curve
AVR	aortic valve replacement
BMI	body mass index
BSA	body surface area
BVF	bioprosthetic valve failure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCA	common carotid access
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
CVI	cerebrovascular insults
DAA	direct aortic access
EACTS	European Association for Cardio-Thoracic Surgery
EAPCI	European Association for Percutaneous Cardiovascular Intervention
ECMO	extracorporeal membrane oxygenation
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
MI	myocardial infarction
MR	mitral regurgitation
NOTION	Nordic aortic valve intervention
NYHA	New York Heart Association
PARTNER	placement of aortic transcatheter valves by Edwards
PPI	permanent pacemaker implantation
PVL	paravalvular leak
RCT	randomized controlled trials
SAVR	surgical aortic valve replacement

STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
SVD	structural valve deterioration
TAVR	transcatheter aortic valve replacement
TA	transapical
TF	transfemoral
THV	transcatheter heart valve
TR	tricuspid regurgitation
TS	transsubclavian
VARC	Valve Academic Research Consortium

8.2 List of figures

8.3 List of images

8.4 List of tables

8.4 Bibliography

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