Thesis

The development and structured evaluation of the TAVI program between 2016 and 2022

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 20.08.2024 Raffael Geissler m.p.

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Zusammenfassung

Einleitung:

Aufgrund der weltweit steigenden Inzidenz der sklerosierenden Aortenstenose (AS) und des immer weiter steigenden Bedarfs an Transkatheter-Aortenklappen-Implantationen (TAVI) wurden die strukturellen, organisatorischen und interprozeduralen Veränderungen von TAVI-Implantationen im Zeitraum von 2016 bis 2022 am Universitätskrankenhaus Graz analysiert.

Ziel dieser Studie war es, die Veränderungen von Wartezeiten auf TAVI-Implantationen der letzten Jahre aufzuzeigen und den Einfluss von individuellen Merkmalen und Vorerkrankungen der Patienten auf die Mortalität festzuhalten. Darüber hinaus sollte diese Studie die echokardiographischen Verbesserungen nach TAVI-Eingriffen analysieren und unterschiedliche TAVI-assoziierte Komplikationen aufzeigen.

Methoden:

In dieser Studie wurde eine retrospektive Analyse von 1090 Patient*innen durchgeführt, die zwischen 2016 und 2022 an der Abteilung für Kardiologie am Medizinischen Universitätskrankenhaus Graz eine TAVI erhielten. Es wurden individuelle Charakteristika, diverse echokardiographische Parameter und Operationsberichte gesammelt und analysiert. Darüber hinaus wurden die Follow-up Daten der Patient*innen bis zu einem Jahr nach dem Eingriff gesammelt und Wartezeiten für eine TAVI, sowie die Dauer des Krankenhausaufenthalts nach dem Eingriff erhoben und statistisch ausgewertet.

Ergebnisse:

Die Analyse der Ergebnisse ergab eine signifikante Verbesserung der linksventrikulären Ejektion Fraktion (LVEF) bei Patient*innen, welche vor dem Eingriff LVEF-Werten zwischen 0-30% und 31-50% hatten. Auch der mittlere Druckgradient (MDG) über der Aortenklappe verringerte sich signifikant von 46 mmHg vor dem Eingriff auf 8,6 mmHg nach dem Eingriff.

Die Wartezeiten für den Erhalt einer TAVI-Operation nahmen für Patient*innen im Zeitraum von 2016 bis 2019 jährlich ab, stiegen jedoch während und nach der COVID 19-Pandemie von 2020 bis 2022 signifikant an.

Die durchschnittliche Krankenhausverweildauer nach TAVI sank signifikant von 9,7 ± 7 Tagen im Jahr 2016 auf 7,3 ± 4,6 Tage im Jahr 2022.

Es wurde kein signifikant erhöhter Zusammenhang zwischen der prozentuellen Rate an permanenten Schrittmachern (PSM) und selbstexpandierenden oder ballonexpandierenden- Klappen, sowie eine Aortenklappendilatation vor oder nach der Implantation der neuen Klappenprothese festgestellt.

Obwohl die 30-, 90- und 360-Tage-Überlebensrate progressiv von 95,7 %, 95,0 % und 93,5 % im Jahr 2016 auf 97,3, 95,8 % und 93,2 % im Jahr 2022 anstiegen sind, wurde kein signifikanter Unterschied innerhalb der beobachteten Jahre festgestellt.

Diese Studie zeigt auch einen signifikanten Zusammenhang erhöhten Sterblichkeitsraten bei Patienten mit einer GFR < 30 ml/min/1,73, einem sPAP > 51 mmHg, einem MPG $\leq$ 30 oder einer LVEF $\leq$ 40%.

Schlussfolgerung:

Diese Studie zeigt einerseits einen Rückgang der Dauer des Krankenhausaufenthaltes von Patient*innen nach TAVI-Eingriffen innerhalb der letzten Jahre auf und andererseits einen signifikanten Anstieg der Wartezeiten während der COVID-19-Pandemie. Außerdem wird der Einfluss von Vorerkrankungen und spezifischen echokardiographischen Parametern auf die Erfolgsrate sowie das Überleben nach TAVI-Eingriffen bestätigt.

Diese Studie unterstreicht die Bedeutung individueller Entscheidungsfindung vor jedem TAVI-Eingriff, lässt jedoch einen positiven Trend bei TAVI-Verfahren der letzten 7 Jahren erkennen.

Abstract in English

Introduction:

Due to the worldwide rising incidence of calcified aortic stenosis (AS) and the increasing need for Transcatheter Aortic Valve Implantation (TAVI), we analyzed the structural, organizational, and procedural evolution of TAVI implantations from 2016 to 2022.

The aim of this study was to assess waiting times, patient characteristics and pre-existing comorbidities, while providing insights into factors that predict the outcome after TAVI. Additionally, this study examines changes in echocardiographic parameters before and after the intervention and investigates TAVI-associated complications.

Methods:

This retrospective study analyzed 1090 patients who received TAVI between 2016 and 2022 at the Division of Cardiology at the Medical University Hospital of Graz. Patient individual characteristics, echocardiographic parameters, intra-procedural information, and follow-up data up to 360 days after the procedure were collected and analyzed. In addition, waiting times for TAVI and the duration of post-procedural hospitalization duration were obtained and statistically evaluated.

Results:

Our analysis revealed significant post-procedural improvements in left ventricular ejection fraction (LVEF) for patients with pre-procedural LVEF values between 0-30% and 31-50%. Mean aortic pressure gradient (MPG) also significantly decreased from a pre-procedural average of 46 mmHg to a post-procedural average of 8.6 mmHg.

Although, waiting times to receive TAVI decreased progressively from 2016 to 2019, they significantly increased during the COVID-19 pandemic from 2020 to 2022.

Additionally, the average post-TAVI hospitalization duration decreased from 9.7 ± 7 days in 2016 to 7.3 ± 4.6 in 2022.

Moreover, no significant association was found between an increased rate of permanent pacemaker (PPM) implantation and the use of either self- or balloon-expanding valves or pre- or post-implantation aortic valve dilation.

While 30-, 90-, and 360-day survival rates gradually improved from 95.7%, 95.0% and 93.5% in 2016 to 97.3%, 95.8% and 93.2% in 2022, but no statistically significant differences were identified.

This study also noted a significant association between increased mortality rates in patients with GFR < 30 ml/min/1.73m^2, sPAP > 51 mmHG, MPG $\leq$ 30 mmHg or LVEF $\leq$ 40%.

Conclusion:

This study demonstrates a notable reduction in post-TAVI hospitalization duration over the last years and a significant increase in waiting times to receive during the COVID-19 pandemic. It underscores the impact of comorbidities, and specific echocardiographic parameters on patient outcomes and survival after TAVI.

Finally, this study highlights the importance of individual decision-making prior to every TAVI procedure and identifies a positive trend in TAVI procedures over the past seven years.

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Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
AINS	Aortic Valve Insufficiency
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVR/MVR	Aortic/Mitral Valve Reconstructions
BAV	Bicuspid Aortic Valve
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CMR	Cardiac Magnetic Resonance
CTT	Cardiac Computer Tomography
DM	Diabetes Mellitus
ECG	Electrocardiography
EOA	Effective Orifice Area
ESC	European Society of Cardiology
GFR	Glomerular Filtration Rate
HLP	Hyperlipidemia
HTN	Hypertension
LVEF	Left Ventricular Ejection Fraction
MINS	Mitral Valve Insufficiency
MPG	Mean Aortic Pressure Gradient
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PPM	Permanent Pacemaker
SFAR	Sheath-to-Femoral Arterial Ratio
sPAP	Systolic Pulmonary Artery Pressure
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography

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1. Introduction

Transcatheter aortic valve implantation, also known as TAVI, is an alternative treatment for patients with severe aortic stenosis (AS), for whom the individual surgical risk of an open surgical aortic valve replacement is too high. Due to various factors such as multimorbidity, concomitant valve diseases, anomalies of the coronary arteries and cardiac or vascular anatomical restrictions, TAVI is often the only option for many patients (55).

On the 16th of April 2002, Alain Cribier performed the first aortic valve replacement by using a catheter-based system, fundamentally changing the treatment of patients with aortic stenosis. From that day on, AS could be treated through a minimally invasive procedure (1).

In the initial years, TAVI was only used for a few selected inoperable and multimorbid patients and the results were poor with many complications and adverse events. Over the following years, the TAVI procedure underwent numerous improvements and became increasingly adopted by physicians all over the world. As a result of the progressions, TAVI is now considered far more frequently and has become indispensable in modern cardiology (56).

In 2014, a milestone was achieved in Europe when cardiologists in Germany performed more TAVI-procedures than surgical aortic valve replacements over the course of a whole calendar year (57).

2. Transcatheter Aortic Valve Implantation (TAVI)

2.1. Indication

The primary indication for TAVI is severe Aortic Stenosis (AS), but multiple aspects must be considered. Various individual factors, such as the patient's individual peri-operative risk, contributing risk factors, limitations due to anatomical conditions and pre-existing diseases play a crucial role in the decision-making process. To help with these decisions, the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) have provided guidelines with indications for the correct treatment of severe AS with TAVI (56).

The ACC/AHA and ESC guidelines are nearly fully congruent and provide recommendations supported by clinical trial evidence (46). While the ESC-2021 guidelines primarily recommend TAVI for patients with severe AS who are over 75 years, the ACC/AHA guidelines consider TAVI as a reasonable option for patients aged over 65 years (2, 63).

The ACC/AHA provides four Class 1 recommendations for using TAVI, which indicate that the treatment is clinically tested, effective and beneficial for most patients in most situations.

The first TAVI Class 1 recommendation refers to patients with "severe AS and high or prohibitive surgical risk", and a predicted "acceptable life-quality" after the procedure, regardless of their age (56).

This risk classification is determined by using specific risk scores such as the Society-of-Thoracic-Surgeons-Score (STS-Score) or the Euro-Score (10).

The second Class 1 recommendation endorses TAVI for people older than 80 years with "a life expectancy of less than 10 years". The third guideline suggests TAVI as an option for all AS patients aged 65 to 80 years with typically TAVI-associated symptoms. Lastly, the fourth Class 1 guideline recommends TAVI for asymptomatic patients under 80 years of age with a left ventricular ejection fraction (LVEF) of 50% or less. Other scenarios receive lower or no grades, and especially complex and exceptional cases require specific individual decisions.

According to the ESC guidelines, absolute contraindications to receive TAVI include active endocarditis, the presence of thrombi in the left ventricle or in the ascending aorta, an aortic annulus diameter of less than 18 mm or larger than 29 mm, the absence of in-hospital- cardiac surgery facilities, no expected improvement in life quality after the procedure and overall inadequate vascular access methods (61).

With the help of these guidelines, most cases are covered, but every final decision need further case-based information and remains by the multidisciplinary heart team and the patient (56).

2.2. Aortic stenosis (AS)

2.2.1. Definition and Classification

AS is defined by the ACA/ACC as a reduction of the aortic valve area (AVA) and an increased mean pressure gradient (MPG) or an elevation of the aortic valve velocity flow and there are three different severity grades of AS. Mild stenosis means an AVA of 1.5 cm^2 or more and a MPG of less than 25 mmHg or a velocity flow between 2 and 3 m/s. Moderate AS is defined as an AVA of 1,5 - 1 cm^2 and a MPG of 25 – 40 mmHg or a velocity flow between 3 to 4 m/s. Severe AS is diagnosed when the AVA is 1 cm^2 or less and the MPG is more than 40 mmHg or the aortic velocity flow is above 4 m/s (10).

2.2.2. Epidemiology

Valve diseases are one of the major reasons for reduction in physical performance and loss in quality of life. Especially the most common one, Aortic Stenosis (AS), plays an increasingly important role in modern cardiology and its global incidence is on the rise (6). There are two main types of AS, the calcified AS and the rheumatic AS.

In high-income countries the most common type is the calcified AS, whereas in low-income countries the rheumatic AS predominates (5).

A meta-analysis of 7 studies found an estimated prevalence of 3.4% for severe AS among people aged 75 or older (4).

A further study in Norway and Sweden involving 30 000 people, showed that 7.2% of their observed population had some grade of calcified AS and nearly 2.8% were diagnosed with a severe calcified AS. The prevalence of the pre-stage of AS, aortic valve sclerosis, is more challenging to estimate. However, studies have found a varying prevalence of 9 to 42% and found any grade of aortic sclerosis in over 50% of people over 85 years of age.

The prevalence of rheumatic AS ranges from 5 to 350 cases per 100 000 people and is one of the leading causes of mortality in low-income countries (55). Rheumatic AS particularly affects children and adolescents and accounts for nearly 20% of all heart failure cases in low-income countries (9).

Contrary to calcified AS, the incidence of rheumatic AS is slowly decreasing, primarily due to rising medical standards and a more frequent use of antibiotics in low-income countries (55).

2.2.3. Etiology and risk factors

The etiology and risk factors of aortic stenosis (AS) vary depending on the different types and circumstances of AS.

The calcification of the aortic valve is a multifactorial process with several risk factors including valve abnormalities, advanced age, and the metabolic syndrome (55).

Among all congenital aortic valve abnormalities, the most common is the Bicuspid Aortic Valve (BAV), which is found in 1 to 2% of the world's population and in nearly 50% of people diagnosed with AS. BAV can occur as a standalone abnormality or as part of other diseases and syndromes (2, 55).

Arterial hypertension is a primary risk factor for developing calcified AS, with research indicating that for every 20 mmHg increase of arterial systolic pressure, the risk of developing AS rises by 40% (41).

Additionally, high levels of lipoprotein (a) (Lp (a)) and low-density lipoprotein (LDL) significantly elevate this risk. Also, smoking increases the risk factor of developing calcified AS by 35% and there is a notable correlation between diabetes mellitus and the development of calcified AS. The SALTIRE study found diabetes mellitus in 20% of people with a diagnosed severe AS. Furthermore, diabetes mellitus is also associated as a risk factor for chronic kidney disease (CKD) and coronary artery disease (CAD), both are also implicated as risk factors in the development of AS (40, 61).

Men have a higher prevalence of AS, tend to have faster disease progression, and often develop AS at younger ages compared to women (39).

Also, age is an important risk factor for developing calcified AS and with the world-wide progressively increasing age, the number of people over the age of 65 with severe AS and an indication for aortic valve replacement rose from 24 568 in 1989 to 31 380 in 2011. The same ascent was observed between 2007 and 2009, where the number of patients with AS increased by about 27% compared to the years 1989 to 1991. During this period, the patients' mean age at AS diagnosis increased by four years (8).

The second major type of AS, the rheumatic AS, is caused by a systemic abnormal immune reaction, with molecular mimicry targeting components of the heart, especially the valves. This reaction is mostly triggered by a throat infection with beta-hemolytic streptococci and symptoms typically manifesting weeks after the infection (9).

However, due to rising medical standards in low-income countries, rheumatic AS has been overcome by the calcified AS, as the worldwide most common form of AS (55).

2.2.4. Symptoms

The symptoms of AS can vary between patients and depend on various individual factors. Initially, most patients experience a long asymptomatic period, with symptoms typically manifesting between the age of 70 to 80 years. Early symptoms include vertigo, fatigue, and a decrease in physical performance (8).

As the disease progresses, most patients develop more AS-specific symptoms such as dyspnea, syncope, and severe fatigue, often in combination with hemodynamic decompensation and the clinical picture of nocturnal paroxysmal dyspnea, also known as asthma cardiale. Due to the decreased coronary perfusion pressure, more than 50% of patients develop coronary insufficiency and angina pectoris symptoms even without a pre-existing coronary artery disease.

With increasing wall tension caused by high aortic peak velocity, patients often develop hemolytic anemia, which typically worsens fatigue and decompensation symptoms (58). Other symptoms can be pulmonary hypertension, orthopnea, edema, and intestinal bleeding.

Once a patient starts developing symptoms, there is a significant increase in mortality and valve replacement becomes urgently needed (9).

2.2.5 Pathophysiology

A physiological aortic valve has an average aortic valve area (AVA) of 2.6 to 3.5 cm^2 and symptoms typically occur when the AVA is below 1.5 cm^2. Due to the progressive reduction of AVA, the heart must overcome increasingly high pressure to maintain blood flow and cardiac output through the aortic valve (59). Over time, this continuous increase in left ventricular afterload compensatory leads to a concentric heart hypertrophy. This hypertrophy can persist for several years until it results in decreased cardiac output and severe hemodynamical dysfunctions. This continuous left-ventricular mass gain often worsens pre-existing arterial hypertension and can lead to subendocardial ischemia (58).

Arterial hypertension is associated with negative impacts on ventricle remodeling and accelerates the degeneration process of the aortic valve (12).

As symptoms progress, patients also develop diastolic dysfunctions, including myocardial fibrosis and decreased left ventricular preload reserve, causing blood backflow from the left ventricle into the left atrium and the veins of the lung (58).

Left-ventricular hypertrophy and blood backflow can result in a dilation of the left atrium, leading to arrhythmias, especially atrial fibrillation (11).

With further AS progression, it becomes impossible to overcome the prevailing pressure gradients and maintain adequate central and coronary perfusion (58).

2.3. Diagnostic

The diagnosis and evaluation of AS is a process that includes clinical examinations and a combination of invasive and non-invasive diagnostic tools. The diagnostic procedure involves anatomic and hemodynamic assessments of the aortic valve, alongside the consideration of specific cardiac parameters. Gathering medical history, current medication, individual risk factors, comorbidities, family cardiac history, comprehensive anamnesis and detailed information about the patient’s symptoms are essential (55, 56).

2.3.1. Clinical examination

For diagnosing and differentiating AS from other valve diseases, it is useful to examine the patient's carotid pulse. In severe AS a "parvus and tardus" carotid pulse is typically present. This "slow-rising, late-peaking, low amplitude" pulse is relatively specific for AS, although its absence does not rule out the existence of AS (56).

Another essential diagnostic tool is auscultating the patient. The typical finding is a spindle-shaped systolic murmur, heard parasternal over the right second intercostal space, often with a radiation to the carotids and the aortic arch (58). In some cases, this murmur can be displaced, and in 15% of the patients, the acoustic peak is found near the apex. If this AS-specific murmur has a "musical quality", it is called the "Gallavardin-Phenomen", making it complicated to differentiate this sound from the murmur of mitral regurgitation (13).

There may also be a splitting second heart sound, resulting from the premature closure of the pulmonic valve before the stenotic aortic valve (56). Additionally, a fourth heart sound can be observed, indicating hypertrophic diastolic dysfunction of the left ventricle (58).

A louder murmur typically refers to further AS progression and higher AS severity. However, with even further increasing severity and decreasing cardiac output, the murmur can soften and sometimes disappears completely. This condition demonstrates the complexity of AS and the need for specific diagnostic tools (56).

2.3.2. ECG

The ECG serves as an important, non-invasive tool to diagnose AS. It provides a quick and practical assessment, but comes with limited sensitivity. One of the main characteristic findings in patients with severe AS is left ventricular hypertrophy, evidenced by high left-precordial R-wave amplitudes with a Sokolow-Lyon Index over 3.5 mV. ST-segment elevations and T-wave inversions can be found, as a sign of subendocardial ischemia, particularly in ECG-leads I, aVL, V_5 and V_6 (14, 58). Due to the changes in pressure gradients, a shift to left heart axis deviation and cardiac arrhythmias can be found in ECG of AS patients (15, 53).

Following a successful aortic valve intervention, these ECG signs often regress or even resolve entirely (14).

2.3.3. X-Ray

Aortic valve calcification, a dilated aorta ascendence distal to the valve stenosis and pulmonary congestion are typical findings in X-rays of patients with severe AS. Additionally, concentric hypertrophy and a dilation of the left atrium can be observed in further projections. With the progression of AS and cardiac decompensation, an enlarged cardiac silhouette may be present.

X-ray is a quick, but non-specific and not very sensitive diagnostic method, but it helps to substantiate the suspected diagnosis (6, 59).

2.3.4. Echocardiography

Echocardiography is the most specific tool for diagnosing and confirming the presence of AS. It is the gold standard for quantifying pressure conditions and evaluating cardiac functions in most AS patients (58). Various echocardiographic techniques offer a comprehensive assessment of the presence of valve calcifications, valve anomalies and other pathological cardiac structures (60). In addition, assessing pulmonary pressure, right ventricular function and aortic structures are essential parts of echocardiographic diagnostics.

Echocardiography is typically performed using two primary methods, transthoracic (TTE) and transesophageal (TEE). TTE is used for the initial evaluation of cardiac structures, while TEE is used for intraoperative echocardiography and for assessing complex valve diseases, providing a more detailed image of heart structures (23).

Echocardiography incorporates several essential modes to diagnose AS in a quick, non-invasive, and sensitive way. Starting with the Motion-mode (M-mode), a one-dimensional mode used for measuring heart structures, displaying heart motions, and indicating valve separations. The second mode is the Brightness-mode (B-mode), which provides a two-dimensional view of the heart, primarily used for detecting valve sclerosis, anomalies and malposition of valve leaflets, and a dilation of the ascending aorta.

Another echocardiographic feature is the Doppler echocardiography, which is used to determine pressure conditions and assess blood flow velocities. It includes two sub-types, color Doppler and spectral Doppler. Color Doppler visualizes blood flow through heart structures, helping to detect “turbulent blood flow”, which is a typical finding in stenotic valves. Spectral Doppler mode is used to detect “frequency shifts” in the physiological blood flow, providing quantitative information about the flow across valves or in blood vessels.

These techniques are crucial for calculating the aortic peak jet velocity, mean pressure gradient and aortic valve area (AVA), essential metrics for diagnosing AS and classifying their severity (60).

2.3.5. MRT/CT

Cardiac magnetic resonance (CMR) is specifically used for measuring myocardial perfusion and assessing the dynamics of the left ventricle. It plays an important role in evaluating myocardial damage and prognosticating the outcome of heart diseases. CMR is particularly important for evaluating, monitoring, and staging the progression of AS, especially in patients with “poor acoustic echocardiographic windows, misaligned left ventricles and asymmetrical cardiac hypertrophy” (16).

CMR provides more precise planimetry of the AVA than other diagnostic methods, delivering measurements approximately 10.7% larger than obtained by echocardiography, which enables better pre-operative planning and enhanced post-procedural outcomes (17, 58).

Limitations exist in providing inaccurate measurements in patients with highly calcified valves or very high flow velocities. High costs, limited availability, often-required use of gadolinium contrast medium and individual risk factors, are additional considerations against using CMR (16).

Cardiac computer tomography (CCT) is one of the premier diagnostic tools for diagnosing AS, providing accurate assessments and essential information for pre-procedural screening before TAVI (18). CCT is the inevitable standard for making measurements in patients with “low flow, low gradient AS and preserved LVEF” and for situations where stress tests are contraindicated or AS cannot be diagnosed by other diagnostic tools. Beyond providing detailed insights into the calcification and anatomy of the valve, CCT also gives information about the calcification of the coronary arteries, indicating the necessity of coronary artery revascularization before an aortic valve replacement (58).

CTT can be compromised in patients with very high heart rates, morbid obesity or artifacts can occur, due to stents or metal implants (19). Another limiting factor is the need of iodine contrast medium, which poses a risk of contrast-induced nephropathy (20).

Although the popularity and usage of CTT and CMT is rising, it is important to note that they are not intended to diagnose AS solely. For a comprehensive diagnostic and evaluation, additional diagnostic methods are required (19).

2.3.6. Stress Test

Stress tests are considered as the gold standard for diagnosing AS in asymptomatic patients. Over 50% of all AS patients have unmasked symptoms at the time of their diagnosis. Patients may appear asymptomatic either because they underestimate their symptoms or unconsciously reduce their activities to compensate their decreased physical performance. Stress tests can be conducted using special medication, such as low-dose dopamine, or through an exercise stress test, which is typically performed on a treadmill. During these tests, patients are always under the attendance of a physician and under continuous monitoring of blood pleasure, ECG and eventually echocardiography. Before every stress test, it is essential to rule out clear contraindication such as “uncontrolled hypertension, symptomatic or hemodynamically significant arrhythmias, and global disabilities” (21).

In physical stress tests, AS is detected when patients do not reach their expected performance level based on their age and personal characteristics (22). The patient’s physical performance level is measured by their highest achieved heart rate, their progression of systolic pressure and the potential onset of typical AS symptoms such as dypnone and fatigue (21).

Stress test with medications are preferred for patients with “low gradient and low velocity” AS and significant impaired left ventricular ejection fraction (LVEF) (23).

Although stress tests exhibit only a specificity of 57 to 79% for diagnosing AS, they are a crucial diagnostic tool for uncovering symptoms in patients believed to be asymptomatic (21).

2.3.7. Cardiac Catheterization

Cardiac catheterization is an invasive diagnostic tool used for diagnosing AS when non-invasive diagnostics are inconclusive. Its goal is to specifically address the discrepancies between the patient symptoms and non-invasive findings (24).

It is used to define the peak-to-peak pressure gradient, mean aortic pressure gradient and cardiac output with higher sensitivity compared to most non-invasive diagnostic tools. It enables accurate determination of the severity of the calcification and facilitates precise calculation of the aortic valve. Additionally, cardiac catheterization is indicated for AS when there is a need for combined coronary angiography to assess the need of coronary artery revascularization before the valve reconstruction (59).

The decision for cardiac catheterization should be carefully considered due to its invasiveness and the risk of embolic events caused by the catheter (61). With continuous advancements in echocardiography, the usage of cardiac catheterization has decreased over the last years but remains indispensable for specific questions and indications (59).

2.4. Procedure

After assessing the patient’s characteristics, anatomy and individual situation, a multidisciplinary heart team including cardiologists, heart surgeons, interventional specialists, ancillary specialists, logistic support, and both clinical and non-clinical supporting staff, holds a conference to discuss and decide if a patient is a suitable candidate for TAVI. This decision is made to the individual patient profile with a focused consideration on the urgency of the procedure, aiming to determine the optimal timing to ensure the best possible outcome for the patient. It is important for the multidiscilplinary team to thoroughly evaluate each individual TAVI candidate and always consider surgical aortic valve replacement as an reasonable option, especially in patients under the age of 75 years and low surgical risk (49, 63).

2.4.1. Access methods

For a successful TAVI and a favorable post-procedural prognosis, it is crucial to choose the right access method. It is essential to understand the anatomy and course of the aorta and peripheral arteries of every patient. Pre-operative CT scans, which include advanced vascular reconstruction tools, along with echocardiography, supports physicians in making this decision (25).

Most TAVI procedures are performed via transfemoral access, with approximately 80% not requiring surgery for the punction and insertions afterwards (26).

Transaortic, transapical, transaxillary, transcarotid and transcaval are alternative methods and can be considered in specific cases, such as anatomical anomalies, severe peripheral arterial diseases (PAD), or a sheath-to-femoral arteria ratio (SFAR) exceeding 1.05 (25).

Although, femoral access has the lowest rates of 30- and 360-day mortality and accounts for over 95 percent of all TAVI procedures, due to the increasing age and evolving criteria for TAVI eligibility, alternative accessing methods are being considered more frequently. However, further clinical trials are needed to identify their risks and benefits (26).

2.4.2. Valves

The valves used in TAVI are trileaflet valves made from bovine or porcine pericardium (56). There are currently two common types of TAVI systems, self-expanding and balloon-expanding valves systems. Self-expanding valves expand autonomously until they are correctly deployed and positioned at the aortic annulus, whereas balloon-expending valves use inflatable balloons to expand and secure the correct position of the valve (27).

In 2002, the first-in-man implantation was the balloon-expanding Edwards prothesis and the self-expanding CoreValve-Evolut prothesis was launched shortly afterwards. Over the years, certain TAVI valves have undergone significant developments and innovations, leading to newer generations and the approval of several slightly different models (61, 64).

Self-expanding and balloon-expanding valves show no significant difference in mortality at 30 and 360 days, although self-expanding valves are associated with slightly better post-procedural hemodynamic outcomes.

Studies have either shown that balloon-expending valves have a lower incidence of paravalvular leakage (PVL) than self-expanding valves, but in terms of mean aortic pressure gradient (MPG), self-expanding valves generally provide better post-procedural results and typically offer larger effective orifice areas (EOA) compared to balloon-expanding valves (27, 52).

Despite other observations such as life-threatening bleeding, obstruction of the coronary arteries and kidney injury did not significantly differ between these two types, their different benefits and risk factors make individual decisions for each patient and every procedure necessary (27).

2.4.3. TAVI

The fundamental elements of a TAVI system include the trileaflet valve affixed on an expandable metal frame or scaffold and a catheter delivery system (56).

After the appropriate access method is selected and all preoperative diagnostics are completed, a percutaneous or surgical puncture is made to commence the TAVI procedure. This puncture is used to advance a pigtail-catheter to the aortic root and to position a guidewire retrograde behind the aortic valve. Preoperative and perioperative CT scans are utilized to determine an accurate and suitable implantation plane for the new aortic valve. The delivery system carrying the aortic valve is then navigated following the path of the guiding wire to get into the right position (28).

If the physician chooses the transapical access, the implantation is performed through an anterolateral minithoracotomy. In this technique, the patient's pericardium is longitudinally incised, and the valve replacement is performed antegrade, relative to the aortic valve (28).

In certain cases, a dilation of the aortic valve is needed either before or after the implantation.

Pre-implantation valve dilation facilitates the delivery of the new valve and ensures a secure positioning in highly calcified areas (29). However, studies found that pre-implantation valve dilation is associated with an increased risk of hemodynamical instability, damaging the cardiac conduction system, producing embolic events and a prolonged time of the procedure.

Post-implantation dilation is used to optimize the positioning of the new aortic valve prothesis and to minimize the severity of potential paravalvular leakages (PVL). Like pre-implantation dilation, it carries the risk of producing embolic events and damaging the cardiac conduction system. Furthermore, post-implantation dilation can damage aortic structures and embolizes the new aortic valve prothesis.

Despite the severe compilations, both pre- and post-implantation dilation are indispensable for ensuring the optimal position of the valve, correcting PVL`s and enhancing long-term durability of the valve prothesis (53).

Additionally, in almost every procedure a temporary pacemaker is implanted, facilitating short tachycardic stimulations during the procedure. This is used to reduce cardiac movement to enable a stable positioning of the new aortic valve.

After implantation, a postoperative ultrasound is made, and the puncture is sealed, either surgically or with a vascular closure system (28).

Vascular closure systems seal the puncture site quickly, non-invasively and in a safe way, preventing vascular complications such as critical site bleeding and serious vascular damage. The Multiclose study, which involved over 630 TAVI procedures with vascular closure systems, reported major vascular complications in fewer than 1% of all procedures (45).

2.5. Cardiac Improvement

Serval positive cardiac, hemodynamic and clinical effects have been observed after TAVI. Notably, there is a significant reduction in left-ventricular pressure overload and a substantial decrease in the pressure gradient across the aortic valve (42). Further important improvements include enhancements of the left ventricular ejection fraction (LVEF) and significant reduction of left ventricular end-systolic and end-diastolic volume (LVESV/LVEDV) (43).

These improvements in systolic and diastolic functions contribute to a reduction in systolic pulmonary artery pressure (sPAP), leading to a reduced right ventricular function, milder tricuspid regurgitation along with a decreased risk of heart failure and cardiovascular death (44).

Another positive aspect is the reverse remodeling effect after TAVI. Due to the significantly improved hemodynamical conditions and reduced volume overload, remarkable improvements of damaged heart structures, especially in the myocardial layers can be found (42).

2.6. Complications

Although TAVI is generally considered a safe procedure with a low rate of complications, but there are certain TAVI-associated complications that often require further interventions and can potentially lead to fatal events (56). These complications often prolong the patient’s hospital stay and increase the risk of hospital-acquired diseases (47). Prolonged hospitalization also worsens the post-procedural outcomes, consumes more hospital resources and is associated with significantly higher in-hospital mortality (48).

2.6.1. Perioperative Complications

Perioperative complications during TAVI procedures often present dreaded challenges. One of them is a malposition of the new aortic valve, where the TAVI prosthesis is either placed incorrectly or shifts after positioning within the aortic annulus. This complication occurs in approximately 2% of all TAVI implantations (31).

Further perioperative complications may include damage to heart structures, including chamber perforation, annulus rupture and aortic dissection (56).

Annulus rupture often results from pre- or post-implantation dilation in highly calcified valves or from incorrect sizing of the new valve prothesis. According to the German register IQTIG, the incidence of annulus rupture is less than 0.1%, but has a mortality rate of up to 63% and often necessitates emergency cardiac surgery with extracorporeal circulation support. Similar incidence-rates apply to aortic dissections, another feared complication with inter-hospital mortality rates of up to 80%. To avoid this potentially fatal event, precise knowledge of the anatomy, anomalies and calcification of cardiac and vascular structures is essential. Another perioperative complication is coronary ostium obstruction, caused by wrong placement of the aortic valve prothesis, appearing in 0.16% of all TAVI interventions (31).

With an incidence ranging up to 23%, the most common intraoperative complications are various types of vascular damage. Severe vascular damage can lead to life-threading site-bleeding and often requires blood transfusions (61).

Despite these risks, the need for emergency open-heart surgery and cardiopulmonary bypass support during TAVI is very low, significantly less than 0.5% among all procedures (56).

2.6.2. Postoperative Complications

Paravalvular regurgitation (PVR) is the most frequent TAVI-associated post-procedural complication. The PARTNER Study involving 2 434 TAVI-patients, found some degree of PVR in over 47% of their study population. Among these, 38% exhibited a mild form while 9.1% had even higher grades. Patients with higher grades of PVR showed significantly increased re-hospitalization and mortality rates (32).

However, with the increasingly common use of post-implantation dilation and specific transcatheter device closure systems, most severe PVR can be reduced or even completely resolved (56).

Another postoperative TAVI-associated complication is stroke. The SURTAVI Trial, which included 1 746 patients with severe aortic stenosis, found severe stroke occurrence in 2.6% of patients within the span of 24 months after TAVI implantation (8).

Furthermore, potential damage of the atrioventricular conduction can result in arrhythmias and the need for permanent pacemaker (PPM) implantation after the procedure (33). Risk factors for damaging these conduction pathways are anatomically short membranous septa or very deep valve implantations (50).

Permanent pacemaker rates (PPM) range from 7 to 25% but differ strongly among the different valves and implanters (51). The CONDUCT registry, with a study population of 300 people treated with balloon-expandable TAVI systems, demonstrated that 14% of the study population required a PPM after the interventions (33). Further studies, such as the Evolut R FORWARD study, found increased PPM rates in self-expanding valve systems compared to balloon-expanding valve systems (27).

Further less frequent postoperative complications include acute kidney injury and endocarditis, both occurring in less than 1% of all TAVI interventions (56).

2.7. Mortality

The overall TAVI mortality varies strongly among all patients and depends on certain pre- and post-operative factors, including comorbidities and individual characteristics. Mortality rates are difficult to define and are constantly changing due to progressive advancements in valve development, increasing expertise of physician and improved diagnostic methods (61).

A strong determining factor is the patient's pre-procedural left ventricular ejection fraction (LVEF). Pre-procedural LVEF of 50% or less worsens the outcome and significantly increases all-cause and cardiovascular mortality (34).

Also, a low mean aortic pressure gradient (≤ 40 mmHg)(MPG) is a decisive negative predictor for the outcome after TAVI. Patients with a combination of low LVEF and low MPG have the highest mortality rate among all patients. With a 1-year mortality of up to 40%, this group has a significantly worse outcome compared to people with an isolated reduced LVEF or isolated reduced MPG (35).

Systolic pulmonary arterial pressure (sPAP) over 40 mmHg also significantly increases the mortality in TAVI patients. A study of the FRANCE 2 Registry found that especially patients with sPAP values of more than 60 mmHg had significantly increasing all-cause mortality rates (36).

Further studies proved that also pre-procedural chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) under 45ml/min/1.73m^2 have significantly higher all-cause mortality rates (38).

Another important predictor of 1-year mortality is the patients' waiting time to receive TAVI after their diagnosis. Prolonged waiting times are often the result of the progressively rising demand for TAVI over the last years. This situation leads to an increased need for more medical and organizational resources and in certain situations, this can be challenging and often leads to postponement or even cancelation of planned procedures (46). Studies have shown that longer waiting times are associated with further disease progression and a concomitant decrease in individual mobility and cognition. Additionally, the 1-year mortality increases by 2% for every 2 additional weeks of waiting time. Myocardial volume overload and chronical kidney disease (CKD) worsen with longer waiting times, which are also key factor for increased mortality rates (37).

Other previous studies identified pre-procedural moderate or severe mitral insufficiency, previous myocardial infarction and COPD as factors that increase mortality and hospitalization in TAVI patients (36).

In consideration of all these factors, multiple trials have found mortality rates varying from 0.49% to 0.96% during the TAVI procedure, 1.7% to 5.3% after 30 days and 8.6% to 24.3% after 360 days (62, 53).

3. Aim of the study

The aim of the study is to illustrate the structural and organizational changes in TAVI implantations from 2016 to 2022 at the Department of Cardiology in the Medical University Hospital of Graz.

Additionally, this study should analyze individual characteristics, pre-existing comorbidities and waiting times of TAVI patients and assess the impact on patients' health.

3.1. Collection of data

In this retrospective thesis we collected data from 1090 patients diagnosed with AS and an indication for TAVI between 2016 and 2022.

All patients received different types of TAVI and all data were pseudonymized and recorded in a Microsoft Excel spreadsheet.

Preoperative baseline characteristics such as age, gender, pre-existing comorbidities including arterial hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLP), peripheral artery disease (PAD), previous valve reconstructions of the mitral or aortic valve (AVR/MVR), previous aortic valve balloon valvuloplasty (BV), previous percutaneous coronary interventions (PCI) and coronary artery bypass graft (CABG) surgeries were gathered from the hospital information system, openMedocs. The patients' renal functions were assessed by using the estimated glomerular filtration rate (eGFR) and pulmonary hypertension by measuring the systolic pulmonary arterial pressure (sPAP).

Echocardiographic reports were collected before and after the procedure and the observed parameters included pre- and post-procedural metrics such as aortic valve area (AVA), mean pressure gradient (MPG), left ventricular ejection fraction (LVEF), the specific grade of mitral valve insufficiency (MINS) and potential aortic valve insufficiency (AINS). Information of the specific TAVI system, vascular closure system and intra-procedural complications were obtained from the surgical report. Mortality rates were gathered for up to 1 year after the procedure and organizational key dates including the time between the heart team meeting to the procedures and the post-procedural hospitalization time were analyzed and facilitated.

3.2. Statistical Analysis

The statistical analysis and all diagrams were created by using the software programs GraphPad Prism Version 8.0.2 and IBM SPSS Statistic Version 29. The data were descriptively analyzed, presenting mean, median, standard deviation, range, minimum and maximum parameters. To assess whether the metric values followed a normal distribution, either the D'Agostino-Pearson or Shapiro-Wilk test was used. To evaluate specific differences in metric data with normal distribution, paired and unpaired t-tests were performed. Metric data, which did not follow normal distribution, were analyzed by using the Wilcoxon rank-sum test, Mann-Whitney U test and Kruskal-Wallis test.

To analyze the association between two binary data values, the Chi-Square (Chi^2) test was used, and Kaplan-Meier curves were created to visualize mortality rates.

Not every parameter could be collected for each patient, so the number of values varies in the statistics.

In this study, a p-value of <0.05 was considered as statistically significant.

4. Ethics Vote

The approval for this study was made on 14th of April 2023 by the Ethic Committee of the Medical University of Graz. (35-002 ex 22/23)

5. Results

5.1. Characteristics of the Study Population

5.1.1. General Demographics and Comorbidities

The study population included a total of 586 (53.8%) females and 504 (46.2%) males, with a mean age of 81 ± 7 years and a range from 38 to 95 years.

Arterial hypertension (HTN) was observed in 1016 (93.2%) patients, diabetes mellitus (DM) in 293 (26.9%) and hyperlipidemia in 739 (67.8%). Notably, 260 (23.9%) patients had undergone a previous percutaneous coronary intervention (PCI), 98 (9%) had coronary bypass grafts (CABG) and 123 (11.3%) patients received PCI between the heart team conference and the TAVI procedure. Prior valve reconstructions, either mitral or aortic valve reconstruction, were documented in 41 (3.8%) patients and 33 (3%) had undergone aortic balloon valvuloplasty (BV) prior to the procedure. The mean glomerular filtration rate (GFR) was 53.0 ± 19.4 ml/min/1.73m^2 and severe renal impairment, defined as a GFR of 30 ml/min/1.73m^2 or less, was found in 142 (13.2%) patients.

There were no significant differences in the distribution of the observed characteristics among all patients. All parameters are shown in Table 1.

	n	Yes	%
Gender (Male)	1090	504	46.2
Diabetes mellitus (DM)	1090	293	26.9
Hyperlipidemia (HLP)	1090	739	67.8
Arterial hypertension (HTN)	1090	1016	93.2
Percutaneous coronary intervention (PCI)	1090	260	23.9
Coronary artery bypass graft (CABG)	1090	98	9.0
Mitral/Aortic valve reconstruction (MVR/AVR)	1090	41	3.8
Pre-procedural TAVI PCI*	1090	123	11.3
Glomerular filtration rate <30 (GFR) (ml/min/1.73m^2)	1090	142	13.2
Balloon aortic valvuloplasty (BV)	1090	33	3.0

Table 1: Demographics and comorbidities *n= number of patients*

**PCI between heart team meeting and the TAVI procedure*

5.1.2. Pre-TAVI Echocardiography Characteristics

Table 2 presents parameters from echocardiography prior to the TAVI procedure. The mean left ventricular ejection fraction (LVEF) was 51 ± 13 % and 166 (22.7%) patients had an LVEF of 40% or less. The mean pressure gradient (MPG) was 46 ± 15 mmHg and mild mitral insufficiency (MINS) was observed in 683 (67.7%) patients, while 150 (15.9%) exhibited moderate to severe MINS prior to the intervention.

The aortic valve area (AVA) had a mean of 0.69 ± 0.19 cm^2, which was measured by echocardiography or extracted from the cardiac catheterization report. The mean systolic pulmonary artery pressure (sPAP) was 45 ± 14 mmHg and 95 (15.8%) people in the study population had sPAP values of 60 mmHg or higher (Table 2).

	n	Min.	Max.	Mean ± SD
Ejection fraction (%)	732	10	86	51 ± 13
Mean pressure gradient (mmHg)	1044	5	120	46 ± 15
Systolic pulmonary artery pressure (sPAP) (mmHg)	601	15	107	46 ± 14
Aortic valve area (cm^2)	1031	0.1	1.8	0.69 ± 0.19

Table 2: Pre-TAVI echocardiography characteristics *n= number of patients*

5.2. Valves

During the observed period, 752 (69.9%) of 1076 patients received self-expanding valves, while the other 324 (30.1%) received balloon-expanding valves.

The most implanted self-expanding valve was the "CoreValve", which accounts for 42.3% of all valves, while "Edwards" was the leading valve among the balloon-expanding valves, accounting for 27.4% of all implants (see Table 3).

Among all implanted valves, 146 (13.6%) were classified as small-sized valves, 703 (65.5%) as medium-sized valves and 224 (20.9%) as large-sized valves.

Additionally, Table 4 shows that intraoperative aortic valve dilation was performed in 384 (35.8%) cases and post-implantation dilation was necessary in 409 (38.1%). Furthermore, both pre- and post-implantation dilation were required in 158 (14.7%) people of the study population.

		Type	n (%)
Self-expanding	Supra-annular		
		Corevalve	455 (42.3)
	Intra-annular		
		Symetis	170 (15.8)
		Lotus	7 (0.7)
		Portico	120 (11.2)
Balloon-expanding		Edwards	295 (27.4)
		Direct Flow	29 (2.7)
		Total	1076 (100)
Size			
		S	146 (13.6)
		M	703 (65.5)
		L	224 (20.9)
		Total	1073 (100

Table 3: Valves *n= number of patients*

	n	%
Pre-implantation valve dilation	225	21
Post-implantation TAVI dilation	251	23.4
Pre- + post-implantation dilation	158	14.7
No valve dilation	440	41
	1074	100

Table 4: Intra-procedural valve dilation   n= number of patients

5.3. Echocardiographic Analysis

To observe changes in left ventricular ejection fraction (LVEF) before and after the procedure, the study population was divided into two groups: patients with an LVEF of 0-30% and patients with an LVEF of 31-50%. These groups were compared to each other using the Wilcoxon rank-sum test and both showed significant improvement in LVEF following TAVI ((p = <0.001).

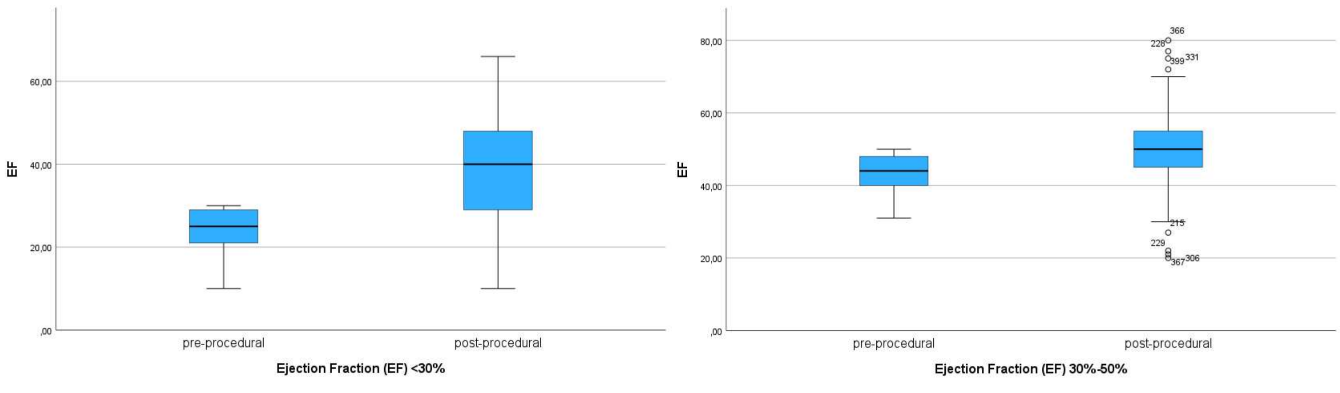

Figure 1: Patients with pre-procedural LVEF <30% (left) / LVEF 30-50% (right) before and after TAVI

The mean aortic pressure gradient (MPG) decreased from pre-procedural 46 mmHg to 8.6 mmHg post-procedural and was determined with a significant improvement by the Wilcoxon rank-sum test (p = <0.001). (see Table 5)

The MPG after TAVI was significantly lower in procedures with self-expanding valves compared to procedures where balloon-expanding valves were used (see Table 6).

	MPG before TAVI	MPG after TAVI
n (patients)	856	856
Mean (mmHg)	46 ± 15	8.6 ± 5
Range (mmHg)	115	72
Minimum (mmHg)	5	2
Maximum (mmHg)	120	74
p-value		<0.001

Table 5: Pre- and post-procedural aortic mean pressure gradient (MPG)

	Self-expanding	Balloon-expanding
n (patients)	646	235
Mean (mmHg)	7 ± 5.1	10 ± 4.6
p-value		<0.001

Table 6: Aortic mean pressure (MPG) of self-expanding valves vs balloon-expanding valves

5.4. Waiting Periods Analysis

Another important parameter in this thesis, is the change in waiting times from diagnosis to receive TAVI over the last years.

5.4.1. Conference to Procedure

Data from 1000 patients were analyzed and grouped by the year they underwent TAVI. Waiting times from the heart team conference to the procedure were calculated and the patients were divided into 7 groups, from Group 1 (2016) through group 7 (2022). As seen in Table 7 and Figure 2, patients in Group 4 (2019) experienced the shortest waiting time between the heart team conference and the procedure averaging 69 ± 69 days, while those in Group 7 (2022) had the longest waiting time, averaging 129 ± 112 days. Significant differences were observed between the groups, but notably, Group 4 (209) compared to Group 6 (2021), Group 3 (2018) compared to Group 7 (2022), Group 4 compared to Group 7(2022) and Group 5 to Group 7 showed all highly significant differences (p = <0.001). (

Group	n	Mean ± SD (days)
1 (2016)	127	100 ± 100
2 (2017)	127	103 ± 111
3 (2018)	129	93 ± 127
4 (2019)	144	69 ± 69
5 (2020)	158	87 ± 86
6 (2021)	181	118 ± 106
7 (2022)	134	140 ± 112
Total	1000	102 ± 104

Table 7: Days from conference to procedure
n= number of patients

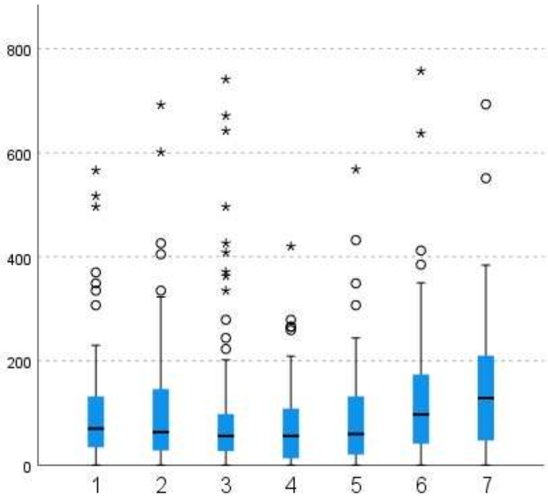

Figure 2: Boxplot: Days from conference to procedure

5.4.2. Hospitalization

In this thesis, the hospitalization duration is defined as the time period from procedure to hospital discharge. For the analysis, the patients were again divided into 7 groups based on the year they underwent TAVI.

As demonstrated in Table 8 and Figure 3, the average hospitalization duration decreased from 9.7 ± 7 days in Group 1 (2016) to 7.3 ± 4.6 days in group 7 (2022). There was a reduction in hospitalization each year, except for 2020 following 2019.

Especially, Group 6 (2021) and Group 7 (2022) exhibited statistically significant reductions in hospitalization duration compared to Group 1 (2016), Group 2 (2017) and Group 3 (2018) (p = < 0.001).

Group	n	Mean ± SD (days)
1 (2016)	136	9.7 ± 7
2 (2017)	135	9.4 ± 6
3 (2018)	131	9 ± 4.5
4 (2019)	154	7.9 ± 4.6
5 (2020)	161	8.4 ± 10.9
6 (2021)	197	7.6 ± 5
7 (2022)	147	7.3 ± 4.6
Total	1061	8.3 ± 6.5

Table 8: Days from procedure to hospital discharge
n= number of patients

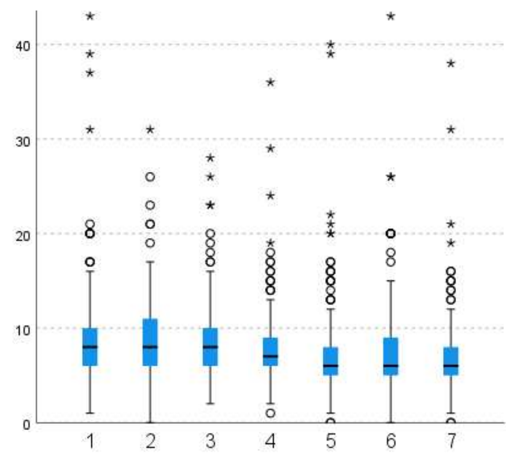

Figure 3: Boxplot: Days from procedure to hospital discharge

5.5. Complications

Table 9 provides an overview of all recorded TAVI-associated complications during and after the procedure. The intra-procedural complications were originated from the TAVI procedural report and the assessment of potential paravalvular regurgitation (PVR) was conducted from the first post-procedural echocardiography.

Post-procedural paravalvular regurgitation (PVR) was the most common complication of all 1019 TAVI implantations, with an incidence of mild paravalvular regurgitation (PVR) of 34.2% among the study population and higher grades of 2.2%.

Out of 1083 patients, 133 (12.3%) required a permanent pacemaker (PPM) during or after the TAVI procedure. There was no statistical difference between balloon- and self-expanding valves in terms of the need for permanent pacemakers (PPM) observed. Additionally, no significant association between pre-, post- or pre- and post-implantation dilation and increased PPM rates was found.

During the procedure 11 (1%) patients died, 12 (1.1%) experienced post-operative bleedings with unstable blood pressure and 16 (1.5%) suffered peripheral vascular complications. (See Table 9)

		Type	n (%)
Complications	Intra-procedural (N=1090)		
		Exitus	11 (1)
		Bleeding with RR-problems	12 (1.1)
		Site bleeding and peripheral vascular damage	16 (1.5)
	Permanent Pacemaker (n=1083)		
		Permanent Pacemaker (PPM)	133 (12.3)
		PPM - Self-expanding vs Balloon-expanding valves	P = 0.96
		PPM - pre-implantation valve dilation	50 (13.0) [p = 0.31]
		PPM - post-implantation valve dilation	52 (12.7) [p = 0.46]
		PPM - pre- versus post-implantations	24 (15.2) [p= 0.43]
	Paravalvular regurgitation (n=1019)		
		Mild	349 (34.2)
		Moderate or Severe	22 (2.2)

Table 9: TAVI complications *n= number of patients*

5.6. Survival

5.6.1. General survival

As presented in Table 10 and Figure 4 we assessed the survival rates of all patients and found overall survival rates of 97.3% at 30 days, 95.8% at 90 days and 93.2% at 360 days. Although, notable variances were observed within the years, especially when comparing the 90-day survival rates of 2021 to those in 2018 and the 360-day survival rates of 2021 to those in 2017 (p = 0.085 / 0.052), no statically significant differences between the years were found.

In Figure 5, the entire study population was divided into 2 groups and the 360-day survival rates were compared to each other. Group 1 included all available mortality rates from the first half of the patients and Group 2 the data of the second half.

Although the survival rate was higher in Group 2, again no statistical significance was found (p = 0.434).

Year	30-days	90-days	360-days
2016	95,7%	95,0%	93,5%
2017	96,3%	95,5%	90,3%
2018	96,9%	93,9%	91,6%
2019	97,4%	95,5%	92,3%
2020	97,0%	95,2%	92,8%
2021	98,5%	98,0%	96,1%
2022	98,6%	96,6%	94,6%
Total	97,3%	95,8%	93,2%

Table 10: Survival-rates 30-, 90- and 360- days after TAVI

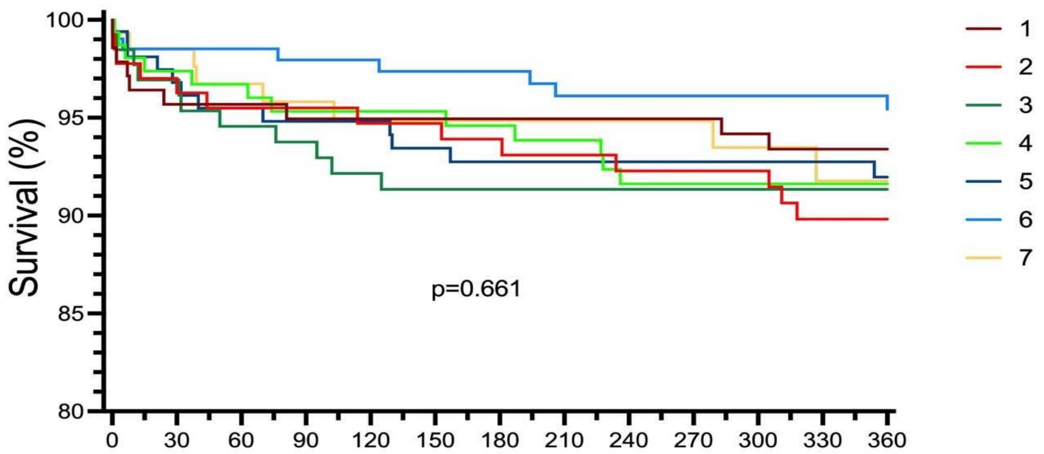

Figure 4: Kaplan-Meier survival rates after TAVI. (days)
1=2016, 2=2017, 3=2018, 4=2019, 5=2020, 6=2021, 7=2022

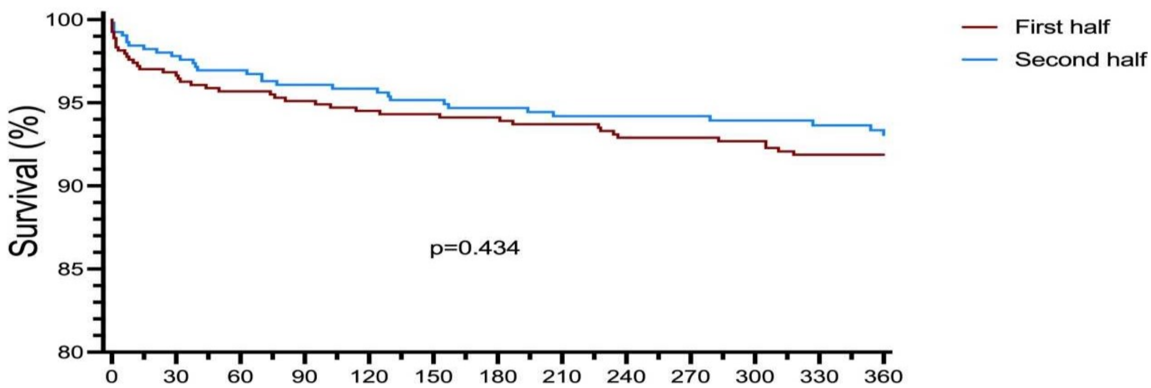

Figure 5: 360-days survival-rate of the first and second half of all TAVI patients.

5.6.2. Factors that influence mortality

Chi-Square (chi2) and Fisher-exact tests were used to determine the influence of individual characteristics, comorbidities, and pre-existing diseases on the 360-day mortality of the patients. The analysis indicated that pre-existing arterial hypertonus (HTN), diabetes mellitus (DM), peripheral artery diseases (PAD), moderate or severe mitral insufficiency (MINS) and gender did not show a statistically significant impact on patients' mortality. Also, the mortality rates of patients with previous percutaneous coronary interventions (PCI) or coronary arterial bypass grafts (CABG) did not differ significantly from those without these interventions. Additionally, there was no significant difference in mortality rates when comparing the patients' ages. We analyzed the mortality rate of people younger and older than 70 years, younger and older than 80 years and younger and older than 90 years.

However, statistically significant higher mortality rates were observed in patients with glomerular filtration rate (GFR) of 30 ml/min/1.73m^2 or less, left ventricular ejection fraction (LVEF) of 40% or less, mean aortic pressure gradient (MPG) of 40 mmHg or less and systolic pulmonary artery pressure (sPAP) exceeding 51 mmHg. The exact mortality rates and significance levels for all analyses are shown in Table 11.

	Yes (%)	No (%)	p-value
Arterial hypertension (HTN)	6.77	6.76	1.00
Diabetes mellitus (DM)	7.56	6.48	0.53
Peripheral arterial diseases (PAD)	8.86	5.91	0.08
Gender (yes = male)	6.80	6.75	1.00
Previous percutaneous coronary intervention (PCI)	9.02	6.08	0.12
Previous coronary artery bypass graft (CABG)	5.10	6.94	0.67
Left ventricular ejection fraction ≤ 40% (LVEF)	12.20	6.27	0.02
Glomerular filtration rate ≤ 30 ml/min/1.73m^2 (GFR)	11.97	5.98	0.01
Systolic pulmonary arterial pressure > 51 mmHg (sPAP)	11.54	5.67	0.02
Moderate or severe mitral insufficiency	10.74	6.37	0.08
Mean aortic pressure gradient ≤40 mmHg (MPG)	9.95	5.00	0.003
Age ≥ 70 years	6.58	6.79	1.00
Age ≥ 80 years	6.82	6.74	1.00
Age ≥ 90 years	6.56	10.64	0.24

Table 11: Impact of characteristics and comorbidities on mortality rates

6. Discussion

This study provides an overview of the individual characteristics and comorbidities of over 1000 patients with aortic stenosis (AS) who received TAVI between 2016 and 2022. We analyzed the changes in echocardiography parameters before and after the intervention and provided insights in factors that predict the outcome. It also determines waiting times during the entire TAVI process and analyses changes within the years. Furthermore, 30-, 90-, and 360-day mortality rates were evaluated, compared and the influence of certain parameters and factors gathered. Certain diagrams and tables were created to illustrate the results and provide a better overview of the findings.

6.1. Study Design

The design of this study is a retrospective single-center study with a population of 1090 people who received TAVI from 2016 to 2022. The sample size and observation duration make it possible to draw adequate conclusions and provide reliable statistical results. This study design is also used in many comparable studies and enables a valid comparison with the results of others.

6.2. Study Population

This study included a population with a mean age of 81 ± 7 years, which is the typical age where patients with AS becoming symptomatic and candidates for TAVI (55, 58). The gender distribution was 46.2% male and 53.8% female, which is slightly different from studies in the literature, where men are more commonly affected by AS and there are often higher rates of men in studies with aortic valve diseases. In case of TAVI, studies have found that women tend to develop AS at an older age than men, which may imply that they are more likely to receive TAVI instead of open surgery. This factor, along with the longer lifespan of women, may explain the higher percentage of females in this study (39, 62).

The study population showed a high prevalence of patients with hypertension (93.2%), diabetes mellitus (26.9%) and hyperlipidemia (67.8%), which are associated risk factors for developing aortic stenosis and are typically observed in TAVI candidates. All further assessed echocardiographic parameters and comorbidities are typical characteristics for TAVI patients and can be similarly found in the literature and in comparable studies (61,40,41).

The average mean aortic valve area (AVA) was 0.69 ± 0.19 cm^2 and the mean pressure gradient (MPG) was 46 ± 15 mmHg, both indicative parameters for severe AS (10, 46). The study population had an average systolic pulmonary arterial pressure (sPAP) of 46 ± 14 mmHg and left ventricular ejection fraction (LVEF) values of 51 ± 13 %.

6.3. Change in Waiting-Times within the Years

One of the primary objectives of our analysis was to assess the duration of various time periods during the whole TAVI procedure. We focused on the waiting times from heart team conference to the procedure and the duration of hospitalization of every patient.

Various former studies suggest that shorter intervals between diagnosis and procedure are associated with a better outcome and lower mortality rates, as they prevent further disease progression and further cardiovascular damage (37, 46).

Initially, we found average waiting times between the heart team conference to the procedure of 100 ± 100 days in 2016, found the shortest waiting times of 69 ± 69 days in 2019 and the longest with 140 ± 112 days in 2023.

This pattern should be carefully interpreted due to the impact of the COVID-19 pandemic from 2020 to early 2022. At the Medical University Hospital of Graz, this time was marked by government-imposed public health lockdowns, organizational challenges, staff shortages due to illness and rescheduling of several TAVI procedures. These circumstances had a significant impact on the waiting times and led to postponements of TAVI interventions up to several months.

To apply these data representatively, further research and analysis without a pandemic setting needs to be done.

Hospitalization time, defined as the period between the procedure and the hospital discharge, decreased nearly every year from 9.7 ± 7 days in 2016 to 7.3 ± 4.6 days in 2022. Shorter hospitalization time have been linked to reduced hospital-mortality, improved patient outcomes and a more efficient use of hospital resources (47, 48).

This improvement could be attributed to improvements in the valve prothesis, more experience among the implanters and improved pre-procedural planning. Additionally, the increased use of improved vascular closure systems may be a factor for the decreasing hospitalization time in our study (56, 61).

6.4. Outcome

Looking at the cardiac outcome after TAVI, we analyzed the change in echocardiographic parameters after the procedure and examined differences between the types of valves used by the Medical University Hospital Graz.

Our study found statistically significant improvements in left ventricular ejection fraction (LVEF) in patients with pre-procedural LVEF values of 0-30% ($p < 0.001$) and those with values of 31-50% ($p = < 0.001$).

We observed a significant reduction in mean aortic pressure gradient (MPG), which went from pre-procedural 46 ± 15 mmHg to 8.6 ± 5 mmHg post-procedural ($p = < 0.001$).

Consistent with findings in the literature, the MPG was with 7 ± 5.1 mmHg in self-expanding valves significantly lower than with the MPG of 10 ± 4.6 mmHg in balloon expanding valves ($p = < 0.001$) (27, 52).

These cardiac improvements are strongly associated with various positive cardiovascular effects and lower mortality rates after the procedure significantly (42).

6.5. Complications

The most common observed complications during TAVI were side bleeding and severe peripheral vascular damage, which occurred in 1.5% of all procedures. This prevalence is nearly consistent with the vascular complication rate found in similar studies, such as the Multiclose study (45). The intraprocedural death rate was observed at 1%, again aligning with the findings reported in the literature (53).

Compared to the Evolut R FORWARD and CONDUCT studies, we observed similar rates of permanent pacemaker (PPM) implantation at 12.3 %. Unlike their results we detected no statistical difference in the need for PPM implantation between self-expanding and balloon expanding valves (p = 0.96) (27, 33).

Furthermore, we found no significant correlation between an increased need of PPM in either pre-, post- or pre- and post-implantation valve dilation, contrary to studies in the literature. (table4 and 11) (29, 53).

6.6. Mortality

To determine mortality rates, we assessed the 30-, 90- and 360-day mortality of the study population and compared them within the years.

We then looked at various individual characteristics, comorbidities and echocardiographic parameters and analyzed their impact on the observed mortality rates.

Looking the baseline characteristics, studies in the literature indicate a significantly increased 360-day mortality rates among patients with a left ventricular ejection fraction (LVEF) of 50% or less (34).

According to their findings, we only noted a significant increase in patients with LVEF values of 40% or below (p = 0.02).

Additionally, we observed significantly higher 360-day mortality rates in patients with mean aortic pressure values (MPG) of 40 mmHg or less (p = 0.003), corroborating with the literature.

Regarding to renal function, we reported a significant increase in 360-day mortality in patients with a preprocedural glomerular filtration rate (GFR) of 30 ml/min/1.73m^2 or less (p = 0.01), while Ferro et.al.'s findings in the UK TAVI registry, had similar significant association, but only in patients with glomerular filtration rates of 45 ml/min/1.73m^2 or below (38).

Our study found a correlation between elevated mortality rates and elevated systolic pulmonary artery pressure (sPAP) values over 51 mmHg, while a study from the FRANCE 2 Registry indicated a threshold of 60 mmHg.

This study also reported that preexisting percutaneous coronary intervention (PCI), coronary arterial bypass graft (CABG) and moderate to severe mitral insufficiency (MINS) have a significant impact on the mortality rates of TAVI patients. However, our findings diverge from theirs, although we found that the impact of moderate or severe MINS was nearly significant, we could not determine statistically significant results (36).

Additionally, to the results in the literature, our study found no significant difference in mortality rates among patients with arterial hypertension (HTN), diabetes mellitus (DM), or peripheral arterial disease (PAD) compared to patients without these conditions.

We reported 30-day, 90-day and 360-day survival rates of 97.3 %, 95.8% and 93.2% and these align with the usual observed survival rates in TAVI procedures (62). Although no statistically significant improvement was noted, we observed rising survival rates nearly annually. With continued analysis over the following years, we suggest significant improvement in these rates. This rise may be the result of advances in diagnostic, procedural and follow-up methods for TAVI patients (61).

7. Limitations

A key limitation in gathering the patient data was that specific parameters or characteristics were sometimes not precisely recorded in openMedocs and being unusable. In such cases, we excluded these patients with missing parameters for certain analyses and relied on the other available data. Consequently, the number of patients is different among the several statistical evaluations.

Another limitation was that the echocardiographic parameters were assessed by different physicians, which might have led to bias in the interpretations of certain values and data.

8. Conclusion

This study documents a consistent decrease in hospitalization duration following TAVI procedures in the years from 2016 to 2022.

It shows the annual change in waiting times to receive TAVI and highlights the impact of the COVID 19 pandemic on them.

We noted rising survival rates almost every year and found significant associations between increased mortality rates and patients with GFR <30 ml/min/1.73m^2, sPAP > 51 mmHG, MPG $\leq$ 30 mmHg or LVEF $\leq$ 40%.

This study demonstrates a significant post-procedural decrease in MPG and significantly improved LVEF in patients with initial LVEF values of $\leq$ 30% and 30 - 50%. TAVI-associated complications were also explored and we additionally showing that self-expanding valves have a significantly lower MPG after TAVI, compared to balloon-expanding valves.

We found no significant correlation between elevated mortality and arterial hypertension, diabetes mellitus, moderate or severe MINS, previous PCI or CABG, or an age over 70, 80 or 90 years.

In summary, our findings observed a positive trend in TAVI procedures over the last years. Furthermore, this study underscores the importance of considering each patient's individual baseline characteristics and parameters and highlights the urgent need for individual decision making in every TAVI intervention.

9. Literature

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