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Transfemoral access in trans-catheter aortic valve implantation: surgical cut-down vs. percutaneous with the ProGlide system. Evaluation of 1,600 patients

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Abbreviations

AHT	Arterial Hypertension
AOA	Alpha-amino Oleic Acid
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVB	Atrioventricular Block
BAV	Bicuspid Aortic Valve
BE	Balloon-Expandable
BMI	Body Mass Index
CE	Conformité Européenne
CI	Confidence Interval
CT	Computed Tomography
DFM	Direct Flow Medical
DM	Diabetes Mellitus
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
ESC	European Society of Cardiology
Fr	French
GARY	German Aortic Valve Registry
LVOT	Left Ventricular Outflow Tract
MRI	Magnetic Resonance Imaging
NOAC	Novel Oral Anticoagulants
OAD	Oral Antidiabetic Drug
OR	Odds Ratio
PAD	Peripheral Artery Disease
PPI	Permanent Pacemaker Implantation
PVL	Paravalvular Leak
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation

SE	Self-Expandable
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TF	Transfemoral
TTE	Transthoracic Echocardiogram
VC	Vascular Complications
VHD	Valvular Heart Disease

1 Introduction

1.1 Anatomy of the Aortic Valve and its Surrounding Structures

Located between the left ventricle and the ascending aorta, the aortic valve could be viewed as the cardiac centerpiece, with the mitral valve located posterior and to the left, the tricuspid valve inferiorly posterior and to the right and with the pulmonary valve located superiorly anterior and to the left (Piazza et al., 2008; Ho, 2009).

The aortic root, positioned at the junction of the left ventricular outflow tract (LVOT) and the ascending aorta, consists of three components: the valvular leaflets, the sinuses of Valsalva and the aortic commissures (Piazza et al., 2008; Ho, 2009) and contains at least three circular rings (virtual ring formed by joining basal attachments of aortic valvar leaflets, anatomic ventriculo-arterial junction and sinotubular junction) (Anderson, 2007). (Fig. 1)

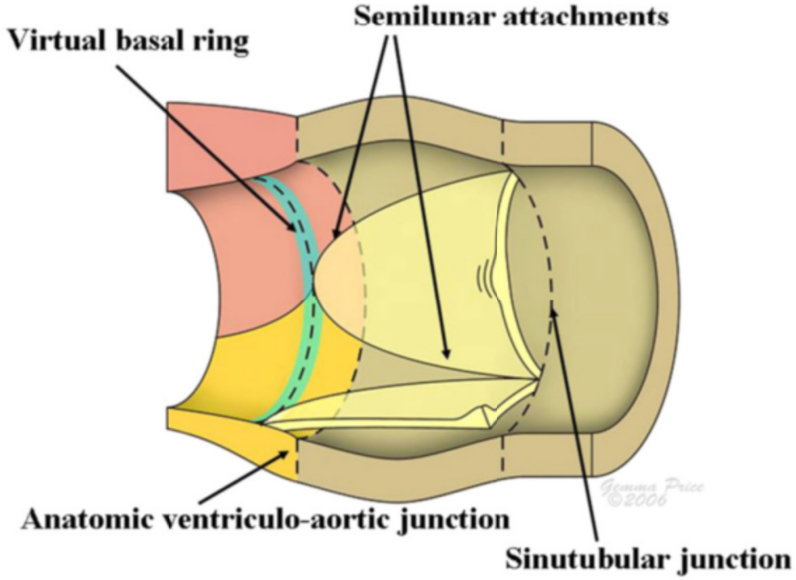

Figure 1: Bisected Aortic Root: The illustration shows three circular rings – the virtual ring formed by joining the basal attachments of the aortic valve leaflets, the anatomic ventriculo-arterial junction, and the sinotubular junction. The crown-like attachments of the leaflets extend through the entire length of the root from the sinotubular junction to the virtual basal ring.
(Anderson et al., 2013)

The aortic valve comprise of three cusps (right coronary, left coronary and non-coronary) composed of thin fibrous connective tissue core with endothelial linings. The leaflets are attached to the fibrous ring, which provides structural support and has a crown-like shape (Piazza et al., 2008).

The adjacent aortic wall is slightly dilated to help form the three sinuses of Valsalva (Ho, 2009). In most cases, the orifices of the coronary arteries arise from the two anterior sinuses, just below the sinotubular junction (Berdajs, Lajos and Turina, 2002).

As a result of the semilunar attachment of the aortic valvular leaflets, there are 3 triangular extensions of the LVOT that reach to the level of the sinotubular junction. These interleaflet triangles are formed of the thinned fibrous wall of the aorta, and are known as aortic commissures (Sutton III, Ho and Anderson, 1995).

The larger part of the non-coronary leaflet along with part of the left coronary leaflet is in fibrous continuity with the anterior leaflet of the mitral valve, the so-called aortic-mitral curtain (Piazza et al., 2008). Therefore, the implantation of the valvular prosthesis too low within the left ventricular outflow tract may affect the anterior leaflet of the mitral valve and impair its function (Piazza *et al.*, 2008).

The interleaflet triangle located between the right coronary and non-coronary aortic leaflets is confluent with the membranous septum. The membranous septum located beneath the right and non-coronary commissure is where the atrioventricular conduction bundle can be located.

The atrioventricular node, located within the triangle of Koch in the right atrium, is in close proximity to the subaortic region and membranous septum of the left ventricular outflow tract (Anderson, 2007) (Fig. 2). Procedures involving the aortic valve can lead to complete heart block or intraventricular conduction abnormalities, if this delicate structure is offended during aortic valve procedures (Anderson, 2007).

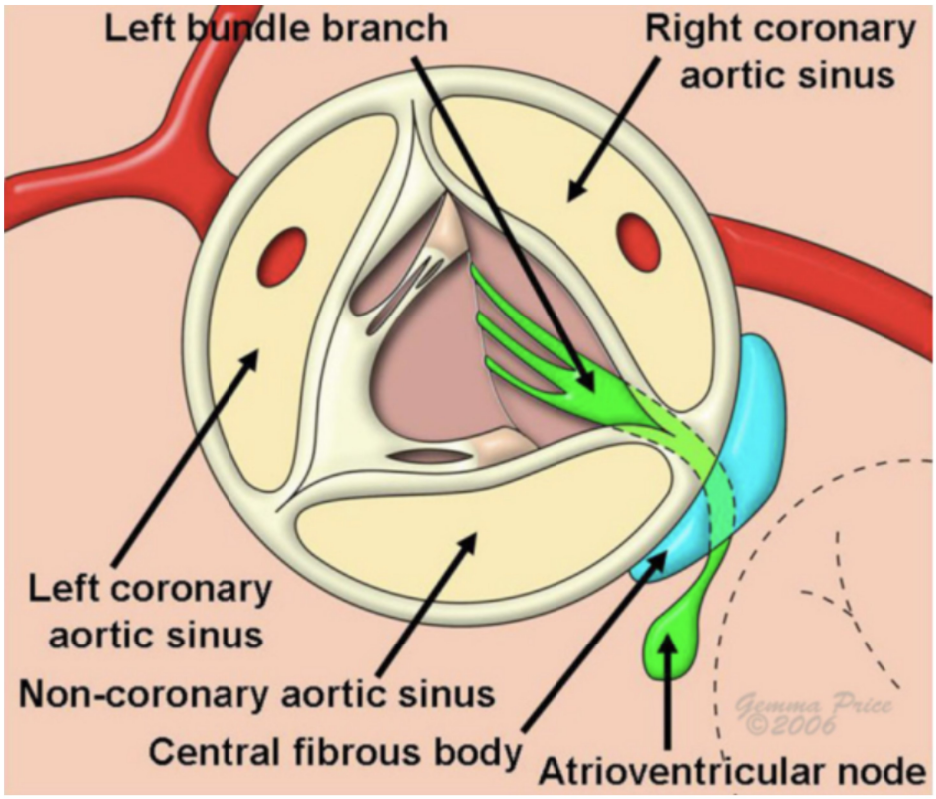

Figure 2: Aortic sinuses, coronary arteries and the location of the atrioventricular conduction axis, as seen by looking down through the aortic root. (Anderson et al., 2013) Copyright 2013 by Gemma Price, used with permission.

1.2 Aortic Stenosis

1.2.1 Epidemiology and Etiology

Aortic stenosis (AS) is an obstruction of blood flow across the aortic valve due to a pathological narrowing. It is the most common valvular heart disease in Western countries and is usually caused by degenerative calcific valvular disease (Nathaniel, Saligram and Innasimuthu, 2010). The prevalence of aortic sclerosis increases with age: It is seen in 25% of patients at 65 years of age, rising to 48% in patients older than 75 years; moderate to severe AS for those aged over 65 years is 4–5% (Baumgartner and Walther, 2018).

Risk factors for degenerative aortic stenosis are male gender, nicotine abuse, hypertension, hypercholesterolemia, diabetes mellitus, and hypercalcemia (Kamath and Pai, 2008; Rajamannan, 2009).

The bicuspid aortic valve (BAV) is the second most frequent cause of aortic stenosis and the most common congenital cardiac malformation, affecting approximately 1-2% of the population (Wedin *et al.*, 2019). The development of BAV arises from irregular aortic cusp formation during valvulogenesis, where adjacent cusps fuse, resulting in a single aberrant cusp, larger than one cusp but smaller than the combination of two normal cusps (Paloschi, 2013). Notably, a majority of patients, aged 15 to 65 years, afflicted with significant aortic stenosis exhibit bicuspid valves, indicating a tendency for premature fibrosis, stiffening, and calcium deposition within these abnormally functioning valves (Fedak *et al.*, 2002).

Post-rheumatic aortic stenosis, as a late consequence of rheumatic fever, occurs nowadays in industrialized countries much less often. Initially normal valve leaflets thicken, shorten, merge, and then calcify secondarily. This type of aortic stenosis is characteristically accompanied by aortic insufficiency and a concomitant mitral valve defect (Nkomo *et al.*, 2006).

1.2.2 Pathogenesis of Hypertrophic Cardiomyopathy Based on Aortic Stenosis

The normal opening area of the aortic valve is 2 to 4 cm^2. Narrowing under 2 cm^2 causes an increase in pressure afterload and ventricular wall stress. According to the law of Laplace (wall stress = [pressure x radius]/2 x wall thickness), as the left ventricular pressure rises, the ventricular wall thickness must also increase (Czarny and Resar, 2014). The hypertrophy of myocytes aims to restore wall stress and for a time preserves overall left ventricular function. The increasing thickness of the left ventricular wall leads to relative coronary insufficiency. This, together with the increased afterload results in reduced oxygen supply and causes fibrosis of subendocardial wall layers (Schiattarella and Hill, 2015). As the disease progresses, the left ventricle dilates and heart failure develops. Both the severity of valve narrowing and the myocardial hypertrophic response determine onset of symptoms and the indication for intervention (Lester *et al.*, 1998; Dweck, Boon and Newby, 2012).

1.2.3 Clinical Symptoms and Evaluation

The classic physical finding of aortic stenosis is a harsh, late-peaking crescendo-decrescendo systolic murmur that is loudest over the second right intercostal space and radiates to the carotid arteries. However, in older persons, the murmur may be less intense and often radiates to the apex instead of to the carotid arteries (Grimard, Safford and Burns, 2016). An electrocardiogram (ECG) might illustrate left axis deviation as a sign of left ventricle hypertrophy. The typical clinical manifestations of AS are angina pectoris, syncope, and dyspnea (Nishizaki et al., 2013).

Angina pectoris as a sign of myocardial ischemia, is the result of increased oxygen demands by the hypertrophic myocardium in combination with a reduction in oxygen delivery resulting from the excessive compression of the coronary arteries (Bertrand *et al.*, 1981). Syncope can occur due to the heart's inability to increase cardiac output in response to systemic hypotension, leading to cerebral hypoperfusion, particularly during situations like exercise where skeletal muscle vasodilation lowers blood pressure and the heart cannot compensate adequately due to the fixed cardiac output caused by the stenotic valve (Maharaj and Teelucksingh, 2023). Dyspnoe on exertion is usually the first symptom associated with AS. Dyspnoe can also present itself late in AS, as a symptom of heart failure (David, 1999).

A transthoracic echocardiogram (TTE) and in many centers a transesophageal echocardiogram as well, is the gold-standard non-invasive method to evaluate aortic valve anatomy and function. The aortic valve area can be calculated using echocardiographic flow velocities. Using the velocity of blood flow through the valve, the pressure gradient across the valve can also be calculated. A decreased valvular area causes an increased pressure gradient (Vahanian et al., 2022). These parameters are used to classify and grade aortic stenosis as mild, moderate, or severe (Tab. 1). The pressure gradient can be abnormally low in the presence of mitral stenosis, heart failure, co-existent aortic regurgitation, as well as ischemic heart disease (Vahanian et al., 2022).

Table 1: Aortic Stenosis Grades of Severity as Assessed Using Echocardiography and Computed Tomography (Calcium Scoring) (Messika-Zeitoun' and Lloyd', 2018)

Abbreviations: AS, aortic stenosis; AU, Agatston Units; AVA, aortic valve area.

Echo parameters	Sclerosis	Mild AS	Moderate AS	Severe AS
Peak velocity, m/sec	<2.5	2.5-3	3-4	>4
Mean gradient, mmHg	Normal	<20	20-40	40
AVA, cm^2	Normal	≥1.5	1-1.5	<1
Calcium scoring, AU				Male 2,065 Female 1,275

1.2.4 Therapy

Severe symptomatic AS, as well as severe asymptomatic AS with ejection fraction less than 50% without another cause, typically requires prompt valve intervention (Vahanian et al., 2022). Neither balloon valvuloplasty nor drug therapy has shown satisfactory results, but they can be used as a bridge to intervention or palliation (Vahanian et al., 2022).

For almost 60 years, surgical aortic valve replacement (SAVR) has been the gold standard treatment for severe symptomatic aortic stenosis. In low-risk patients with isolated aortic valve disease, SAVR has mortality of 2% (Möllmann *et al.*, 2016). For higher risk patients and those incapable of cardiopulmonary bypass and general anesthesia, percutaneous transcatheter aortic valve implantation (TAVI) represents a less invasive approach for treating AS. This approach has been implemented successfully in high-risk patients with severe symptomatic AS who were not considered candidates for conventional surgery (Grube *et al.*, 2007). After implementing TAVI procedures in high risk patients, the range of indications has been extended to intermediate and low risk patients (Vahanian *et al.*, 2022).

The choice between surgical and transcatheter intervention should be based on a thorough evaluation by a Heart Team, considering clinical, anatomical, and

procedural factors. This recommendation should be discussed with the patient to enable an informed treatment choice (Vahanian et al., 2022). The intervention itself should be performed in a Heart Valve Center with proven expertise, active interventional cardiology and cardiac surgery programs, and the aforementioned collaborative Heart Team (Vahanian et al., 2022).

The current 2021 European Society of Cardiology/ European Association for Cardio-Thoracic Surgery guidelines recommend surgical therapy for patients under 75 years of age and at low risk or those unsuitable for TAVI. Patients over 75 years of age or those who are high risk or unsuitable for operation should be treated with TAVI. Other patients are recommended to undergo either SAVR or TAVI according to individual clinical, anatomical, and procedural characteristics (Vahanian *et al.*, 2022).

Characteristics favoring TAVI include higher surgical risk, older age, previous cardiac surgery, frailty, anatomy suited for transfemoral access, sequelae of chest radiation, porcelain aorta, and severe chest deformation or scoliosis (Vahanian *et al.*, 2022). Conversely, lower surgical risk, younger age, active or suspected endocarditis, aortic annular dimensions unsuitable for TAVI devices, BAV, valve morphology unfavorable for TAVI such as low coronary ostia or heavy leaflet/LVOT calcification, thrombus in the aorta or left ventricle, and the need for concomitant cardiac surgery favor SAVR (Vahanian *et al.*, 2022).

Specific therapy for mild, asymptomatic aortic stenosis is usually not necessary, but regular echocardiographic check-ups should take place (Vahanian *et al.*, 2022).

1.2.5 Prognosis

Patient prognosis depends largely on the severity of disease, comorbidities, and the therapy option chosen. Patients with asymptomatic aortic stenosis have a very good prognosis (Rosenhek *et al.*, 2010). The life expectancy of patients with severe aortic stenosis is significantly reduced when left untreated, with more than one third dying within the first year after diagnosis (Varadarajan *et*

al., 2006). Therefore, surgical or minimally invasive treatments are urgently indicated in these cases.

1.3 Transcatheter Aortic Valve Implantation

The first TAVI was performed in 2002 by Alain Cribier in Rouen, France, using the antegrade trans-septal access route (Cribier *et al.*, 2002). The 57-year-old patient suffered from aortic valve stenosis, subacute leg ischemia, and cardiogenic shock. The atrial septum and mitral valve had to be crossed to get into the stenotic aortic valve (Cribier *et al.*, 2002). In 2006 John Webb, in cooperation with Edwards Lifesciences, developed the retrograde trans-arterial implantation technique with a deflectable pusher sheath to allow easy passage through the aortic arch and the stenotic valve. He also performed the first transapical aortic valve implantation (Webb *et al.*, 2007).

Transcatheter aortic valve implantation is nowadays a treatment option for patients with symptomatic aortic valve stenosis. Although originally designed to provide an alternative, safer treatment option for patients with a high surgical risk, its indication broadens to the population of patients with an intermediate or even low risk (Agma *et al.*, 2022).

Since 2002, TAVI has experienced a significant surge in popularity, and new valves and sheaths have been steadily developed and improved upon, to decrease the amount of procedural complications (Mariathas, Rawlins and Curzen, 2017).

1.3.1 Preoperative Planning

Since there is no direct view or access to the affected anatomy, comprehensive preoperative planning is crucial for a successful procedural outcome (Swee and Grbić, 2014).

1.3.1.1 Patient Examination and Evaluation

Complete medical history and thorough physical examination, in particular auscultation and search for heart failure signs, are crucial (Munt *et al.*, 1999). Patient frailty is carefully assessed. Frailty is defined as a decrease of physiologic reserve and ability to maintain homeostasis leading to an increased

vulnerability to stresses and conferring an increased risk of morbidity and mortality after both surgery and TAVI (Afilalo, 2017). Anatomical aspects, malnutrition, cognitive dysfunction and major organ dysfunction / failure not included in below mentioned risk scores should be all taken into consideration (Vahanian *et al.*, 2022).

Risk stratification is required for weighing the risk of intervention against the expected natural history of valvular heart disease (VHD) and for choosing the type of intervention (Nishimura *et al.*, 2014). The Society of Thoracic Surgeons (STS) predicted risk of mortality score and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) accurately discriminate high-risk (STS score / EuroSCORE II > 8%) and low-risk (STS score / EuroSCORE II < 4%) surgical patients and show good calibration to predict postoperative outcome after valvular surgery in the majority of the patients (Osnabrugge *et al.*, 2014).

The EuroSCORE II takes into account factors related to the patient, the patient's heart condition and the proposed operation and its urgency (Nashef *et al.*, 2012). The patient’s EuroSCORE is the probability, expressed as a percentage, of the patient dying during or shortly after the proposed surgery (Nashef *et al.*, 2012).

In addition to predicting patient’s mortality, as the EuroSCORE does, the STS score also estimates the probabilities of morbidity and of some operative complications such as stroke or renal failure (Kozower *et al.*, 2010).

1.3.1.2 Imaging Studies

Transthoracic and transesophageal echocardiography are the key techniques used to confirm the diagnosis of VHD, to assess its etiology, mechanisms, function, severity, and prognosis, as well as to evaluate the feasibility of a TAVI (Vahanian *et al.*, 2022). Immediately before the procedure, a baseline morphological and hemodynamic assessment should be performed using TEE, assessing all four valves and chambers, examining chamber size and wall motion, and quantifying heart valve regurgitation (Onishi *et al.*, 2018).

Standardized, ECG-synchronized computed tomography (CT) is used to assess the aortic valve and the distribution of its calcifications, to select a suitable valve size and to evaluate the feasibility of a transfemoral access (Blanke, Schoepf and Leipsic, 2013). All computed tomography data are transferred to a dedicated computer program (in our clinic 3mensio Structural Heart by Pie Medical Imaging). This program is able to automatically generate transverse, coronal, and sagittal sections of the valve (Blanke, Schoepf and Leipsic, 2013). The size of the aortic valve prosthesis is chosen based on the average of the measured valve diameters ((largest diameter + smallest diameter) / 2) (Kasel *et al.*, 2013). The CT scan is also used to determine the location of the coronary arteries ostia, measuring the height of the coronary arteries takeoff. This knowledge is essential for appropriate TAVI prosthesis selection and implantation (Blanke, Schoepf and Leipsic, 2013). If they are too low within the sinus of Valsalva and/or the prosthesis is placed too high, the skirt may obstruct their orifices and thus impede coronary arterial flow. Furthermore, the prosthesis crushes the leaflets of the native valve against the aortic wall during deployment, meaning, that in combination with a relatively low-lying coronary artery ostium, a large native aortic valvular leaflet can obstruct the flow into the coronary arteries (Webb *et al.*, 2006).

Finally, coronary angiography is recommended for the assessment of coronary artery disease, and to determine if concomitant coronary revascularization is needed (Knuuti *et al.*, 2020).

1.3.1.3 Indication

It is recognized that low risk patients with severe AS should be directly referred for SAVR and those who are inoperable should be offered TAVI if their life expectancy is more than one year (Vahanian *et al.*, 2022). The therapy for symptomatic patients at higher risks for SAVR should be determined by a Heart Team, taking into account the available scientific evidence, as well as recommendations from the 2021 ESC/EACTS Guidelines for the management of valvular disease and center-specific outcomes of various treatment options (Vahanian *et al.*, 2022).

The risk of the intervention using STS and/or EuroSCORE II should be predicted. As the risk scores have major limitations in patients undergoing transcatheter intervention – they do not include major risk factors such as frailty, anatomical factors with impact on the procedure (porcelain aorta, previous chest radiation, mitral annular calcification) – the Heart Team should assess potential procedure impediments, compromised major organs, and the frailty of the patient (Vahanian *et al.*, 2022).

1.3.1.4 Prosthesis Selection

There are two main categories of transcatheter aortic valve prostheses: balloon-expandable (BE) and self-expandable (SE) (Kasel *et al.*, 2013). Balloon expandable valves are designed to reach a definite diameter and shape after deployment meaning they can substantially change the shape of the annulus after deployment. In contrast, SE prostheses are more prone to accommodate native anatomies (Kasel *et al.*, 2013).

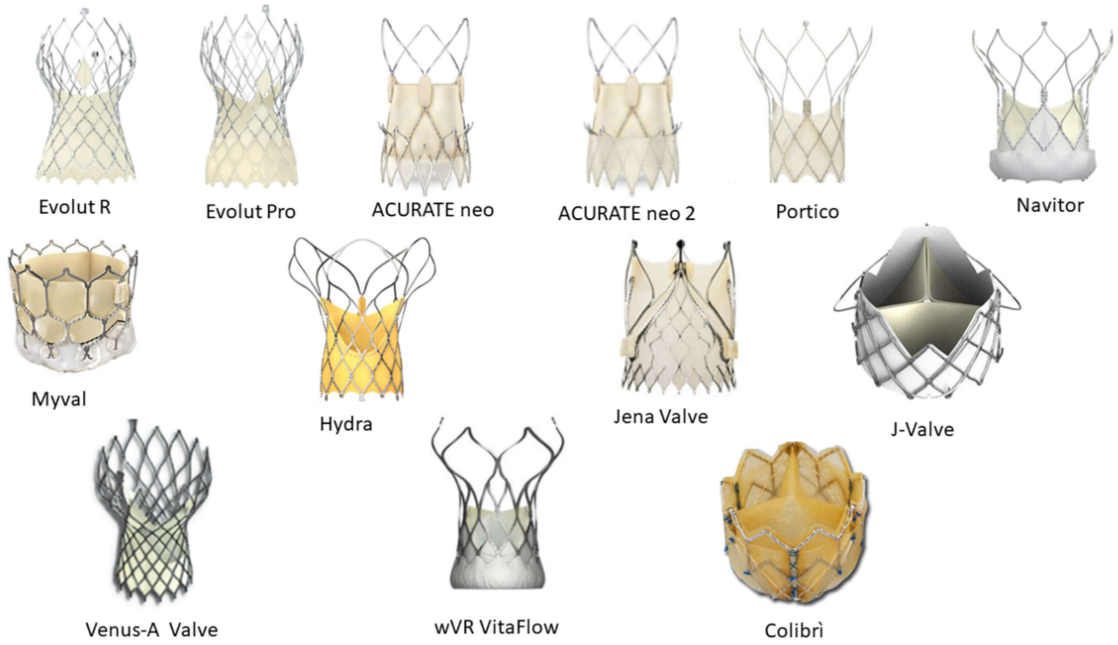

Figure 3: Commercially available and investigational devices for transcatheter aortic valve implantation (Santangelo et al., 2022)

There are charts and dedicated applications available to help determine the correct size of transcatheter aortic valves, as well as industry guidance on valve dimensions and aortic annuli measurements. Insufficient sizing of either self-

expanding or balloon-expandable transcatheter valves has been associated with more frequent paravalvular leaks (PVL), valve migration, and patient-prosthesis mismatch (Ki *et al.*, 2020). To avoid such complications, transcatheter prostheses are designed to be deployed in annuli that are slightly smaller than the prostheses. However, careful attention to oversizing is essential, as excessive oversizing can lead to complications such as annular rupture and postoperative conduction abnormalities (Elnwagy *et al.*, 2024). The appropriate degree of TAVI oversizing is prosthesis specific (the best cutoff value for the Evolut system being >17.6% and for the Sapien system >10.2%) and is greatly influenced by the imaging modality (echocardiographic vs. computed tomography (CT)) and by the method of diameter calculation (i.e., area, mean diameter, and perimeter) (Mylotte *et al.*, 2013; Chodór *et al.*, 2017; Ki *et al.*, 2020).

1.3.1.4.1 Balloon-expandable Valves

Edwards Sapien

The Edwards SAPIEN heart-valve was the first commercially available TAVI prosthesis and has received CE Mark approval for European sales in 2007. It consists of a trileaflet bovine pericardial valve and a stainless-steel support frame. A 22 or 24 Fr sheath is needed, depending on the selected size of the valve (23 mm or 26 mm) (*Edwards Lifesciences Receives CE Mark for Edwards SAPIEN Transcatheter Heart Valve*).

Edwards Sapien XT

The Edwards Sapien XT valve has been approved in Europe since 2010 and is made of a cobalt chromium alloy frame with high radial strength. The valve leaflets consist of bovine pericardial tissue and are treated with ThermaFix procedures to minimize the risk of calcification. The disadvantage of this valve is the caliber size of the insertion sheaths required. Those vary from 16 Fr with a valve diameter of 23 mm to a size of 20 Fr with a valve diameter of 29 mm (*Transcatheter pulmonic heart valves | Edwards Lifesciences*).

Edwards Sapien 3

The Edwards Sapien 3 transcatheter heart valve was approved for clinical use in Europe in 2014. It incorporates an optimized cobalt chromium alloy frame (which allows for an extremely low-crimped profile with high radial strength), bovine pericardial leaflets treated with ThermaFix process, and an adaptive external polyethylene terephthalate fabric seal (Edwards SAPIEN 3 Transkatheter-Herzklappe | Edwards Lifesciences). The transfemoral Commander delivery catheter provides a stable platform allowing for controlled coaxial alignment and accurate positioning of the Sapien 3 within the native valve (Edwards SAPIEN 3 Transkatheter-Herzklappe | Edwards Lifesciences). The system is compatible with 14-Fr (20-26 mm diameter S3) and 16-Fr (29 mm S3) expandable introducer sheaths and incorporates a central balloon marker, which is the primary landmark for positioning during Sapien 3 expansion (Webb et al., 2014; Edwards SAPIEN 3 Transkatheter-Herzklappe | Edwards Lifesciences).

1.3.1.4.2 Self-expandable Valves

Medtronic CoreValve

The CoreValve system was first approved in Europe in March 2007. The bioprosthesis is manufactured by suturing 3 valve leaflets and a skirt, made from a single layer of porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of nitinol. The bioprosthesis is processed with alpha-amino oleic acid, which is an antimineralization treatment. The outer diameter of the valve capsule is 18 Fr, an 18-Fr hemostatic vessel introducer sheath is therefore necessary (Medtronic, 2014).

Medtronic CoreValve Evolut R

The CoreValve Evolut R valve has been approved in Europe since 2012. In contrary to CoreValve, this valve is retrievable and repositionable. The frame is tailored to reduce overall height to 45 mm, approximately 10 mm shorter than the original CoreValve frame, while preserving the height of the pericardial skirt (12 mm) to provide a seal against paravalvular leakage (Sinning *et al.*, 2012).

This valve is made of porcine pericardial tissue treated with alpha-amino oleic acid to inhibit calcification (Sinning *et al.*, 2012). The built-in sheath enables the insertion of the entire system without the need of an additional access sheath, thereby reducing the overall profile of the delivery system down to 14-Fr equivalent sheath (Medtronic, 2019).

Medtronic CoreValve Evolut PRO

Approved in Europe since 2017, this valve consists of an external pericardial wrap which ensures reduction in paravalvular regurgitation. Low delivery profile, self-expansion, and the ability to recapture and reposition remain the same as in the previous generation (Mahtta, Elgendy and Bavry, 2017). The Evolut Pro system is indicated for vessels down to 5.5 mm and its delivery system with the InLine sheath allows for a delivery profile as low as 16-Fr equivalent (Mahtta, Elgendy and Bavry, 2017).

New Valve Technology Allegra

The prosthesis, approved in Europe since 2017, incorporates a trileaflet, bovine pericardial valve attached to a nitinol stent frame. The diamond-shaped configuration with a variable cell size distribution allows improved coronary perfusion and easy access for possible percutaneous coronary intervention at a later stage (Wenaweser *et al.*, 2016). Different levels of radial force enhance a safe anchoring of the prosthesis within the native aortic annulus. Six radiopaque gold markers are placed at the level of the valve plane to indicate the distal part of the semilunar valve and to assist correct valve positioning. The ventricular part of the prosthesis is covered by a bovine pericardial sealing skirt in order to mitigate paravalvular prosthetic regurgitation. The delivery of this valve requires an 18Fr sheath (Wenaweser *et al.*, 2016).

Saint Jude Medical Portico

The Portico transcatheter heart valve was approved for clinical use in Europe in 2012. Its self-expanding stent is fully re-sheathable, repositionable and retrievable (Manoharan *et al.*, 2012). The low leaflet-cuff within the stent allows for sealing without the valve extending deep within the left ventricular outflow

tract (LVOT) - potentially causing heart block. The large stent cells in the annulus section allow for tissue to conform around calcific nodules — potentially minimizing PVL (Manoharan *et al.*, 2012). Bovine leaflets and the porcine cuff are treated with Linx™ anti-calcification treatment. Rapid pacing is not required to deploy this valve. The valve is typically inserted using an 18 Fr (23 and 25 mm valve) and 19 Fr (27 mm and 29 mm valve) sheath (Manoharan *et al.*, 2012).

Boston Scientific Symetis Acurate neo

This bioprosthesis is composed of a porcine pericardial tissue valve sewn into a self-expanding nitinol stent covered with an anti-leak porcine pericardial skirt. The flexible stabilization arches are responsible for the self-aligning properties of the valve ensuring predictable coaxial alignment. The valve leaflets are placed supra-annularly yielding low gradients (Möllmann *et al.*, 2013). It has been available in Europe since 2014. The 18 Fr delivery system was later exchanged for a smaller one (14 Fr).

Boston Scientific Lotus

The Lotus valve consisted of braided nitinol frame, bovine pericardium leaflets treated with anticalcification technology and Adaptive seal TM technology that promotes annular sealing and prevents paravalvular leak. It was repositionable and retrievable after being fully deployed. The delivery system diameter varied between 18-20 Fr. It was available on the European market between 2013 and 2020 (*Boston Scientific Lotus™ Valve System demonstrates strong performance - Boston Scientific*).

JenaValve Trilogy Valve

Available since 2011, this porcine pericardial valve, attached to a self-expanding nitinol frame, can be fixated in a native, non-calcified aortic annulus, using a unique paper clip-like anchorage mechanism. This makes it the only TAVI system approved not only for aortic stenosis, but since 2021 for the aortic regurgitation as well (Poschner *et al.*, 2021).

Direct Flow Medical

The Direct Flow Medical (DFM) prosthesis was a non-metallic bovine pericardial valve with an expandable Dacron polyester double ring design. It utilized non-compliant angioplasty balloon technology and the upper and lower ring could be pressurized independently through position-fill lumens. After aortic valvuloplasty, the DFM delivery catheter was positioned in the left ventricle and the rings were pressurized with a saline and contrast media mixture. After deflation of the aortic ring, the operator retracted and/or advanced the three positioning wires, ensuring ventricular ring alignment to the aortic annulus, followed by aortic ring balloon pressurization. Once this position was achieved, pulling on the other two wires aligned the entire ventricular ring with the aortic annulus. After assessment of the valve hemodynamics, the valve could be permanently implanted or could be depressurized for prosthesis repositioning or completely retrieved. When an optimal position had been obtained, a polymer was infused into the bioprosthesis, solidifying it for permanent implantation. This valve required an 18 Fr introducer sheath and was available on European market between 2014 and 2017 (Naber *et al.*, 2016).

1.3.1.5 Vascular Access Route

There are several routes to implant a transcatheter aortic valve as depicted in Fig. 4, however transfemoral puncture is the only one that can be performed completely percutaneously. All the other routes require a surgical cut-down of the artery. Overall, 70% of TAVI patients are treated using the minimally invasive transfemoral puncture technique (Bleiziffer *et al.*, 2013; Branny *et al.*, 2017).

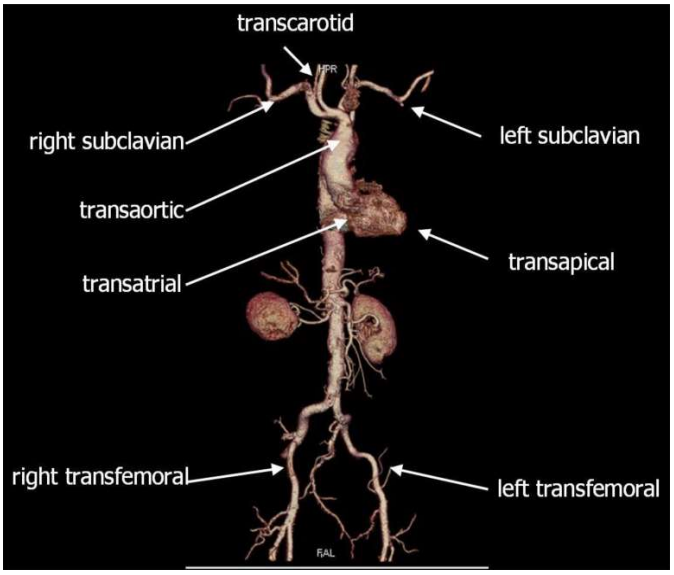

Figure 4: CT scan of the thoracic and abdominal aorta, demonstrating the various access options for transcatheter valve procedures. (Bleiziffer et al., 2013)

Antegrade transseptal access

Alain Cribier used this approach in 2002 for the first TAVI. A 24 Fr sheath was inserted into the right femoral vein, and the interatrial septum was balloon-dilated. A percutaneous heart valve was advanced through the sheath, across the interatrial septum and the mitral valve, and was positioned within the stenotic aortic valve. Because of the complexity of this approach, it was abandoned after the introduction of the transfemoral and transapical routes (Bleiziffer *et al.*, 2013; Branny *et al.*, 2017).

Transapical access

Transapical access is the only antegrade implantation route still in use. The advantages are the short distance from the sheath to the annulus, the ability to accommodate larger sheaths (up to 36 Fr), “no-touch aorta principle” and essentially no access limitations, since the apex can be exposed in almost every patient. On the other hand, it is the only method, with direct invasion to the left ventricle myocardium and is therefore considered the most invasive. The transapical technique is nowadays well standardized and is used in most centers as the second option, in case the transfemoral implantation is not feasible (Branny *et al.*, 2017).

Transsubclavian access

This access route, first reported in 2008, is considered to be a second least invasive. A surgical cut-down is performed to access the left subclavian artery and to introduce the sheath after placement of purse-string sutures. The right subclavian artery is used less routinely due to its inconvenient anatomical implantation angle. Before the procedure, there are several things to be considered, for example, a patent left internal thoracic artery graft may be put at risk with an occlusive sheath, a previously implanted permanent pacemaker at the access site whose wires could be damaged, and the anatomical proximity to the brachial nerve plexus, that requires special attention to avoid neurological complications (Bleiziffer *et al.*, 2013; Branny *et al.*, 2017).

Transaortic access

The direct transaortic route for TAVI was first described in 2009 as a bail-out strategy in a patient with unfeasible transfemoral, subclavian, or transapical access (Bleiziffer *et al.*, 2013). A full or partial upper sternotomy, or a right anterolateral thoracotomy, can be used to access the ascending aorta. The purse-string sutures are placed, to obtain safe hemostasis. In case of porcelain aorta or calcified atherosclerotic plaques on the anterior wall of the aorta ascendens, this access is contraindicated (Bleiziffer *et al.*, 2013; Branny *et al.*, 2017).

Transfemoral access

The transfemoral access, first described in 2005, is considered the first choice in many TAVI centers because of its minimal invasiveness and is currently the most common form of access in the world (Ando, Takagi and Grines, 2017). Since 2005, technological improvements have resulted in reduced sheath diameters (14-18 Fr) for the new generation prostheses, and as such, vascular complications (VC) rates decreased from up to 22.9% (Thomas *et al.*, 2011; Linke *et al.*, 2012) to 5.9% (Adams *et al.*, 2014; Thourani *et al.*, 2016).

Vascular complications are rare, but include vessel rupture, dissection of the iliac artery or the aorta, vessel stenosis, bleeding, and hematoma, or false aneurysm with the potential need for vascular intervention, either per catheter or

surgical, as well as a transfusion (Branny *et al.*, 2017). To reduce the risk of those complications, the access vessel diameter should be at least 6 mm (5mm in the CoreValve Evolut R), without significant tortuosity, stenosis, or calcifications (Bleiziffer *et al.*, 2013; Branny *et al.*, 2017).

1.3.1.6 Intubation Anesthesia versus Sedation

Prosthesis implantation via femoral access can be done under general anesthesia or light sedation. Both anesthesia procedures, in the presence of an experienced cardio-anesthesiologist, show similar results in terms of short-term and long-term mortality (Mayr *et al.*, 2015).

Sedation can be initiated and maintained with propofol or midazolam. Analgesia is ensured with remifentanil at a dose of 0.025-0.1 µg/kg/min. Local anesthesia is achieved using lidocaine 2% injections, 20 ml bilaterally.

Intraprocedurally, the vital signs are monitored using a 3-channel ECG, continuous oxygen saturation measurements, and invasive blood pressure measurements.

Sedation is associated with shorter procedures, shorter stays in the intensive care unit, and less intraprocedural use of vasopressors. On the other hand, up to 17% of patients undergoing TAVI under sedation require conversion to general anesthesia during the procedure and urgent intubation is frequently associated with hemodynamic instability (Mayr *et al.*, 2015).

1.3.2 The Transfemoral Transcatheter Aortic Valve Implantation Procedure

Transcatheter Aortic Valve Implantation is usually performed in a catheterization laboratory or a hybrid operating room. During the procedure, a specialized multidisciplinary team is required to ensure the procedure's success and manage any potential complications. This team typically includes an interventional cardiologist, a cardiothoracic surgeon, an anesthesiologist, an echocardiographer, nurses, and, in some cases, a perfusionist. A representative from the company that manufactures the prosthesis being implanted is often present to provide technical support and to ensure that the device is handled and deployed correctly. The collaboration of this team ensures that all aspects

of the TAVI procedure are handled expertly, promoting the best possible outcomes for the patient.

As the first step of the procedure, a temporary pacing wire is positioned in the right ventricle via the jugular or femoral vein. A femoral artery is then punctured, and a 6 Fr pigtail catheter is inserted into the right coronary sinus, to be used for the injection of contrast media during the procedure (Jones *et al.*, 2017). The appropriate main intervention site is selected prior to the procedure, and is based on multi-slice computed tomography (Kronzon *et al.*, 2015). It should be above the bifurcation and below the inguinal ligament. If possible, the part of the anterior wall with the least degree of calcification should be used (Jones *et al.*, 2017). The native aortic valve is then crossed with a soft-tipped straight wire with the help of an Amplatzer catheter. Once it is crossed, the soft-tipped straight wire is exchanged for a stiff wire with a curved tip, to minimize the risk of ventricular injury. The TAVI device is then advanced over this wire.

To ensure accurate navigation and positioning, the procedure relies heavily on fluoroscopy and echocardiography. Fluoroscopy provides real-time X-ray imaging for visualizing the catheter's progress, while transesophageal echocardiography offers detailed images of the heart and the aortic valve, ensuring the precise location and alignment of the catheter (Kronzon et al., 2015). Once the prosthesis is correctly positioned, the valve is deployed under fluoroscopic and echocardiographic guidance. By inflating a balloon (BE valves) (Fig. 5) or removing the valve sheath (SE valves), the valve unfolds and is anchored in the native valve ring. The native valve is not removed, but instead is pushed aside by the new prosthesis (Ruparelia and Prendergast, 2016). To be deployed, BE valves require rapid ventricular pacing (180-220 beats per minute) to reduce cardiac output and avoid inaccurate valve implantation (Jones *et al.*, 2017). Self-expandable valves may not routinely require ventricular pacing, although this may still be useful in cases when valve positioning presents a challenge (Vlastra *et al.*, 2019).

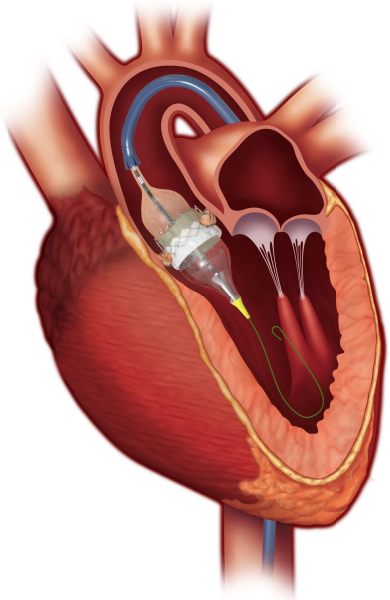

Figure 5: Transcatheter aortic valve implantation (TAVI)
(Edwards Lifesciences SAPIEN 3)
Image courtesy of Edwards Lifesciences Corporation.

Recommendations on the optimal positioning of the prosthesis within the aortic root vary according to the design of the valve. Its ventricular end should be 2 to 6 mm below the basal attachment of the aortic valvular leaflets (Piazza *et al.*, 2008).

Proper placement and function of the new valve are verified through angiography and echocardiography. If post implantation aortic regurgitation is more than mild, attempts should be made to reduce its severity. If a repositionable valve has been used, then it may be realigned to achieve a more optimal position. Alternatively, the valve may be post-dilated to improve the apposition of the valve with the aortic annulus (Ruparelia and Prendergast, 2016). Once proper position and function are confirmed, the catheter and other instruments are removed, and the access site is closed.

1.3.2.1 ProGlide Closure System

The ProGlide closure system was developed to close vascular lesions of the femoral artery after catheter interventions or diagnostics, and functions by supplying a monofilament polypropylene suture.

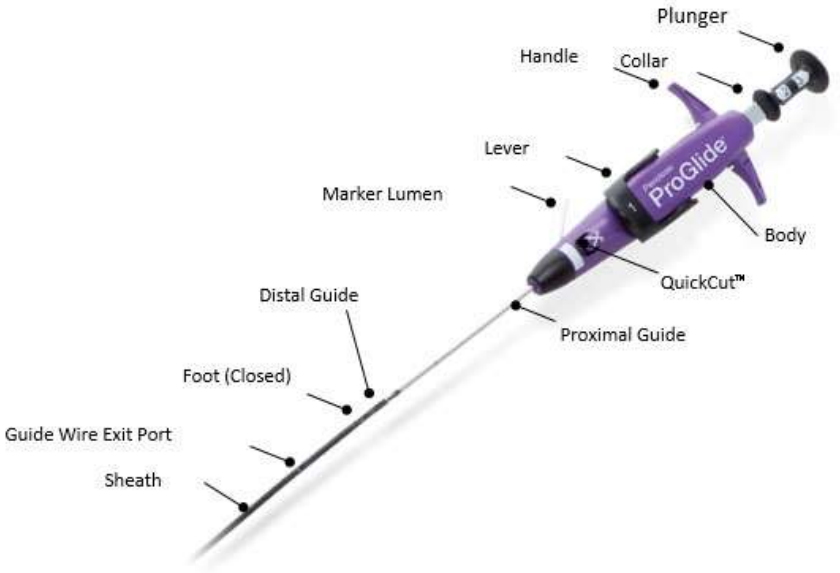

Figure 6: Illustration of ProGlide Vascular Closure System (ProGlide device)
Image courtesy of Abbott. © 2024. All rights reserved.

At the beginning of the procedure, the ProGlide is advanced over a guide-wire within the arterial lumen (Fig. 7A), after which the “feet” are deployed within the lumen to abut the artery wall and temporarily occlude the vessel (Fig. 7B). The plunger is then depressed to deploy two needles within the subcutaneous tissue (Fig. 7C). Further depression of the plunger advances the needles through feet inside the lumen, thus forming a loop of suture (Fig. 7D). The feet latch on to the needles and the device is removed as a whole, leaving behind two suture tails (*Overview of Perclose ProGlide | Abbott*; *Single Perclose ProGlide Suture-Mediated Closure System | Abbott*).

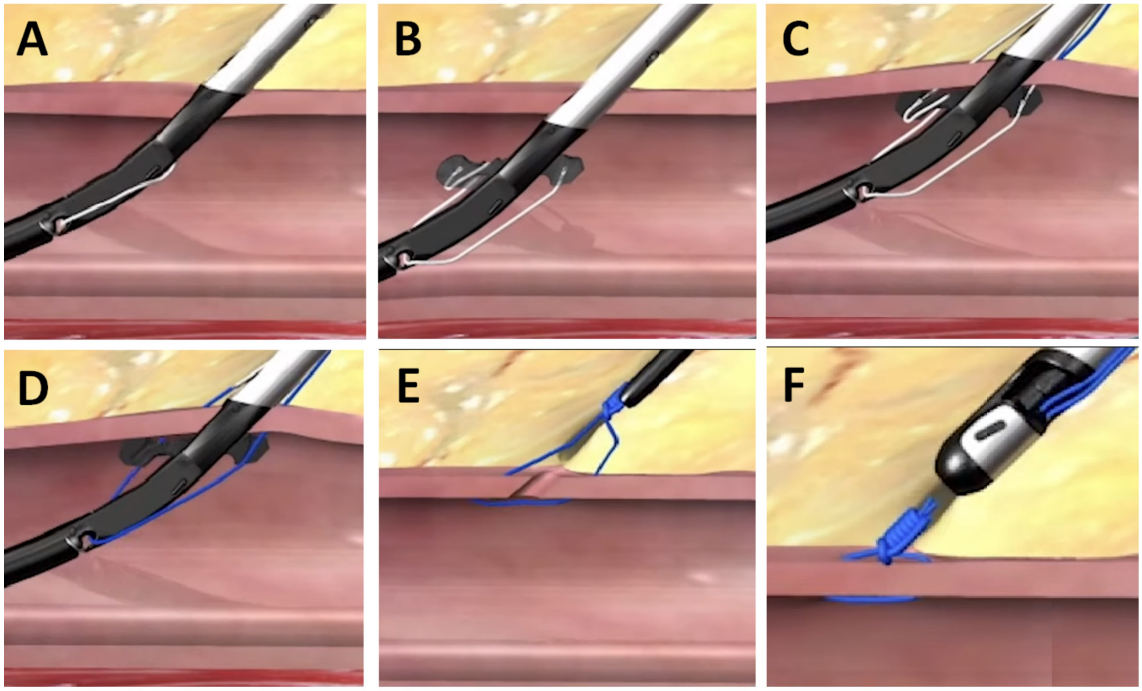

Figure 7: Phases of ProGlide deployment.

A) The ProGlide is advanced over a guide-wire within the arterial lumen.
B) The "feet" are deployed within the lumen
C) Two needles puncture the subcutaneous tissue and the arterial wall..
D) The suture is deployed.
E) The knot is tightened with the help of a knot pusher.
F) Finally, the knot is trimmed.

adapted from (How to: Perclose ProGlide Single Device Deployment, 2023)

The ProGlide is used for 5 Fr to 8 Fr sheath procedures; for sheaths between 8 Fr and 21 Fr (max. 26 Fr), two closure devices are often used. The large sheath used for access is removed over the wire. The site is then closed by using the knot pusher on the blue threads (Fig. 7E). The wire is then removed, and the knot is set by retracting on the white threads. Finally, the suture tails are trimmed close to the arteriotomy (Fig. 7F). (*Overview of Perclose ProGlide | Abbott*; *Single Perclose ProGlide Suture-Mediated Closure System | Abbott*)

1.3.2.2. Surgical Cut down

If a surgical cut down is used, the common femoral artery is exposed via 3 cm incision in the groin. Two purse-string stay sutures are prepared and guide-

wires and access sheaths are introduced. The TAVI delivery system is then advanced over the guide-wires and deployed under radiographic control. Angiography and echocardiography are used to confirm satisfactory deployment of the prosthesis, following which all catheters, sheaths and guide-wires are removed. The purse-string stitches are tied and when the hemostasis is achieved, the cut-down incision is closed.

1.3.3 Complications associated with Transcatheter Aortic Valve Implantation

The most common complications of the TAVI procedure involve higher-grade atrioventricular blockages (AVB) with a subsequent indication for pacemaker implantation and paravalvular insufficiency (Sinning *et al.*, 2013; Margolina *et al.*, 2016). The vascular complications after TAVI, especially bleeding from the arterial access area, have shown to be serious complications as they affect both the morbidity as well as mortality of the patients (Steinvil *et al.*, 2015). Rare but dangerous complications can include neurological events, ruptures in the area of the prosthesis landing zone and a closure of the coronary ostia (Hamm *et al.*, 2014).

1.3.3.1 Stroke

Stroke is a serious complication of transcatheter aortic valve replacement with a clinically relevant incidence and is associated with up to a five-fold increased 30-day mortality and increased morbidity of the patients. A study by the German TAVI Register, which included 1413 patients, showed postoperative incidence of stroke of 3.2%. 40% of the cases were classified as transitory ischemic attack (*Incidence and Clinical Impact of Stroke Complicating Transcatheter Aortic Valve Implantation: Results From the German TAVI Registry - Werner - 2016 - Catheterization and Cardiovascular Interventions - Wiley Online Library*). The SANITY study (The Silent and Apparent Neurological Injury in TAVI) was able to detect new ischemic brain lesion using MRI in 76% of the patients (Fanning *et al.*, 2014).

1.3.3.2 Arrhythmias

The most common complication of a TAVI procedure with the first generation of prosthesis was the left bundle branch block with AVB. This combined conduction disturbance often requires pacemaker implantation (Cribier, 2012). The incidence of a permanent pacemaker implantation (PPI) after the use of a new-generation TAVI prosthesis ranges between 2.3% and 36.1% (van Rosendael, Delgado and Bax, 2018). For balloon-expandable prostheses, with the SAPIEN 3 device, the PPI rate is between 4.0% and 24.0%. For self-expandable prostheses, the PPI rates are higher, (14.7-26.7%) with the new Evolut R (van Rosendael, Delgado and Bax, 2018).

1.3.3.3 Paravalvular Insufficiency

Paravalvular leak (PVL) after TAVI is relatively common. More than moderate PVL is associated with increased mid-term all-cause mortality (Ando *et al.*, 2018). The PARTNER A-study even demonstrated an impact on mortality with a mild paravalvular insufficiency (Leon *et al.*, 2010). With the emergence of newer-generation prosthetic valves, the incidence of more than moderate PVL has declined dramatically, however, the rate of mild PVL remains relatively high (Ando *et al.*, 2018). For example the most sealant Sapien 3 valve has an incidence of none-trace PVL 55.7%, mild 32.6%, mild to moderate 8.2%, and at least moderate PVL 3.5% at 30 days (Pibarot *et al.*, 2017).

1.3.3.4 Vascular Complications

Since large-caliber sheaths are required to advance the prosthesis, iliofemoral complications are the most frequent VC in transfemoral TAVI. The vessels of elderly patients are often severely calcified and thus particularly susceptible to vascular injury. Small vessel dimensions, moderate or severe calcification, and center experience are the major predictors (Toggweiler *et al.*, 2013).

Aortic complications are rare, but serious complications and are associated with a high mortality rate, particularly if emergent surgery is performed. Reported rates of (major) vascular complications range from 1.9% to 23% (Toggweiler et al., 2013; Leon et al., 2011; Généreux et al., 2012). This considerable variety is

mainly due to using various criteria and the constant improvement or reduction of the required diameter of the sheaths. Recently published data have described improvements in VC, mainly due to newer device generations, smaller delivery systems, and the use of adjunctive techniques, together with better screening and increased surgeon experience (Walas *et al.*, 2020).

1.3.3.5 Other Complications

Serious complications of a TAVI procedure can lead to conversion, in which an emergency median sternotomy is required to manage complications. Particularly threatening complications are aortic annulus rupture, aortic dissections, ventricular perforations, pericardial tamponades, coronary obstructions and embolization of the bio-prosthesis (*Qualitätskriterien zur Durchführung der transvaskulären Aortenklappenimplantation (TAVI)*). Overall, the need for an emergency surgical conversion is very rare. The data here range from 0.4 to 1.3% (Gilard *et al.*, 2012; Hamm *et al.*, 2014). An annular rupture occurs very rarely. A study with 1,000 patients showed an annulus rupture in 0.6% of cases (Schymik *et al.*, 2014). Dissection or perforation of the aorta, embolization of the valve prosthesis and closure or dissection of the coronary arteries are also very rare. The GARY register has observed those complications in 0, 24%, 0.6% and 0.3% of the cases, respectively (Walther *et al.*, 2014). Like any intervention or diagnostic measure, with the potentially nephrotoxic contrast agent used, the TAVI also harbors the risk of deteriorating kidney function and in the worst case, acute kidney failure requiring dialysis, in the sense of contrast-induced nephropathy (1.4-1.9%) (Bagur *et al.*, 2010).

1.4 Working Hypothesis

In view of the increasing life expectancy in the western states is expected an increase of patients with degenerative aortic stenosis. Many patients are considered inoperable because of their old age and the multiple comorbidities. TAVI has already become an established alternative therapy option for this patient population. To expand the indication of catheter-based procedures in the future, treatment options must be optimized. Vascular complications are a common event after a TF-TAVI and limit due to the associated increased

morbidity and mortality, the indication of such an intervention. Some studies have already shown a link between the vascular complication rate and the caliber size of the sheaths required, which in turn depends on the selected prosthesis (Van Mieghem et al., 2012).

2 Materials and Methods

2.1 Study Design

This single center, retrospective cohort study was designed to compare two methods for femoral artery access during TF-TAVI procedures: surgical cut-down versus percutaneous vascular closure. Specifically, the risks of vascular, bleeding, and wound complications were assessed.

This study was approved by the ethics committee of the Eberhard Karls University with the project number 814/2019BO2 by decision of 06.12.2019.

2.2 Patient Population

The study size was determined by the number of patients undergoing TF-TAVI between 2010 and 2020 at Heart Center Klinikum Stuttgart. No patients were excluded from the study.

2.3 Variables

2.3.1 Data Collection

2.3.1.1 Preoperative Data

Following preoperative data were extracted retrospectively from the clinic's data bank: name, date of birth, sex, age, height, weight, peripheral artery disease, diabetes mellitus (no DM, DM on diet, DM on Oral Antidiabetic Drug (OAD), DM on insulin), high blood pressure and blood thinners (mono-antiaggregation, dual-antiaggregation, Marcoumar/Warfarin, NOAC, triple-anticoagulation).

2.3.1.2 Intraoperative Data

Operation reports provided following intraoperative data: date of operation, valve type, valve size, technique of vascular closure, vascular/bleeding/other

complications (use of an additional closure system such as AngioSeal or another ProGlide was not considered a complication) and intraoperative mortality.

2.3.1.3 Postoperative Data

The following postoperative data from discharge letters supplement the dataset: intrahospital mortality, bleeding (any mention of hematoma or bleeding), wound healing complications (any mention of complications such as lymphatic fistula), vascular stenosis, vascular dissection, number of red blood cell (RBC) transfusions and any other complication during hospitalization. No other vascular complications, aside from the aforementioned stenosis and dissection, were present. Only the complications related to the main intervention vascular access site were considered.

2.3.2 Data Transformations and Dataset Preparation

Dataset was anonymized by removal of name and date of birth.

2.3.2.1 Independent Variables

The set of independent variables included three numeric ones: age, BMI and sheath size; and following binary ones: sex, DM without insulin (DM on diet or DM on OAD), DM on insulin, arterial hypertension, PAD, antiaggregation (mono-antiaggregation or dual-antiaggregation), anticoagulation (Marcoumar/Warfarin or NOAC or triple-anticoagulation), percutaneous/surgical vascular closure.

2.3.2.2 Endpoints

The binary endpoints were: intraoperative mortality, intrahospital mortality, dissection, stenosis, bleeding and wound healing complications. Number of RBC transfusions endpoint was defined as an ordinal variable with three levels: 0-1, 2-3, ≥4.

2.4 Statistical Methods

First, propensity matching was performed to identify a match in surgical closure patients for each patient with percutaneous closure. The propensity scores were calculated on the basis of the preoperative variables (sex, age, BMI, periphery

artery disease, diabetes mellitus on/without insulin, hypertension and anticoagulation therapy). Propensity matching was performed without replacement and with caliper of 0.2 Standard Deviation (SD) (Austin, 2011). The unmatched cases and remaining controls were discarded.

Then the independence of the choice of vascular closure system was tested using Fisher's exact test for categorical variables and Student's t-test for continuous variables. Additionally, the non-parametric Whitney-Mann U test was calculated in case some of the continuous variables were not normally distributed.

For each endpoint, univariate logistical or ordinal regressions (depending on the endpoint) were performed to identify a subset of independent variables associated with the endpoint at $p<0.1$. Subsequently, multivariate logistical or ordinal regression was conducted for the factors identified in the previous step to calculate adjusted odds ratios, with p-values considered significant at $p<0.05$.

The same approach was then used to analyze subgroups determined by sheath size (Wang *et al.*, 2018). Bonferroni correction was applied, decreasing the p value for significant effect to $p<0.02$.

The analysis was performed with Python programming language (version 3.10.8) and following packages: numpy 1.23.5, pandas 1.5.2, scipy 1.9.3, psmpy 0.3.13 (Kline and Luo, 2022), statsmodels 0.13.2, seaborn 0.12.1 and forestplot 0.3.1.

3 Results

3.1 Participants

Between 2010 and 2020, 1,600 TF-TAVI procedures were recorded. A total of 716 (45%) implants were closed percutaneously, and the remaining 884 (55%) underwent surgical cut-down. There were 3 patients who received two separate TF-TAVI operations, these were not matched and were treated as separate data points.

After propensity matching, 12 unmatched percutaneous implantations were discarded along with the remaining surgical cut-downs. The resulting dataset contains 704 matched pairs, for a total of 1408.

3.2 Descriptive Data

Descriptive statistics of independent variables are shown in Tab. 2, with age, BMI, and sheath size distributions visualized in Fig. 8, Fig. 9, and Fig. 10, respectively.

Table 2: Descriptive data

Abbreviations: aHT, arterial hypertension; BMI, body mass index; DM, diabetes mellitus; PAD, peripheral artery disease; SD, standard deviation.

	Mean (SD) or Number (Percentage)	
Variable	**Percutaneous Closure (n = 704)**	**Surgical Closure (n = 704)**
Age (years) (SD)	81.76 (5.39)	81.67 (5.61)
Sex (male)	334 (47.4%)	338 (48.0%)
BMI (SD)	26.93 (4.69)	26.90 (5.01)
DM without Insulin	143 (20.3%)	147 (20.9%)
DM on Insulin	81 (11.5%)	74 (10.5%)
aHT	539 (76.6%)	529 (75.1%)
PAD	75 (10.7%)	72 (10.2%)
Antiaggregation	570 (81.0%)	579 (82.2%)
Anticoagulation	189 (26.8%)	197 (28.0%)

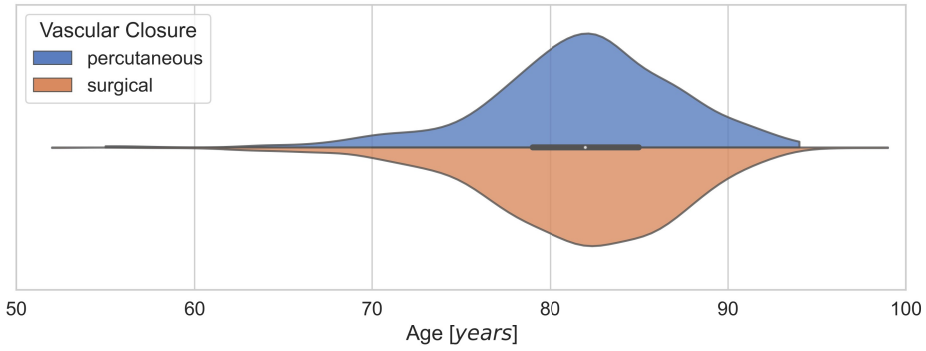

Figure 8: Age distributions for percutaneous and surgical groups after propensity matching

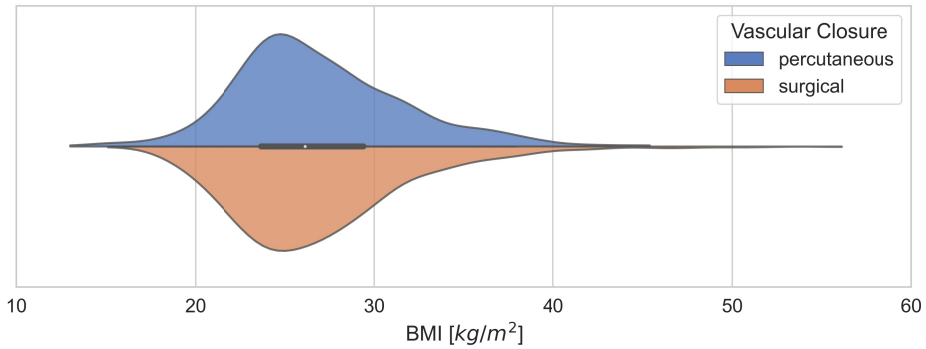

Figure 9: Body Mass Index (BMI) distributions for percutaneous and surgical groups after propensity matching

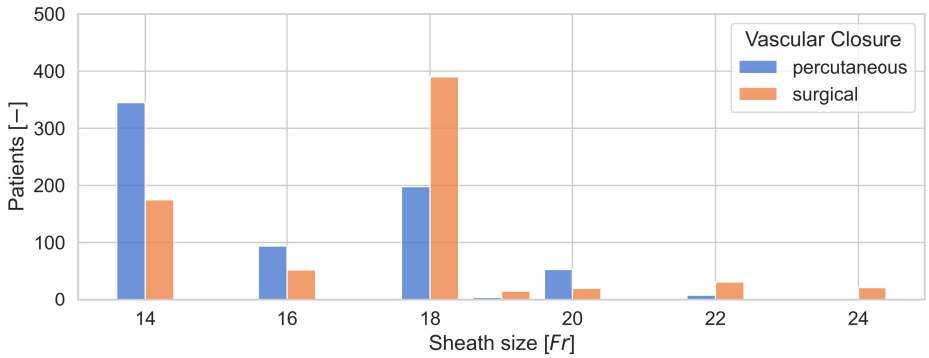

Figure 10: Sheath size distributions for percutaneous and surgical groups after propensity matching

3.3 Outcome Data

Similarly, the statistics for endpoints are presented in Tab. 3.

Table 3: Outcome data

Abbreviation: RBC, red blood cells.

	Number (Percentage)	
Endpoint	**Percutaneous Closure (n = 704)**	**Surgical Closure (n = 704)**
Intraoperative Mortality	2 (0.3%)	4 (0.6%)
Intrahospital Mortality	5 (0.7%)	19 (2.7%)
Dissection	4 (0.6%)	5 (0.7%)
Bleeding	31 (4.4%)	9 (1.3%)
Stenosis	15 (2.1%)	14 (2.0%)
Wound Healing Complications	1 (0.1%)	3 (0.4%)
RBC transfusions		
0-1	614 (83.0%)	598 (80.8%)
2-3	55 (7.4%)	70 (9.5%)
≥4	35 (4.7%)	36 (4.9%)

3.4 Main Results

The outcomes of Fisher's exact test for categorical independent variables, as well as the results obtained from Student's t-test and the Mann-Whitney U test (also referred to as the Wilcoxon rank-sum test) for continuous independent variables, collectively reveal no statistically significant differences between these independent variables when comparing the surgical group to the percutaneous group. (Tab. 4)

Table 4: Results of statistical tests of independence of the choice of vascular closure on the independent variables (after propensity matching) Abbreviations: aHT, arterial hypertension; BMI, body mass index; DM, diabetes mellitus; PAD, peripheral artery disease.

	P-value		
Variable	**Fisher's exact test**	**Student's t-test**	**Mann-Whitney U test**
Age (years)	-	0.75	0.99
Sex	0.87		
BMI	-	0.90	0.41
DM without Insulin	0.84	-	-
DM on Insulin	0.61	-	-
aHT	0.58	-	-
PAD	0.86	-	-
Antiaggregation	0.58	-	-
Anticoagulation	0.68	-	-

The results of the multivariate logistical regression do not indicate a significant association between vascular closure and any of the following endpoints: intraoperative mortality, dissection, stenosis or wound healing complications.

A significant association was indicated between surgical closure and the intrahospital mortality with adjusted odds ratio (OR)=3.88 (95% CI 1.44 – 10.44, p=0.01). This suggests that a patient with surgical closure is almost 4 times as likely to die during hospitalization than one with percutaneous closure.

A significant association was also indicated between surgical closure and vascular bleeding with adjusted odds ratio (OR)=0.28 (95% CI 0.13 – 0.59, p<0.001). Meaning that a patient with percutaneous closure is over 3 times as likely to bleed than one with surgical closure.

Table 5: Main results

Abbreviation: CI, confidence interval.

	Percentage (Number)		
Endpoint	**Percutaneous Closure (n = 704)**	**Surgical Closure (n = 704)**	**Odds Ratio (95% CI)**
Intrahospital Mortality	0.7% (5)	2.7% (19)	3.88 (1.44 to 10.44)
Bleeding	4.4% (31)	1.3% (9)	0.28 (0.13 to 0.59)

The analysis of sheath size subgroups was mostly inconclusive, with one exception. For the 18 Fr sheath size, there was a significant association between the method of closure and the risk of bleeding. Specifically, 5.0% (12 out of 239) of patients with percutaneous closure experienced bleeding, compared to just 0.4% (1 out of 239) of those with surgical closure. The adjusted odds ratio was (OR)=0.08 (95% CI 0.01 – 0.61, p=0.01), meaning that during procedures, where an 18 Fr sheath is used, the patient with percutaneous closure is over 12 times as likely to bleed than one with surgical closure.

Table 6: Subgroup results

Abbreviation: CI, confidence interval.

	Percentage (Number)		
Endpoint	**Percutaneous Closure (n = 239)**	**Surgical Closure (n = 239)**	**Odds Ratio (95% CI)**
Bleeding (Sheath size 18 Fr)	5.0% (12)	0.4% (1)	0.08 (0.05 to 0.66)

The results are summarized in Fig. 11.

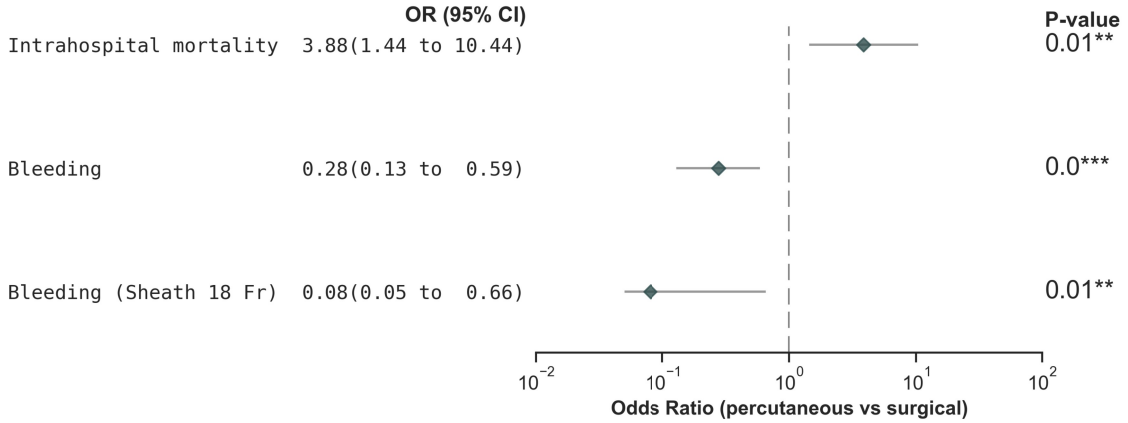

Figure 11: Effect comparison

4 Discussion

Many patients presenting with degenerative aortic stenosis are considered unsuitable for surgical aortic valve replacement due to their advanced age and multiple comorbidities. For this patient population, TAVI has become a well-established therapeutic option. However, it is crucial to holistically evaluate all aspects of the TAVI procedure before its use is extended to intermediate- and low-risk patients as well. Although the rates of vascular and bleeding complications have decreased over the years due to smaller sheath sizes and increased experience, they remain relatively high (Avvedimento *et al.*, 2023). The data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry on 34 893 patients show a vascular complication rate of 9.3% and a bleeding complication rate of 7.6% (Sherwood *et al.*, 2020). Since vascular and bleeding complications increase morbidity and mortality (Steinvil *et al.*, 2015), our study aimed to determine whether one of the two established methods for vascular closure, surgical cut-down or percutaneous closure using ProGlide, results in fewer vascular, bleeding, and healing complications.

In the early years of TAVI, surgical cut-down was predominantly used in our institution, but this has changed over the years and in contemporary practice, the percutaneous closure approach dominates, as depicted in Fig. 12. However, there is surprisingly little evidence in the literature to support this shift. This study, with a relatively large sample size (n=1600) compared to most others, sought to address this gap. However, the generalizability of our findings is limited by the retrospective and monocentric nature of the study.

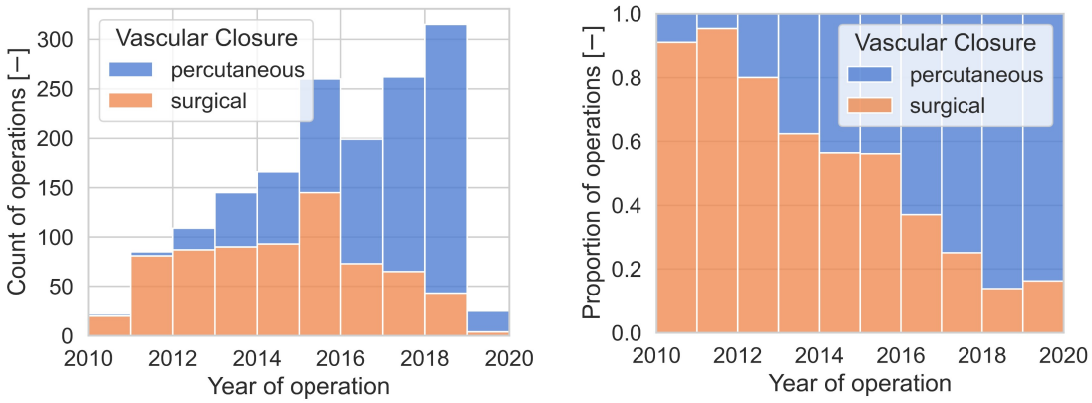

Figure 12: Percutaneous vs surgical closure over the years

4.1 Key Results

Our study observed increased odds of intrahospital mortality for surgical closure compared to percutaneous one, with an odds ratio (OR)=3.88 (95% CI 1.44 – 10.44, p=0.01). In the surgical arm, there were 19 deaths, of which only two had access site complications. In contrast, the percutaneous arm had five deaths, none of which with access site complications. The discharge letters were reviewed to determine the exact cause of all deaths, and only a single death in the surgical cohort was caused by access site complications.

One possible explanation for this mortality trend is the change in the TAVI patient population over time combined with the shift from surgical to percutaneous vascular closure. TAVI was first introduced for the high-risk/inoperable patients and subsequently indicated for lower risk patients. Since frailty, STS score, EuroSCORE II, organ failure, etc. were not collected in preoperative data, the propensity score matching would not be able to control

those differences in the underlying population. Another possible confounder could be the learning curve of the TAVI procedure. Therefore, a randomized controlled trial (RCT) is recommended to test the validity of this observed mortality trend, especially since no other study has observed it.

A significant association was also found between percutaneous closure and bleeding, with an adjusted odds ratio (OR)=3.57 (95% CI 1.69 – 7.69, p<0.001). This observation aligns with findings from Ceresa et al. (Ceresa *et al.*, 2020), Spitzer et al. (Spitzer *et al.*, 2016), and the retrospective study on 1680 patients from the POL-TAVI registry by Walas et al. (Walas *et al.*, 2020). While Ceresa et al. reported a drop of hemoglobin after the procedure and the need for blood transfusions, making quantitative comparison challenging, the other two studies respectively report odds ratios of 4.1 and 1.9, both of which fall within the 95% confidence interval of our result, corroborating the observed effect's magnitude.

Notably, the association between percutaneous closure and bleeding was also seen in the analysis of sheath size subgroups but only for sheath size 18 Fr (OR)=12.5 (95% CI 1.64 – 100, p=0.01). It was not observed in any other subgroup. Although most subgroups lacked sufficient samples for statistical analysis, the subgroup with sheath size 14 Fr (n=356) had a comparable sample size to the 18 Fr subgroup (n=478), and the effect was not observed for it. This suggests that bleeding complications are more likely with percutaneous closure in the case of larger sheath sizes, while the difference may be negligible for smaller sheaths. Similarly, Van Mieghem et al. (Van Mieghem *et al.*, 2012) found that life-threatening or disabling bleeding was associated with the use of >19 Fr systems, though with a lower effect magnitude (OR)=2.39 (95% CI 1.16 – 4.89).

In addition to percutaneous access strategy, Van Mieghem et al. (Van Mieghem *et al.*, 2012) also identified female gender, peripheral arterial disease, and the learning effect as associated with bleeding. In contrast, our multivariate logistic regression model identified the choice of vascular closure technique as the only significant factor for both the bleeding and the intrahospital mortality results.

Curiously, all four studies mentioned above also found an association between percutaneous closure and an increased risk of vascular complications, which we did not observe. We also did not see any significant differences for any other endpoint, including intraoperative mortality, wound healing complications, or number of RBC transfusions.

It is important to note that neither Eckner et al. (Eckner *et al.*, 2021) nor Stathogiannis et al. (Stathogiannis *et al.*, 2021) observed any significant difference in risks between the two closure techniques concerning vascular or bleeding complications. While a meta-analysis might provide further insights into these conflicting results, only a proper RCT will be able to determine the relationship between vascular access systems and both bleeding and vascular complications. Only then can any recommendation for medical practice be made.

4.2 Limitations

Several limitations should be acknowledged, primarily the retrospective design of the study. Secondly, data was collected from a single center. Additionally, under-reporting of endpoint data cannot be ruled out. Furthermore, wound healing complications often occur after patients are discharged, and there was no follow-up data available for this study.

4.3 Conclusions

In conclusion, our study suggests that surgical closure in TF-TAVI operations is associated with increased odds of intrahospital death but decreased odds of bleeding with larger sheaths compared to the percutaneous system. However, to establish a more definitive understanding, a well-designed randomized controlled trial encompassing a broader range of confounding variables is required.

Furthermore, wound healing complications are mostly not reported in the literature. Future research should consider this endpoint as well to guide clinical decision-making in the choice of vascular closure technique.

5 Abstract

Background: Percutaneous vascular closure has increasingly become the preferred standard over the surgical cut-down technique in transcatheter aortic valve implantations (TAVI). However, this shift lacks sufficient evidence-based support.

Objective: To evaluate incidence of vascular, bleeding and wound complications associated with two vascular closure methods for TAVI: the completely percutaneous method with ProGlide closure system, and the conventional cut-down technique.

Design: Retrospective cohort study.

Setting: All TF-TAVI between 2010 and 2020 at Heart Center Klinikum Stuttgart.

Patients: Propensity score-based matching was employed to balance the percutaneous and surgical closure cohorts using preoperative variables, including age, BMI, diabetes mellitus, and other relevant factors.

Methods: Adjusted odds ratio for endpoints were computed using multivariate logistic regression, with factors identified via univariate logistic regression. This approach was applied to the entire dataset and subsequently to analyze subgroups based on sheath size.

Results: Out of 1600 TAVI procedures, 704 samples remained in both percutaneous and surgical cohorts after propensity matching. Surgical closure was associated with increased intrahospital mortality (OR)=3.88 (95% CI 1.44 – 10.44, p=0.01), while percutaneous closure had increased odds of bleeding (OR)=3.57 (95% CI 1.69 – 7.69, p<0.001). Choice of vascular closure had no significant effect on intraoperative mortality, vascular complications, or wound healing complications. The only significant observation in subgroup analysis was the association between percutaneous closure with sheath size 18 Fr and bleeding (OR)=12.5 (95% CI 1.64 – 100, p=0.01).

Limitations: Monocentric, retrospective design. Some of the input data such as pre- and postoperative hemoglobin, STS score and EuroSCORE II are lacking. Missing follow-up data for wound healing complication assessment.

Conclusions: The surgical closure system in TAVI operations is associated with higher odds of intrahospital death but lower odds of bleeding with larger sheaths compared to the percutaneous system. However, to establish a more definitive understanding, a well-designed randomized controlled trial encompassing a broader range of confounding variables is required.

5.1 Deutsche Zusammenfassung

Hintergrund: Die perkutane Gefäßverschlussmethode hat sich zunehmend als bevorzugter Standard im Vergleich zur chirurgischen cut-down bei Transkatheter-Aortenklappenimplantationen (TAVI) etabliert. Allerdings fehlt dieser Wandel ausreichende evidenzbasierte Unterstützung.

Zielsetzungen: Ziel dieser retrospektiven Kohortenstudie war es, die Häufigkeit vaskulärer-, blutungs- und wundheilung- Komplikationen bei zwei Gefäßverschlussmethoden für TAVI zu bewerten: die vollständig perkutane Methode mit dem ProGlide-Verschlusssystem und die chirurgische cut-down Technik.

Studiendesign: Retrospektive Kohortenstudie.

Rahmen: Alle TF-TAVI-Eingriffe zwischen 2010 und 2020 im Herzzentrum Klinikum Stuttgart.

Studienteilnehmer: Die Ausgleichung der perkutanen und chirurgischen Verschlusskohorten erfolgte unter Verwendung präoperativer Variablen wie Alter, BMI, Diabetes mellitus und anderen mittels Propensity-Score-Abgleich.

Messmethoden: Die adjustierten Chancenverhältnisse für Endpunkte wurden mithilfe multivariater logistischer Regression unter Verwendung von Faktoren, die mittels univariater logistischer Regression identifiziert wurden, berechnet. Dieser Ansatz wurde auf den gesamten Datensatz angewendet und anschließend zur Analyse von Untergruppen basierend auf der Schleusengröße verwendet.

Ergebnisse: Von den 1600 TAVI-Eingriffen blieben nach Propensity-Matching 704 Patienten sowohl in den perkutanen als auch in den chirurgischen Kohorten erhalten. Die chirurgische Verschlussmethode war mit einer erhöhten innerklinischen Sterblichkeitsrate assoziiert (OR=3,88, 95%-KI 1,44–10,44, p=0,01), während der perkutane Verschluss ein erhöhtes Blutungsrisiko aufwies (OR=3,57, 95%-KI 1,69–7,69, p<0,001). Die Wahl des Gefäßverschlusses hatte keine signifikante Auswirkung auf die intraoperative Mortalität, vaskuläre

Komplikationen oder Wundheilungskomplikationen. Die einzige signifikante Beobachtung in der Untergruppenanalyse war die Assoziation zwischen dem perkutanen Verschluss mit Schleusengröße 18 Fr und Blutungen (OR=12,5, 95%-KI 1,64–100, p=0,01).

Einschränkungen: Monozentrisches, retrospektives Design. Einige der Eingabedaten, wie zum Beispiel prä- und postoperative Hämoglobinwerte, der STS-Score und der EuroSCORE II, fehlen. Fehlende Follow-up-Daten zur Beurteilung von Wundheilungskomplikationen.

Schlussfolgerungen: Das chirurgische Verschlusssystem bei TAVI-Eingriffen ist mit einem höheren Sterblichkeitsrisiko während des Krankenhausaufenthalts, aber einem geringeren Blutungsrisiko bei größeren Schleusen im Vergleich zum perkutanen System assoziiert. Allerdings ist zur Festigung des Verständnisses eine gut konzipierte, randomisierte kontrollierte Studie erforderlich, die eine breitere Palette von Störfaktoren einbezieht.

6 References

Adams, D.H. *et al.* (2014) 'Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis', *New England Journal of Medicine*, 370(19), pp. 1790–1798. Available at: https://doi.org/10.1056/NEJMoa1400590.

Afilalo, J. (2017) 'The clinical frailty scale: upgrade your eyeball test', *Circulation*. Am Heart Assoc.

Agma, H.U. *et al.* (2022) 'From an Unfolding Emergency Treatment to a Universal Shift in Therapy: The History and Evolution of the Catheter-Based Treatment of Aortic Valve Stenosis', *Reviews in Cardiovascular Medicine*, 23(10), p. 349. Available at: https://doi.org/10.31083/j.rcm2310349.

Anderson, R.H. (2007) 'The surgical anatomy of the aortic root.', *Multimedia manual of cardiothoracic surgery: MMCTS*, 2007(102), p. mmcts-2006.

Anderson, R.H. *et al.* (2013) *Wilcox's Surgical Anatomy of the Heart*. 4th edn. Cambridge: Cambridge University Press. Available at: https://doi.org/10.1017/CBO9781139028561.

Ando, T. *et al.* (2018) 'Does mild paravalvular regurgitation post transcatheter aortic valve implantation affect survival? A meta-analysis', *Catheterization and Cardiovascular Interventions*, 91(1), pp. 135–147. Available at: https://doi.org/10.1002/ccd.27336.

Ando, T., Takagi, H. and Grines, C.L. (2017) 'Transfemoral, transapical and transcatheter aortic valve implantation and surgical aortic valve replacement: a meta-analysis of direct and adjusted indirect comparisons of early and mid-term deaths', *Interactive CardioVascular and Thoracic Surgery*, 25(3), pp. 484–492. Available at: https://doi.org/10.1093/icvts/ivx150.

Austin, P.C. (2011) 'Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies', *Pharmaceutical Statistics*, 10(2), pp. 150–161. Available at: https://doi.org/10.1002/pst.433.

Avvedimento, M. *et al.* (2023) ‘Bleeding Events After Transcatheter Aortic Valve Replacement: JACC State-of-the-Art Review’, *Journal of the American College of Cardiology*, 81(7), pp. 684–702. Available at: https://doi.org/10.1016/j.jacc.2022.11.050.

Bagur, R. *et al.* (2010) ‘Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement’, *European Heart Journal*, 31(7), pp. 865–874. Available at: https://doi.org/10.1093/eurheartj/ehp552.

Baumgartner, H. and Walther, T. (2018) ‘Aortic stenosis’, in H. Baumgartner et al. (eds) *The ESC Textbook of Cardiovascular Medicine*. Oxford University Press, p. 0. Available at: https://doi.org/10.1093/med/9780198784906.003.0766.

Berdajs, D., Lajos, P. and Turina, M. (2002) ‘The anatomy of the aortic root’, *Cardiovascular surgery*, 10(4), pp. 320–327.

Bertrand, M.E. *et al.* (1981) ‘Coronary sinus blood flow at rest and during isometric exercise in patients with aortic valve disease. Mechanism of angina pectoris in presence of normal coronary arteries’, *The American Journal of Cardiology*, 47(2), pp. 199–205. Available at: https://doi.org/10.1016/0002-9149(81)90384-2.

Blanke, P., Schoepf, U.J. and Leipsic, J.A. (2013) ‘CT in Transcatheter Aortic Valve Replacement’, *Radiology*, 269(3), pp. 650–669. Available at: https://doi.org/10.1148/radiol.13120696.

Bleiziffer, S. *et al.* (2013) ‘Which way in? The Necessity of Multiple Approaches to Transcatheter Valve Therapy’, *Current Cardiology Reviews*, 9(4), pp. 268–273. Available at: https://doi.org/10.2174/1573403X09666131202123326.

Boston Scientific Lotus™ Valve System demonstrates strong performance - Boston Scientific (no date) *www.bostonscientific.com*. Available at: https://www.bostonscientific.com/en-EU/news/newsroom-uk/aortic-valve-

disease/press-releases-2014/boston-scientific-lotus-valve-system-demonstrates-strong-perform1.html (Accessed: 23 July 2023).

Branny, M. *et al.* (2017) 'Alternative access routes for transcatheter aortic valve implantation (TAVI)', *Cor et Vasa*, 59(1), pp. e10–e16. Available at: https://doi.org/10.1016/j.crvasa.2017.01.024.

Ceresa, F. *et al.* (2020) 'Could Surgical Cut-down Avoid Vascular Complications in Patients Undergoing Transfemoral TAVI?', *Structural Heart*, 4, p. 12. Available at: https://doi.org/10.1080/24748706.2020.1713638.

Chodór, P. *et al.* (2017) 'Impact of CoreValve size selection based on multi-slice computed tomography on paravalvular leak after transcatheter aortic valve implantation', *Cardiology Journal*, 24(5), pp. 467–476. Available at: https://doi.org/10.5603/CJ.a2017.0014.

Cribier, A. *et al.* (2002) 'Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description', *Circulation*, 106(24), pp. 3006–3008. Available at: https://doi.org/10.1161/01.cir.0000047200.36165.b8.

Cribier, A. (2012) 'Development of transcatheter aortic valve implantation (TAVI): A 20-year odyssey', *Archives of Cardiovascular Diseases*, 105(3), pp. 146–152. Available at: https://doi.org/10.1016/j.acvd.2012.01.005.

Czarny, M.J. and Resar, J.R. (2014) 'Diagnosis and Management of Valvular Aortic Stenosis', *Clinical Medicine Insights. Cardiology*, 8(Suppl 1), pp. 15–24. Available at: https://doi.org/10.4137/CMC.S15716.

David, T.E. (1999) 'Surgery of the aortic valve', *Current problems in surgery*, 36(6), pp. 421–501.

Dweck, M.R., Boon, N.A. and Newby, D.E. (2012) 'Calcific aortic stenosis: a disease of the valve and the myocardium', *Journal of the American College of Cardiology*, 60(19), pp. 1854–1863. Available at: https://doi.org/10.1016/j.jacc.2012.02.093.

Eckner, D. *et al.* (2021) ‘Comparison between Surgical Access and Percutaneous Closure Device in 787 Patients Undergoing Transcatheter Aortic Valve Replacement’, *Journal of Clinical Medicine*, 10(7), p. 1344. Available at: https://doi.org/10.3390/jcm10071344.

Edwards Lifesciences Receives CE Mark for Edwards SAPIEN Transcatheter Heart Valve (no date). Available at: https://ir.edwards.com/news/news-details/2007/Edwards-Lifesciences-Receives-CE-Mark-for-Edwards-SAPIEN-Transcatheter-Heart-Valve/default.aspx (Accessed: 26 July 2023).

Edwards Lifesciences SAPIEN 3 (no date). Available at: https://mma.prnewswire.com/media/961768/Edwards_Lifesciences_SAPIEN_3_valve.jpg (Accessed: 17 August 2024).

Edwards SAPIEN 3 Transkatheter-Herzklappe | Edwards Lifesciences (no date). Available at: https://www.edwards.com/de/devices/Heart-Valves/Transcatheter-Sapien-3 (Accessed: 26 July 2023).

Elnwagy, M.M. *et al.* (2024) ‘Impact of prosthesis oversizing on clinical outcomes of transcatheter aortic valve implantation using a self-expandable Evolut R valve’, *The Egyptian Heart Journal*, 76(1), p. 20. Available at: https://doi.org/10.1186/s43044-024-00450-0.

Fanning, J.P. *et al.* (2014) ‘The silent and apparent neurological injury in transcatheter aortic valve implantation study (SANITY): concept, design and rationale’, *BMC Cardiovascular Disorders*, 14(1), p. 45. Available at: https://doi.org/10.1186/1471-2261-14-45.

Fedak, P.W.M. *et al.* (2002) ‘Clinical and pathophysiological implications of a bicuspid aortic valve’, *Circulation*, 106(8), pp. 900–904. Available at: https://doi.org/10.1161/01.cir.0000027905.26586.e8.

Gilard, M. *et al.* (2012) ‘Registry of transcatheter aortic-valve implantation in high-risk patients’, *The New England Journal of Medicine*, 366(18), pp. 1705–1715. Available at: https://doi.org/10.1056/NEJMoa1114705.

Grimard, B.H., Safford, R.E. and Burns, E.L. (2016) ‘Aortic stenosis: diagnosis and treatment’, *American family physician*, 93(5), pp. 371–378.

Grube, E. *et al.* (2007) ‘Percutaneous Aortic Valve Replacement for Severe Aortic Stenosis in High-Risk Patients Using the Second- and Current Third-Generation Self-Expanding CoreValve Prosthesis’, *Journal of the American College of Cardiology*, 50(1), pp. 69–76. Available at: https://doi.org/10.1016/j.jacc.2007.04.047.

Hamm, C.W. *et al.* (2014) ‘The German Aortic Valve Registry (GARY): in-hospital outcome’, *European Heart Journal*, 35(24), pp. 1588–1598. Available at: https://doi.org/10.1093/eurheartj/eht381.

Ho, S.Y. (2009) ‘Structure and anatomy of the aortic root’, *European journal of echocardiography*, 10(1), pp. i3–i10.

How to: Perclose ProGlide Single Device Deployment (2023). Available at: https://www.youtube.com/watch?v=AjWFDCBJbec (Accessed: 17 August 2024).

Incidence and Clinical Impact of Stroke Complicating Transcatheter Aortic Valve Implantation: Results From the German TAVI Registry - Werner - 2016 - Catheterization and Cardiovascular Interventions - Wiley Online Library (no date). Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ccd.26612 (Accessed: 23 July 2023).

Jones, B.M. *et al.* (2017) ‘Transfemoral Aortic Valve Implantation: Preparation, Implantation, and Complications’, in G.D. Dangas et al. (eds) *Interventional Cardiology*. 1st edn. Wiley, pp. 558–568. Available at: https://doi.org/10.1002/9781118983652.ch59.

Kamath, A.R. and Pai, R.G. (2008) ‘Risk factors for progression of calcific aortic stenosis and potential therapeutic targets’, *The International Journal of Angiology: Official Publication of the International College of Angiology, Inc*, 17(2), pp. 63–70. Available at: https://doi.org/10.1055/s-0031-1278283.

Kasel, A.M. *et al.* (2013) ‘Standardized imaging for aortic annular sizing: implications for transcatheter valve selection’, *JACC. Cardiovascular imaging*, 6(2), pp. 249–262. Available at: https://doi.org/10.1016/j.jcmg.2012.12.005.

Ki, Y.-J. *et al.* (2020) ‘Optimal Oversizing Index Depending on Valve Type and Leakage-Proof Function for Preventing Paravalvular Leakage after Transcatheter Aortic Valve Implantation’, *Journal of Clinical Medicine*, 9(12), p. 3936. Available at: https://doi.org/10.3390/jcm9123936.

Kline, A. and Luo, Y. (2022) ‘PsmPy: A Package for Retrospective Cohort Matching in Python’, *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, 2022, pp. 1354–1357. Available at: https://doi.org/10.1109/EMBC48229.2022.9871333.

Knuuti, J. *et al.* (2020) ‘2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)’, *European heart journal*, 41(3), pp. 407–477.

Kozower, B.D. *et al.* (2010) ‘STS database risk models: predictors of mortality and major morbidity for lung cancer resection’, *The Annals of thoracic surgery*, 90(3), pp. 875–883.

Kronzon, I. *et al.* (2015) ‘Optimal Imaging for Guiding TAVR: Transesophageal or Transthoracic Echocardiography, or Just Fluoroscopy?’, *JACC: Cardiovascular Imaging*, 8(3), pp. 361–370. Available at: https://doi.org/10.1016/j.jcmg.2015.01.003.

Leon, M.B. *et al.* (2010) ‘Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery’, *New England Journal of*

Medicine, 363(17), pp. 1597–1607. Available at: https://doi.org/10.1056/NEJMoa1008232.

Lester, S.J. *et al.* (1998) 'The natural history and rate of progression of aortic stenosis', *Chest*, 113(4), pp. 1109–1114. Available at: https://doi.org/10.1378/chest.113.4.1109.

Linke, A. *et al.* (2012) 'Treatment of high risk aortic stenosis patients with transcatheter medtronic corevalve implantation: results from the international multi-center advance study', *Journal of the American College of Cardiology*, 59(13_Supplement), pp. E8–E8. Available at: https://doi.org/10.1016/S0735-1097(12)60009-6.

Maharaj, A. and Teelucksingh, J. (2023) 'Syncope in Aortic Stenosis: Not Always What It Seems', *Cureus*, 15(3), p. e36716. Available at: https://doi.org/10.7759/cureus.36716.

Mahtta, D., Elgendy, I.Y. and Bavry, A.A. (2017) 'From CoreValve to Evolut PRO: Reviewing the Journey of Self-Expanding Transcatheter Aortic Valves', *Cardiology and Therapy*, 6(2), pp. 183–192. Available at: https://doi.org/10.1007/s40119-017-0100-z.

Manoharan, G. *et al.* (2012) 'St Jude Medical Portico valve', *EuroIntervention*, 8 Suppl Q, pp. Q97-101. Available at: https://doi.org/10.4244/eijv8sqa18.

Margolina, A.A. *et al.* (2016) '[Complications After Transcatheter Aortic Valve Implantation]', *Kardiologiia*, 56(2), pp. 35–39. Available at: https://doi.org/10.18565/cardio.2016.2.35-39.

Mariathas, M., Rawlins, J. and Curzen, N. (2017) 'Transcatheter aortic valve implantation: where are we now?', *Future Cardiology*, 13(6), pp. 551–566. Available at: https://doi.org/10.2217/fca-2017-0056.

Mayr, N.P. *et al.* (2015) 'Sedation or general anesthesia for transcatheter aortic valve implantation (TAVI)', *Journal of Thoracic Disease*, 7(9), pp. 1518–1526. Available at: https://doi.org/10.3978/j.issn.2072-1439.2015.08.21.

Medtronic (2014) 'CoreValve™ System Instructions for Use (M333433D001 Rev. 1B)'.

Medtronic (2019) 'CoreValve™ Evolut™ R System Instructions for Use (M970312A001 Rev. AA)'.

Messika-Zeitoun', 'David and Lloyd', 'Guy (2018) 'Aortic valve stenosis: evaluation and management of patients with discordant grading', *e-Journal of Cardiology Practice*, 15(26). Available at: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Aortic-valve-stenosis-evaluation-and-management-of-patients-with-discordant-grading, https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Aortic-valve-stenosis-evaluation-and-management-of-patients-with-discordant-grading (Accessed: 24 July 2023).

Möllmann, H. *et al.* (2013) 'Symetis ACURATE TF™ aortic bioprosthesis', *EuroIntervention*, 9 Suppl, pp. S107-10. Available at: https://doi.org/10.4244/eijv9ssa22.

Möllmann, H. *et al.* (2016) 'In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany', *Clinical Research in Cardiology*, 105(6), pp. 553–559. Available at: https://doi.org/10.1007/s00392-016-0962-4.

Munt, B. *et al.* (1999) 'Physical examination in valvular aortic stenosis: correlation with stenosis severity and prediction of clinical outcome', *American heart journal*, 137(2), pp. 298–306.

Mylotte, D. *et al.* (2013) 'TCT-745 CoreValve Oversizing Using Multislice Computed Tomography and Clinical Outcomes: A Comparison with Transesophageal Echocardiography', *Journal of the American College of Cardiology*, 62(18_Supplement_1), pp. B227–B227. Available at: https://doi.org/10.1016/j.jacc.2013.08.1497.

Naber, C. *et al.* (2016) 'Real-world multicentre experience with the Direct Flow Medical(R) repositionable and retrievable transcatheter aortic valve implantation

system for the treatment of high-risk patients with severe aortic stenosis', *EuroIntervention*, 11, pp. e1314-20. Available at: https://doi.org/10.4244/EIJV11I11A254.

Nashef, S.A. *et al.* (2012) 'Euroscore ii', *European journal of cardio-thoracic surgery*, 41(4), pp. 734–745.

Nathaniel, S., Saligram, S. and Innasimuthu, A.L. (2010) 'Aortic stenosis: An update', *World Journal of Cardiology*, 2(6), pp. 135–139. Available at: https://doi.org/10.4330/wjc.v2.i6.135.

Nishimura, R.A. *et al.* (2014) '2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines', *Circulation*, 129(23), pp. 2440–2492. Available at: https://doi.org/10.1161/CIR.0000000000000029.

Nishizaki, Y. *et al.* (2013) 'Clinical factors associated with classical symptoms of aortic valve stenosis', *The Journal of Heart Valve Disease*, 22(3), pp. 287–294.

Nkomo, V.T. *et al.* (2006) 'Burden of valvular heart diseases: a population-based study', *Lancet (London, England)*, 368(9540), pp. 1005–1011. Available at: https://doi.org/10.1016/S0140-6736(06)69208-8.

Onishi, T. *et al.* (2018) 'The role of echocardiography in transcatheter aortic valve implantation', *Cardiovascular Diagnosis and Therapy*, 8(1), pp. 3–17. Available at: https://doi.org/10.21037/cdt.2018.01.06.

Osnabrugge, R.L. *et al.* (2014) 'Performance of EuroSCORE II in a large US database: implications for transcatheter aortic valve implantation', *European Journal of Cardio-Thoracic Surgery*, 46(3), pp. 400–408.

Overview of Perclose ProGlide | Abbott (no date). Available at: https://www.cardiovascular.abbott/us/en/hcp/products/peripheral-intervention/vessel-closure/perclose-proglide-suture-mediated-closure-system/overview.html (Accessed: 24 July 2023).

Paloschi, V. (2013) ‘BICUSPID AORTIC VALVE-ASSOCIATED AORTOPATHY’. Available at: https://core.ac.uk/download/pdf/70340662.pdf (Accessed: 23 October 2023).

Piazza, N. *et al.* (2008) ‘Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve’, *Circulation: Cardiovascular Interventions*, 1(1), pp. 74–81.

Pibarot, P. *et al.* (2017) ‘Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve’, *JAMA Cardiology*, 2(11), pp. 1208–1216. Available at: https://doi.org/10.1001/jamacardio.2017.3425.

Poschner, T. *et al.* (2021) ‘The JenaValve pericardial transcatheter aortic valve replacement system to treat aortic valve disease’, *Future Cardiology*, 18(2), pp. 101–113.

ProGlide device (no date). Available at: https://www.cardiovascular.abbott/content/dam/cv/cardiovascular/hcp/products/peripheral-intervention/prostyle/product-images/pi-prostyle-compare-proglide-device.jpg (Accessed: 17 August 2024).

Qualitätskriterien zur Durchführung der transvaskulären Aortenklappenimplantation (TAVI) (no date) *springermedizin.de*. Available at: https://www.springermedizin.de/qualitaetskriterien-zur-durchfuehrung-der-transvaskulaeren-aorte/9178910 (Accessed: 23 July 2023).

Rajamannan, N.M. (2009) ‘Calcific aortic stenosis: lessons learned from experimental and clinical studies’, *Arteriosclerosis, Thrombosis, and Vascular Biology*, 29(2), pp. 162–168. Available at: https://doi.org/10.1161/ATVBAHA.107.156752.

van Rosendael, P.J., Delgado, V. and Bax, J.J. (2018) ‘Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review’, *European heart journal*, 39(21), pp. 2003–2013.

Rosenhek, R. *et al.* (2010) ‘Natural history of very severe aortic stenosis’, *Circulation*, 121(1), pp. 151–156. Available at: https://doi.org/10.1161/CIRCULATIONAHA.109.894170.

Ruparelia, N. and Prendergast, B.D. (2016) ‘Technical aspects of transcatheter aortic valve implantation (TAVI)’, *EJ Cardiol Pract*, 14.

Santangelo, G. *et al.* (2022) ‘An Update on New Generation Transcatheter Aortic Valves and Delivery Systems’, *Journal of Clinical Medicine*, 11(3), p. 499. Available at: https://doi.org/10.3390/jcm11030499.

Schiattarella, G.G. and Hill, J.A. (2015) ‘Inhibition of Hypertrophy Is a Good Therapeutic Strategy in Ventricular Pressure Overload’, *Circulation*, 131(16), pp. 1435–1447. Available at: https://doi.org/10.1161/CIRCULATIONAHA.115.013894.

Schymik, G. *et al.* (2014) ‘Ruptures of the device landing zone in patients undergoing transcatheter aortic valve implantation: an analysis of TAVI Karlsruhe (TAVIK) patients’, *Clinical Research in Cardiology: Official Journal of the German Cardiac Society*, 103(11), pp. 912–920. Available at: https://doi.org/10.1007/s00392-014-0729-8.

Sherwood, M.W. *et al.* (2020) ‘Incidence, Temporal Trends, and Associated Outcomes of Vascular and Bleeding Complications in Patients Undergoing Transfemoral Transcatheter Aortic Valve Replacement’, *Circulation: Cardiovascular Interventions*, 13(1), p. e008227. Available at: https://doi.org/10.1161/CIRCINTERVENTIONS.119.008227.

Single Perclose ProGlide Suture-Mediated Closure System | Abbott (no date). Available at: https://www.cardiovascular.abbott/us/en/hcp/products/peripheral-intervention/vessel-closure/perclose-proglide-suture-mediated-closure-system/single-device-deployment.html (Accessed: 26 July 2023).

Sinning, J.-M. *et al.* (2012) ‘Medtronic CoreValve Evolut valve’, *EuroIntervention*, 8, pp. Q94–Q96. Available at: https://doi.org/10.4244/EIJV8SQA17.

Sinning, J.-M. *et al.* (2013) ‘Evaluation and Management of Paravalvular Aortic Regurgitation After Transcatheter Aortic Valve Replacement’, *Journal of the American College of Cardiology*, 62(1), pp. 11–20. Available at: https://doi.org/10.1016/j.jacc.2013.02.088.

Spitzer, S.G. *et al.* (2016) ‘Surgical cut-down or percutaneous access-which is best for less vascular access complications in transfemoral TAVI?’, *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*, 88(2), pp. E52-58. Available at: https://doi.org/10.1002/ccd.26361.

Stathogiannis, K. *et al.* (2021) ‘Percutaneous access versus surgical cutdown in TAVI: vascular and bleeding complications’, *European Heart Journal*, 42(Supplement_1), p. ehab724.2253. Available at: https://doi.org/10.1093/eurheartj/ehab724.2253.

Steinvil, A. *et al.* (2015) ‘Vascular Complications After Transcatheter Aortic Valve Implantation and Their Association With Mortality Reevaluated by the Valve Academic Research Consortium Definitions’, *The American Journal of Cardiology*, 115(1), pp. 100–106. Available at: https://doi.org/10.1016/j.amjcard.2014.09.047.

Sutton III, J.P., Ho, S.Y. and Anderson, R.H. (1995) ‘The forgotten interleaflet triangles: a review of the surgical anatomy of the aortic valve’, *The Annals of thoracic surgery*, 59(2), pp. 419–427.

Swee, J.K.Y. and Grbić, S. (2014) ‘Advanced Transcatheter Aortic Valve Implantation (TAVI) Planning from CT with ShapeForest’, in P. Golland et al. (eds) *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2014*. Cham: Springer International Publishing (Lecture Notes in Computer Science), pp. 17–24. Available at: https://doi.org/10.1007/978-3-319-10470-6_3.

Thomas, M. *et al.* (2011) ‘One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards

SAPIEN valve', *Circulation*, 124(4), pp. 425–433. Available at: https://doi.org/10.1161/CIRCULATIONAHA.110.001545.

Thourani, V.H. *et al.* (2016) 'Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis', *The Lancet*, 387(10034), pp. 2218–2225. Available at: https://doi.org/10.1016/S0140-6736(16)30073-3.

Toggweiler, S. *et al.* (2013) 'Management of Vascular Access in Transcatheter Aortic Valve Replacement', *JACC: Cardiovascular Interventions*, 6(8), pp. 767–776. Available at: https://doi.org/10.1016/j.jcin.2013.05.004.

Transcatheter pulmonic heart valves | Edwards Lifesciences (no date). Available at: https://www.edwards.com/gb/devices/heart-valves/transcatheter-sapien-xt-valve-pulmonic (Accessed: 23 July 2023).

Vahanian, A. *et al.* (2022) '2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)', *European Heart Journal*, 43(7), pp. 561–632. Available at: https://doi.org/10.1093/eurheartj/ehab395.

Van Mieghem, N.M. *et al.* (2012) 'Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation', *The American Journal of Cardiology*, 110(9), pp. 1361–1367. Available at: https://doi.org/10.1016/j.amjcard.2012.06.042.

Varadarajan, P. *et al.* (2006) 'Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis', *The Annals of Thoracic Surgery*, 82(6), pp. 2111–2115. Available at: https://doi.org/10.1016/j.athoracsur.2006.07.048.

Vlastra, W. *et al.* (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), pp. 456–465.

Walas, R.L. *et al.* (2020) 'Vascular access site complications after transfemoral transcatheter aortic valve implantation in the POL-TAVI Registry: surgical versus percutaneous approach', *The Journal of Cardiovascular Surgery*, 61(1), pp. 117–122. Available at: https://doi.org/10.23736/S0021-9509.19.11087-7.

Walther, T. *et al.* (2014) 'Incidence of procedural complications in 9271 consecutive tavi patients: analysis from the german aortic valve registry', *Journal of the American College of Cardiology*, 63(12_Supplement), pp. A1942–A1942. Available at: https://doi.org/10.1016/S0735-1097(14)61945-8.

Wang, S.V. *et al.* (2018) 'Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses', *American Journal of Epidemiology*, 187(8), pp. 1799–1807. Available at: https://doi.org/10.1093/aje/kwy049.

Webb, J. *et al.* (2014) 'Multicenter Evaluation of a Next-Generation Balloon-Expandable Transcatheter Aortic Valve', *Journal of the American College of Cardiology*, 64(21), pp. 2235–2243. Available at: https://doi.org/10.1016/j.jacc.2014.09.026.

Webb, J.G. *et al.* (2006) 'Percutaneous aortic valve implantation retrograde from the femoral artery', *Circulation*, 113(6), pp. 842–850.

Webb, J.G. *et al.* (2007) 'Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis', *Circulation*, 116(7), pp. 755–763. Available at: https://doi.org/10.1161/CIRCULATIONAHA.107.698258.

Wedin, J. *et al.* (2019) '[Bicuspid aortic valve - a common congenital cardiac malformation associated with serious complications]', *Lakartidningen*, 116, p. FHWP.

Wenaweser, P. *et al.* (2016) 'Transcatheter aortic valve implantation with the NVT Allegra transcatheter heart valve system: first-in-human experience with a

novel self-expanding transcatheter heart valve', *EuroIntervention*, 12(1), pp. 71–77. Available at: https://doi.org/10.4244/eijv12i1a13.

7 Erklärung zum Eigenanteil

Die Arbeit wurde im Herzzentrum Klinikum Stuttgart unter Betreuung von Prof. Dr. Nicolas Doll durchgeführt und konzipiert.

Sämtliche Datenerhebungen wurden von mir eigenständig durchgeführt. Die Daten wurden mir mit Genehmigung des Chefarztes des Herzzentrums Klinikum Stuttgart, Prof. Dr. Nicolas Doll, zur Verfügung gestellt.

Die statistische Auswertung erfolgte sowohl eigenständig durch mich als auch mit Unterstützung von Jan Tužil, PhD, Berater an der 1. Medizinischen Fakultät, Karls-Universität Prag.

Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

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