Aus der medizinischen Klinik II
Kardiologie, Angiologie und Intensivmedizin
der Universität zu Lübeck
Direktor: Prof. Dr. med. Ingo Eitel

„Performance Of Transcatheter Heart Valves In Severely Calcified Aortic Valve Stenoses “

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Osama Mohammed Masoud Bisht
Aus

Kafrelshikh, Ägypten

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1. Berichterstatter*in: PD Dr. med. Mohammed Elsayed Abuelnour Saad

Ko-Betreuer*in: Prof. Dr. med. Karl-Friedrich Klotz

2. Berichterstatter*in: Prof. Dr. med. Matthias Heringlake

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Contents

Anatomy, pathology, pathophysiology, diagnosis, and treatment of aortic stenosis

Definition

Aortic Stenosis (AS) is defined as increased resistance to the blood flow across the left ventricular outflow tract (the aortic valve); this obstruction may be either congenital or acquired. The obstruction my occur at different levels, including the LVOT, aortic valve leaflets, or above the aortic valve leaflets. The obstruction may be fixed, e.g., leaflet calcification or dynamic occurring only in certain phases of the cardiac cycle, e.g., hypertrophic obstructive cardiomyopathy (HOCM). The most likely cause is the valvular obstruction.

Epidemiology

AS was found to be the most prevalent valvular heart disease in western countries; the increase in the incidence of AS will increase the burden on health resources and public health due to the aging western population. (Nkomo et al., 2006) (Iung & Vahanian, 2011)

About 67,500 surgical aortic operations (SAVR) are done in the United States per annum (Clark et al., 2012). It is approximated that there are about 180000 potential candidates for transcatheter aortic valve replacement in Europe (Durko et al., 2018).

There are roughly 189,836 TAVI procedures in the EU and 102,558 in North America. The incidence of AS in the general population is 12.4%, whereas the prevalence of high-grade AS in people >75 years and older is 3.4%. As illustrated in a meta-analysis of earlier research carried out in Europe, the United States, and Taiwan, there are 17,712 new potential TAVI patients yearly in European countries and 9,189 in North America. (Osnabrugge et al., 2013)

Intervention is the only valid treatment option available to individuals with AS, and the anticipated 5-year survival for those with high-grade AS if left untreated is only 15% to 50%.(Vahanian et al., 2012)

Etiology and Pathogenesis

The Euro-Heart Survey on valvular heart disease, which was published in 2006, divided the valvular AS into four major types with varying prevalence:

1. Age-related (degenerative or calcific)

2- post-rheumatic.

3- Congenital is mostly caused by the bicuspid aortic valve.

4- post-endocarditis.

The most common form of aortic stenosis in the developed world is caused by age-related calcific aortic valve stenosis. However, in developing nations, the rheumatic affection of cardiac valves may significantly contribute to AS.

The calcified AS's pathogenesis strangely resembles that of arterial atherosclerosis, being a slowly progressive fibro-calcific process with clinically different manifestations that correlate with disease progression. The disease's process exhibits different phases; the first phase starts with the aortic valve being affected by fibrosis and calcification, which usually starts at the hinge points of the valve (point of attachment to the annulus); clinically there is no significant obstruction of the blood outflow, thus no clinical manifestations. This phase is termed aortic sclerosis; over the years, the calcification process of the aortic valve continues with leaflet motion's impairment and blood outflow obstruction, which is the hallmark of calcific aortic stenosis; the later phase is characterized by flow obstruction, and hemodynamic effects are called aortic valve stenosis. (Rajamannan et al., 2011b)

Calcific valve disease involves multiple mechanisms and pathways, such as chronic inflammation, lipoprotein deposition, an osteoblastic transformation of interstitial cells, and widespread calcification of the leaflets. In contrast to prior belief, calcific valve disease is a consequence of degeneration induced via both passive calcium deposition and time-dependent tear-and-wear of the leaflets.(Freeman & Otto, 2005; Rajamannan et al., 2007)

Fibrosis and calcification are the two main features of Calcific AS after inspection of surgically explanted valves; those features change the Aortic valve leaflets' biomechanical features. Progressive osteogenic metaplasia with chondrocytes, bone marrow, and osteoblast-like cells was noted in a minor percentage (10–15%) of calcific AS valves(Steiner et al., 2007)

Dense inflammatory infiltrates consisting mainly of macrophages are found in the calcific valve.(Coté et al., 2013; Helske et al., 2006)

Mineralization and lipid deposition start in and around the fibrosa, so we can conclude that Calcific aortic stenosis is a fibro-calcific process in response to an injury triggered by lipid-derived species and inflammation(Mathieu & Boulanger, 2014)

Renin-Angiotensin Signaling cascade

Angiotensin-converting enzyme (ACE) was found to be expressed and localized together with LDL in the calcific aortic valve(O'Brien et al., 2002)

Additionally, it was discovered that those taking angiotensin-converting enzyme inhibitors had more obvious aortic valve stenosis than those who weren't receiving the medication.(Shavelle et al., 2002)

The initial phase of oxidative injury:

Abnormalities in the oxidative stress pathway are one of the early events in the onset of AS. These problems include disorder of the endothelial nitric oxide synthesis, which in turn reduces the bioavailability of the generated naturally NO along the valve endothelium in the atherosclerotic risk factors' existing akin to vascular atherosclerosis.(Rajamannan, 2011; Rajamannan et al., 2005)

Contrary to the atherosclerotic plaques in which the increase of oxidative stress activity is primarily due to elevations in NAD(P)H oxidase action (Fukai et al., 1998), in calcified aortic stenosis disease, it is due to a marked increase in the superoxide and hydrogen peroxide levels.(Miller et al., 2008)

In addition, the crucial part is that nitric oxide synthase's uncoupling may play a role in the superoxide's production in calcified aortic valves.(Rajamannan et al., 2005)

Calcification-Bone Formation

The primary cause of the chemomechanical alterations in aortic valve stenosis is calcification; these modifications in the aortic valve's cells are characterized by cell expansion, osteoblast expression, and atherosclerosis (Mohler et al., 2001; Rajamannan et al., 2003)

Osteopontin (OP), collagen, and other minor bone matrix proteins make up the matrix on which the hydroxyapatite that makes up cardiovascular calcification is deposited and has the appearance of bone. (Mohler et al., 1997, 2001; O'Brien et al., 1995; Rajamannan et al., 2003)

Specific transcription factors, notably Runx245, MSX252, and Sox945, are activated to affect the regulation. When calcified aortic valves are eliminated during surgical valve replacement, bone development (osseous metaplasia) is visible. (Caira et al., 2006; Shao et al., 2005) Figure 1

Numerous cardiovascular risk factors, such as advanced age, metabolic risk factor, serum Lp(a) and LDL levels, height, male gender, smoking, and hypertension, are shared by atherosclerosis and aortic stenosis. (Pohle et al., 2001) Figure 1.

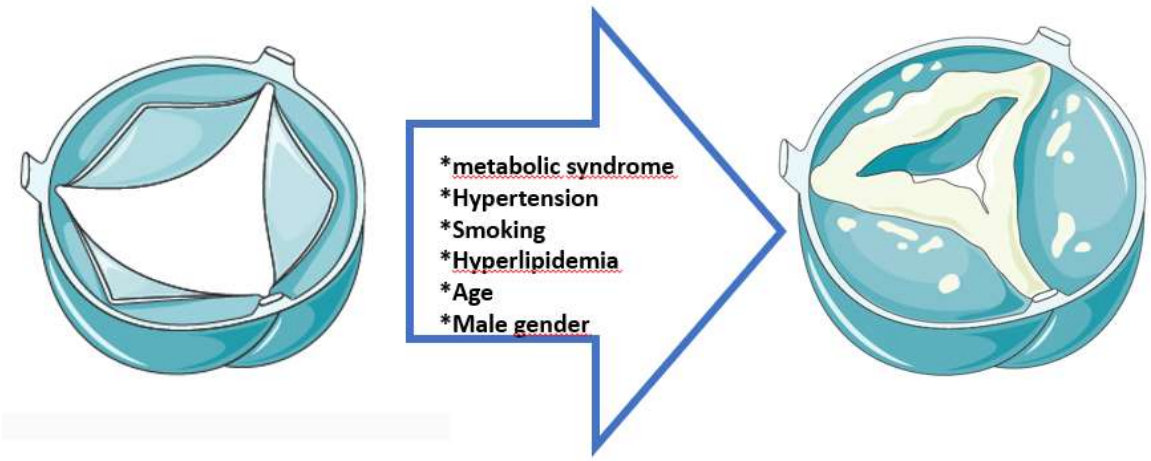


Figure 1: pathophysiology of aortic stenosis

Figure 1 classical atherosclerotic risk factors are associated with the progression of aortic stenosis adapted from Jashari et al. (Rajamannan et al., 2011a)

Bicuspid Aortic valve:

The bicuspid aortic valve (BAV) is the most common congenital anomaly of the aortic valve. The prevalence of BAV. The prevalence of BAV has been estimated to be between 0.6 and 1.4%, with a higher prevalence in males.(Jashari et al., 2009; Movahed et al., 2006). The bicuspid aortic valve is considered one of the prevalent causes of early degeneration of the aortic valve. Aortic stenosis' Progression relies on numerous factors involving valve-related factors like the number and degree of fusions of the cusps and patient-related factors like hyperlipidemia or hypertension(Fedak et al., 2002).

The bicuspid aortic valve can be classified according to Sievers classification (Sievers & Schmidtke, 2007)

1- Type 0 BAV: purely bicuspid valve: has two equally-sized cusps with two raphes and two commissures.

2- Type 1: has three cusps that are unequally developed, with one fully developed cusp and two underdeveloped cusps.

3-Type 2: has 2 raphes.

Pathophysiology.

The cornerstone for managing patients with aortic valve stenosis (AS), risk stratification, and allocating specific symptoms is through investigations to aid in the exact quantification of AS.

The main technique for determining the severity of AS is echocardiography. It depends on three variables: the aortic valve area (AVA), the mean pressure gradient (MPG), and the peak velocity (Vmax). According to the European Society of Cardiology (2018), AS severity was rated according to the categories in Table 1.

Peak velocity, m/sec	<2.5	2.5-3	3-4	>4
Mean gradient, mmHg	Normal	<20	20-40	40
AVA, cm²	Normal	≥1.5	1-1.5	<1 cm²
Calcium scoring, HU	Male 2,065 Female 1,275			

Table 1 Echocardiography and computed tomography severity grades for aortic stenosis (calcium grading)(Otto et al., 2021a)

AS has a prolonged latent period during which valve conditions, including fibrosis and stenosis, occur in addition to progressive worsening of the left ventricular function (LV) in the form of progressive hypertrophy and eventually dilatation form due to the outflow obstruction.(Pantely et al., 1978; Tobin et al., 1967)

The elevation in LV systolic function due to hypertrophy sustains appropriate systematic pressure; nevertheless, this hypertrophy results in LV diastolic dysfunction as a result of the decrease and the resistance in LV filling(Grossman et al., 1975; Hess et al., 1984, 1993)

As the AS develops over time, these adjustments become insufficient to defeat the resistance and preserve normal systolic function. To overcome the filling resistance, left atrial contraction becomes stronger in order to produce enough LV diastolic filling and

stroke volume. Clinical heart impairment may be brought on by a combination of systolic and diastolic dysfunction. (Hess et al., 1993) Figure 3,4

The progressive LV hypertrophy leads to elevated myocardial oxygen demand in addition to compressing the intramural coronary arteries; these events, in addition to LV diastolic dysfunction, may cause an imbalance between oxygen demand and supply, causing rest angina even in patients with normal coronary arteries.(Johnson et al., 1978; Marcus et al., 1982)

Additionally, as AS worsens, exercise no longer causes an increase in cardiac output. It, in turn, causes a decrease in systemic vascular resistance with activity, which could result in severe hypotension and syncope.(Bache et al., 1971; Kulbertus, 1988)

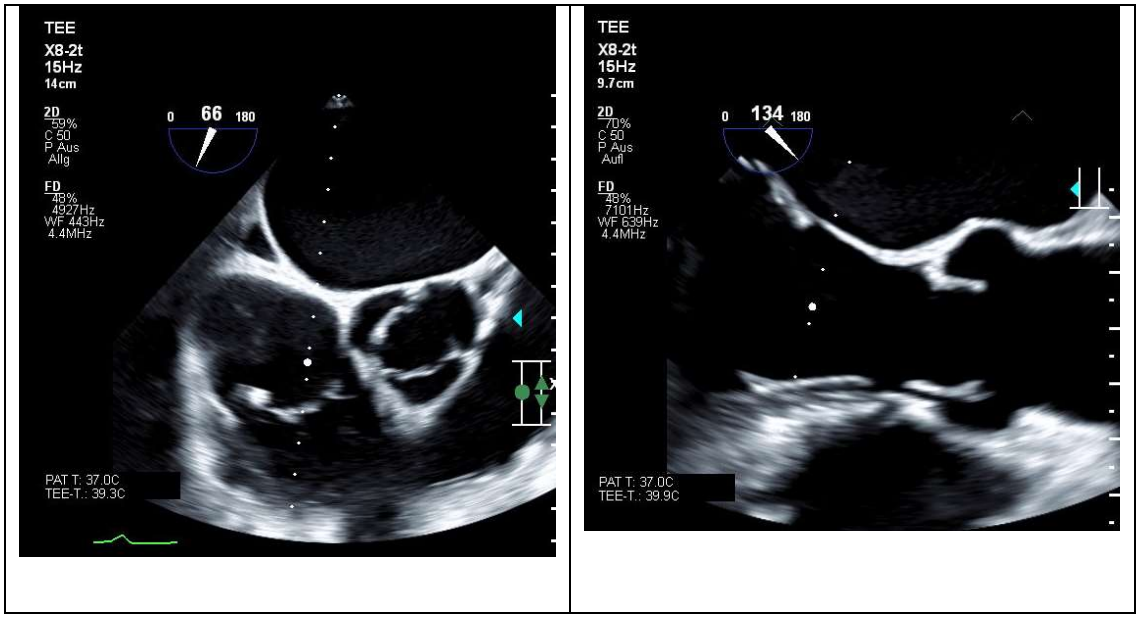


Figure 2

demonstrates a standard TEE view of a healthy aortic valve; on the left-sided panel, there is a typical short axis view of a normal trileaflet aortic valve, displaying normal leaflets, not

absence of calcification; on the right side, there is a long axis LVOT view displaying normal separation of the aortic cusps. Adapted from Larson et al. (6)

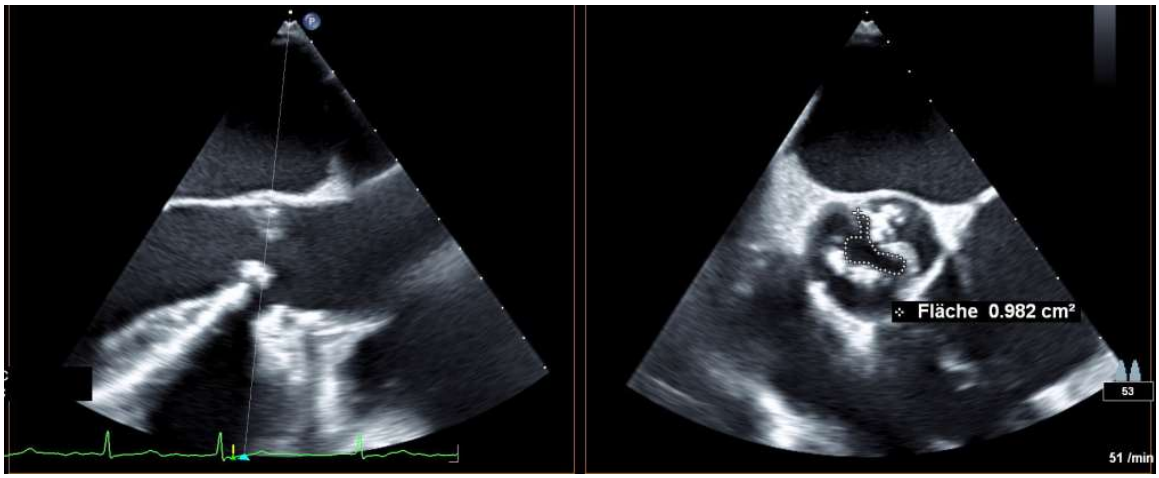


Figure 3: Significant aortic stenosis detected by transesophageal echocardiograms. The axial view in theleft-handed panel demonstrates symmetrically thickened and calcified leaflets that have a reduced excursion, and the right panel demonstrates a reduced aortic valve area of ca. 1 cm-2, demonstrated: diagnosis and treatment, adapted from Larson JM (6).

Diagnosis

Stages of Valvular AS

Accurate diagnosis and evaluation of the AS stage are essential for the proper management of the case, (table 2) demonstrates the different phases of AS that range from stage A (at risk) to stage D (symptomatic). Case indications, valve hemodynamics, valve anatomy, and alterations in the vasculature and LV are the criteria utilized to identify each stage of AS(Otto et al., 2021a).

1- **Stage A:** patients with morphologically abnormal valves (e.g., bicuspid aortic valve) but with preserved motion and normal transvalvular velocity < 2m/s.
2- **Stage B:** those patients have morphologically abnormal valves with calcification and restricted motion. Those patients are further divided according to the maximal velocity and mean gradient into mild (Vmax between 2- 2.9 m/s and mean pressure below 20 mm Hg) or moderate (Vmax between 3.0-3.9 m/s and mean pressure between 20-39 mmHg).

3- **Stage C (asymptomatic):** severe aortic valve stenosis characterized by severely affected aortic valve morphology with heavy calcification and severely decreased leaflet motion. This is diagnosed by increased Vmax >4/ms and/or mean gradient >= 40 mmHg. The index aortic valve is usually less than 0.6 cm-2/m-2, which supports but is not needed for the diagnosis. This can be further categorized according to hemodynamics as follows:
Stage C1: the EF remains normal, and some LV abnormalities like hypertrophy or diastolic dysfunction are observed.
Stage C2: this is characterized by mildly depressed LV function (EF<50%)

4- **Stage D (symptomatic):** presents with typical symptoms of aortic valve stenosis. This may include effort angina, dyspnea, or syncope. This stage can be further classified to
Stage D1 (symptomatic severe high gradient aortic valve stenosis): echocardiographic criteria are similar to stage C1.
Stage D2 (low-flow, low gradient aortic valve stenosis): characterized by the occurrence of overt heart failure symptoms and reduced ejection fraction <50%. The reduction of the ejection fraction leads to consequently lower mean gradients and peak velocities across the aortic valve. However, upon dobutamine stress echocardiography, the gradients increase to meet the definition of classical aortic valve stenosis.
Stage D3 (severe low-flow, low-gradient aortic valve stenosis with preserved ejection fraction): although the ejection fraction is preserved in those patients, the echocardiographic criteria are not met in those patients. This occurs because of a small LV cavity and reduced stroke volumes (usually <35 ml/m2).

Diagnosis

On normal physical examination, a systolic murmur frequently discloses the AS diagnosis; hence, transthoracic echocardiography (TTE) is advised.

A significant community-based investigation found that auscultation-based valvular heart disease identification has low sensitivity and specificity via both general practitioners (specificity 69%, sensitivity 44%) and cardiologists (specificity 81%, sensitivity 31%). Regrettably, a systolic murmur on the physical investigation is an inaccurate finding both for the suspected diagnosis or for the assessment of the degree of stenosis severity (Gardezi et al., 2018)

TTE is suggested in the following conditions: cases with a newly diagnosed systolic murmur, a history of the bicuspid aortic valve (BAV), a single-second heart sound, or any other symptoms suggesting AS.

Structurally abnormal valve (either calcified and thickened or with congenital abnormality) that results in motion restriction and evidence of hemodynamics obstruction made by Doppler assessment.

Repeat TTEs are recommended for asymptomatic patients with AS to monitor the progression of disease severity from mild to severe.

According to the degree of AS, TTE can be repeated according to the following time intervals: every three to five years, one to two years, and every six to twelve months (unless previous imaging is necessary for an alteration in clinical symptoms or signs) for mild, moderate and severe degrees consecutively. (Harris et al., 2020)

Treatment

Medical Therapy

Symptoms of AS do not appear as AS is a deliberately advanced disease, so significant indications seem late in the way of AS after the development of sclerosis and obstruction. The aim of medical therapy is to slow the progressive calcification and fibrosis so as to prevent the obstruction of the Aortic valve; however, there is no single medical therapy that has proved to be significantly beneficial in treating or even preventing the progress of AS. (Yan et al., 2017)

No benefit from statin in valve-associated consequences in adults with asymptomatic stenosis regardless of the stenosis severity except in very severe (critical) stenosis, according to published Randomized trials; however, statin therapy played an essential role in the reduction of rates of ischemic events.

One crucial factor to point to is that these trials were after the detection of the obstruction, and the follow-up was for a short period, so the long-term effect was not assessed, and so is unknown. The control of the precipitating cardiovascular factor may attenuate the disease's course.(Chan et al., 2010; Cowell et al., 2005; Rossebø et al., 2008)

The existing guidelines focus on controlling cardiovascular factors and comorbid conditions, mainly hypertension. (Table 3) Angiotensin receptor-blocking drugs and angiotensin-converting enzyme inhibitors may be beneficial in decreasing left ventricular (LV) fibrosis in AS. Also, smoking cessation is recommended to protect against atherosclerotic events.

Guideline Recommendations	AHA/ACC
Optimal treatment of hypertension in patients with AS reduces cardiovascular event rates	I
Lipid lowering therapy has not been shown to be beneficial for valve-related outcomes in patients with mild-moderate AS	III: No benefit
Evidence Gaps	
Does control of cardiovascular risk factors over a patient's lifetime lead to decreased likelihood or later onset of development of AS?	
Are there medical therapies that can target the specific pathophysiology of AS to prevent or slow progression of AS?	

AHA/ACC Recommendations for medical therapy in patients with AS.[1] European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines do not include recommendations for medical therapy in AS.
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AS, aortic stenosis.
Class I (green) indicates a strong recommendation with benefit greatly exceeding risk.
Class III (red) indicates there is no benefit and this treatment is not recommended.

Table 2 ACC/AHA recommendation for medical treatment of aortic stenosis(Otto et al., 2021b)

Timing of Intervention

Intervention's ideal timing for AS requires evaluation and consideration of different factors, so the decision is complex. For the asymptomatic patient, if left untreated, there is a risk of sudden death from cardiac events or left progressive worsening in the form of fibrosis, calcification, and, finally, obstruction.

On the other hand, both open surgical, minimally invasive surgical, and catheter-based (TAVI) are efficient and safe, but these therapies are not without risk.

Also, endocarditis, thromboembolic events, and bleeding from anti-coagulation treatment are risks of intervention. (Harris et al., 2020)

In the last ten years, there have been a series of trials contrasting TAVI with surgical standard treatment (SAVR) as an established standard of treatment with available long-term data, including the whole surgical risk spectrum. (Leon et al., 2016; Mack et al., 2019; Popma et al., 2019; Reardon et al., 2017, 2017; Smith et al., 2011; Thyregod et al., 2015) Surprisingly, the less invasive TAVI valves were associated with excellent short and mid-range outcomes, which led to a paradigm shift, at least in the US guidelines.

In the results shown, there were comparable 5- years of midterm follow-up when contrasted to SAVR. TAVI had a lower rate of stroke (Windecker et al., 2022)

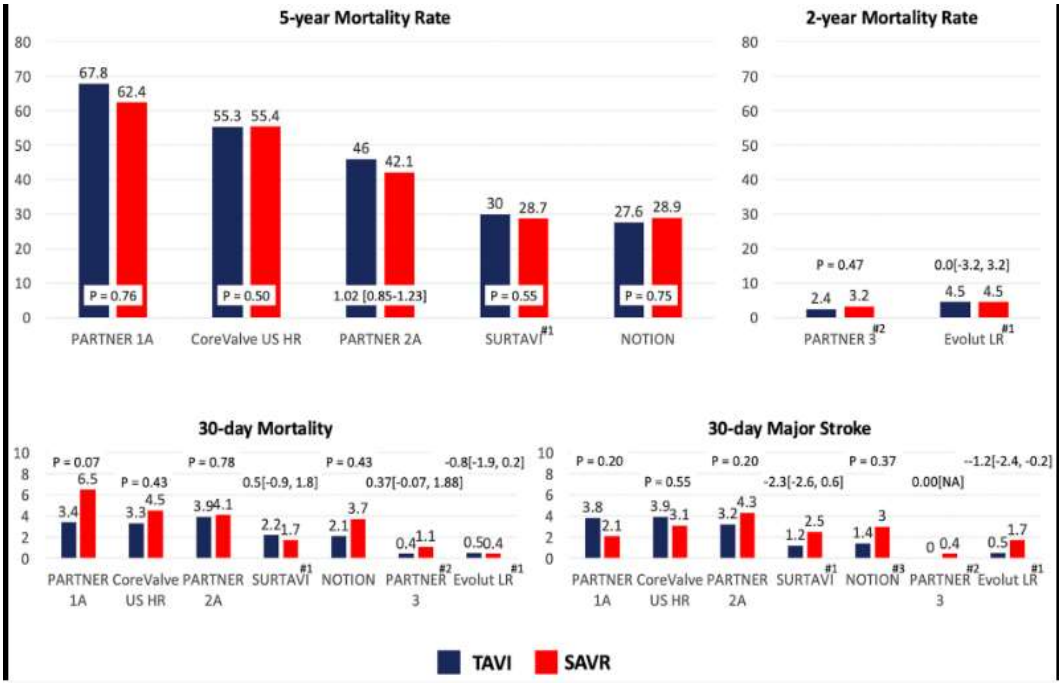
This led to guidelines for transcatheter technology for patients above 65 in the USA, leading to the wide adoption of transcatheter technology(Otto et al., 2021b). The ESC guidelines still use 75 years as the cut-off for decision-making(*2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease | European Heart Journal | Oxford Academic*, n.d.).

Table 3 Summary of ESC/EACTS and ACC/AHA recommendation(Windecker et al., 2022)

2020 ACC/AHA Guideline for Valvular Heart Disease's Management				
Individuals with severe AS, symptoms, and any indication of AVR who are under 65 years old or who have a life expectancy of more than 20 years.			I	A
Individuals with severe AS symptoms between the ages of 65 and 80 who are not ineligible for transfemoral TAVI anatomically	I	A	I	A
Age>80 or younger individuals with severe AS who have a life expectancy 10 years and no anatomical contraindication to transfemoral TAVI	I	A	IIa	A
Ages 65 to 80, asymptomatic patients with a severe LVEF and AS <50%, and no anatomical contraindications to transfemoral TAVI	I	B-NR	I	B-NR
Fast progression, very severe AS, a high BNP level, or asymptomatic cases of severe AS with an irregular exercise test			I	B-NR
Transfemoral TAVI is not appropriate in cases with an AVR sign but with abnormal valve or vascular anatomy or other reasons.			I	A
Symptomatic cases of any age with severe AS and a great or prohibitive surgical risk (anticipated life expectancy >12 months)	I	A		
2021 ESC/EACTS instructions for the Valvular Heart Disease's Management				
Younger (<75 years) cases who are low risk for surgery (STS-PROM/EuroSCORE II <4%) or cases who are operable and inappropriate for transfemoral TAVI			I	B
Older (≥75 years) cases, or those who are at risk (STS-PROM/EuroSCORE II >8%) or inappropriate for surgery	I	A		
Residual cases, as per individual anatomical, clinical, and procedural features	I	B	I	B

*The table is adapted from (56)

Figure 4 Outcome of RCT comparing TAVI vs. SAVR (Windecker et al., 2022)



Consequences of significant randomized clinical trials in the short- and long-term. Intention-to-treat analyses produced outcomes for PARTNER and SURTAVI trials. The outcomes of the as-treated analyses for U.S. CoreValve High Risk, NOTION, and Evolut Low Risk are presented. Findings are presented with differences (SAVR vs. TAVI) and a 95% Bayesian credible interval in item #1. #2: Results are shown with 95% confidence intervals and hazard ratios. 3. Any spark.

Besides surgical risk, as calculated with standardized risk scores like STS and Euro-SCOREs, the heart team should take multiple factors into account. This includes concomitant cardiac morbidity and extracardiac factors, as well as patients' wishes. It is of utmost importance to consider lifetime management in the case of younger patients treated with transcatheter technology, as it is likely that the patient requires a 2nd TAVI procedure. This is summarized in Figure 6 (Windecker et al., 2022)

Table 4 Factors that favor TAVI vs. SAVR

	Favors surgery	Intermediate group	favors TAVI
Age	65 or less	65 to 75	over 75
Surgical risk	low	intermediate	high
Frailty	absent to low	moderate	severe
Femoral vessels	prohibitive	intermediate	suitable
concomitant valvular pathology	severe (AR/MR/TR)	Severe 2ry MR or moderate MS/AR/MR/TR	mild
CAD	3-vessel with SYNTAX-SCORE>22 or LM Disease >SYNTAX 32	intermediate	mild
Other factors	other factors that should be considered are porcelain aorta, previous radiotherapy to the mediastinum, previous sternotomy, chest deformation, previous stroke, severe COPD		

TAVI Procedure:

Once the heart team has decided whether the patient should be eligible for TAVI implantation, the patient should go through a standardized preprocedural workup. It encompasses the following:

1- Transthoracic cardiac echocardiography

2- Proper computerized tomography with a 3-D reconstruction of the access location and landing zone. It is highly recommended to utilize standardized reporting methodologies and checklists to eliminate primary procedural considerations, which can be mitigated by thorough preprocedural assessment. A standardized TAVI approach should include the following:

1- Vascular assessment: this should include the vessel's diameter, degree of tortuosity, and calcification. To avoid unintended high puncture and to alleviate the risk of vascular issues, the level of femoral bifurcation should also be noted. A bare minimum of 5.5 mm diameter is required for current-generation devices to enable safe sheath placement

(Cahill et al., 2018). In the case of complex vascular anatomy, a preparatory vascular surgery consult should be sought. When dealing with vascular complications, it is crucial to have the proper equipment. Among these are various vascular closure devices (for example, Perclose or MANTA systems), covered stents, peripheral wires, and sheaths. In instances of limited diameter or calcification, it is safe to predilate the iliac vessel using particular balloons, such as intravascular lithotripsy balloons(Sawaya et al., 2021).

2-Aorta assessment: notice the degree of calcification and tortuosity. Excessive aortic calcification elevates the likelihood of stroke and should be handled in advance. If there is extensive angulation between the aortic root and the annular plane, such as a horizontal aorta, then further techniques might be needed to realign the valve to the annular plane. Utilizing a deflectable sheath (e.g., Edwards Inc.'s commander system) might offer some advantages for getting coaxially with the annulus.

3- Measurement of the annulus:

- annular dimensions, encompassing minimal, maximal, and average diameters; the annulus is often epileptoid in shape, which cause additional difficulty in sizing the prosthesis. To overcome those challenges, several methods are used by different manufacturers, including area-derived perimeter and perimeter methods.

-Valsalva sinus diameter: a minimum of 30 mm is necessary, and a height of 15mm (Piazza et al., 2012). A narrower SOV increases the likelihood of coronary occlusion.

-Diameter of the sinotubular junction:

-LVOT diameter and degree of calcification: the degree of calcification raises the probability of annular rupture.

4- Valve morphology: identify the valve morphology, such as bicuspid vs. tricuspid. It is crucial to highlight the degree and propagation of calcification.

5- Membranous septum length: due to its close interaction with the conduction system, certain studies have found that a short membranous septum corresponds with the onset of conduction problems.

6- Coronary height: a minimum coronary height of 9 mm is required; a smaller size could result in coronary obstruction after implantation due to the native leaflet obstructing the coronary ostium.

7- Fluoroscopic implantation angle reconstruction. It is possible to mimic the fluoroscopic implantation angles using 3D reconstruction. Different methods, including the coplanar view frequently used for balloon-expandable valves, are explained. This view (usually LAO/Cranial) aligns the three cusps with the non-coronary cusp on the left side, with the aim of implanting the valve 2-3 mm below the annular plane. A recently reported approach is the cusp overlap view, in which the operator overlaps both the left and right coronary cusps to allow for shorter implantation. This has been shown to allow shallow implantation with a lower number of postoperative conduction disturbances and pacemaker implantations without increased risk for valve embolization. This approach has been useful, especially in the case of self-expanding valves.

TAVI Prosthesis Types:

1- Self-expandable valves (for example, the Medtronic Evolut platform): These prostheses require appropriate general pre-dilatation to allow valve delivery.

2- Balloon-expandable prosthesis (such as the Edwards SAPIEN valve): this prosthesis is pre-mounted on balloons. These valves prevent prosthesis recapture.

When selecting a prosthesis, it is best to follow the manufacturer's recommendations. These instructions vary depending on the type of implanted prosthesis. Several factors should be considered throughout the prosthesis selection process.

Procedures for Implantation

1. Obtaining femoral access: This is traditionally accomplished using palpation and fluoroscopy, with the goal of aiming for the femoral head's middle and avoiding bifurcation. Several strategies for reducing complication rates are presented, including ultrasound-guided puncture and micropuncture techniques. It is feasible to execute a surgical cut-down of the femoral vessel if access is problematic. Secondary arterial access is necessary to advance the angiography catheter (e.g., Pigtail catheter) to the aortic root. The contralateral femoral artery is the most common entry point. Radial access, on the other hand, is conceivable. Secondary access is also essential in the case of endovascular access site difficulties.

2- Preclosure techniques: planning ahead for the vascular closure strategy is critical. Suture-based closure with the Proglide-device is the most widely utilized approach. Many

different combinations have been described (for example, double Proglide or single Proglide in combination with a plug-based device, such as Angioseal). Suture-based closure is correlated with a decreased incidence of significant vascular problems when contrasted to plug-based systems, according to recent research (Manta device). The scope of this study does not allow for detailed discussions of both procedural steps.

3- Access sheath placement: the large bore sheath is often advanced over the stiff wire (for example, Safari wire). The Medtronic core valve also allows for a sheathless approach.

4- Crossing the aortic valve: the standard method involves probing the surface of the valve with a straight hydrophilic wire (e.g., Terumo wire). The standard catheter is a curved tip catheter, such as the Amplatz left catheter. To avoid unintentional ventricular puncture, take care not to advance the wire. Following the catheter passage, the stiff wire should be carefully positioned in the ventricle, making a loop and avoiding contact with the papillary muscles.

5- Rapid pacing preparation: a conventional transvenous pacemaker is implanted in the RV apex and checked to ensure appropriate pacing. Fast pacing is essential for implantation to cause transient circulatory arrest, thus preventing valve aortic embolization.

6- Balloon valvuloplasty: aortic valve pre-dilatation is at the discretion of the operator. It helps with valve expansion and simplifies valve distribution over the native aortic valve, but it bears a minor risk of aortic annulus rupture and severe acute valve regurgitation. It is an optional procedure that depends on the degree of valve calcification, valve area, and prosthesis type.

7- Implantation techniques: the standard implantation techniques vary according to manufacturer recommendations. In general, the aim is to implant the valve to ensure a stable postimplant position without the risk of embolization. Without implanting the valve deep in the LVOT, it can lead to conduction disturbance and paravalvular regurgitation. Another important target of the implantation is to preserve coronary access. This is highly relevant in the case of known CAD or younger patients who may need coronary intervention in their lifetime.

Complications of TAVI Procedure:

1- Access-Site Issues

The fundamental factor behind vascular access-site complications is the mismatch between the delivery system's sheaths and the diameter access artery. The presence of calcification and severe tortuosity elevates the risk of issues in the case of a diameter less than 6 mm, which is an alternative TAVI-Access (e.g., transapical). In case of unexplained hypotension, it is advisable to perform angiography of the access site. Treatment options include endovascular treatment and surgical repair.

2- Annular injury or rupture.

Although a rare (1%) preventable consequence, the device landing zone's rupture carries a significant mortality risk of 48–50% (Barbanti et al., 2013). Significant valve oversizing and considerable annular, sub-annular, and left ventricular outflow tract calcifications were found to be predictors of this complication (Blanke et al., 2012). In case of hypotension immediately after valve implantation or after post-dilatation, TTE and /or TEE should be performed immediately to confirm the diagnosis. In the case of aortic wall hematoma, conservative management may be tried; however, in the case of severe.

3- The aortic valve of the aorta regurgitation

There are primarily two types of aortic valve regurgitation seen with TAVI.

Leaks in most subjects (between 50% and 85%) have paravalvular leakage. Up to 24% of them have moderate or severe leakage, which can increase the procedure's mortality rate by up to 4 times in the first year (Athappan et al., 2013) despite the fact that the majority of them have minor leaks. Paravalvular leaks can be produced by three factors: (3) inadequate stent apposition brought on by malformed native structure. (1) A mismatch in size between the prosthetic valve and the annulus. (2) An improper placement of the prosthetic valve.

The degree of aortic root calcification and its geometrical distribution have the biggest effects on the native structure. Paravalvular leaking could result from significant, asymmetrical calcifications that damage the prosthesis and induce deformation. By employing an echocardiographic examination and/or the Agatston score to assess the aortic

root calcification, it would be feasible to lower the risk of paravalvular leak(Ryś et al., 2018).

If there are any issues, an aortic root angiography is carried out to determine the degree of leak. For the purpose of validating the leak's severity and the prosthetic valve, intra-procedural echocardiography's location may be used. Additional evidence that the diagnosis is accurate is provided by the increased left ventricular end-diastolic pressure and decreased aortic diastolic blood pressure. If the leak is central, the problem might be fixed, depending on the situation, by gently probing the leaflets with a soft wire and/or catheter or by inserting a second prosthetic valve. The best way to handle paravalvular leakage is up for debate. While being considered non-progressive, moderate degrees are permitted when they are accompanied by clinical supervision. Larger leaks may need additional care as well. The first option, which makes use of a somewhat bigger balloon, is known as balloon post-dilatation.

Other treatment possibilities include implanting a second artificial valve, repositioning the prosthetic valve already in place, and percutaneous vascular occlusion devices.

4- Malposition and Embolization

Incorrect positioning of the valve typically happens throughout or right after valve implantation; nevertheless, in very rare occurrences, a late malposition has been described. In the event of problems, trans-esophageal echocardiography and aortography are done to validate the prosthetic valve’s position and confirm any mispositioning or migration.

Treatment outcomes depend on the kind of prosthetic valve, the patient's final positioning, and their hemodynamic status. The prosthetic valve for a self-expanding one may be deployed or recaptured to the descending aorta if it is still connected to the delivery system. If not, it might be caught in the aortic direction, or a second artificial valve could be placed through a surgery called a valve-in-valve. An inflated balloon inside the prosthetic valve might move it towards the descending aorta to aid in the balloon-expandable valves' migration. The prosthetic valve and SAVR must be quickly removed surgically; if bailout methods are unsuccessful, the surgical explanation should be performed.

5- Coronary obstruction

The risk reasons for coronary obstruction involve a small sinotubuler junction, a narrow sinus Valsalva, a low sinus Valsalva height (30 mm), a large prosthetic valve, and a short coronary ostium height.

The most popular reason for coronary obstruction is calcific aortic valve leaflets sealing the coronary ostium, and it has also been observed that women and individuals who have already had surgical bio-prosthesis are more likely to develop this problem.

Signs of coronary occlusion can include acute hypotension, segment (ST) elevation, cardiac arrest, and/or ventricular arrhythmias. An urgent aortogram or targeted coronary angiography with stent placement should be done owing to the great risk of hemodynamic collapse. The case might be given mechanical circulatory support to give the medical staff more time to react. Since percutaneous coronary intervention was unable to solve this issue, coronary bypass grafting is required.

6- Stroke: 1.1% of procedures result in cerebral infarction (1.9% with transapical techniques versus 0.8% with trans-arterial approaches) (Khatri et al., 2013) Peri-procedural stroke can be brought on by a number of things, such as hypotension, micro-embolism in the coronary arteries, the myocardium's compression owing to the prosthetic valve's enlargement, and injury to the ventricular apex brought on by the trans-apical technique. Stroke can occur within a month of TAVI Implantation. The principal sources of embolic material, according to studies, were the aortic wall or native aortic valve leaflets (Van Mieghem et al., 2013).

7- Pericardial tamponade

As a result of pericardial hemorrhage, around 3%–4% of patients who undergo TAVI develop cardiac tamponade, which has a significant Death risk (24%) (Rezq et al., 2012).

8- Conduction disturbance

Damage to the conduction system is one of the main side effects of TAVI, which can result in the following: (1) extended atrioventricular (AV) conduction time; (2) AV block; (3) left bundle branch block; and (4) the requirement for a pacemaker implant. Conduction anomalies can happen after TAVI at a rate of 5.7% to 42.5% (Bates et al., 2011). Transvenous pacemaker implantation with conversion to a constant pacemaker is the most typical course of medication for these complications.

9- Acute renal failure:

It occurs in about 22% of TAVI patients, and 8.4% of those patients (8.4%) have stage 2 or stage 3 acute renal injuries (Takagi et al., 2013). Chronic renal disease, peripheral vascular disorder, diabetes mellitus, hypoperfusion throughout fast ventricular pacing, and aortic plaque embolism in the renal arteries are all risk factors for acute renal damage. In the event of any renal difficulties, nephrotoxic pharmaceutical use should be halted and hydration treatments initiated. If necessary, hemodialysis may be an alternative for therapy.

Methodology & statistical analysis

Aim of the Study

The aim of the study is to evaluate the performance of different transcatheter valve technologies, i.e., (balloon-expandable vs self-expanding valves). In cases with severe aortic valve calcification, it is defined as calcium volume that is higher than 700 mm/cm-2 in the preplanning CT. The study included two groups of valves, which are the balloon-expandable valves (SAPIEN S3/Ultra Valve, Edward) and self-expanding valve prosthesis (Evolut Pro and Evolut R, Medtronic). The incidence of the paravalvular leak is the main endpoint for determining the performance of the valve. For the secondary end points, we chose the hemodynamic performance of the valves. As secondary endpoints, we registered all VARC-3 criteria.

Study Design and patient population

We carried out a retrospective, non-randomized cohort analysis with cases who underwent TAVI at five high-volume heart centers in Germany (University clinic Kiel, Cardiac center Bad Segeberg, University Clinic Düsseldorf, University Clinic Köln, Heart and Diabetes Center Bad Oeynhausen) between July 2013 and January 2021 and had symptomatic aortic stenosis with severely calcified aortic valves. By employing the FDA- approved 3Mensio software (Pie Medical Imaging) or an Agatston score higher than 3000 HU by conventional CT-analysis. We were able to identify 1517 individuals with a severely calcific aortic valve annulus, which is indicated by a calcium score of more than 700 mm2 (Pawade et al., 2018). The final analysis included 1513. The incidence and severity of the paravalvular leak (PVL) after TAVI served as the primary outcome. Secondary endpoints included clinical outcomes in accordance with the VARC-3 definition, as well as the hemodynamic performance of the valve as assessed by THV- Area and pressure gradients inside the THV. (null et al., 2021)

Device selection: The selection of the device and access was left to a multidisciplinary heart team comprising cardiac surgeons experienced in TAVI procedures and interventional cardiologists. The sizing recommendation was dependent on the company's recommendation and based on preoperative cardiac CT.

The study, which was done in accordance with the Declaration of Helsinki, received permission from the local ethics board. Before any action was taken, each patient gave their informed consent for the intervention.

To summarize the inclusion criteria

1-severe symptomatic aortic valve stenosis

2- heavily calcified aortic valve as defined per calcium score >700

3- undergoing TAVI procedure after multidisciplinary heat team discussion

4-Undergoing TAVI procedure using the following prosthesis 1- Evolut R 2- Evolut Pro and 3-SAPIEN-3/3 Ultra

Exclusion criteria were

Valve-in valve procedures.

Prosthesis other than the above-mentioned prosthesis

Missing valve type

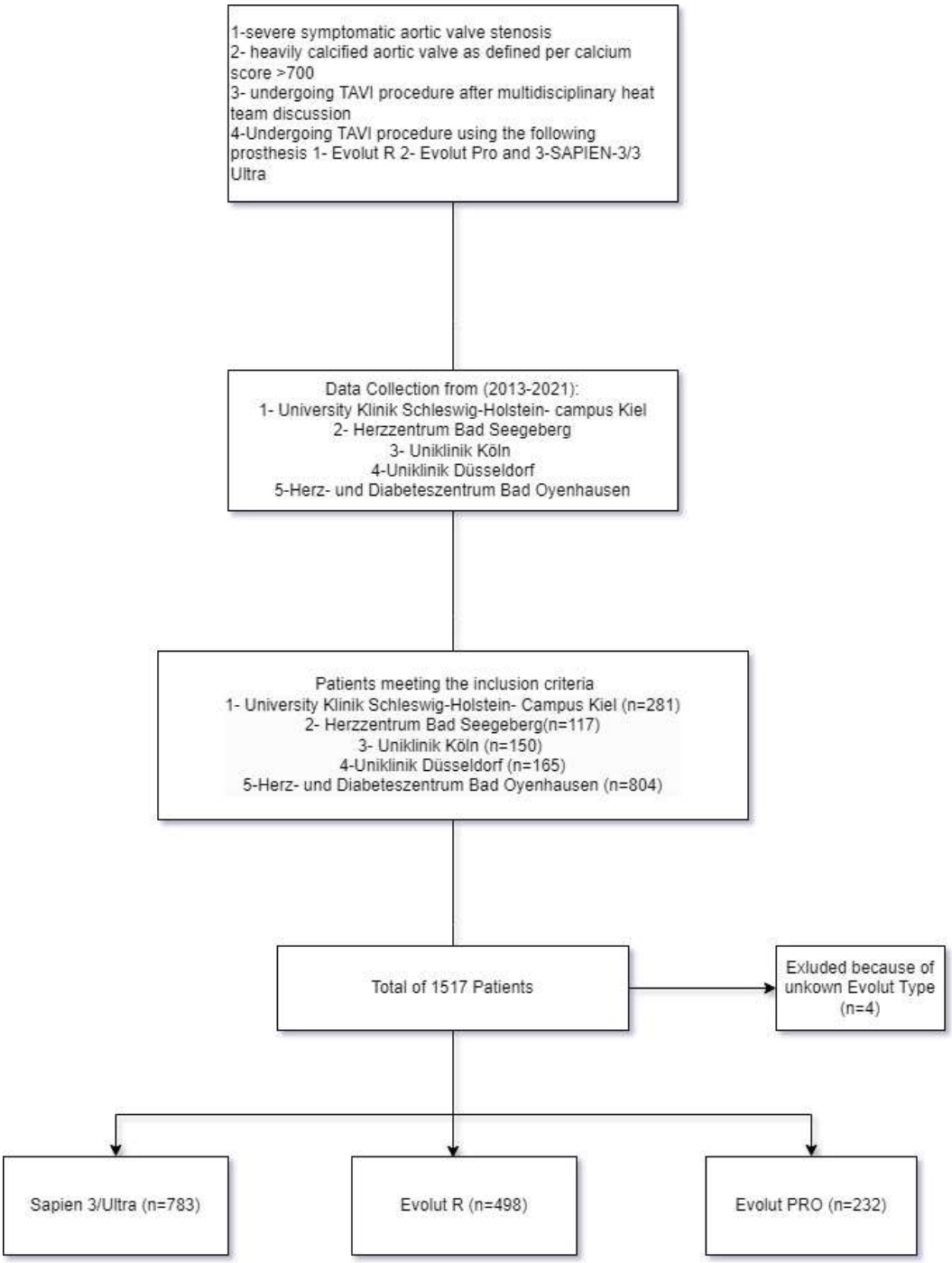


Figure 5: Study design

Endpoints of the Study

1- Primary endpoints were: is the presence or absence and degree of paravalvular regurgitation in postoperative echocardiography,
2- The secondary endpoint was the valve hemodynamics (peak gradient, mean gradient) across the THV, which detected the THV area, and the clinical endpoints, which were standardized using VARC-3 criteria.

Definition of endpoints:

The VARC 3 consensus document was utilized to categories procedural endpoints and adverse events. In-hospital deaths, pericardial tamponade, device embolization, strokes, significant bleeding, and vascular access issues were among the periprocedural complications.

Procedural details

All TAVI procedures were performed by experienced and certified operators according to the standards of best clinical practice using either the SAPIEN-3/3 Ultra THV or CoreValve Evolut R/PRO. The selection of THV type was left at the implanting operator's discretion after a standardized comprehensive preprocedural workup. Therefore, the implanting operator also decided whether pre-dilatation and post-dilatation were necessary. Unfractionated heparin was given throughout the TAVI surgery to raise an active clotting time of 250–300 s, achieving effective systematic anticoagulation. The MANTA® vascular closure device (Teleflex, Morrisville, NC, USA) or two Perclose ProGlideTM vascular closure systems (Abbott Laboratories, Chicago, IL, USA) were typically utilized to close the vascular access.

All patients underwent assessment and consent by a qualified anesthetist. The choice of different anesthetic modalities was left to the discretion of the local heart team. After a comprehensive risk assessment, each patient received either general anesthesia or conscious sedation. A cardiac anesthetist was present during all the procedures as it is a legal requirement by the German Federal Health Authority (GBA-Beschluss). The choice of anesthetic agents in the TAVI procedure was left to each local team member.

Transthoracic echocardiography, contrast angiography, and, in certain cases, transesophageal echocardiography were utilized to guide the implantation.

Pre- and postoperative assessment:

Prior to the approach, all cases received a comprehensive assessment of the aortic valve, which included transthoracic echo (TTE) for assessment of ejection fraction by Simpson's methods, mean and peak aortic valve gradients by continuous wave Doppler, assessment of aortic valve area (AVA) utilizing the continuity equation. Validation of mitral valve with the quantification of mitral regurgitation. The standardized validation included a left heart cauterization and comprehensive cardiac CT assessment of the aortic root. Measurements were obtained to validate the calcification degree of the leaflet and LVOT.

All Patients underwent standard risk assessment utilizing the Society of Thoracic Surgeons Score (STS-Score) and EuroSCORE. Each patient was discussed in the interdisciplinary heart team conference, which included an interventional cardiologist, cardiac surgeon, and cardiac anesthesiologist.

Data collection:

The demographic data of all cases involved in the study were collected retrospectively, including age and sex; also, the comorbidities and risk factors correlated with both groups of the study were collected and analyzed.

Based on preoperative MSCT scans, we evaluated the level of the aortic valve cusps' calcification and the left ventricular outflow tract (LVOT) using FDA-approved software from 3mensiow Medical Imaging (Bilthoven, the Netherlands). With the Biograph mCT 128 (Siemens Healthcare, Siemens AG, Erlangen, Germany), cardiac MSCT that was triggered by electrocardiography (ECG) was captured at an RR interval of 60–70%. Pomerol was injected intravenously in an amount of 60–70 mL, with a 0.6 mm slice thickness. The region of interest for calcium measurement was the aortic valve cusps, which spanned from the basal plane to the origin of the lower coronary artery or 15 mm above the basal plane (whichever was nearer the basal plane). The volume extending from the basal plane to 10 mm below the basal plane made up the LVOT window. Each voxel that was more than 450 Hounsfield units (HU) was considered to have "calcium. "The threshold was manually modified if this value did not effectively capture the calcium.15

To determine the calcium volume, all voxels above the cutoff were added together (Figure 1). 3mensiow provides a mask in the form of a three-pointed "Mercedes" star with adjustable arms that adjust to different patient anatomy, allowing for the assessment of each cusp separately (Figure 1B). The data were examined to see if there were any connections between the calcium load on the valve cusps, LVOT, and the requirement for PPI. Two representative individuals were selected for an ex vivo simulation on the basis of these findings: one with a high risk of PPI who received PPI and one with a low risk who did not need PPI. The simulation did not include patients who had known patient- or procedure-associated risk factors (RBBB, severe oversizing, post-dilation).

Statistical analysis

Continuous normally distributed were summarized using mean (M)/standard error (SE) while categorical variables were summarized by numbers (n)/ total (N) (percentages (%)). To balance baseline patient characteristics as well as missingness in those covariates, we used inverse propensity-score weighting (IPSW) to equalize pretreatment differences between groups. To do this, we used the R programming language (The R Project for Statistical Computing, Vienna, Austria) and the Toolkit for Weighting and Analysis of Nonequivalent Groups package.

To achieve balance, we used a generalized boosted model with multinomial inverse propensity-score weighting using an average treatment effect (ATE) design for propensity scoring and the largest mean pairwise effect size, as described by McCaffrey et al., which included age, sex, BMI, presence of medical conditions such as hypertension (HTN), diabetes mellitus (DM), Hyperlipoproteinemia, coronary artery disease, peripheral artery disease, history of stroke, NYHA class, permanent pacemaker, mean pressure gradient (pre-valve implantation), aortic valve area, Agastone score, preoperative left-ventricular ejection fraction, and the presence and absence of bicuspid aortic valve, LVOT calcification, preoperative NT-proBNP, preoperative, hsTNT and preoperative glomerular filtration rate (GFR).

The effect of IPSW analysis on sample size was assessed by determining the effective sample size. The assumption that the three experimental cohorts had a non-zero

probability of receiving each treatment was confirmed by inspecting the overlap of the empirical propensity score distributions. Variables differing between groups were identified using either the Chi-square or Fisher's exact test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. All analyses were conducted twice: once unadjusted and once IPSW-adjusted.

The maximum pairwise standardized mean differences (SMD) of baseline attributes were identified to determine the balance among the three cohorts. To correct residual imbalances (SMD > 0.1), a double adjustment logistic regression analysis with all unbalanced covariates as predictors and sequentially using each outcome as a dependent variable were used. This strategy was proven to be successful in removing the residual confounding bias[4]. Results of the logistic regression analyses performed on the outcomes were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Hospital Assessment of Adverse Events

For 24 hours after the approach, all cases were followed up for periprocedural negative events involving deaths, stroke, major bleeding, systemic embolization, transient ischemic attack (TIA), device embolization, and significant pericardial effusion or cardiac tamponade by transthoracic echocardiography early after the approach, 3 hours later and later according to the clinical picture.

Major bleeding is described as bleeding that is fatal, obvious bleeding with a drop in hemoglobin level of at minimum two g/dL, needing transfusion of at minimum two units of retroperitoneal hemorrhage, packed blood cells, or bleeding results in hemodynamic instability.

Post-procedural Follow-Up:

All patients underwent a routine standard postoperative assessment. The assessment included standard laboratory panels, including renal function tests and cardiac troponin, electrocardiography, and transthoracic echocardiography. In case of suspected vascular complications, the patients underwent assessment with duplex sonography.

Results

The present study involved an overall of 1517 patients with heavily calcified AS receiving TAVI. In 4 patients, the exact type of Evolut prosthesis could not be determined and thus were excluded. Thus, the final analysis included 1513 patients. The CoreValve Evolut R was implanted in 498 cases (33.0%), the Evolut PRO in 232 patients (15.3%), and the SAPIEN-3/3 Ultra THV in 783 cases (51.8%). 2

IPSW Adjustment The optimal number of iterations used in the generalized boosted model was identified after initially running the mnps() command using the default 10,000 iterations; then, observing the average pairwise SMD-number of iterations plot, it was found that the minimum average pairwise SMD was achieved at 2000 iterations, after which, a higher number of iterations increased the average SMD (Figure 6).

Figure 6: balance of S against others

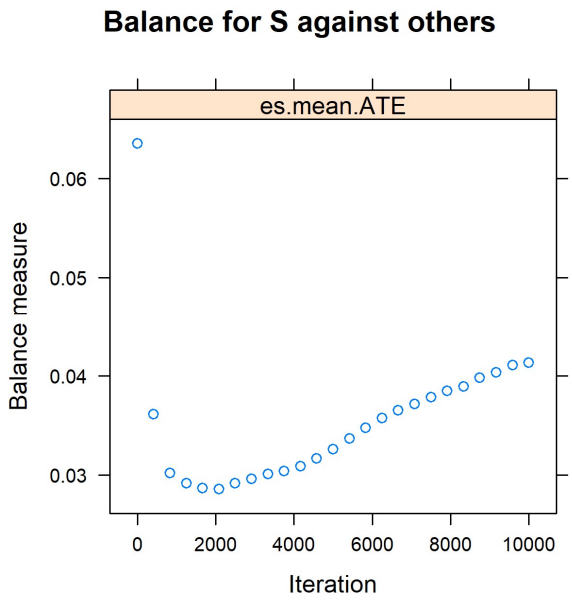
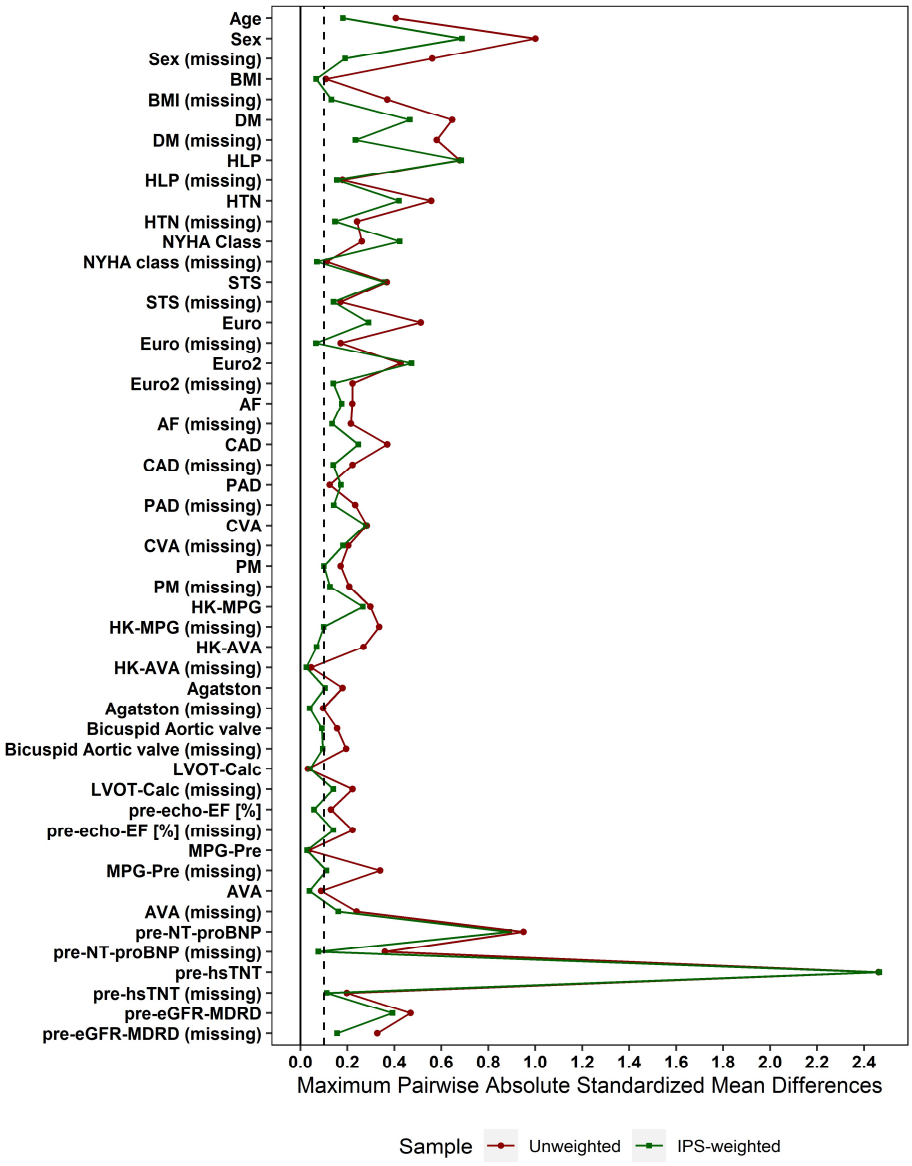


Figure 6 and Figure 7 represent the decrease in the maximum pairwise SMD and the increase in the minimum t- and chi-square p values for the pairwise comparisons between the three cohorts after IPSW, respectively. The three experimental cohorts had a non-zero

probability of receiving each treatment; this was confirmed by the overlap of the empirical propensity score distributions

Figure 7: maximum pairwise absolute standardized mean differences



Abbreviations: BMI: Body Mass Index, DM: Diabetes Mellitus, HLP: Hyperlipidemia, HTN: Hypertension, NYHA Class: New York Heart Association Class, STS: Society of Thoracic Surgeon Score, Euro: European risk Score, Euro2: European risk score 2, AF: atrial fibrillation, CAD: coronary artery disease, PAD: peripheral vascular disease, CVA: cerebrovascular accident, PM: pacemaker, HK-

Figure 8: Rank of the p-value for Pretreatment variables

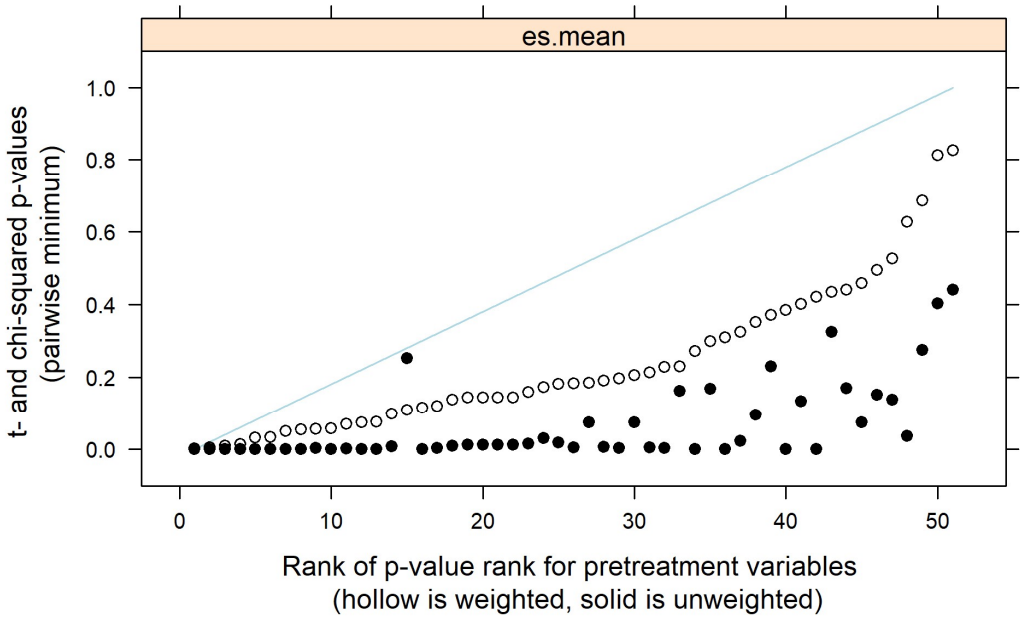


Figure 5

The effective sample sizes for the treatment groups after IPSW adjustment were found at 652 for Sapien3, 392 for Evolut R, and 141 for Evolut Pro, while the weighted counts generated by the model by considering the weights for each observation were 1319 for Sapien3, 1214 for Evolut R, and 947 for Evolut Pro.

Baseline Characteristics

Table 5 illustrates the baseline characteristics of patients undergoing transcatheter aortic valve replacement (TAVR) using the three different valve types: Sapien3 (S), Evolut R (ER), and Evolut Pro (Epro). The analysis revealed statistically significant differences among these groups in several variables, highlighting the need for adjustment.

Age and Sex: Patients in the Evolut R group were significantly older (82.4 ± 0.2 years) compared to those in the Sapien3 (81.4 ± 0.2 years) and Evolut Pro (81.8 ± 0.3 years)

groups ($p = 0.012$). Additionally, there was a higher proportion of female patients in the Evolut Pro group (50%) compared to Evolut R (42%) and Sapien3 (26%) ($p < 0.001$).

Body Mass Index (BMI): The Sapien3 group had a higher BMI (26.9 ± 0.2) compared to Evolut R (26.2 ± 0.2) and Evolut Pro (26.5 ± 0.3) groups, with the difference being statistically significant ($p = 0.014$).

Hyperlipoproteinemia and Atrial Fibrillation: The prevalence of hyperlipoproteinemia was highest in the Evolut Pro group (80%), followed by Evolut R (78%) and Sapien3 (66%) ($p < 0.001$). Atrial fibrillation was more common in the Sapien3 group (41%) compared to Evolut R (36%) and Evolut Pro (30%) ($p = 0.014$).

Log Euro Score and Euro Score 2: The Log Euro Score was significantly lower in the Evolut Pro group (15.6 ± 0.8) compared to Sapien3 (19.7 ± 0.5) and Evolut R (19.0 ± 0.6) ($p = 0.001$). Similarly, the Euro Score 2 was lower in the Evolut Pro group (4.5 ± 0.3) compared to Sapien3 (5.8 ± 0.3) and Evolut R (5.4 ± 0.3) ($p = 0.037$).

Agatston Score and LVOT Calcification: The Agatston Score, which measured the extent of aortic valve calcification, was significantly higher in the Sapien3 group (1422.0 ± 25.7) compared to Evolut R (1179.4 ± 26.3) and Evolut Pro (1354.9 ± 43.0) ($p < 0.001$). Left ventricular outflow tract (LVOT), calcification was most prevalent in the Evolut Pro group (75%) compared to Evolut R (62%) and Sapien3 (70%) ($p = 0.002$).

After the IPSW adjustment, only the Sex and Agatston Scores remained significantly different among the groups. A significant difference remained in the proportion of female patients across the groups. The Evolut Pro group had the highest percentage of females (45%), followed by Evolut R (42%) and Sapien3 (32%) ($p = 0.007$). Agatston's Score remained significantly different among the groups even after adjustment. The Evolut Pro group had the highest mean Agatston Score (1477.9 ± 176.7), followed by Evolut R (1253.8 ± 128.0) and Sapien3 (1035.9 ± 50.8) ($p = 0.030$). For the other variables, the IPSW-adjusted analysis showed no significant differences across the groups.

Table 5: Baseline characteristics of the overall cohort with comparison between the Sapien3, Evolut R, and Evolut Pro subsets before and after inverse propensity score weighting (IPSW)

Variable	Unadjusted Analysis					IPSW-Adjusted Analysis				
	Total (1513)	Sapien 3 (783)	Evolut R (498)	Evolut Pro (232)	p	Total (3480)	Sapien 3 (1319)	Evolut R (1214)	Evolut Pro (947)	p
	n/N (%) or Mean ± SE	n/N (%) or Mean ± SE	n/N (%) or Mean ± SE	n/N (%) or Mean ± SE		n/N (%) or Mean ± SE	n/N (%) or Mean ± SE	n/N (%) or Mean ± SE	n/N (%) or Mean ± SE	
Age, years	81.8 ± 0.1	81.4 ± 0.2	82.4 ± 0.2	81.8 ± 0.3	**0.012***	82.4 ± 0.7	81.3 ± 1.1	84.1 ± 1.3	81.4 ± 0.9	0.174
Sex, female	513/1465 (35)	198/761 (26)	206/485 (42)	109/219 (50)	**< 0.001***	1296/3346 (39)	404/1267 (32)	489/1174 (42)	403/905 (45)	**0.007***
Body mass index	26.6 ± 0.1	26.9 ± 0.2	26.2 ± 0.2	26.5 ± 0.3	**0.014***	25.9 ± 0.9	25.4 ± 1.0	24.5 ± 1.3	28.8 ± 2.0	0.471
Diabetes mellitus	389/1426 (27)	202/748 (27)	117/468 (25)	70/210 (33)	0.077	928/3231 (29)	329/1240 (27)	317/1130 (28)	282/861 (33)	0.299
Hyperlipoproteinemia	1023/1427 (72)	492/749 (66)	364/468 (78)	167/210 (80)	**< 0.001***	2401/3233 (74)	872/1241 (70)	872/1130 (77)	657/861 (76)	0.210
Hypertension	1273/1425 (89)	680/748 (91)	412/468 (88)	181/209 (87)	0.110	2885/3228 (89)	1124/1239 (91)	1005/1130 (89)	756/859 (88)	0.551
NYHA class										
Asymptomatic	1/1424 (0)	1/747 (0)	0/467 (0)	0/210 (0)	0.246	2/3227 (0)	2/1238 (0)	0/1128 (0)	0/861 (0)	0.736
I	57/1424 (4)	32/747 (4)	16/467 (3)	9/210 (4)		127/3227 (4)	52/1238 (4)	37/1128 (3)	39/861 (5)	
II	446/1424 (31)	239/747 (32)	129/467 (28)	78/210 (37)		1034/3227 (32)	388/1238 (31)	356/1128 (32)	291/861 (34)	
III	821/1424 (58)	420/747 (56)	287/467 (61)	114/210 (54)		1872/3227 (58)	712/1238 (58)	658/1128 (58)	502/861 (58)	
IV	99/1424 (7)	55/747 (7)	35/467 (7)	9/210 (4)		192/3227 (6)	85/1238 (7)	78/1128 (7)	29/861 (3)	
STS score, %	5.0 ± 0.1	5.1 ± 0.2	4.9 ± 0.2	5.0 ± 0.2	0.748	3.1 ± 0.5	2.7 ± 0.3	4.1 ± 1.2	2.2 ± 0.5	0.970
Log Euro Score	18.8 ± 0.4	19.7 ± 0.5	19.0 ± 0.6	15.6 ± 0.8	**0.001***	14.4 ± 1.8	12.4 ± 1.8	17.9 ± 4.0	12.2 ± 1.5	0.703
Euro Score 2, %	5.5 ± 0.2	5.8 ± 0.3	5.4 ± 0.3	4.5 ± 0.3	**0.037***	5.6 ± 1.5	4.8 ± 1.0	8.0 ± 3.4	2.9 ± 0.6	0.191
Atrial fibrillation	520/1375 (38)	294/719 (41)	166/456 (36)	60/200 (30)	**0.014***	1139/3103 (37)	464/1182 (39)	420/1093 (38)	255/827 (31)	0.111
Coronary artery disease	874/1427 (61)	467/749 (62)	284/468 (61)	123/210 (59)	0.583	1943/3233 (60)	766/1241 (62)	679/1130 (60)	498/861 (58)	0.694
Peripheral vascular disease	188/1427 (13)	109/749 (15)	59/468 (13)	20/210 (10)	0.148	415/3233 (13)	164/1241 (13)	137/1130 (12)	114/861 (13)	0.922
History of stroke	98/1232 (8)	52/592 (9)	33/434 (8)	13/206 (6)	0.499	237/2842 (8)	100/1049 (10)	80/1018 (8)	57/776 (7)	0.610
Permanent pacemaker	157/1426 (11)	89/749 (12)	50/468 (11)	18/209 (9)	0.395	363/3228 (11)	146/1241 (12)	134/1130 (12)	84/856 (10)	0.743
Mean pressure gradient (MPG), mmHg	44.4 ± 0.7	45.4 ± 0.8	41.8 ± 1.0	45.8 ± 2.9	0.065	46.8 ± 3.4	49.3 ± 4.4	36.5 ± 3.9	59.0 ± 7.0	0.337
Aortic valve area – before TAVR, cm2	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.5 ± 0.1	0.272	0.6 ± 0.0	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.447
Agatston Score	1341.7 ± 17.8	1422.0 ± 25.7	1179.4 ± 26.3	1354.9 ± 43.0	**< 0.001***	1227.3 ± 73.6	1035.9 ± 50.8	1253.8 ± 128.0	1477.9 ± 176.7	**0.030***
Bicuspid Aortic valve	54/1221 (4)	24/581 (4)	23/434 (5)	7/206 (3)	0.492	110/2831 (4)	52/1037 (5)	39/1018 (4)	20/776 (3)	0.300
LVOT calcification	768/1132 (68)	349/498 (70)	265/428 (62)	154/206 (75)	**0.002***	1806/2690 (67)	633/946 (67)	632/969 (65)	541/776 (70)	0.555
LVEF – echo before TAVR, %	52.5 ± 0.3	52.0 ± 0.4	53.1 ± 0.5	53.0 ± 0.6	0.246	51.6 ± 2.1	53.9 ± 2.5	48.7 ± 4.2	52.6 ± 3.1	0.660
MPG-Pre	48.9 ± 0.4	48.4 ± 0.6	49.2 ± 0.8	50.3 ± 1.1	0.330	46.4 ± 2.2	51.3 ± 3.8	40.6 ± 2.3	48.3 ± 4.9	0.766
Aortic valve area post	0.7 ± 0.0	0.7 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	**0.010***	0.7 ± 0.0	0.7 ± 0.0	0.8 ± 0.1	0.7 ± 0.1	0.317
NT-proBNP – before TAVR	5340.0 ± 499.6	4708.0 ± 400.7	5580.6 ± 1094.1	6765.0 ± 1415.5	0.360	3894.8 ± 1225.1	2200.3 ± 449.5	5370.5 ± 2431.6	4153.5 ± 3027.3	0.360
hsTNT – before TAVR	105.7 ± 19.2	125.0 ± 36.3	63.7 ± 11.3	141.1 ± 42.0	0.252	98.1 ± 3.1	124.5 ± 38.3	68.8 ± 17.2	99.9 ± 25.0	0.316
GFR – before TAVR, ml/min	57.0 ± 0.6	57.9 ± 0.9	56.1 ± 0.9	56.1 ± 1.4	0.315	57.6 ± 3.1	60.4 ± 3.2	52.6 ± 6.4	61.4 ± 5.4	0.514

Table 6: PVL and THV hemodynamic

Variable	Unadjusted Analysis					IPSW-Adjusted Analysis				
	Total (1513)	Sapien 3 (783)	Evolut R (498)	Evolut Pro (232)	p	Total (3480)	Sapien 3 (1319)	Evolut R (1214)	Evolut Pro (947)	p
	n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)	
PVL										
None	571/1099 (52)	333/566 (59)	141/341 (41)	97/192 (51)	**< 0.001***	1242/2486 (50)	560/921 (61)	328/782 (42)	354/783 (45)	**0.036***
Mild	385/1099 (35)	167/566 (30)	152/341 (45)	66/192 (34)		849/2486 (34)	271/921 (29)	321/782 (41)	258/783 (33)	
Moderate	136/1099 (12)	66/566 (12)	42/341 (12)	28/192 (15)		345/2486 (14)	89/921 (10)	113/782 (14)	143/783 (18)	
Severe	7/1099 (1)	0/566 (0)	6/341 (2)	1/192 (1)		49/2486 (2)	0/921 (0)	20/782 (3)	28/783 (4)	
Moderate/Severe	143/1099 (13)	66/566 (12)	48/341 (14)	29/192 (15)	0.368	394/2486 (16)	89/921 (10)	133/782 (17)	172/783 (22)	**0.012***
Hemodynamics										
PPG		20±7	14±6	15±7	**< 0.001***		22±9	16±9	17±7	**< 0.001***
MPG		11±4	7±4	9±3	**< 0.001***		13±6	8±5	9±5	**< 0.001***
THV-Area (Echo)		1.7±0.49	2.1±0.6	1.9±0.55	**< 0.001***		1.6±0.38	2.0±0.57	1,9±0,4	**< 0.001***

Table 7: Outcomes comparison between the Sapien3, Evolut R, and Evolut Pro subsets before and after inverse propensity score weighting (IPSW)										
Variable	Unadjusted Analysis					IPSW-Adjusted Analysis				
	Total (1513)	Sapien 3 (783)	Evolut R (498)	Evolut Pro (232)	p	Total (3480)	Sapien 3 (1319)	Evolut R (1214)	Evolut Pro (947)	p
	n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)	
Mortality (30 days)	59/1427 (4)	43/749 (6)	9/468 (2)	7/210 (3)	**0.004***	110/3233 (3)	56/1241 (5)	24/1130 (2)	30/861 (3)	0.239
Cardiovascular mortality	27/204 (13)	17/102 (17)	6/68 (9)	4/34 (12)	0.323	56/483 (12)	24/173 (14)	12/176 (7)	20/134 (15)	0.390
Myocardial infarction	2/1232 (0)	1/592 (0)	1/434 (0)	0/206 (0)	1.000	4/2842 (0)	1/1049 (0)	3/1018 (0)	0/776 (0)	0.560
Stroke	31/1427 (2)	13/749 (2)	8/468 (2)	10/210 (5)	**0.021***	91/3233 (3)	21/1241 (2)	20/1130 (2)	50/861 (6)	**0.004***
Disabling stroke	16/955 (2)	9/464 (2)	3/288 (1)	4/203 (2)	0.657	32/2361 (1)	13/840 (2)	7/788 (1)	12/733 (2)	0.714
Bleeding	156/1427 (11)	75/749 (10)	62/468 (13)	19/210 (9)	0.136	347/3233 (11)	117/1241 (9)	143/1130 (13)	87/861 (10)	0.445
Disabling bleeding	77/498 (15)	39/226 (17)	22/225 (10)	16/47 (34)	**< 0.001***	193/1048 (18)	65/392 (17)	57/435 (13)	70/222 (32)	**0.012***
Major bleeding	31/433 (7)	15/197 (8)	16/205 (8)	0/31 (0)	0.275	61/872 (7)	24/339 (7)	36/381 (10)	0/152 (0)	0.112
Minor bleeding	50/438 (11)	21/197 (11)	26/208 (13)	3/33 (9)	0.767	97/887 (11)	28/340 (8)	52/390 (13)	17/157 (11)	0.599
Acute kidney injury	105/1513 (7)	65/783 (8)	31/498 (6)	9/232 (4)	**0.050***	203/3480 (6)	87/1318 (7)	63/1214 (5)	52/947 (5)	0.776
Access site Complications	137/1427 (10)	55/749 (7)	63/468 (13)	19/210 (9)	**0.002***	321/3233 (10)	96/1241 (8)	139/1130 (12)	87/861 (10)	0.172
Major Access site Complications	54/466 (12)	24/212 (11)	23/216 (11)	7/38 (18)	0.380	131/969 (13)	46/369 (13)	46/410 (11)	39/190 (20)	0.324
Minor Access site Complications	82/477 (17)	31/213 (15)	39/222 (18)	12/42 (29)	0.087	189/989 (19)	49/366 (13)	92/435 (21)	48/188 (26)	0.160
Conduction disturbance	83/311 (27)	14/83 (17)	62/197 (31)	7/31 (23)	**0.036***	195/688 (28)	44/212 (21)	97/325 (30)	54/152 (36)	0.396
Persistent AV Block	34/311 (11)	4/83 (5)	25/197 (13)	5/31 (16)	0.066	101/688 (15)	15/212 (7)	42/325 (13)	44/152 (29)	0.058
Transient AV Block	10/311 (3)	2/83 (2)	6/197 (3)	2/31 (6)	0.539	22/688 (3)	4/212 (2)	10/325 (3)	9/152 (6)	0.437
Permanent pacemaker	208/1427 (15)	100/749 (13)	77/468 (16)	31/210 (15)	0.328	478/3233 (15)	161/1241 (13)	190/1130 (17)	128/861 (15)	0.446
Atrial fibrillation	201/1232 (16)	117/592 (20)	50/434 (12)	34/206 (17)	**0.002***	471/2842 (17)	205/1049 (20)	137/1018 (13)	129/776 (17)	0.117
conversion	4/1427 (0)	3/749 (0)	0/468 (0)	1/210 (0)	0.378	8/3233 (0)	6/1241 (1)	0/1130 (0)	2/861 (0)	0.209
Coronary obstruction	1/1232 (0)	0/592 (0)	0/434 (0)	1/206 (0)	0.170	2/2842 (0)	0/1049 (0)	0/1018 (0)	2/776 (0)	0.332
Tamponade	8/1232 (1)	8/592 (1)	0/434 (0)	0/206 (0)	**0.017***	15/2842 (1)	15/1049 (1)	0/1018 (0)	0/776 (0)	**0.014***
Endocarditis	5/1232 (0)	4/592 (1)	1/434 (0)	0/206 (0)	0.483	6/2842 (0)	4/1049 (0)	1/1018 (0)	0/776 (0)	0.142
TAVI thrombosis	5/428 (1)	5/193 (3)	0/204 (0)	0/31 (0)	0.087	6/864 (1)	6/334 (2)	0/378 (0)	0/152 (0)	0.299
Malposition	6/311 (2)	0/83 (0)	6/197 (3)	0/31 (0)	0.344	7/688 (1)	0/212 (0)	7/325 (2)	0/152 (0)	0.314
Migration	0/311 (0)	0/83 (0)	0/197 (0)	0/31 (0)		0/688(1)	0/212 (0)	0/325 (0)	0/152 (0)	
embolization	3/1115 (0)	1/482 (0)	2/427 (0)	0/206 (0)	0.792	5/2667 (0)	2/927 (0)	3/964 (0)	0/776 (0)	0.495
Ectopic	0/311 (0)	0/83 (0)	0/197 (0)	0/31 (0)		0/688 (0)	0/212 (0)	0/325 (0)	0/152 (0)	
Valve-in-valve Bailout	8/1115 (1)	6/482 (1)	1/427 (0)	1/206 (0)	0.216	26/2667 (1)	13/927 (1)	1/964 (0)	13/776 (2)	0.253
TAVI Dysfunction	17/312 (5)	2/84 (2)	15/197 (8)	0/31 (0)	0.108	22/689 (3)	4/213 (2)	19/325 (6)	0/152 (0)	**0.032***
success	301/428 (70)	137/193 (71)	159/204 (78)	5/31 (16)	**< 0.001***	555/864 (64)	226/334 (68)	278/378 (73)	51/152 (34)	**0.001***
safety	168/327 (51)	39/99 (39)	126/197 (64)	3/31 (10)	**< 0.001***	319/706 (45)	110/230 (48)	165/325 (51)	43/152 (28)	0.179
efficiency	197/355 (55)	63/124 (51)	131/200 (66)	3/31 (10)	**< 0.001***	367/754 (49)	137/258 (53)	188/344 (55)	43/152 (28)	0.087

Outcomes

Primary Endpoints

Table 2 presents the comparison of outcomes between the Sapien3 (S), Evolut R (ER), and Evolut Pro (Epro) subsets before and after inverse propensity score weighting (IPSW). Before IPSW adjustment, significant differences were observed across several outcomes among patients undergoing TAVR with Sapien3, Evolut R, and Evolut Pro devices.

In terms of aortic regurgitation (AR), the proportion of patients with no AR was highest in the Sapien3 group (59%), followed by Evolut Pro (51%) and Evolut R (41%) ($p < 0.001$). After adjustment, these differences persisted, with Sapien3 at 61%, Evolut R at 42%, and Evolut Pro at 45% ($p = 0.036$). Mild AR was most prevalent in the Evolut R group before adjustment (45%) and after adjustment (41%), indicating a shift in the Evolut Pro group from 34% to 33% and Sapien3 from 30% to 29%. Moderate AR showed a similar pattern, with the highest prevalence in the Evolut Pro group before (15%) and after adjustment (18%). Severe AR, though rare, was more frequent in the Evolut R and Evolut Pro groups after adjustment (3% and 4%, respectively), with none observed in the Sapien3 group pre- and post-adjustment. The combined moderate/severe AR category remained significantly different after adjustment, increasing from 13% to 16% overall, with Sapien3 at 10%, Evolut R at 17%, and Evolut Pro at 22% ($p = 0.012$).

Secondary Endpoints:

Regarding the predicted transcatheter valve area (TVH-Area) the area was greater in the Evolut R (2.1 ± 0.6 cm^{-2}) group, followed by Evolut Pro (1.9 ± 0.55 cm^{-2}) with the Sapien group (1.7 ± 0.49 cm^{-2}) showing the lowest predicted valve area, after adjustment the effect remained significant. In accordance with the predicted area, the lowest mean gradients were measured in the Evolut R group 7 ± 4 mm Hg followed by Evolut P 9 ± 3 mm Hg, the group with the highest gradients measured in the Sapien 3 group11 ± 4 mm Hg; this effect remained significant after inverse propensity scoring.

VARC-3 Outcomes

Table 2 presents the comparison of outcomes between the Sapien3 (S), Evolut R (ER), and Evolut Pro (Epro) subsets before and after inverse propensity score weighting (IPSW). Before IPSW adjustment, significant differences were observed across several outcomes among patients undergoing TAVR with Sapien3, Evolut R, and Evolut Pro devices.

Regarding 30-day mortality, the Sapien3 group initially had the highest rate (6%) compared to Evolut R (2%) and Evolut Pro (3%) ($p = 0.004$). After adjustment, these differences were not significant, with mortality rates at 5% for Sapien3, 2% for Evolut R, and 3% for Evolut Pro ($p = 0.239$). Stroke incidence before adjustment was significantly higher in the Evolut Pro group (5%) compared to Sapien3 and Evolut R (both 2%) ($p = 0.021$). Post-adjustment, stroke rates were still highest in the Evolut Pro group (6%) compared to 2% for both Sapien3 and Evolut R ($p = 0.004$). Disabling bleeding initially showed a high prevalence in the Evolut Pro group (34%), significantly higher than in Sapien3 (17%) and Evolut R (10%) ($p < 0.001$). After adjustment, the rates remained highest for Evolut Pro (32%) compared to Sapien3 (17%) and Evolut R (13%) ($p = 0.012$). Acute kidney injury rates were initially higher in the Sapien3 group (8%) compared to Evolut R (6%) and Evolut Pro (4%) ($p = 0.050$), but post-adjustment, no significant differences were found, with rates at 7% for Sapien3 and 5% for both Evolut R and Evolut Pro ($p = 0.776$). Access site complications were significantly different before adjustment, highest in the Evolut R group (13%) compared to Sapien3 (7%) and Evolut Pro (9%) ($p = 0.002$). After adjustment, these differences were not significant, with 12% for Evolut R, 10% for Evolut Pro, and 8% for Sapien3 ($p = 0.172$).

Conduction disturbances were more frequent in the Evolut R group (31%) compared to Sapien3 (17%) and Evolut Pro (23%) ($p = 0.036$) before adjustment. After adjustment, the rates were 21% for Sapien3, 30% for Evolut R, and 36% for Evolut Pro ($p = 0.396$), indicating no significant differences. Atrial fibrillation was initially highest in the Sapien3 group (20%) compared to Evolut R (12%) and Evolut Pro (17%) ($p = 0.002$). Post-adjustment, differences were not significant, with rates of 20% for Sapien3, 13% for

Evolut R, and 17% for Evolut Pro ($p = 0.117$). Cardiac tamponade, initially observed only in the Sapien3 group (1%) ($p = 0.017$), remained significant after adjustment, with occurrences only in Sapien3 (1%) ($p = 0.014$). TAVI dysfunction was higher in the Evolut R group before adjustment (8%) compared to Sapien3 (2%) and Evolut Pro (0%) ($p = 0.108$), and post-adjustment, it was significantly different, with 6% for Evolut R, 2% for Sapien3, and none for Evolut Pro ($p = 0.032$).

Device success rates before adjustment were highest for Evolut R (78%) compared to Sapien3 (71%) and Evolut Pro (16%) ($p < 0.001$). After adjustment, the success rates were 68% for Sapien3, 73% for Evolut R, and 34% for Evolut Pro ($p = 0.001$). Device safety, initially highest for Evolut R (64%) compared to Sapien3 (39%) and Evolut Pro (10%) ($p < 0.001$), showed no significant difference post-adjustment, with 48% for Sapien3, 51% for Evolut R, and 28% for Evolut Pro ($p = 0.179$). Efficiency rates were initially highest for Evolut R (66%) compared to Sapien3 (51%) and Evolut Pro (10%) ($p < 0.001$). Post-adjustment, the rates were 53% for Sapien3, 55% for Evolut R, and 28% for Evolut Pro ($p = 0.087$)

Discussion

This was a real-world, industry-independent, multicenter study including 1514 patients with heavily calcified AS undergoing TAVI using either the CoreValve Evolut PRO, Evolut R, or the Edwards SAPIEN-3/3 Ultra transcatheter heart valves. The major results of the study are: (1) when compared to the SAPIEN-3/3 Ultra, mild PVL was more often found in the CoreValve Evolut R, but not Evolut PRO; (2) both Medtronic Evolut PRO and Evolut R showed a better postoperative hemodynamic performance than the SAPIEN-3/3 Ultra; (3). All VARC-3 outcomes were comparable.

Prevalence and prognostic influence of PVL after TAVI

According to the result of published trials, there is a general agreement among authors that PVL after TAVI is significantly correlated with the severity of aortic valve calcification (Ewe et al., 2011; Koos et al., 2011; Mauri et al., 2018; Milhorini Pio et al., 2020; Pavicevic et al., 2015). This may be explained by the constriction of the THV to be adequately and symmetrically expanded in the presence of heavy calcification, which might interfere with adequate sealing. In a large meta-analysis examining post-TAVI-PVL with first-generation THVs, the self-expanding valve had a higher rate of moderate to severe PVL in comparison to balloon-expandable THVs (Athappan et al., 2013). Because of continuous technical innovation and improvement, the rates of PVL have dramatically decreased with newer-generation THVs compared to first-generation THVs. Lower rates of PVL were documented in the newer-generation group in contrast to the first-generation group in a study that examined the prevalence of PVL among those who received TAVI with first-generation and new-generation prostheses (Akodad et al., 2018). In this work, the primary endpoint was met as there was a significantly higher number of PVL in the Evolut R followed by Evolut Pro then the Sapien. Similarly, another study reported that more than mild PVL occurs less frequently in cases implanted with newer generation THVs, with a grade of 5.3% for the CoreValve Evolut R and none for the SAPIEN-3 (Stundl et al., 2019). The incidence of moderate to severe PVL is correlated with a greater incidence of heart failure hospitalization(Athappan et al., 2013; Sá et al., 2023). These higher incidences of PVL in our cohort can be explained by the severe aortic valve calcifications in our patient

population. This may prevent the perfect alignment of the valve frame to the native annulus, thus allowing the passage of blood between the two annuli. The additional sealing outer skirt of the Evolut Pro reduced this effect by sealing the gap in the diastole. Another factor may be the under-expansion of the valve frame, resulting eventually in a smaller frame.

However, the incidence of PVL is not merely a function of a certain device but is associated with multiple anatomical, device, and operator factors. John et al. provided evidence that the LVOT and native valve calcium are squeezed between the device's nitinol frame and the aortic wall. This element creates gaps, which, following successful implantations, result in multiple diastolic PVL jets (John et al., 2010). The exitance of further pericardial outskirt may aid in closing the gap between the prosthesis frame and the native valve, decreasing the regurgitation amount.

The distribution and pattern of calcification may act a role in the incidence and severity of PVL. Previous studies demonstrated that the exitance of calcification in the landing zone of the device, calcification of the commissures, and extension of the calcification in the LVOT are predictors of PVL(Khalique et al., 2014).

Azzalini et al. introduced the TAVI community to the concept of the AVC nodule score. This score incorporates not only the total calcium volume but also the volume of the largest individual calcium nodules. Those cases with a higher score exhibited a greater likelihood of greater than mild PVL (odds ratio [OR] 2.269, 95% CI: 1.433-3.593; $p<0.001$) (Azzalini et al., 2014). This was supported by a recent study that found a substantial correlation between the occurrence of PVL following TAVI and the volume of the greatest calcium nodules, calcium perimeter, and calcium burden (measured by Feret's diameter) (P=0.012, P=0.001, and P=0.045, respectively). According to the perdition model, a ten mm^{-2} rise in the local AVC quantity was linked to a 9.8% (95% CI: 2-18%; P=0.019) rise in the likelihood of PVL occurring in that area following TAVI (Wiktorowicz et al., 2021).

In the present study, the prevalence of significant LVOT calcification was recorded in 70%, 62%, and 75% of patients treated with S3, EVOLUT R, and Pro, respectively. This was partially due to the operator's preference not to implant a balloon-expandable valve in the existence of severe LVOT calcification, as the existence of LVOT calcification and valve oversizing are one of the most widely recognized factors for annular rupture, especially with balloon-expandable valves. It is a common practice to implant SE THV in patients presenting with severe LVOT calcification. After performing propensity matching for LVOT calcification, the occurrence of PVL was still higher in the SE THV than in the BE THV. In our study, we could not identify a particular pattern of calcification that could be the culprit in the paravalvular leak.

Notably, the CoreValve Evolut PRO displayed much lower PVL rates when compared to the CoreValve Evolut R. The third generation self-expanding THV, known as the CoreValve Evolut PRO, is based on the CoreValve Evolut R valve platform but has been improved by the sewing of an exterior pericardial tissue wrap around the valve inflow in order to reduce PVL. In the CoreValve Evolut PRO's initial research, which involved 60 patients in the US, 72.4% of patients had no or trace PVL, while 27.6% had mild PVL (Forrest et al., 2018). There was no sign of moderate or severe PVL. A report from the STS/ACC TVT registry found that the rate of moderate or severe PVL was 5.4% in the CoreValve Evolut R group and 3.4% in the CoreValve Evolut PRO group (Forrest et al., 2020). Our research supports the previously released results, which show that the CoreValve Evolut R has a greater rate of PVL than the CoreValve Evolut PRO and SAPIEN-3/3 Ultra (Mosleh et al., 2019; Modolo et al., 2020; Thiele et al., 2020). The total rate of PVL across all THV types was significantly higher in our study than previously published studies in patients with the whole spectrum of aortic valve anatomies, which, again, is explained by the severe aortic valve calcifications in our patient cohort.

THV hemodynamics

In our analysis, both CoreValve Evolut R and CoreValve Evolut PRO groups demonstrated superior post-implant hemodynamics compared to the SAPIEN-3/3 Ultra with regard to peak and mean pressure gradients, as well as effective orifice area. This difference in the hemodynamics is primarily related to the CoreValve system's supra-

annular design, which had previously been demonstrated to yield superior hemodynamics compared to balloon-expanding valve systems such as the SAPIEN-3/3 Ultra platform (Reardon et al., 2017; Hahn et al., 2019). Consistent with our results, the OCEAN-TAVI registry reported a better post-implant hemodynamic profile of the CoreValve Evolut R compared to the SAPIEN-3 in cases with a small aortic annulus (Hase et al., 2021). Another study demonstrated that the CoreValve Evolut R achieved a larger efficient orifice area and lower mean pressure gradients than the SAPIEN-3 (Hahn et al., 2019). Similar outcomes were noted in the CHOICE-Extend registry, where the mean pressure gradient was 7 ± 3 mm Hg for the CoreValve Evolut R compared to 12 ± 4 mm Hg for SAPIEN-3 (Abdelghani et al., 2018). It's interesting to note that even in the high-risk group of individuals with substantially calcified AS, the inclusion of the outer pericardial wrap did not demonstrate an adverse effect on the hemodynamic performance of the CoreValve Evolut PRO when contrasted to the SAPIEN-3. This is in line with the results of the original CoreValve Evolut PRO Study as well as data from the STS/ACC TVT registry regarding the overall TAVI population (Forrest et al., 2018, 2020).

Whether the inferior hemodynamics of the SAPIEN-3/3 Ultra may translate into worse long-term outcomes, such as earlier valve deterioration in patients with heavily calcified AS, is beyond the scope of our study and thus warrants further investigation. The latest investigation by Herrmann et al. indicated that TAVI cases with severe but not moderate patient-prosthesis mismatch are impacted by greater rates of heart failure rehospitalization and elevated late mortality contrasted to patients without patient-prosthesis mismatch (Herrmann et al., 2018). Supplementary, long-term, head-to-head comparisons utilizing standardized criteria between intra-annular and supra-annular valves are required.

Short-term clinical outcomes according to VARC-3 Criteria

In our study, SAPIEN-3/3 Ultra demonstrated significantly greater rates of pericardial tamponade when contrasted to the CoreValve Evolut R/P, and this became insignificant after IPSW. However, there is a higher likelihood for BEV to cause more annular injury because of the higher radial force in this type of valve. Our findings are mainly consistent with two previous studies demonstrating similar clinical consequences

between the SAPIEN-3 and CoreValve Evolut R (Abdelghani et al., 2018; Thiele et al., 2020). Interestingly, however, the overall rate of new permanent pacemaker implantation in our case cohort was lower than in the previously mentioned studies. This could be explained by the recent improvement of implantation techniques using the cusp-overlap technique, allowing shallower implants, which reduces the risk of injury to the conduction system. In contrast, the CENTER-collaboration registry contrasting the CoreValve Evolut R to the SAPIEN-3 demonstrated a greater rate of conversion to open heart surgery, stroke, and new permanent pacemaker implantation in the CoreValve Evolut R group, while major or life-threatening bleeding was more frequent in the SAPIEN-3 group (Vlastra et al., 2019). Mortality did not vary between the two groups.

Limitations

Because the analysis is retrospective, a potential selection bias cannot be completely ruled out. A randomized study comparing the performance of different devices in different anatomies and degrees of calcification still needs to be designed. Such a study could result in a better knowledge of the advantages and disadvantages of different devices in different anatomies.

Deutsche Zusammenfassung

Einleitung:

Signifikante Verkalkungen bei Patienten, die sich einer Transkatheter-Aortenklappenimplantation (TAVI) unterziehen, stellen eine erhebliche Herausforderung dar. Es gibt nur wenige Studien, die sich mit der Performance von Transkatheter-Herzklappen (THV) bei Patienten mit schwerer Aortenstenose und ausgeprägten Verkalkungen befassen.

Methodik

Ziel der Studie: Das Ziel der Studie ist es, die Performance ballon-expandierbarer versus selbstexpandierender Transkatheter-Klappentechnologien bei starker Aortenklappenverkalkung zu bewerten. Diese Verkalkung ist definiert durch ein Kalziumvolumen von mehr als 700 mm/cm² im präoperativen CT. Die Studie umfasst zwei Gruppen von Klappen: ballon-expandierbare Klappen (SAPIEN S3/Ultra Valve, Edwards) und selbstexpandierende Klappenprothesen (Evolut Pro und Evolut R, Medtronic).

Studienaufbau und Patientenpopulation: Es wurde eine retrospektive, nicht-randomisierte Kohortenanalyse durchgeführt, die Fälle umfasste, die zwischen Juli 2013 und Januar 2021 in fünf Herzzentren in Deutschland (Universitätsklinikum Kiel, Herzzentrum Bad Segeberg, Universitätsklinikum Düsseldorf, Universitätsklinikum Köln, Herz- und Diabeteszentrum Bad Oeynhausen) eine TAVI erhielten und eine symptomatische Aortenklappenstenose mit stark verkalkten Aortenklappen aufwiesen. Mittels der von der FDA zugelassenen 3Mensio-Software (Pie Medical Imaging) oder einem Agatston-Score von über 3000 HU durch konventionelle CT-Analyse wurden 1517 Patienten mit einer stark verkalkten Aortenklappe identifiziert, was durch einen Kalziumscore von mehr als 700 mm² angezeigt wird. Die endgültige Analyse umfasste 1513 Patienten. Als primären Endpunkt definierten wir die Inzidenz und den Schweregrad der paravalvulären Leckage (PVL) nach TAVI. Sekundäre Endpunkte umfassten klinische Ergebnisse gemäß der VARC-3-Definition sowie die hämodynamische Leistung der Klappe, gemessen anhand der THV-Fläche und Druckgradienten der THV.

Klappenauswahl : Die Auswahl des Klappentyps und des Zugangswegs wurde einem interdisziplinären Herzteam überlassen. Die Größenempfehlung basierte auf den Empfehlungen des Herstellers und präoperativen kardialen CTs.

Einschlusskriterien:

1. Schwere symptomatische Aortenklappenstenose
2. Stark verkalkte Aortenklappe, definiert durch einen Kalziumscore >700
3. Durchführung der TAVI nach Diskussion im interdisziplinären Herzteam
4. Durchführung der TAVI mit den folgenden Prothesen: Evolut R, Evolut Pro, SAPIEN-3/3 Ultra

Ausschlusskriterien:

1. Valve-in-Valve-Verfahren
2. Andere Prothesen, die oben nicht genannten sind
3. Unbekannter Klappentyp

Statische Auswertung : Kontinuierliche normalverteilte Variablen wurden mittels Mittelwert (M)/Standardfehler (SE) zusammengefasst, während kategoriale Variablen durch Anzahl (n)/Gesamt (N) (Prozentsätze (%)) dargestellt wurden. Um die Ausgangsmerkmale der Patienten sowie fehlende Werte in diesen Kovariaten auszugleichen, verwendeten wir die inverse Propensity-Score-Gewichtung (IPSW), um die Unterschiede zwischen den Gruppen vor der Behandlung auszugleichen. Hierzu nutzten wir die Programmiersprache R (The R Project for Statistical Computing, Wien, Österreich) und das Toolkit for Weighting and Analysis of Nonequivalent Groups.

Um ein Gleichgewicht zu erreichen, verwendeten wir ein generalisiertes Boosted-Modell mit multinomialer inverser Propensity-Score-Gewichtung unter Verwendung eines Average Treatment Effect (ATE)-Designs für das Propensity-Scoring und der höchsten mittleren paarweisen Effektgröße.

Die Ergebnisse der logistischen Regressionsanalysen zu den Ergebnissen wurden als Odds Ratio (OR) mit 95% Konfidenzintervallen (CI) ausgedrückt.

Ergebnisse

Die vorliegende Studie umfasste insgesamt 1517 Patienten mit stark verkalkter Aortenklappenstenose, die eine TAVI erhielten. Bei 4 Patienten konnte der genaue

Typ der Evolut-Prothese nicht bestimmt werden, weshalb sie ausgeschlossen wurden. Somit umfasste die endgültige Analyse 1513 Patienten. Die CoreValve Evolut R wurde in 498 Fällen (33,0%) implantiert, die Evolut PRO in 232 Patienten (15,3%) und die SAPIEN-3/3 Ultra THV in 783 Fällen (51,8%).

Nach IPSW-Anpassung blieben nur Geschlecht und Agatston-Score signifikant unterschiedlich zwischen den Gruppen. Der Anteil weiblicher Patienten war in der Evolut Pro-Gruppe am höchsten (45%), gefolgt von Evolut R (42%) und Sapien3 (32%) ($p = 0,007$). Der Agatston-Score blieb auch nach der Anpassung signifikant unterschiedlich zwischen den Gruppen. Die Evolut Pro-Gruppe hatte den höchsten mittleren Agatston-Score (1477,9 ± 176,7), gefolgt von Evolut R (1253,8 ± 128,0) und Sapien3 (1035,9 ± 50,8) ($p = 0,030$). Für die anderen Variablen zeigte die IPSW-adjustierte Analyse keine signifikanten Unterschiede zwischen den Gruppen.

Primäre Endpunkte: Bezüglich der Aortenklappeninsuffizienz (AR) war der Anteil der Patienten ohne AR in der Sapien3-Gruppe am höchsten (59%), gefolgt von Evolut Pro (51%) und Evolut R (41%) ($p < 0,001$). Nach der Anpassung blieben diese Unterschiede bestehen, mit Sapien3 bei 61%, Evolut R bei 42% und Evolut Pro bei 45% ($p = 0,036$). Leichte AR war vor der Anpassung am häufigsten in der Evolut R-Gruppe (45%) und nach der Anpassung (41%), was auf eine Verschiebung in der Evolut Pro-Gruppe von 34% auf 33% und Sapien3 von 30% auf 29% hinweist. Moderate AR zeigte ein ähnliches Muster, mit der höchsten Prävalenz in der Evolut Pro-Gruppe vor (15%) und nach der Anpassung (18%). Schwere AR, obwohl selten, war nach der Anpassung häufiger in den Evolut R- und Evolut Pro-Gruppen (3% bzw. 4%), wobei in der Sapien3-Gruppe weder vor noch nach der Anpassung beobachtet wurde. Die kombinierte Kategorie moderater/schwerer AR blieb nach der Anpassung signifikant unterschiedlich und stieg insgesamt von 13% auf 16%, mit Sapien3 bei 10%, Evolut R bei 17% und Evolut Pro bei 22% ($p = 0,012$).

Sekundäre Endpunkte: Bezüglich der Klappenfläche (TVH-Fläche) war die Fläche in der Evolut R-Gruppe (2,1±0,6 cm^2) größer, gefolgt von Evolut Pro (1,9±0,55 cm^2), wobei die Sapien3-Gruppe (1,7±0,49 cm^2) die kleinste vorhergesagte Klappenfläche aufwies. Nach der Anpassung blieb der Effekt signifikant. Entsprechend der vorhergesagten Fläche wurden die niedrigsten mittleren Gradienten in der Evolut R-Gruppe gemessen (7±4 mm Hg), gefolgt von Evolut Pro (9±3 mm Hg), wobei die

höchsten Gradienten in der Sapien3-Gruppe gemessen wurden (11±4 mm Hg). Dieser Effekt blieb nach der inversen Propensity-Score-Gewichtung signifikant.

VARC-3 Ereignisse: Bezüglich der 30-Tage-Mortalität hatte die Sapien3-Gruppe anfänglich die höchste Rate (6%) im Vergleich zu Evolut R (2%) und Evolut Pro (3%) (p = 0,004). Nach Anpassung waren diese Unterschiede nicht signifikant mit Mortalitätsraten von 5% für Sapien3, 2% für Evolut R und 3% für Evolut Pro (p = 0,239). Die Schlaganfallinzidenz war vor der Anpassung in der Evolut Pro-Gruppe signifikant höher (5%) im Vergleich zu Sapien3 und Evolut R (jeweils 2%) (p = 0,021). Nach der Anpassung waren die Schlaganfallraten in der Evolut Pro-Gruppe immer noch am höchsten (6%) im Vergleich zu 2% für sowohl Sapien3 als auch Evolut R (p = 0,004). Die Prävalenz für schwerwiegende Blutungen war anfänglich in der Evolut Pro-Gruppe (34%) signifikant höher als in Sapien3 (17%) und Evolut R (10%) (p < 0,001). Nach der Anpassung blieben die Raten für Evolut Pro am höchsten (32%) im Vergleich zu Sapien3 (17%) und Evolut R (13%) (p = 0,012). Die Raten für akutes Nierenversagen waren in der Sapien3-Gruppe höher (8%) im Vergleich zu Evolut R (6%) und Evolut Pro (4%) (p = 0,050), aber nach der Anpassung wurden keine signifikanten Unterschiede gefunden mit Raten von 7% für Sapien3 und 5% für sowohl Evolut R als auch Evolut Pro (p = 0,776). Komplikationen an der Zugangsseite waren vor der Anpassung signifikant unterschiedlich, am höchsten in der Evolut R-Gruppe (13%) im Vergleich zu Sapien3 (7%) und Evolut Pro (9%) (p = 0,002). Nach der Anpassung waren diese Unterschiede nicht signifikant mit 12% für Evolut R, 10% für Evolut Pro und 8% für Sapien3 (p = 0,172). Leitungsstörungen waren vor der Anpassung häufiger in der Evolut R-Gruppe (31%) im Vergleich zu Sapien3 (17%) und Evolut Pro (23%) (p = 0,036). Nach der Anpassung lagen die Raten bei 21% für Sapien3, 30% für Evolut R und 36% für Evolut Pro (p = 0,396), damit bestanden keine signifikanten statistischen Unterschiede mehr. Vorhofflimmern war anfänglich in der Sapien3-Gruppe am höchsten (20%) im Vergleich zu Evolut R (12%) und Evolut Pro (17%) (p = 0,002). Nach der Anpassung waren die Unterschiede nicht signifikant, mit Raten von 20% für Sapien3, 13% für Evolut R und 17% für Evolut Pro (p = 0,117). Herzbeuteltamponade, die anfänglich nur in der Sapien3-Gruppe beobachtet wurde (1%) (p = 0,017), blieb nach der Anpassung signifikant mit Vorkommen nur in Sapien3 (1%) (p = 0,014). TAVI-Dysfunktion war vor der Anpassung in der Evolut R-Gruppe höher (8%) im Vergleich zu Sapien3 (2%)

und Evolut Pro (0%) (p = 0,108), und nach der Anpassung war sie signifikant unterschiedlich, mit 6% für Evolut R, 2% für Sapien3 und keiner für Evolut Pro (p = 0,032).

Die Erfolgsraten der Geräte waren vor der Anpassung am höchsten für Evolut R (78%) im Vergleich zu Sapien3 (71%) und Evolut Pro (16%) (p < 0,001). Nach der Anpassung lagen die Erfolgsraten bei 68% für Sapien3, 73% für Evolut R und 34% für Evolut Pro (p = 0,001). Die Gerätesicherheit, anfänglich am höchsten für Evolut R (64%) im Vergleich zu Sapien3 (39%) und Evolut Pro (10%) (p < 0,001), zeigte nach der Anpassung keinen signifikanten Unterschied mit 48% für Sapien3, 51% für Evolut R und 28% für Evolut Pro (p = 0,179). Die Effizienzraten waren anfänglich am höchsten für Evolut R (66%) im Vergleich zu Sapien3 (51%) und Evolut Pro (10%) (p < 0,001). Nach der Anpassung lagen die Raten bei 53% für Sapien3, 55% für Evolut R und 28% für Evolut Pro (p = 0,087).

Diskussion:

Studien zeigen, dass PVL signifikant mit dem Schweregrad der Verkalkung der Aortenklappe korreliert (Ewe et al., 2011; Koos et al., 2011; Mauri et al., 2018; Milhorini Pio et al., 2020; Pavicevic et al., 2015). Diese Verkalkung kann die symmetrische Expansion der Transkatheter-Herzklappen (THV) verhindern und somit das Abdichten beeinträchtigen. Eine Metaanalyse ergab, dass selbstexpandierende Klappen der ersten Generation eine höhere Rate an mäßigen bis schweren PVL aufweisen als ballon-expandierbare Klappen (Athappan et al., 2013). Dank technischer Innovationen und Verbesserungen sind die PVL-Raten bei neueren THV-Generationen im Vergleich zu den ersten Generationen deutlich gesunken (Akodad et al., 2018).

Höheren PVL-Raten in der untersuchten Kohorte können durch die schwere Verkalkung der Aortenklappen in der Patientengruppe erklärt werden, was die perfekte Ausrichtung des Klappenrahmens auf den nativen Anulus verhindert. Die zusätzliche äußere Dichtungsmanschette des Evolut Pro reduziert diesen Effekt, indem sie die Lücke in der Diastole abdichtet.

Die Inzidenz von PVL hängt nicht nur von einem bestimmten Implantat ab, sondern wird auch durch anatomische und operatorbedingte Faktoren beeinflusst. John et al. zeigten, dass das Kalzium des linksventrikulären Ausflusstrakts (LVOT) und der

nativen Klappe zwischen dem Nitinolrahmen des Implantats und der Aortenwand eingeklemmt wird, was Lücken entstehen lässt, die nach erfolgreicher Implantation zu mehreren diastolischen PVL-Jets führen (John et al., 2010). Eine zusätzliche perikardiale Außenhülle kann helfen, die Lücke zwischen dem Prothesenrahmen und der nativen Klappe zu schließen und so die Regurgitationsmenge zu verringern.

Die Verteilung und das Muster der Verkalkung spielen ebenfalls eine Rolle bei der Inzidenz und Schwere von PVL. Frühere Studien zeigten, dass Verkalkungen in der Landungszone des Devices, Verkalkungen der Kommissuren und die Ausdehnung der Verkalkung in den LVOT Prädiktoren für PVL sind (Khalique et al., 2014). Azzalini et al. führten das Konzept des AVC-Knotenscores ein, der das gesamte Kalziumvolumen berücksichtigt. Fälle mit einem höheren Score zeigten eine größere Wahrscheinlichkeit für PVL (Azzalini et al., 2014).

In der vorliegenden Studie wurde eine signifikante LVOT-Verkalkung bei 70 %, 62 % und 75 % der Patienten, die mit S3, EVOLUT R und Pro behandelt wurden, festgestellt. Dies lag teilweise daran, dass der Operateur es vorzog, bei schwerer LVOT-Verkalkung keine ballon-expandierbare Klappe zu implantieren, da LVOT-Verkalkung und Klappenüberschreitung Faktoren für einen Anulusabriss sind, insbesondere bei ballon-expandierbaren Klappen. Es ist gängige Praxis, selbstexpandierende THV bei Patienten mit schwerer LVOT-Verkalkung zu implantieren.

Die CoreValve Evolut PRO zeigte deutlich niedrigere PVL-Raten im Vergleich zur CoreValve Evolut R. Die dritte Generation der selbstexpandierenden THV, bekannt als CoreValve Evolut PRO, basiert auf der CoreValve Evolut R-Plattform, wurde jedoch durch das Annähen einer äußeren perikardialen Gewebehülle um den Klappeneinlass verbessert, um PVL zu reduzieren. In der initialen Forschung zur CoreValve Evolut PRO hatten 72,4 % der Patienten keine oder nur geringe PVL, während 27,6 % leichte PVL aufwiesen (Forrest et al., 2018). Ein Bericht aus dem STS/ACC TVT-Register fand eine Rate von mäßiger oder schwerer PVL von 5,4 % in der CoreValve Evolut R-Gruppe und 3,4 % in der CoreValve Evolut PRO-Gruppe (Forrest et al., 2020).

In unserer Analyse zeigten sowohl die CoreValve Evolut R als auch die CoreValve Evolut PRO-Gruppen eine überlegene postimplantative Hämodynamik im Vergleich zur SAPIEN-3/3 Ultra hinsichtlich der Spitzen- und mittleren Druckgradienten sowie der effektiven Öffnungsfläche. Diese hämodynamischen Unterschiede sind hauptsächlich auf das supra-anuläre Design des CoreValve-Systems zurückzuführen (Reardon et al., 2017; Hahn et al., 2019). Ob die schlechtere Hämodynamik der SAPIEN-3/3 Ultra langfristig zu schlechteren Ergebnissen führt, wie zum Beispiel einem früheren Klappenverschleiß, muss weiter untersucht werden.

Kurzfristige klinische Ergebnisse zeigten, dass die SAPIEN-3/3 Ultra signifikant höhere Raten von Perikardtamponaden aufwies, was nach IPSW jedoch nicht mehr signifikant war. Es besteht jedoch eine höhere Wahrscheinlichkeit, dass BEV aufgrund der höheren radialen Kraft mehr Anulusverletzungen verursacht. Unsere Ergebnisse stimmen weitgehend mit zwei früheren Studien überein, die ähnliche klinische Konsequenzen zwischen der SAPIEN-3 und der CoreValve Evolut R zeigten (Abdelghani et al., 2018; Thiele et al., 2020).

Zusammenfassung: die identifizierten Unterschiede in den paravalvulären Leckraten (PVL) und die verbesserte Hämodynamik des CoreValve Evolut R im Vergleich zum SAPIEN-3/3 Ultra könnten für interventionelle Kardiologen von entscheidender Bedeutung sein, dennoch unterstreicht die Studie die Notwendigkeit weiterer Forschung, um diese Ergebnisse mit den anderen Studien zu vergleichen.

Englische Zusammenfassung:

Background: Severe aortic valve calcification presents a significant challenge in Transcatheter Aortic Valve Implantation (TAVI) procedures. This study aimed to evaluate the performance of balloon-expandable versus self-expanding transcatheter heart valve (THV) technologies in patients with severe aortic stenosis and extensive calcification.

Methods: A retrospective, non-randomized cohort analysis was conducted on 1513 patients who underwent TAVI between July 2013 and January 2021 across five German heart centers. Patients with severe aortic valve calcification (calcium score >700 mm^2) were included. The study compared balloon-expandable valves (SAPIEN S3/Ultra, Edwards) with self-expanding valves (Evolut Pro and Evolut R, Medtronic). The primary endpoint was the incidence and severity of paravalvular leakage (PVL) post-TAVI. Secondary endpoints included clinical outcomes as per VARC-3 definition and hemodynamic valve performance.

Results: After inverse propensity score weighting (IPSW) adjustment, the SAPIEN-3 group showed the highest proportion of patients without aortic regurgitation (AR) (61%), compared to Evolut R (42%) and Evolut Pro (45%) (p=0.036). Moderate/severe AR was significantly different post-adjustment, with SAPIEN-3 at 10%, Evolut R at 17%, and Evolut Pro at 22% (p=0.012). The Evolut R group demonstrated larger valve areas (2.1±0.6 cm^2) and lower mean gradients (7±4 mmHg) compared to SAPIEN-3 (1.7±0.49 cm^2, 11±4 mmHg). Post-adjustment, 30-day mortality rates were not significantly different. Stroke incidence remained highest in the Evolut Pro group (6%) post-adjustment (p=0.004).

Conclusion: In patients with severely calcified aortic valves undergoing TAVI, balloon-expandable valves (SAPIEN-3/3 Ultra) demonstrated lower rates of paravalvular leakage compared to self-expanding valves (Evolut R and Pro). However, self-expanding valves, particularly Evolut R, showed superior hemodynamic performance with larger valve areas and lower gradients. These findings provide valuable insights for interventional cardiologists in valve selection for patients with severe aortic valve calcification, though further research is needed to corroborate these results[1].

List of abbreviations

AS	Aortic stenosis
ACC	American college of cardiology
ACE	Angiotensin-Converting-Enzyme
AHA	American Heart Association
AR	Aortic Regurgitation
AV Block	Atrioventricular block
AVA	Aortic Valve Area
AVAi	Aortic Valve Area index
AVC	Aortic valve calcification
AVR	Aortic valve replacement
BAV	bicuspid aortic valve
BE	balloon expandable
BP	blood pressure
CAD	coronary artery disease
CENTER-Registey	Cerebrovascular EveNts in Patients Undergoing TranscathetER Aortic Valve Implantation
CHOICE	Randomized Comparison of Transcatheter Heart Valves in High-Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT
COPD	chronic obstructive pulmonary disease
CT	computerized tomography
EACTS	European Association for Cardio-Thoracic Surgery
EF	Ejection fraction
eGFR	estimated glomerular filtration rate
ESC	European society of cardiology
Euro-SCORE	
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HOCM	hypertrophic obstructive cardiomyopathy
hsTNT	high sensitivity troponin-T
HU	Housefield Unit
LAO	Left anterior oblique
LBBB	left bundle branch block
LDL	low density lipoprotein
LM	left main
Lp(a)	lipoprotein A
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MPG	mean pressure gradient

MR	mitral regurgitation
MS	mitral stenosis
MSCT	Multislice computerised tomography
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NO	Nitric oxide
NOTION	Nordic Aortic Valve Intervention
NYHA	New York heart association
OCEAN-TAVI	Optimized transCathEter vAlvular iNtervention
PARTNER	The Placement of Aortic Transcatheter Valves
PM	pacemaker
PPG	peak pressure gradient
proBNP	PRO–B-TYPE NATRIURETIC PEPtide
PVel	Peak velocity
PVL	paravalvular leak
SAVR	surgical aortic valve replacement
SE	self expanding
SOV	sinus of Valsalva
STS	Society of thoracic surgeons
SURTAVI	Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients
SYNTAX-Score	Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
TAVI	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement
TEE	transesophageal echocardiography
THV	transcatheter heart valve
TIA	transient ischemic attack
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
VARC-3	Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research
Vmax	maximal velocity
ΔP	change (delta) of pressure gradient

References

2021 ESC/EACTS Guidelines for the management of valvular heart disease | European Heart Journal | Oxford Academic. (n.d.). Retrieved April 25, 2023, from https://academic.oup.com/eurheartj/article/43/7/561/6358470?login=false

Abdelghani, M., Mankerious, N., Allali, A., Landt, M., Kaur, J., Sulimov, D. S., Merten, C., Sachse, S., Mehilli, J., Neumann, F.-J., Frerker, C., Kurz, T., El-Mawardy, M., Richardt, G., & Abdel-Wahab, M. (2018). Bioprosthetic Valve Performance After Transcatheter Aortic Valve Replacement With Self-Expanding Versus Balloon-Expandable Valves in Large Versus Small Aortic Valve Annuli: Insights From the CHOICE Trial and the CHOICE-Extend Registry. *JACC. Cardiovascular Interventions*, *11*(24), 2507–2518. https://doi.org/10.1016/j.jcin.2018.07.050

Akodad, M., Lattuca, B., Agullo, A., Macia, J.-C., Gandet, T., Marin, G., Iemmi, A., Vernhet, H., Schmutz, L., Nagot, N., Albat, B., Cayla, G., & Leclercq, F. (2018). Prognostic Impact of Calcium Score after Transcatheter Aortic Valve Implantation Performed With New Generation Prosthesis. *The American Journal of Cardiology*, *121*(10), 1225–1230. https://doi.org/10.1016/j.amjcard.2018.02.004

Athappan, G., Patvardhan, E., Tuzcu, E. M., Svensson, L. G., Lemos, P. A., Fraccaro, C., Tarantini, G., Sinning, J.-M., Nickenig, G., Capodanno, D., Tamburino, C., Latib, A., Colombo, A., & Kapadia, S. R. (2013). Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: Meta-analysis and systematic review of literature. *Journal of the American College of Cardiology*, *61*(15), 1585–1595. https://doi.org/10.1016/j.jacc.2013.01.047

Azzalini, L., Ghoshhajra, B. B., Elmariah, S., Passeri, J. J., Inglessis, I., Palacios, I. F., & Abbara, S. (2014). The aortic valve calcium nodule score (AVCNS) independently predicts paravalvular regurgitation after transcatheter aortic valve replacement (TAVR). *Journal of Cardiovascular Computed Tomography*, *8*(2), 131–140. https://doi.org/10.1016/j.jcct.2013.12.013

Bache, R. J., Wang, Y., & Jorgensen, C. R. (1971). Hemodynamic effects of exercise in isolated valvular aortic stenosis. *Circulation*, *44*(6), 1003–1013. https://doi.org/10.1161/01.cir.44.6.1003

Barbanti, M., Yang, T.-H., Rodès Cabau, J., Tamburino, C., Wood, D. A., Jilaihawi, H., Blanke, P., Makkar, R. R., Latib, A., Colombo, A., Tarantini, G., Raju, R., Binder, R. K., Nguyen, G., Freeman, M., Ribeiro, H. B., Kapadia, S., Min, J., Feuchtner, G., … Leipsic, J. (2013). Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation*, *128*(3), 244–253. https://doi.org/10.1161/CIRCULATIONAHA.113.002947

Bates, M. G. D., Matthews, I. G., Fazal, I. A., & Turley, A. J. (2011). Postoperative permanent pacemaker implantation in patients undergoing trans-catheter aortic valve implantation: What is the incidence and are there any predicting factors? *Interactive Cardiovascular and Thoracic Surgery*, *12*(2), 243–253. https://doi.org/10.1510/icvts.2010.256578

Blanke, P., Reinöhl, J., Schlensak, C., Siepe, M., Pache, G., Euringer, W., Geibel-Zehender, A., Bode, C., Langer, M., Beyersdorf, F., & Zehender, M. (2012). Prosthesis oversizing in balloon-expandable transcatheter aortic valve implantation is associated with contained rupture of the aortic root. *Circulation. Cardiovascular Interventions*, *5*(4), 540–548. https://doi.org/10.1161/CIRCINTERVENTIONS.111.967349

Cahill, T. J., Chen, M., Hayashida, K., Latib, A., Modine, T., Piazza, N., Redwood, S., Søndergaard, L., & Prendergast, B. D. (2018). Transcatheter aortic valve implantation: Current status and future perspectives. *European Heart Journal*, *39*(28), 2625–2634. https://doi.org/10.1093/eurheartj/ehy244

Caira, F. C., Stock, S. R., Gleason, T. G., McGee, E. C., Huang, J., Bonow, R. O., Spelsberg, T. C., McCarthy, P. M., Rahimtoola, S. H., & Rajamannan, N. M. (2006). Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. *Journal of the American College of Cardiology*, *47*(8), 1707–1712. https://doi.org/10.1016/j.jacc.2006.02.040

Chan, K. L., Teo, K., Dumesnil, J. G., Ni, A., & Tam, J. (2010). Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: Results of the aortic stenosis progression observation: Measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation*, *121*(2), 306–314. https://doi.org/10.1161/CIRCULATIONAHA.109.900027

Clark, M. A., Duhay, F. G., Thompson, A. K., Keyes, M. J., Svensson, L. G., Bonow, R. O., Stockwell, B. T., & Cohen, D. J. (2012). Clinical and economic outcomes after surgical aortic valve replacement in Medicare patients. *Risk Management and Healthcare Policy*, *5*, 117–126. https://doi.org/10.2147/RMHP.S34587

Coté, N., Mahmut, A., Bosse, Y., Couture, C., Pagé, S., Trahan, S., Boulanger, M.-C., Fournier, D., Pibarot, P., & Mathieu, P. (2013). Inflammation is associated with the remodeling of calcific aortic valve disease. *Inflammation*, *36*(3), 573–581. https://doi.org/10.1007/s10753-012-9579-6

Cowell, S. J., Newby, D. E., Prescott, R. J., Bloomfield, P., Reid, J., Northridge, D. B., & Boon, N. A. (2005). A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *The New England Journal of Medicine*, *352*(23), 2389–2397. https://doi.org/10.1056/NEJMoa043876

Durko, A. P., Osnabrugge, R. L., Van Mieghem, N. M., Milojevic, M., Mylotte, D., Nkomo, V. T., & Pieter Kappetein, A. (2018). Annual number of candidates for transcatheter aortic valve implantation per country: Current estimates and future projections. *European Heart Journal*, *39*(28), 2635–2642. https://doi.org/10.1093/eurheartj/ehy107

Ewe, S. H., Ng, A. C. T., Schuijf, J. D., van der Kley, F., Colli, A., Palmen, M., de Weger, A., Marsan, N. A., Holman, E. R., de Roos, A., Schalij, M. J., Bax, J. J., & Delgado, V. (2011). Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. *The American Journal of Cardiology*, *108*(10), 1470–1477. https://doi.org/10.1016/j.amjcard.2011.07.007

Fedak, P. W. M., Verma, S., David, T. E., Leask, R. L., Weisel, R. D., & Butany, J. (2002). Clinical and Pathophysiological Implications of a Bicuspid Aortic Valve. *Circulation*, *106*(8), 900–904. https://doi.org/10.1161/01.CIR.0000027905.26586.E8

Forrest, J. K., Kaple, R. K., Tang, G. H. L., Yakubov, S. J., Nazif, T. M., Williams, M. R., Zhang, A., Popma, J. J., & Reardon, M. J. (2020). Three Generations of Self-Expanding Transcatheter Aortic Valves: A Report From the STS/ACC TVT Registry. *JACC. Cardiovascular Interventions*, *13*(2), 170–179. https://doi.org/10.1016/j.jcin.2019.08.035

Forrest, J. K., Mangi, A. A., Popma, J. J., Khabbaz, K., Reardon, M. J., Kleiman, N. S., Yakubov, S. J., Watson, D., Kodali, S., George, I., Tadros, P., Zorn, G. L., Brown, J., Kipperman, R., Saul, S., Qiao, H., Oh, J. K., & Williams, M. R. (2018). Early Outcomes With the Evolut PRO Repositionable Self-Expanding Transcatheter Aortic Valve With Pericardial Wrap. *JACC. Cardiovascular Interventions*, *11*(2), 160–168. https://doi.org/10.1016/j.jcin.2017.10.014

Freeman, V. R., & Otto, C. M. (2005). Spectrum of calcific aortic valve disease: Pathogenesis, disease progression, and treatment strategies. *Circulation*, *111*(24), 3316–3326. https://doi.org/10.1161/CIRCULATIONAHA.104.486738

Fukai, T., Galis, Z. S., Meng, X. P., Parthasarathy, S., & Harrison, D. G. (1998). Vascular expression of extracellular superoxide dismutase in atherosclerosis. *The Journal of Clinical Investigation*, *101*(10), 2101–2111. https://doi.org/10.1172/JCI2105

Gardezi, S. K. M., Myerson, S. G., Chambers, J., Coffey, S., d'Arcy, J., Hobbs, F. D. R., Holt, J., Kennedy, A., Loudon, M., Prendergast, A., Prothero, A., Wilson, J., & Prendergast, B. D. (2018). Cardiac auscultation poorly predicts the presence of valvular heart disease in asymptomatic primary care patients. *Heart (British Cardiac Society)*, *104*(22), 1832–1835. https://doi.org/10.1136/heartjnl-2018-313082

Grossman, W., Jones, D., & McLaurin, L. P. (1975). Wall stress and patterns of hypertrophy in the human left ventricle. *Journal of Clinical Investigation*, *56*(1), 56–64. https://doi.org/10.1172/JCI108079

Hahn, R. T., Leipsic, J., Douglas, P. S., Jaber, W. A., Weissman, N. J., Pibarot, P., Blanke, P., & Oh, J. K. (2019). Comprehensive Echocardiographic Assessment of Normal Transcatheter Valve Function. *JACC. Cardiovascular Imaging*, *12*(1), 25–34. https://doi.org/10.1016/j.jcmg.2018.04.010

Harris, A. W., Pibarot, P., & Otto, C. M. (2020). Aortic Stenosis: Guidelines and Evidence Gaps. *Cardiology Clinics*, *38*(1), 55–63. https://doi.org/10.1016/j.ccl.2019.09.003

Hase, H., Yoshijima, N., Yanagisawa, R., Tanaka, M., Tsuruta, H., Shimizu, H., Fukuda, K., Naganuma, T., Mizutani, K., Yamawaki, M., Tada, N., Yamanaka, F., Shirai, S., Tabata, M., Ueno, H., Takagi, K., Watanabe, Y., Yamamoto, M., Hayashida, K., & OCEAN-TAVI Investigators. (2021). Transcatheter aortic valve replacement with Evolut R versus Sapien 3 in Japanese patients with a small aortic annulus: The OCEAN-TAVI registry. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*, *97*(6), E875–E886. https://doi.org/10.1002/ccd.29259

Helske, S., Syväranta, S., Kupari, M., Lappalainen, J., Laine, M., Lommi, J., Turto, H., Mäyränpää, M., Werkkala, K., Kovanen, P. T., & Lindstedt, K. A. (2006). Possible role for mast cell-derived cathepsin G in the adverse remodelling of stenotic aortic valves. *European Heart Journal*, *27*(12), 1495–1504. https://doi.org/10.1093/eurheartj/ehi706

Herrmann, H. C., Daneshvar, S. A., Fonarow, G. C., Stebbins, A., Vemulapalli, S., Desai, N. D., Malenka, D. J., Thourani, V. H., Rymer, J., & Kosinski, A. S. (2018). Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *Journal of the American College of Cardiology*, *72*(22), 2701–2711. https://doi.org/10.1016/j.jacc.2018.09.001

Hess, O. M., Ritter, M., Schneider, J., Grimm, J., Turina, M., & Krayenbuehl, H. P. (1984). Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation*, *69*(5), 855–865. https://doi.org/10.1161/01.cir.69.5.855

Hess, O. M., Villari, B., & Krayenbuehl, H. P. (1993). Diastolic dysfunction in aortic stenosis. *Circulation*, *87*(5 Suppl), IV73--6.

Iung, B., & Vahanian, A. (2011). Epidemiology of valvular heart disease in the adult. *Nature Reviews Cardiology*, *8*(3), 162–172. https://doi.org/10.1038/nrcardio.2010.202

Jashari, R., Van Hoeck, B., Goffin, Y., & Vanderkelen, A. (2009). The incidence of congenital bicuspid or bileaflet and quadricuspid or quadrileaflet arterial valves in 3,861 donor hearts in the European Homograft Bank. *The Journal of Heart Valve Disease*, *18*(3), 337–344.

John, D., Buellesfeld, L., Yuecel, S., Mueller, R., Latsios, G., Beucher, H., Gerckens, U., & Grube, E. (2010). Correlation of Device Landing Zone Calcification and Acute Procedural Success in Patients Undergoing Transcatheter Aortic Valve Implantations With the Self-Expanding CoreValve Prosthesis. *JACC: Cardiovascular Interventions*, *3*(2), 233–243. https://doi.org/10.1016/j.jcin.2009.11.015

Johnson, L. L., Sciacca, R. R., Ellis, K., Weiss, M. B., & Cannon, P. J. (1978). Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. *Circulation*, *57*(3), 582–590. https://doi.org/10.1161/01.cir.57.3.582

Khalique, O. K., Hahn, R. T., Gada, H., Nazif, T. M., Vahl, T. P., George, I., Kalesan, B., Forster, M., Williams, M. B., Leon, M. B., Einstein, A. J., Pulerwitz, T. C., Pearson, G. D. N., & Kodali, S. K. (2014). Quantity and Location of Aortic Valve Complex Calcification Predicts Severity and Location of Paravalvular Regurgitation and Frequency of Post-Dilation After Balloon-Expandable Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *7*(8), 885–894. https://doi.org/10.1016/j.jcin.2014.03.007

Khatri, P. J., Webb, J. G., Rodés-Cabau, J., Fremes, S. E., Ruel, M., Lau, K., Guo, H., Wijeysundera, H. C., & Ko, D. T. (2013). Adverse effects associated with transcatheter aortic valve implantation: A meta-analysis of contemporary studies. *Annals of Internal Medicine*, *158*(1), 35–46. https://doi.org/10.7326/0003-4819-158-1-201301010-00007

Koos, R., Mahnken, A. H., Dohmen, G., Brehmer, K., Günther, R. W., Autschbach, R., Marx, N., & Hoffmann, R. (2011). Association of aortic valve calcification severity with the degree of aortic regurgitation after transcatheter aortic valve implantation. *International Journal of Cardiology*, *150*(2), 142–145. https://doi.org/10.1016/j.ijcard.2010.03.004

Kulbertus, H. E. (1988). Ventricular arrhythmias, syncope and sudden death in aortic stenosis. *European Heart Journal*, *9 Suppl E*, 51–52. https://doi.org/10.1093/eurheartj/9.suppl_e.51

Leon, M. B., Smith, C. R., Mack, M. J., Makkar, R. R., Svensson, L. G., Kodali, S. K., Thourani, V. H., Tuzcu, E. M., Miller, D. C., Herrmann, H. C., Doshi, D., Cohen, D. J., Pichard, A. D., Kapadia, S., Dewey, T., Babaliaros, V., Szeto, W. Y., Williams, M. R., Kereiakes, D., … Webb, J. G. (2016). Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine*, *374*(17), 1609–1620. https://doi.org/10.1056/nejmoa1514616

Mack, M. J., Leon, M. B., Thourani, V. H., Makkar, R., Kodali, S. K., Russo, M., Kapadia, S. R., Malaisrie, S. C., Cohen, D. J., Pibarot, P., Leipsic, J., Hahn, R. T., Blanke, P., Williams, M. R., McCabe, J. M., Brown, D. L., Babaliaros, V., Goldman, S., Szeto, W. Y., … Smith, C. R. (2019). Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *New England Journal of Medicine*, *380*(18), 1695–1705. https://doi.org/10.1056/nejmoa1814052

Marcus, M. L., Doty, D. B., Hiratzka, L. F., Wright, C. B., & Eastham, C. L. (1982). Decreased coronary reserve: A mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *The New England Journal of Medicine*, *307*(22), 1362–1366. https://doi.org/10.1056/NEJM198211253072202

Mathieu, P., & Boulanger, M.-C. (2014). Basic mechanisms of calcific aortic valve disease. *The Canadian Journal of Cardiology*, *30*(9), 982–993. https://doi.org/10.1016/j.cjca.2014.03.029

Mauri, V., Deuschl, F., Frohn, T., Schofer, N., Linder, M., Kuhn, E., Schaefer, A., Rudolph, V., Madershahian, N., Conradi, L., Rudolph, T. K., & Schäfer, U. (2018). Predictors of paravalvular regurgitation and permanent pacemaker implantation after TAVR with a next-generation

self-expanding device. *Clinical Research in Cardiology: Official Journal of the German Cardiac Society*, *107*(8), 688–697. https://doi.org/10.1007/s00392-018-1235-1

Milhorini Pio, S., Bax, J., & Delgado, V. (2020). How valvular calcification can affect the outcomes of transcatheter aortic valve implantation. *Expert Review of Medical Devices*, *17*(8), 773–784. https://doi.org/10.1080/17434440.2020.1789456

Miller, J. D., Chu, Y., Brooks, R. M., Richenbacher, W. E., Peña-Silva, R., & Heistad, D. D. (2008). Dysregulation of antioxidant mechanisms contributes to increased oxidative stress in calcific aortic valvular stenosis in humans. *Journal of the American College of Cardiology*, *52*(10), 843–850. https://doi.org/10.1016/j.jacc.2008.05.043

Modolo, R., Chang, C. C., Abdelghani, M., Kawashima, H., Ono, M., Tateishi, H., Miyazaki, Y., Pighi, M., Wykrzykowska, J. J., de Winter, R. J., Ruck, A., Chieffo, A., van Mourik, M. S., Yamaji, K., Richardt, G., de Brito, F. S., Lemos, P. A., Al-Kassou, B., Piazza, N., … Serruys, P. W. (2020). Quantitative Assessment of Acute Regurgitation Following TAVR: A Multicenter Pooled Analysis of 2,258 Valves. *JACC. Cardiovascular Interventions*, *13*(11), 1303–1311. https://doi.org/10.1016/j.jcin.2020.03.002

Mohler, E. R. 3rd, Adam, L. P., McClelland, P., Graham, L., & Hathaway, D. R. (1997). Detection of osteopontin in calcified human aortic valves. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *17*(3), 547–552. https://doi.org/10.1161/01.atv.17.3.547

Mohler, E. R. 3rd, Gannon, F., Reynolds, C., Zimmerman, R., Keane, M. G., & Kaplan, F. S. (2001). Bone formation and inflammation in cardiac valves. *Circulation*, *103*(11), 1522–1528. https://doi.org/10.1161/01.cir.103.11.1522

Mosleh, W., Amer, M. R., Joshi, S., Mather, J. F., Gandhi, S., Iyer, V., Curtis, L., Kiernan, F. J., McMahon, S., Duvall, L., & McKay, R. G. (2019). Comparative Outcomes of Balloon-Expandable S3 Versus Self-Expanding Evolut Bioprostheses for Transcatheter Aortic Valve Implantation. *The American Journal of Cardiology*, *124*(10), 1621–1629. https://doi.org/10.1016/j.amjcard.2019.08.014

Movahed, M.-R., Hepner, A. D., & Ahmadi-Kashani, M. (2006). Echocardiographic prevalence of bicuspid aortic valve in the population. *Heart, Lung & Circulation*, *15*(5), 297–299. https://doi.org/10.1016/j.hlc.2006.06.001

Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., & Enriquez-Sarano, M. (2006). Burden of valvular heart diseases: A population-based study. *Lancet*, *368*(9540), 1005–1011. https://doi.org/10.1016/S0140-6736(06)69208-8

null, null, G, énéreux P., Piazza, N., Alu, M. C., Nazif, T., Hahn, R. T., Pibarot, P., Bax, J. J., Leipsic, J. A., Blanke, P., Blackstone, E. H., Finn, M. T., Kapadia, S., Linke, A., Mack, M. J., Makkar, R., Mehran, R., Popma, J. J., Reardon, M., … Leon, M. B. (2021). Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *Journal of the American College of Cardiology*, *77*(21), 2717–2746. https://doi.org/10.1016/j.jacc.2021.02.038

O'Brien, K. D., Kuusisto, J., Reichenbach, D. D., Ferguson, M., Giachelli, C., Alpers, C. E., & Otto, C. M. (1995). Osteopontin is expressed in human aortic valvular lesions. *Circulation*, *92*(8), 2163–2168. https://doi.org/10.1161/01.cir.92.8.2163

O'Brien, K. D., Shavelle, D. M., Caulfield, M. T., McDonald, T. O., Olin-Lewis, K., Otto, C. M., & Probstfield, J. L. (2002). Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation*, *106*(17), 2224–2230. https://doi.org/10.1161/01.cir.0000035655.45453.d2

Osnabrugge, R. L. J., Mylotte, D., Head, S. J., Van Mieghem, N. M., Nkomo, V. T., LeReun, C. M., Bogers, A. J. J. C., Piazza, N., & Kappetein, A. P. (2013). Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. *Journal of the American College of Cardiology*, *62*(11), 1002–1012. https://doi.org/10.1016/j.jacc.2013.05.015

Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P. 3rd, Gentile, F., Jneid, H., Krieger, V. E., Mack, M., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M. 3rd, Thompson,

A., & Toly, C. (2021a). 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, *143*(5), e35--e71. https://doi.org/10.1161/CIR.0000000000000932

Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P. 3rd, Gentile, F., Jneid, H., Krieger, V. E., Mack, M., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M. 3rd, Thompson, A., & Toly, C. (2021b). 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, *143*(5), e35--e71. https://doi.org/10.1161/CIR.0000000000000932

Pantely, G., Morton, M., & Rahimtoola, S. H. (1978). Effects of successful, uncomplicated valve replacement on ventricular hypertrophy, volume, and performance in aortic stenosis and in aortic incompetence. *The Journal of Thoracic and Cardiovascular Surgery*, *75*(3), 383–391.

Pavicevic, J., Nguyen, T. D. L., Caliskan, E., Reser, D., Frauenfelder, T., Plass, A., Stähli, B. E., Maier, W., Seifert, B., Maisano, F., Falk, V., Corti, R., Grünenfelder, J., & Emmert, M. Y. (2015). Aortic valve calcium score is a significant predictor for the occurrence of post-interventional paravalvular leakage after transcatheter aortic valve implantation—Results from a single center analysis of 260 consecutive patients. *International Journal of Cardiology*, *181*, 185–187. https://doi.org/10.1016/j.ijcard.2014.12.032

Pawade, T., Clavel, M.-A., Tribouilloy, C., Dreyfus, J., Mathieu, T., Tastet, L., Renard, C., Gun, M., Jenkins, W. S. A., Macron, L., Sechrist, J. W., Lacomis, J. M., Nguyen, V., Galian Gay, L., Cuéllar Calabria, H., Ntalas, I., Cartlidge, T. R. G., Prendergast, B., Rajani, R., … Dweck, M. R. (2018). Computed Tomography Aortic Valve Calcium Scoring in Patients With Aortic Stenosis. *Circulation. Cardiovascular Imaging*, *11*(3), e007146. https://doi.org/10.1161/CIRCIMAGING.117.007146

Piazza, N., Lange, R., Martucci, G., & Serruys, P. W. (2012). Patient selection for transcatheter aortic valve implantation: Patient risk profile and anatomical selection criteria. *Archives of Cardiovascular Diseases*, *105*(3), 165–173. https://doi.org/10.1016/j.acvd.2012.02.007

Pohle, K., Mäffert, R., Ropers, D., Moshage, W., Stilianakis, N., Daniel, W. G., & Achenbach, S. (2001). Progression of aortic valve calcification: Association with coronary atherosclerosis and cardiovascular risk factors. *Circulation*, *104*(16), 1927–1932. https://doi.org/10.1161/hc4101.097527

Popma, J. J., Deeb, G. M., Yakubov, S. J., Mumtaz, M., Gada, H., O'Hair, D., Bajwa, T., Heiser, J. C., Merhi, W., Kleiman, N. S., Askew, J., Sorajja, P., Rovin, J., Chetcuti, S. J., Adams, D. H., Teirstein, P. S., Zorn, G. L., Forrest, J. K., Tchétché, D., … Evolut Low Risk Trial Investigators. (2019). Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *The New England Journal of Medicine*, *380*(18), 1706–1715. https://doi.org/10.1056/NEJMoa1816885

Rajamannan, N. M. (2011). Bicuspid aortic valve disease: The role of oxidative stress in Lrp5 bone formation. *Cardiovascular Pathology : The Official Journal of the Society for Cardiovascular Pathology*, *20*(3), 168–176. https://doi.org/10.1016/j.carpath.2010.11.007

Rajamannan, N. M., Bonow, R. O., & Rahimtoola, S. H. (2007). Calcific aortic stenosis: An update. *Nature Clinical Practice. Cardiovascular Medicine*, *4*(5), 254–262. https://doi.org/10.1038/ncpcardio0827

Rajamannan, N. M., Evans, F. J., Aikawa, E., Grande-Allen, K. J., Demer, L. L., Heistad, D. D., Simmons, C. A., Masters, K. S., Mathieu, P., O'Brien, K. D., Schoen, F. J., Towler, D. A., Yoganathan, A. P., & Otto, C. M. (2011a). Calcific aortic valve disease: Not simply a degenerative process: A review and agenda for research from the national heart and lung and blood institute aortic stenosis working group. *Circulation*, *124*(16), 1783–1791. https://doi.org/10.1161/CIRCULATIONAHA.110.006767

Rajamannan, N. M., Evans, F. J., Aikawa, E., Grande-Allen, K. J., Demer, L. L., Heistad, D. D., Simmons, C. A., Masters, K. S., Mathieu, P., O'Brien, K. D., Schoen, F. J., Towler, D. A., Yoganathan, A. P., & Otto, C. M. (2011b). Calcific aortic valve disease: Not simply a degenerative process: A review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: Calcific aortic valve disease-2011 update. *Circulation*, *124*(16), 1783–1791. https://doi.org/10.1161/CIRCULATIONAHA.110.006767

Rajamannan, N. M., Subramaniam, M., Rickard, D., Stock, S. R., Donovan, J., Springett, M., Orszulak, T., Fullerton, D. A., Tajik, A. J., Bonow, R. O., & Spelsberg, T. (2003). Human aortic valve calcification is associated with an osteoblast phenotype. *Circulation*, *107*(17), 2181–2184. https://doi.org/10.1161/01.CIR.0000070591.21548.69

Rajamannan, N. M., Subramaniam, M., Stock, S. R., Stone, N. J., Springett, M., Ignatiev, K. I., McConnell, J. P., Singh, R. J., Bonow, R. O., & Spelsberg, T. C. (2005). Atorvastatin inhibits calcification and enhances nitric oxide synthase production in the hypercholesterolaemic aortic valve. *Heart (British Cardiac Society)*, *91*(6), 806–810. https://doi.org/10.1136/hrt.2003.029785

Reardon, M. J., Van Mieghem, N. M., Popma, J. J., Kleiman, N. S., Søndergaard, L., Mumtaz, M., Adams, D. H., Deeb, G. M., Maini, B., Gada, H., Chetcuti, S., Gleason, T., Heiser, J., Lange, R., Merhi, W., Oh, J. K., Olsen, P. S., Piazza, N., Williams, M., … SURTAVI Investigators. (2017). Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *The New England Journal of Medicine*, *376*(14), 1321–1331. https://doi.org/10.1056/NEJMoa1700456

Rezq, A., Basavarajaiah, S., Latib, A., Takagi, K., Hasegawa, T., Figini, F., Cioni, M., Franco, A., Montorfano, M., Chieffo, A., Maisano, F., Corvaja, N., Alfieri, O., & Colombo, A. (2012). Incidence, management, and outcomes of cardiac tamponade during transcatheter aortic valve implantation: A single-center study. *JACC. Cardiovascular Interventions*, *5*(12), 1264–1272. https://doi.org/10.1016/j.jcin.2012.08.012

Rossebø, A. B., Pedersen, T. R., Boman, K., Brudi, P., Chambers, J. B., Egstrup, K., Gerdts, E., Gohlke-Bärwolf, C., Holme, I., Kesäniemi, Y. A., Malbecq, W., Nienaber, C. A., Ray, S., Skjaerpe, T., Wachtell, K., & Willenheimer, R. (2008). Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *The New England Journal of Medicine*, *359*(13), 1343–1356. https://doi.org/10.1056/NEJMoa0804602

Ryś, M., Hryniewiecki, T., Michałowska, I., Stokłosa, P., Różewicz-Juraszek, M., Chmielak, Z., Dąbrowski, M., Mirota, K., & Szymański, P. (2018). Quantitative estimation of aortic valve calcification in multislice computed tomography in predicting the development of paravalvular leaks following transcatheter aortic valve replacement. *Postepy W Kardiologii Interwencyjnej = Advances in Interventional Cardiology*, *14*(1), 85–89. https://doi.org/10.5114/aic.2018.74359

Sá, M. P., Jacquemyn, X., Van den Eynde, J., Tasoudis, P., Erten, O., Sicouri, S., Macedo, F. Y., Pasala, T., Kaple, R., Weymann, A., Ruhparwar, A., Clavel, M.-A., Pibarot, P., & Ramlawi, B. (2023). Impact of Paravalvular Leak on Outcomes After Transcatheter Aortic Valve Implantation: Meta-Analysis of Kaplan-Meier-derived Individual Patient Data. *Structural Heart*, *7*(2), 100118. https://doi.org/10.1016/j.shj.2022.100118

Sawaya, F. J., Bajoras, V., Vanhaverbeke, M., Wang, C., Bieliauskas, G., Søndergaard, L., & De Backer, O. (2021). Intravascular Lithotripsy-Assisted Transfemoral TAVI: The Copenhagen Experience and Literature Review. *Frontiers in Cardiovascular Medicine*, *8*, 739750. https://doi.org/10.3389/fcvm.2021.739750

Shao, J.-S., Cheng, S.-L., Pingsterhaus, J. M., Charlton-Kachigian, N., Loewy, A. P., & Towler, D. A. (2005). Msx2 promotes cardiovascular calcification by activating paracrine Wnt signals. *The Journal of Clinical Investigation*, *115*(5), 1210–1220. https://doi.org/10.1172/JCI24140

Shavelle, D. M., Takasu, J., Budoff, M. J., Mao, S., Zhao, X. Q., & O'Brien, K. D. (2002). HMG CoA reductase inhibitor (statin) and aortic valve calcium. *Lancet (London, England)*, *359*(9312), 1125–1126. https://doi.org/10.1016/S0140-6736(02)08161-8

Sievers, H.-H., & Schmidtke, C. (2007). A classification system for the bicuspid aortic valve from 304 surgical specimens. *The Journal of Thoracic and Cardiovascular Surgery*, *133*(5), 1226–1233. https://doi.org/10.1016/j.jtcvs.2007.01.039

Smith, C. R., Leon, M. B., Mack, M. J., Miller, D. C., Moses, J. W., Svensson, L. G., Tuzcu, E. M., Webb, J. G., Fontana, G. P., Makkar, R. R., Williams, M., Dewey, T., Kapadia, S., Babaliaros, V., Thourani, V. H., Corso, P., Pichard, A. D., Bavaria, J. E., Herrmann, H. C., … PARTNER Trial Investigators. (2011). Transcatheter versus surgical aortic-valve replacement in high-risk patients. *The New England Journal of Medicine*, *364*(23), 2187–2198. https://doi.org/10.1056/NEJMoa1103510

Steiner, I., Kasparová, P., Kohout, A., & Dominik, J. (2007). Bone formation in cardiac valves: A histopathological study of 128 cases. *Virchows Archiv : An International Journal of Pathology*, *450*(6), 653–657. https://doi.org/10.1007/s00428-007-0430-7

Stundl, A., Lucht, H., Shamekhi, J., Weber, M., Sedaghat, A., Mellert, F., Grube, E., Nickenig, G., Werner, N., & Sinning, J.-M. (2019). Early versus newer generation transcatheter heart valves for transcatheter aortic valve implantation: Echocardiographic and hemodynamic evaluation of an all-comers study cohort using the dimensionless aortic regurgitation index (AR-index). *PloS One*, *14*(5), e0217544. https://doi.org/10.1371/journal.pone.0217544

Takagi, H., Niwa, M., Mizuno, Y., Goto, S.-N., Umemoto, T., & All-Literature Investigation of Cardiovascular Evidence Group. (2013). Incidence, predictors, and prognosis of acute kidney injury after transcatheter aortic valve implantation: A summary of contemporary studies using Valve Academic Research Consortium definitions. *International Journal of Cardiology*, *168*(2), 1631–1635. https://doi.org/10.1016/j.ijcard.2013.01.273

Thiele, H., Kurz, T., Feistritzer, H.-J., Stachel, G., Hartung, P., Eitel, I., Marquetand, C., Nef, H., Doerr, O., Lauten, A., Landmesser, U., Abdel-Wahab, M., Sandri, M., Holzhey, D., Borger, M., Ince, H., Öner, A., Meyer-Saraei, R., Wienbergen, H., … Desch, S. (2020). Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve

implantation: The randomized SOLVE-TAVI trial. *European Heart Journal*, *41*(20), 1890–1899. https://doi.org/10.1093/eurheartj/ehaa036

Thyregod, H. G. H., Steinbrüchel, D. A., Ihlemann, N., Nissen, H., Kjeldsen, B. J., Petursson, P., Chang, Y., Franzen, O. W., Engstrøm, T., Clemmensen, P., Hansen, P. B., Andersen, L. W., Olsen, P. S., & Søndergaard, L. (2015). Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *Journal of the American College of Cardiology*, *65*(20), 2184–2194. https://doi.org/10.1016/j.jacc.2015.03.014

Tobin, J. R. J., Rahimtoola, S. H., Blundell, P. E., & Swan, H. J. (1967). Percentage of left ventricular stroke work loss. A simple hemodynamic concept for estimation of severity in valvular aortic stenosis. *Circulation*, *35*(5), 868–879. https://doi.org/10.1161/01.cir.35.5.868

Vahanian, A., Alfieri, O., Andreotti, F., Antunes, M. J., Barón-Esquivias, G., Baumgartner, H., Borger, M. A., Carrel, T. P., De Bonis, M., Evangelista, A., Falk, V., Iung, B., Lancellotti, P., Pierard, L., Price, S., Schäfers, H.-J., Schuler, G., Stepinska, J., Swedberg, K., … Zembala, M. (2012). Guidelines on the management of valvular heart disease (version 2012). *European Heart Journal*, *33*(19), 2451–2496. https://doi.org/10.1093/eurheartj/ehs109

Van Mieghem, N. M., Schipper, M. E. I., Ladich, E., Faqiri, E., van der Boon, R., Randjgari, A., Schultz, C., Moelker, A., van Geuns, R.-J., Otsuka, F., Serruys, P. W., Virmani, R., & de Jaegere, P. P. (2013). Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement. *Circulation*, *127*(22), 2194–2201. https://doi.org/10.1161/CIRCULATIONAHA.112.001091

Vlastra, W., Chandrasekhar, J., Muñoz-Garcia, A. J., Tchétché, D., de Brito, F. S., Barbanti, M., Kornowski, R., Latib, A., D'Onofrio, A., Ribichini, F., Baan, J., Tijssen, J. G. P., Trillo-Nouche, R., Dumonteil, N., Abizaid, A., Sartori, S., D'Errigo, P., Tarantini, G., Lunardi, M., … Delewi, R. (2019). Comparison of balloon-expandable vs. self-expandable valves in patients undergoing

transfemoral transcatheter aortic valve implantation: From the CENTER-collaboration. *European Heart Journal*, *40*(5), 456–465. https://doi.org/10.1093/eurheartj/ehy805

Wiktorowicz, A., Wit, A., Malinowski, K. P., Dziewierz, A., Rzeszutko, L., Dudek, D., & Kleczynski, P. (2021). Paravalvular leak prediction after transcatheter aortic valve replacement with self-expandable prosthesis based on quantitative aortic calcification analysis. *Quantitative Imaging in Medicine and Surgery*, *11*(2), 652–664. https://doi.org/10.21037/QIMS-20-669

Windecker, S., Okuno, T., Unbehaun, A., Mack, M., Kapadia, S., & Falk, V. (2022). Which patients with aortic stenosis should be referred to surgery rather than transcatheter aortic valve implantation? *European Heart Journal*, *43*(29), 2729–2750. https://doi.org/10.1093/eurheartj/ehac105

Yan, A. T., Koh, M., Chan, K. K., Guo, H., Alter, D. A., Austin, P. C., Tu, J. V, Wijeysundera, H. C., & Ko, D. T. (2017). Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. *Journal of the American College of Cardiology*, *69*(12), 1523–1532. https://doi.org/10.1016/j.jacc.2017.01.025

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The curriculum vitae was removed from the electronic version due to data protection laws.