Diploma Thesis

Comparison of Echocardiographic to Invasive Determination of Aortic Valve Stenosis Severity

submitted by

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Statutory Declaration

I hereby declare that I have authored this diploma thesis fully on my own, that I have not used any other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, 29.09.2022 *Soraya Azizbaig Mohajer eh.*

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List of Abbreviations

ACC/AHA ..... *American College of Cardiology/American Heart Association*
ACEi ..... *Angiotensin-converting enzyme inhibitors*
AF ..... *Atrial fibrillation*
AR ..... *Aortic regurgitation*
ARB ..... *Angiotensin II receptor blockers*
ARNI ..... *Angiotensin receptor-neprilysin inhibitor*
AS ..... *Aortic (valve) stenosis*
AVA ..... *Aortic valve area*
CAD ..... *Coronary artery disease*
CCT ..... *Cardiac computed tomography*
CK ..... *Creatine kinase*
CKD ..... *Chronic kidney disease*
CK-MB ..... *Creatine kinase muscle-brain type*
CMR ..... *Cardiovascular magnetic resonance*
CO ..... *Cardiac output*
CSA ..... *Cross-sectional area*
CSS ..... *Canadian Cardiovascular Society*
CVD ..... *Cardiovascular disease*
CW ..... *Continuous-waved*
DDP-4i ..... *Dipeptidyl peptidase-4 inhibitor (gliptins)*
ECG ..... *Electrocardiogram*
eGFR ..... *Estimated glomerular filtration rate*
EOA ..... *Effective orifice area*
ESC ..... *European Society of Cardiology*
EuroSCORE II ..... *European System for Cardiac Operative Risk Evaluation II*
GLP1 ..... *Glucagon-like peptide-1*
GOA ..... *Geometric orifice area*
Hb ..... *Hemoglobin*
hs-troponin ..... *High-sensitive troponin*
IQR ..... *Interquartile range*
LV ..... *Left ventricle*

LVEDP ..... *Left ventricular end-diastolic pressure*

LVOT ..... *Left ventricular outflow tract*

mean Δp ..... *Mean pressure gradient*

ms ..... *Millisecond*

mV ..... *Millivolts*

NT-proBNP ..... *N-terminal pro-B-type natriuretic peptide*

NYHA ..... *New York Heart Association*

PAD ..... *Peripheral artery disease*

PCI ..... *Percutaneous coronary intervention*

PPI ..... *Permanent pacemaker implantation*, *Proton pump inhibitor*

PROM ..... *Predicted Risk of Mortality*

PVL ..... *Paravalvular leak*

PW ..... *Pulsed-waved*

SAVR ..... *Surgical aortic valve replacement*

SD ..... *Standard deviation*

SGLT2i ..... *Sodium dependent glucose co-transporter 2 inhibitor (gliflozins)*

STS ..... *Society of Thoracic Surgeons*

SV ..... *Stroke volume*

SVi ..... *Stroke volume index*

TAVI ..... *Transcatheter aortic valve implantation*

TEE ..... *Transesophageal echocardiography*

v_{max} ..... *Transvalvular peak jet velocity*

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Zusammenfassung

Einführung: Die kalzifizierte Aortenstenose (AS) ist das häufigste erworbene Klappenvitium in Industrieländern. Die Beurteilung und Klassifizierung der AS wird heutzutage in erster Linie mittels der Echokardiografie durchgeführt. Ergänzend werden manchmal zur Charakterisierung dieser Patient*innen invasive hämodynamische Analysen bei Herzkatheteruntersuchungen durchgeführt. Ziel dieser Diplomarbeit ist es, die AS mittels invasiver hämodynamischer und echokardiografischer Parameter zu klassifizieren und diese miteinander zu vergleichen.

Methoden: In dieser retrospektiven Datenanalyse wurden Patient*innen mit hochgradiger AS untersucht, die zwischen Mai 2007 und Dezember 2019 an der Universitätsklinik Graz, Abteilung für Kardiologie, eine Transkatheter-Aortenklappenimplantation (TAVI) erhielten. Die Patient*innen wurden hinsichtlich der Bevölkerungsdemografie, Komorbiditäten, Medikation, laborchemischen Parameter sowie echokardiografischen und invasiven hämodynamischen Parameter analysiert. Alle Patient*innen, die die Einschlusskriterien erfüllten, wurden anhand von echokardiografischen und invasiven hämodynamischen Parametern jeweils in milde, moderate und schwere AS bzw. in die nicht-klassischen Subtypen „high-gradient“ (HG), „low-flow, low-gradient“ (LF/LG) und „normal-flow, low-gradient“ (NF/LG) AS eingeteilt und miteinander verglichen.

Ergebnisse: Von 1156 Patient*innen erfüllten nur 275 die Einschlusskriterien, d. h. es lagen sowohl echokardiografische als auch alle notwendigen invasiven Parameter vor. 61,1% (168/275) der mit den beiden Messmethoden ermittelten Klassifikationen stimmten überein. 15,3% (42/275) der echokardiografisch ermittelten HG AS wurden bei der Katheteruntersuchung als LF/LG oder NF/LG AS identifiziert. Umgekehrt wurden 5,1% (14/275) der Patient*innen, die bei der Herzkatheteruntersuchung als HG AS klassifiziert wurden, echokardiografisch als LF/LG oder NF/LG AS identifiziert. Bei den milden und moderaten AS gab es keine Übereinstimmung zwischen den beiden Messmethoden.

Schlussfolgerung: In dieser Studie konnte gezeigt werden, dass die Inkonsistenz zwischen Echokardiografie und Herzkatheteruntersuchung sowohl die milden und moderaten AS als auch die nicht-klassischen AS-Subtypen (HG, LF/LG und NF/LG AS) betrafen.

Beide Untersuchungsmethoden sind wichtige Diagnostika zur Beurteilung des AS-Schweregrades und können sich ergänzen. Die finale Beurteilung integriert auch das klinische Bild der Patient*innen sowie die zusätzlich erforderlichen diagnostischen Tests und muss bei der Festlegung des individuellen Therapieplans sowie der Indikation zum Klappenersatz berücksichtigt werden.

Abstract

Introduction: Aortic valve stenosis (AS) is the most common acquired valvular heart defect in developed countries. Nowadays, the assessment and classification of AS are primarily performed through echocardiography. In some centers, invasive hemodynamic analysis is still performed in cardiac catheterizations to characterize these patients. The aim of this study is to classify AS using invasive hemodynamic and echocardiographic parameters and to compare them with each other.

Methods: This retrospective data analysis reviews patients with severe AS, who received transcatheter aortic valve implantation (TAVI) at the Division of Cardiology, Medical University of Graz between May 2007 and December 2019. Descriptive statistics were obtained regarding population demographics, comorbidities, medication, laboratory parameters, and echocardiographic and invasive hemodynamic parameters. Patients who met the inclusion criteria were classified and compared based on echocardiographic and invasive hemodynamic parameters into mild, moderate, severe AS and into the non-classical subtypes high-gradient (HG), low-flow, low-gradient (LF/LG), and normal-flow, low-gradient (NF/LG) AS.

Results: Of 1156 patients, only 275 met the inclusion criteria, i.e., both echocardiographic and all required invasive parameters were available. 61.1% (168/275) of the classifications determined by the two measurement methods were concordant. 15.3% (42/275) of echocardiographically determined HG AS were identified as LF/LG or NF/LG AS on cardiac catheterization. Conversely, 5.1% (14/275) of the patients classified as HG AS on cardiac catheterization were echocardiographically identified as LF/LG or NF/LG AS.

Conclusion: This study showed that inconsistency between echocardiography and cardiac catheterization mainly concerned the non-classical AS subtypes, i.e., HG, LF/LG, and NF/LG AS. Both examination methods are important diagnostic tools for assessing AS severity and can complement one another. The final assessment also integrates the patient's clinical presentation and other required diagnostic tests that have to be considered when determining the individualized treatment plan and the indication for valve replacement.

1. Introduction

1.1. Aortic Stenosis

1.1.1. Definition

Aortic valve stenosis (AS) is the most common valvular heart defect which occurs by narrowing of the aortic valve. This results in obstructed or decreased blood outflow from the left ventricle (LV), leading to impaired blood supply to the end organs (1).

1.1.2. Epidemiology

The prevalence, cause, and mortality vary among communities. The main reason is the different availability of medical resources. In low- and middle-income countries, especially countries in Central America, the Middle East, and Southeast Asia, the dominant cause of AS is rheumatic fever. Worldwide, approximately 30-35 million people are affected by a rheumatic heart disease with 300,000 new cases and 233,000 fatalities per year (2).
On the contrary, in high-income countries (e.g., in North America, Europe, and Australasia) the dominant cause of AS is degenerative alteration. Globally, a prevalence of 9.4 million patients with calcified AS was estimated in 2019 (3). In high-income countries, the age-standardized prevalence is >200 per 100,000 persons, whereas in low- and middle-income countries the prevalence is much lower (<20 per 100,000). The main reason for this difference might be a higher prevalence of other competing diseases and the lack of medical resources for AS diagnosis (4). The prevalence of undiagnosed moderate and severe valvular disease is about 6% in men and women over the age of 65 years. Specific to AS, the prevalence is 3.5% in patients over 75 years and it is still growing due to the aging population (2).

1.1.3. Etiology

There are three main causes that lead to AS in adulthood. The most common one is the degenerative calcification of the aortic valve. This is particularly the case for patients over the age of 70 years and accounts for approximately 50% of AS in western countries (5). There are associations between vascular atherosclerosis and AS risk factors, such as arterial hypertension, low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp(a)), diabetes

mellitus, smoking, chronic kidney disease, and metabolic syndrome (2,6). Based on current knowledge, the development of AS is an active process which includes endothelial dysfunction, chronic inflammation, lipoprotein deposition, renin-angiotensin system activation, osteoblastic transformation of valvular interstitial cells, and active calcification. In addition, genetic factors also play an important role in the manifestation of AS (6).

In younger adults with AS, there may be an underlying congenital cause. Usually, it is a bicuspid aortic valve, which has a lower ability to distribute and endure mechanical stress, ultimately leading to rapid development of stenosis (6). These patients are mostly between 50 and 70 years old (5).

The third important cause of AS is rheumatic disease. This leads to thickening, commissural fusion, and eventually calcification of the aortic leaflets and narrowing of the valve orifice (7). Rheumatic AS is often associated with mitral valve involvement and aortic regurgitation (AR). Due to the sufficient antibiotic treatments for streptococcal infections nowadays, rheumatic disease is a minor cause of AS in developed countries; nevertheless, it still remains a significant cause worldwide (5).

Mediastinal radiation can also cause fibrosis, and eventually calcification of the valve leaflets resulting in AS (2).

1.1.4. Pathophysiology

A normal aortic valve area (AVA) in adults is 2.6-3.4 cm^2. If AVA is less than 1.5 cm^2, hemodynamic effects begin to appear, meaning an increased systolic pressure gradient and peak velocity (5).

The gradually increasing obstruction leads to a pressure overload on the LV. To overcome the increased pressure gradient and to maintain the LV contractility a concentric hypertrophy of the LV occurs as a key adaptive mechanism. This condition may exist for many years without a reduction in cardiac output (CO), or development of LV dilation. However, eventually, this ventricular hypertrophy brings adverse consequences: LV systolic function declines due to increased afterload contributed by reduced systemic arterial compliance in elderly patients. Moreover, diastolic dysfunction, particularly elevated LV end-diastolic pressure (LVEDP), and irreversible myocardial fibrosis develop resulting in diminished compliance of LV and limited preload reserve. In addition, the hypertrophic LV requires a higher oxygen supply. As a result of the impaired coronary blood flow caused by the increased end-diastolic pressure, and the increased oxygen demands of the myocardium,

ischemia occurs. This precipitates angina, even without an underlying obstruction of coronary arteries (2,6).

1.1.5. Symptoms

The appearance and severity of clinical symptoms in patients with AS can vary widely. Usually, they appear in a later course, when severe AS is already present, i.e., AVA has narrowed to < 1 cm^2. However, patients with a severe AS may also be asymptomatic for many years because the hypertrophic LV is able to produce elevated intraventricular pressure to maintain a normal stroke volume. The three cardinal symptoms of AS are exertional dyspnea, angina pectoris, and syncope (2).

The elevated LVEDP present in AS patients causes an increased pulmonary capillary pressure. Along with the reduced LV compliance this leads to dyspnea, especially on exertion (2).

75% of the patients with severe AS report angina pectoris which results from the disproportionally increased myocardial oxygen demands and the reduced oxygen supply. This occurs even without the presence of coronary artery disease (CAD), however, a coexistence of CAD is common (2).

Syncope and dizziness are provoked by diminished cerebral perfusion during physical activity. This can be observed, e.g., in patients standing up due to impaired autonomic responses. Among others, malfunction of the baroreceptors in the LV is an important factor inducing vasodilation in peripheral arteries and thus arterial hypotension. Other causes of syncope and dizziness are arrhythmia and reduced CO (5,8).

1.1.6. Natural History

Patients with severe AS have a latent asymptomatic phase that can last individually long. Once symptoms develop, the disease usually progresses fast. There are several features which predict the development of symptoms and adverse outcomes (6). These include clinical, echocardiographic, and laboratory factors which are described in table 1.

Table 1: Predictors of Symptom Development and Adverse Outcomes Adapted from (6)

Clinical	Older age, presence of atherosclerotic risk factors
Echocardiography	The extent of valve calcification and AVA, maximal aortic transvalvular velocity, amount of LVEF, increase of gradient with exercise, excessive LV hypertrophy, abnormal longitudinal LV function, pulmonary hypertension
Exercise testing	Unmasking of symptoms during exercise in physically active patients predicts a very high likelihood of symptom development within twelve months. Abnormal blood pressure response and/or ST-segment depression have a lower positive predictive value.
Biomarkers	Elevated plasma levels of natriuretic peptides

Symptomatic patients with severe AS have a very poor prognosis, the 2-year survival rate is less than 50% (5). Sudden deaths occur mostly in patients with symptomatic severe AS and rarely in asymptomatic patients (2).

1.2. Diagnosis

Diagnosis of AS begins with a thorough gathering of the patient's medical history including family medical history, all cardiovascular risk factors, comorbidities, and current symptoms. Frequently, the initial symptoms are exertional dyspnea and fatigue. However, it can be difficult to verify the presence of symptoms. It should be considered that elderly patients may deny having symptoms or have unconsciously reduced their activity to avoid the onset of symptoms. Hence, specific questions, such as noticeable lifestyle changes or a decreased resilience with consequently decreased physical activity, are useful to evaluate and objectify the patient's symptoms (9).

1.2.1. Physical Examination

As AS progresses, stroke volume gradually decreases, as does systolic pressure. Consequently, the carotid arterial pulse rises slowly and has a delayed peak, a so-called pulsus tardus et parvus. On physical examination, however, this pulse quality is usually masked due to arterial stiffness in elderly patients (2).

The LV impulse may be broadened because of its concentric hypertrophy in the later course of AS. When the LV is dilated, the impulse may also be laterally displaced (1).

The main finding of AS is a systolic murmur on auscultation. Because this murmur is related to the increased transvalvular pressure gradient and jet velocity, it has crescendo-decrescendo, harsh, and rasping characteristics. Its punctum maximum is in the second right intercostal space, and it is transmitted to the carotid arteries, as well as to the apex of the heart. This radiated murmur is difficult to distinguish from a co-existing mitral regurgitation. In severe AS, the second heart sound is often paradoxically split. Normally, aortic valve closure precedes minimally, however, due to the prolonged outflow phase in AS, the aortic valve closes after the pulmonic valve (2,6).

1.2.2. Chest X-ray

Due to the concentric hypertrophy of the LV, the cardiac apex is rounded in the frontal projection. Also, a dilated ascending aorta instantaneous after the valve stenosis is apparent in this view. In the lateral projection, the LV is slightly enlarged posteriorly into the mediastinum and the aortic valve calcification can be seen in the middle of the heart. Overall, the cardiac shadow is usually not enlarged in chest X-rays. If an enlargement of the heart is present, LV dysfunction or AR already exists (1,2).

1.2.3. Electrocardiogram (ECG)

In approximately 80% of the patients with severe AS LV hypertrophy is evident on ECG (6). This is determined via the Sokolow-Lyon index, in which the largest S wave in V1 or V2 lead and the largest R wave in V5 or V6 lead are added together. If the summation of both waves is equal to or higher than 3.5 mV, LV hypertrophy is present (10). However, the absence of a hypertrophy sign in the ECG does not exclude a severe AS. Furthermore, there may be other ECG signs, such as left axis deviation, or left atrial enlargement, which produces broad, bifid P waves in lead II and enlarges P with a negative portion in lead V1.

Also, a left bundle branch block, whose criteria are prolonged QRS (>120 ms), dominant S wave in V1, and broad monophasic or M-shaped R wave in the lateral leads I, aVL, V5-6, can be detected. At a late stage of AS, ECG may also reveal atrial fibrillation (6,10).

1.2.4. Echocardiography

Echocardiography is the most important diagnostic tool and ultimately confirms the presence of AS. It allows the assessment of aortic valve morphology, concomitant AR and other valve pathologies, severity of AS, LV function, and LV wall thickness.

Furthermore, echocardiography can be used to evaluate whether the LV outflow obstruction is at valvular (such as AS), subvalvular (such as subaortic stenosis or hypertrophic cardiomyopathy), or supravalvular level. The latter is very rare and usually occurs in congenital diseases such as Williams syndrome (11).

Commonly, transthoracic echocardiography is adequate for ascertainment of the above-mentioned conditions and therefore gold standard for the initial AS diagnosis. However, in some cases, when image quality is suboptimal, transesophageal echocardiography (TEE) is required.

The parameters required to determine the AS severity are transvalvular peak jet velocity (v_{max}), mean pressure gradient (mean Δp), and aortic valve area (AVA). A combination of imaging (B-mode) and the Doppler technique is used for this purpose. In addition, using the correct acoustic window is a crucial requirement (11,12).

Peak Jet Velocity

The AS jet velocity is measured by continuous-waved (CW) Doppler ultrasound because this technique allows accurate identification of the highest blood flow velocity in the direction of the ultrasound beam. The disadvantage of CW Doppler is that it cannot determine the exact location of the measured velocity. However, in this case, this is negligible because the highest flow velocity is where the outflow tract and aortic valve are the narrowest (2). Most frequently the apical 5-chamber view is used, but also the suprasternal and right parasternal views yield the highest velocity for measuring the aortic peak velocity (13).

Mean Pressure Gradient

The mean Δp is calculated directly from the velocity by means of the simplified Bernoulli equation:

$$\Delta p = 4v^2 \qquad [1]$$

Aortic Valve Area

AVA is calculated by means of the continuity equation. It is based on the fact that the same stroke volume (SV) that flows into the left ventricular outflow tract (LVOT) also flows through the aortic valve orifice:

$$SV_{AVA} = SV_{LVOT} \qquad [2]$$

Since the SV is defined as any cross-sectional area (CSA) multiplied with the velocity time integral (VTI) – both terms explained below – the equation ($SV = CSA \times VTI$) can be rewritten into:

$$AVA \times VTI_{AVA} = CSA_{LVOT} \times VTI_{LVOT} \qquad [3]$$

For the calculation of AVA, the equation *[3]* must be transformed into:

$$AVA = \frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_{AVA}} \qquad [4]$$

Assuming that the LVOT is cylindrical the CSA_{LVOT} is calculated with the formula for a circular area:

$$A = \pi \times r^2 \qquad [5]$$

Therefore, the diameter of LVOT is needed, which is measured in the parasternal long axis view.

In order to determine LVOT velocity and VTI, pulsed-waved (PW) Doppler is used. In contrast to CW Doppler, PW Doppler can identify the location of the flow velocity. Using the 5-chamber view, the sampling volume of the PW Doppler line is placed in the LVOT just before the aortic valve orifice. For obtaining VTI_{AVA} CW Doppler is needed. In both

ways, it records the flow as a spectral curve. The area under the curve is defined as the VTI and describes how far the blood volume has moved in a certain time (in this case during the systole). This calculated AVA is the so-called effective orifice area (EOA). It is the narrowest area between LV and aorta and is defined by flow velocity. However, this does not correspond to the geometric orifice area (GOA) where the aortic valve leaflets are located. GOA is more proximal and always greater or equal to EOA (11–13).

The echocardiographic classification based on the aforementioned parameters is explained in section 2.2.1.

1.2.5. Stress Tests

Exercise stress testing is an additional recommended diagnostic measure in patients with asymptomatic severe AS. It helps to unveil symptoms or abnormal blood pressure responses and is also useful for risk stratification. These exercise tests determine the patient's capacity, which is particularly important in physically active patients. Exercise testing is considered safe in asymptomatic patients as it is performed under constant supervision by a physician with ECG and blood pressure monitoring. Further important findings during these tests can be exercise-induced arrhythmia or ST-segment abnormalities (6,14).

Exercise stress echocardiography is used to assess hemodynamic changes and to find the origin of the unspecific symptom dyspnea. Possible reasons could be mitral regurgitation, increased aortic mean pressure gradient, or pulmonary artery pressure. In patients with symptomatic AS and/or reduced LV function (EF <50 %) exercise testing is contraindicated (15).

The use of low-dose dobutamine stress echocardiography is recommended in patients with low-flow, low-gradient AS with impaired LV function to assess if they have a flow or contractile reserve. This helps to determine the true severity of AS and the operative risk stratification (15).

1.2.6. Cardiac Computed Tomography (CCT) and Cardiovascular Magnetic Resonance (CMR)

Because of the high spatial resolution of CCT, it provides further information about the aortic valve anatomy, the calcification of valve leaflets, and the annulus size, shape, and its distance to the coronary ostia. It serves as an additional diagnostic tool that helps in evaluating and grading AS, especially in patients with low-flow, low-gradient AS and preserved EF or in patients with poor echocardiography window and uncertain AS severity (13,16).

The calcification is quantified by the calcium score and the values are expressed in arbitrary units using the Agatston method (AU). If the calcium score is < 1600 AU in men and < 800 AU in women, a severe AS is unlikely; calcium score ≥ 2000 AU in men and ≥ 1200 AU in women, a severe AS is likely; calcium score ≥ 3000 AU in men and ≥ 1600 AU in women, a severe AS is very likely (6).

Nevertheless, CCT alone is not recommended for diagnosing AS because it has no information about the hemodynamics and can only determine GOA, and thus does not accurately represent the AS severity (13). However, it plays an important role in the integrated approach to grading AS severity (see figure 2, section 2.2.). Several studies have shown that there is a correlation between high levels of valve calcification and severe AS and that CCT is able to predict disease progression and adverse outcomes (13,16,17). Furthermore, it plays a major role in the pre-procedural work-up for TAVI as well as for SAVR. As the multi-slice computed tomography (MSCT) provides an image of the aortic valve, annulus, coronary arteries, and a detailed mapping of the peripheral vasculature, the interventionist can make accurate decisions about the approach and route of the TAVI procedure, the appropriate prosthesis size, and the need for prior coronary artery revascularization. Essential for SAVR preparation is the exclusion of a severely calcified ascending aorta, the so-called porcelain aorta, that can be determined by MSCT (18).

Concerning CMR, this imaging modality is able to acquire not only anatomical but also hemodynamic measurements throughout the entire heart cycle. Moreover, it can detect and quantify myocardial fibrosis (13,16). Despite these benefits, there are still decisive disadvantages that limit the usage of CMR for diagnosing AS, such as lower spatial resolution compared to CCT, imaging artifacts in case of implanted medical devices, higher costs, and longer scan times (13). Compared with CCT, CMR has less evidence and thus is not yet well established in the assessment and quantification of AS (19).

1.2.7. Cardiac Catheterization

Retrograde left ventricular catheterization, which used to be the gold standard for determining AS severity, is nowadays only performed when there are discrepancies between clinical symptoms and non-invasive findings (16). As with echocardiography, hemodynamic parameters are measured invasively including Δp and CO. Typically, a double-lumen (fluid-filled) catheter is used, with the distal ostium in the LV and the proximal ostium in the ascending aorta, registering maximum systolic LV pressure and maximum systolic aortic pressure simultaneously. The difference between these two peak pressures becomes the transvalvular pressure gradient, the so-called peak-to-peak gradient (20). However, since these peak pressures occur with a time lag, the peak-to-peak pressure difference is not exactly measurable at any moment and does not correspond to the instantaneous maximum pressure gradient in the echocardiography (figure 1). The only comparable value is the mean pressure gradient, which is the surface integral between the LV pressure curve and the aortic pressure curve and is therefore used for the classification of AS (5). Furthermore, the CO needs to be measured so that the AVA can be calculated by means of the Gorlin equation (13).

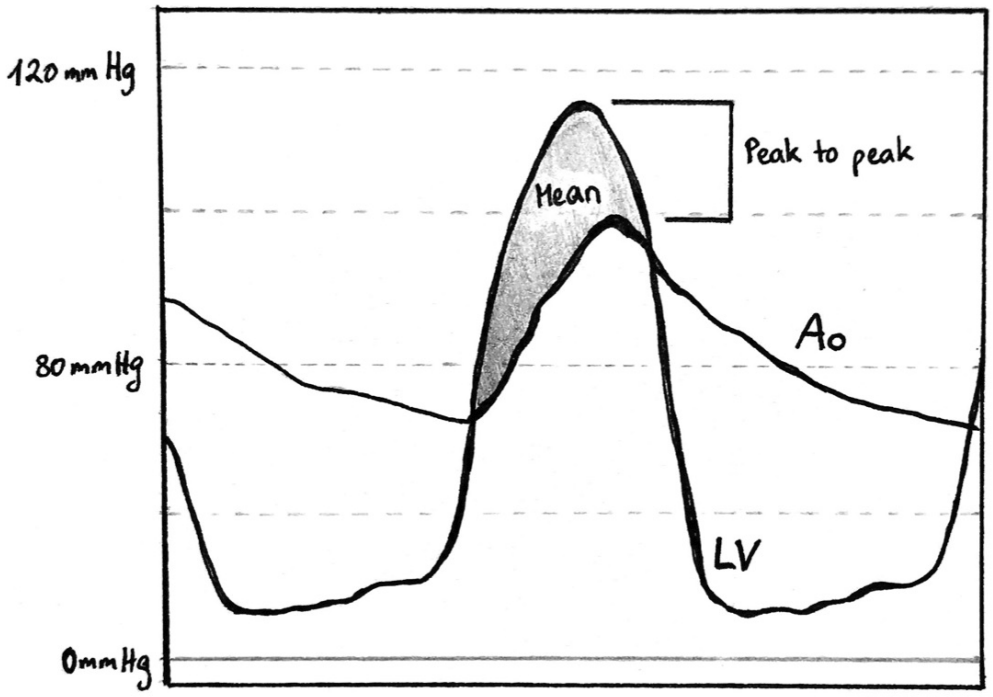

Figure 1: Peak-to-peak gradient and integrated gradient between left ventricular (LV) and aortic (Ao) pressure (mean pressure gradient). Note the time lag between the two peaks. Adapted from (55).

1.3. Therapy

1.3.1. Management of Symptomatic versus Asymptomatic AS

Because of the extremely high mortality rate of untreated severe AS (50% mortality at one year, more than 90% at five years as proven in the prospective study PARTNER trial (21,22)) an accurate diagnosis and therapy are essential. In general, an already symptomatic AS has a poor prognosis and needs to be treated promptly (one to three months after symptom onset (2)). This is done either surgically (surgical aortic valve replacement (SAVR)) or percutaneously (transcatheter aortic valve implantation (TAVI)). In contrast, the management of asymptomatic AS is controversial. Basically, in these cases an intervention is recommended if a severe AS and systolic LV dysfunction (LVEF < 50%) is present without any other cause and when symptoms develop during exercise testing. For the decision whether an intervention is indicated or not, an individualized assessment with careful consideration of all risks and benefits by a heart team (clinical cardiologist,

interventional cardiologist, cardiac surgeon, imaging specialist with expertise in interventional imaging, cardiovascular anesthesiologist) is required. For this, evaluation of unfavorable prognostic factors (as described in table 1, section 1.1.6.) is helpful. If one or more of these factors are present and the procedural risks are low, early intervention in patients with asymptomatic severe AS is recommended, otherwise watchful waiting is the safer option. However, as soon as symptoms appear, immediate intervention is indicated. In these cases, balloon valvuloplasty is also available as an alternative acute measure (16,21,23).

1.3.2. Pharmacological Therapy

According to the latest guidelines, there is no pharmacological therapy that counteracts the progression of degenerative AS. The only effective therapy, which improves the prognosis, is an aortic valve replacement/implantation (16). However, patients, who are waiting for the replacement or for whom an intervention is contraindicated, should still be treated for commonly concomitant heart failure (16). The heart failure therapy usually includes angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, aldosterone-antagonists, and diuretics which should be administered very carefully to avoid adverse hemodynamic effects (5,24). The treatment of co-existing hypertension is also essential since it is a significant factor of valve calcification progression and is associated with higher rates of mortality and ischemic cardiovascular events. However, the dosage of the antihypertensive drugs must be adjusted carefully to avoid hypotension (24,25).

Although the pathogenesis of degenerative AS is similar to vascular atherosclerosis, studies have shown that statins have no favorable effect on the progression of valvular calcification or AS-related events and are therefore not recommended as pharmacological therapy for AS. Nevertheless, statins are indicated in patients with concomitant atherosclerotic cardiovascular disease (26).

1.3.3. Balloon Aortic Valvuloplasty (BAV)

Balloon aortic valvuloplasty, which was the first percutaneous therapy for AS, only brings short-time amelioration of symptoms and hemodynamic measures. The percutaneous approach for BAV is usually via the femoral artery. A balloon catheter is positioned and

inflated across the stenotic aortic valve resulting in fracturing calcific deposits on the leaflets, separation of the fused commissures, and stretching of the aortic annulus. This leads to an increase in AVA and a decrease in the pressure gradient, thus improving severe AS. However, in about 80% of the cases, complaints and restenosis of the aortic valve recur after six to twelve months, and therefore BAV is not recommended as a definitive therapy for AS. In addition, this procedure also entails risks and complications such as stroke, myocardial infarction, severe aortic regurgitation, LV perforation, serious vascular complications, and death. BAV is mainly considered a bridge to the definite valve replacement in hemodynamically unstable patients. It also plays an important role for patients who are not suitable for SAVR and TAVI and those who have a severe AS and need urgent high-risk non-cardiac surgery (21,25,27).

1.3.4. SAVR

For more than 60 years SAVR has been the gold standard therapy for severe AS. For the best access to the heart and the aortic valve, the general approach is a median sternotomy. The surgery requires a full cardiopulmonary bypass and a cardiac arrest. In the following, the aorta is opened and the calcified aortic annulus and valve leaflets are removed. Afterwards, a prosthetic valve is inserted. Basically, there are two groups of prosthetic valves: the mechanical valve, and the biological valve. Concerning mechanical prostheses, most of them are bileaflet and are made from pyrolytic carbon. One of the greatest advantages of a mechanical valve is that it will not gain any structural changes for a lifetime and therefore it is especially used in patients younger than 65 years and with good hemodynamics. However, it must be mentioned that mechanical prosthesis has a risk of blood clotting and requires lifelong anticoagulation, usually with a coumarin derivate, e.g., warfarin or phenprocoumon. This poses a risk of bleeding, which demands caution, especially in elderly patients.

Biological prostheses, in contrast, are made from porcine valve or root or from bovine pericardium. There are two ways of implanting the biological valves: either each valve leaflet is fixated on a stent, which facilitates the valve implantation, or the valve is implanted without a stent. Compared to the stented bioprosthesis, the stentless version provides perfect hemodynamics and thus is superior in patients with smaller aortic annulus. Furthermore, it might even have better durability, however, its implantation is more difficult than the stented

valve. Additionally, a major advantage of all bioprostheses is that there is no need for lifelong anticoagulation (21,28).

Generally, biological valve prostheses are mainly recommended in patients older than 65 years due to their limited durability when compared to mechanical prostheses. Structural deterioration of bioprostheses occurs eight to 20 years after surgery (21). Johnston D. et al. investigated the long-term durability of the Carpentier-Edwards Perimount bioprosthesis made from bovine pericardium. It showed excellent durability of 17 years. However, this study also underlines the fact that there is no uniform definition of valve deterioration and that it is therefore difficult to define the durability of bioprostheses in general (29).

Over the years, there have been advances and improvements in the field of SAVR. Since conventional open surgery is associated with a complete division of the sternum, large wounds, pain, and long recovery time, two new minimally invasive approaches have been developed: the right anterior mini-thoracotomy and the mini-sternotomy (28). Also, since the success of TAVI, sutureless valves have gained importance in the field of SAVR. By eliminating the need for surgeons to secure the prosthesis with sutures in the aortic annulus, a minimally invasive surgical approach is enabled and the cross-clamp time of the aorta and thus the operating time can be shortened. This in turn leads to reduced perioperative morbidity and better postoperative recovery (30). In addition, the expanded clinical practice of reintervention after SAVR (TAVI within a degenerated surgically implanted bioprosthesis) is leading to a shift in age cutoffs. There is a clear trend toward SAVR with bioprostheses in patients of younger age (31).

1.3.5. TAVI

Initially, transcatheter aortic valve implantation has been established for patients who have a high risk for surgery or are considered inoperable. As the average age of patients with AS has increased to date – most are octogenarians – and carry serious concomitant diseases and high or prohibitive surgical risk, the number of TAVI procedures has risen accordingly (21). The implanted transcatheter heart valves are bioprostheses with three integrated leaflets in a stainless-steel stent. There are two different types of valves: a self-expanding bioprosthesis with valve leaflets made from porcine pericardium (Medtronic CoreValve), and a balloon-expandable bioprosthesis with bovine pericardium valve leaflets (Edwards SAPIEN) (32). Both valves had improvements in design and technology and are now available in their third generation (25).

Concerning the access route for this procedure, there are various options. The most frequently used and experienced one is the transfemoral route. However, in case of peripheral vascular diseases or other contraindications for the transfemoral access, there are alternatives such as transapical, transaxillary/subclavian, and transaortic routes.

In transfemoral TAVI, the procedure is as follows: After puncturing the femoral artery (either percutaneously or with prior surgical exposure), normally a pigtail catheter is inserted and placed in the aortic root and the aortic valve is passed retrogradely with a wire. If a balloon-expanded valve prosthesis is implanted, a balloon valvuloplasty is usually performed in advance to loosen calcifications and create space for the prosthesis. For this purpose, a temporary pacemaker is inserted beforehand to stimulate tachycardia for a short phase and thus ensure a brief arrest of cardiac ejection. This is necessary to enable a stable position of the balloon. In contrast to this, implantation of the self-expanding valve can be performed on the normally beating heart. After the procedure, the temporary pacemaker is usually left in place for a few days as there is still a risk of atrioventricular block developing, especially with self-expanding prostheses (33).

In the transapical valve implantation method, the access route is antegrade. Usually, this procedure is performed under general anesthesia or, in case of high risk of anesthesia, while awake under high epidural anesthesia. An anterolateral mini-thoracotomy is performed in the fifth or sixth intercostal space followed by a longitudinal opening of the pericardium so that an apical puncture can be made with the insertion of a guide wire. Finally, a sheath is advanced anterogradely over the aortic valve into the ascending aorta. The further steps are analogous to the transfemoral approach (33).

1.3.6. TAVI versus SAVR

For the choice of intervention, risk stratification is required to accurately assess the risks and benefits of the treatment for each patient individually. Current guidelines recommend the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) score and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) for risk estimation. These surgical risk scores divide patients into low-, intermediate- and high-risk patients, however, they do not include other important factors such as frailty, other major organ failures such as liver disease, and specific anatomical features such as porcelain aorta, previous chest radiation, and mitral annular calcification. These factors also have a crucial impact on both procedure models and need to be taken into account (16).

Multiple trials have assessed both TAVI and SAVR for their efficacy, complications, and mortality. They have shown that TAVI is non-inferior to SAVR in high- and intermediate-risk patients in a follow-up period of five years. Even more recent trials, namely the PARTNER 3 trial (evaluating the third-generation balloon-expandable SAPIEN 3 valve) and the Evolut Low Risk trial (surveying the self-expanding supra-annular bioprosthesis (CoreValve, Evolut R, Evolut PRO)) indicate the same in low-risk patients in a follow-up period of two years (16,34,35).

Nevertheless, there are some complications that occur more frequently after TAVI than SAVR. That includes vascular complications, paravalvular regurgitation/leak (PVL), and cardiac conduction system disorders with the necessity of permanent pacemaker implantation (PPI). On the contrary, SAVR is more associated with severe bleeding, acute kidney injury, and new-onset atrial fibrillation as postprocedural complications (16).

Paravalvular Regurgitation

Moderate and severe PVL, which occur particularly after implanting a self-expanding valve (25), are associated with poorer outcomes and a higher 1-year mortality rate. Factors that predict a PVL may include undersizing or malpositioning of the prosthesis or incomplete contact of the prosthesis with the aortic annulus. However, in the new generation of valve prostheses, e.g., Edwards SAPIEN 3 or CoreValve Evolut PRO, improved valve designs reduce these factors, especially the valve undersizing, and thus the risk of PVL (36).

Permanent Pacemaker Implantation (PPI)

Conduction disorder and PPI are among the most common complications after TAVI. Again, the incidence is higher with the implantation of self-expanding valves. The most important predictor for PPI is the history of a right bundle branch block, but also a left anterior fascicular block. Furthermore, the quantification and location of annulus calcification and procedural features play an important role as predictors. Although studies have demonstrated that PPI does not increase mortality compared to SAVR, it is still problematic inducing many other complications and longer and more frequent hospitalizations (36).

Stroke

One of the most serious complications that can occur after aortic valve replacement is stroke. It not only increases mortality but also, depending on its severity, impairs the quality of life. Early studies, where first-generation devices were used, had shown an increased stroke

incidence after TAVI. However, more recent trials have proven that with the advent of newer and improved devices, stroke rates have decreased in favor of TAVI (36).
In fact, TAVI also has many advantages. On one hand, the transfemoral procedure can be performed without general anesthesia, and on the other hand, TAVI is associated with a short hospital stay and a rapid recovery time (16).
Moreover, studies have proven a better hemodynamic performance with TAVI than with SAVR. Larger AVA and lower mean pressure gradients were measured after TAVI, which remained consistent after a 2-year follow-up (36).

1.4. Aim of the Study

For many years cardiac catheterization has been the gold standard method for assessing the severity of AS by measuring hemodynamic parameters invasively. Nowadays, this method has been mostly replaced by echocardiographic assessment.
Therefore, the aim of this study is to compare invasive and non-invasive parameters and evaluate if the classifications of AS are consistent.

2. Material and Methods

2.1. Study Design

This retrospective data analysis reviews all patients with severe AS, who received a transcatheter aortic valve implantation (TAVI) at the Division of Cardiology, Medical University of Graz between May 2007 and December 2019. All patients gave their consent to use their data for scientific evaluation. The study has been approved by the ethics committee of the Medical University of Graz (27-114 ex 14/15).

The data collection was carried out via the hospital information system (MEDOCS) and added to the TAVI Registry of Graz. This included patients' comorbidities, especially chronic obstructive lung disease (COPD) stage IV, cardiovascular diseases (CVD), like CAD with percutaneous coronary intervention (PCI), and peripheral artery diseases (PAD), arterial hypertension, diabetes, dyslipidemia, end-stage renal disease, and heart failure. The latter was classified according to the New York Heart Association (NYHA)-classification (5). Equivalently, the extension of angina pectoris was assessed using the Canadian Cardiovascular Society (CSS)-classification (5). Furthermore, the patients' medications, particularly medication for heart failure, anticoagulants/platelet aggregation inhibitors, statins as well as oral antidiabetics and insulin, and the routinely performed pre- and post-procedural diagnostics were gathered. These comprised laboratory tests, echocardiography, and electrocardiograms, which were performed shortly before and after TAVI as well as follow-up inquiries three and six months after the procedure. Lastly, invasive hemodynamic parameters obtained from cardiac catheterization, data of the procedure itself, and the 1-year outcome were also collected and evaluated.

We focused on echocardiographic and invasive hemodynamic parameters before implanting the aortic valve prosthesis and compared these two methods regarding the classification of AS subtypes.

In the descriptive analysis for the characterization of the study population (section 3.1.), no inclusion criteria were defined. Despite the incompleteness of patient data, all available parameters were evaluated.

However, for the analysis of AS classification (section 2.2), inclusion criteria were set. These included male and female patients containing a complete set of echocardiographic (v_{max}, mean Δp, AVA, SVi, and EF) and invasive hemodynamic parameters (mean Δp, AVA, and SVi). The exclusion criteria were an incomplete set of the above-mentioned parameters.

2.2. Classification of AS Subtypes

2.2.1. Echocardiography

For assessing the severity of valve calcification echocardiography is the key diagnostic tool. There are three primary parameters that are used for the clinical evaluation of AS severity, namely mean transvalvular pressure gradient (mean Δp), peak transvalvular velocity (v_{max}), and aortic valve area (AVA) (16). The cut-off values in the classification of aortic stenosis are not uniform in the literature. Especially in the classification of mild and moderate AS, there are discrepancies between the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines. However, according to the latest updates, both agree on the cut-off values for severe AS (12,16,37).

Table 2: Classification of AS Adapted from the ACC/AHA Guidelines (12,16,37)

Parameters	**Mild AS**	**Moderate AS**	**Severe AS**
v_{max} (m/s)	2.6 – 2.9	3.0 – 3.9	≥ 4.0
mean Δp (mmHg)	< 20	20 – 39	≥ 40
AVA (cm^2)	> 1.5	1.1 – 1.5	≤ 1.0

Usually, these three criteria should be concordant as shown in table 2. In case of inconsistency, further investigations are necessary. This includes assessment of left ventricular function (LVEF), size, and wall thickness as well as the stroke volume index (SVi), leading to four subtypes of aortic stenosis:

- **High-gradient AS** with mean $\Delta p \geq 40$ mmHg, or $v_{max} \geq 4.0$ m/s – in this case, severe AS can be assumed regardless of flow (defined by SVi) and LVEF.
- **Low-flow, low-gradient AS with reduced EF** (≤ 50%) with AVA ≤ 1 cm^2, mean $\Delta p < 40$ mmHg and SVi ≤ 35 ml/m^2 – in this case a low-dose dobutamine

stress-echocardiography is recommended to distinguish a truly severe AS from a pseudosevere AS. For the latter, flow and AVA (> 1 cm^2) increase after administration of dobutamine, while patients with truly severe AS have neither flow nor contractile reserve.

- **Low-flow, low-gradient AS with preserved EF** (> 50%) with AVA ≤ 1cm^2, mean Δp < 40 mmHg and SVi ≤ 35 ml/m^2 – this occurs mainly for elderly patients with a small and hypertrophic left ventricle and arterial hypertension. However, there may also be other explanations or conditions associated with a low stroke volume, e.g., moderate/severe mitral regurgitation, severe tricuspid regurgitation, severe mitral stenosis, large ventricular septal defect, and severe right ventricular dysfunction. Therefore, diagnosing severe AS with these echocardiographic parameters can be challenging and requires a careful exclusion of measurement errors. In this case, CCT provides additional information of the valve calcification degree through a calcium score which helps to identify the true AS severity.
- **Normal-flow, low-gradient AS with preserved EF** (> 50%) with AVA ≤ 1cm^2, mean Δp < 40 mmHg and SVi > 35 ml/m^2 – this constellation of echocardiographic parameters is considered moderate AS (16).

In this study, the echocardiographic classification of AS subtypes was performed according to the flowchart scheme from the latest ESC/EACTS Guidelines (figure 2) by using the gathered echocardiographic parameters. Any AS with a mean $\Delta p \geq 40$ mmHg or a $v_{max} \geq 4.0$ m/s is classified as a high-gradient AS regardless of AVA and flow status. Cases with a mean Δp < 40 mmHg and v_{max} < 4.0 m/s are either classified as a moderate AS if AVA is greater than 1 cm^2 or a low-gradient AS if AVA is equal to or less than 1 cm^2. The latter is further subdivided depending on the flow status. If the SVi is equal to or less than 35 ml/m^2, it refers to a low-flow, low-gradient AS with reduced or preserved EF (≤ 50% or > 50%). However, if SVi is greater than 35 ml/m^2, it is a normal-flow, low-gradient AS.
Mild AS is defined by a mean Δp < 20 mmHg, v_{max} < 3 m/s, and AVA > 1 cm^2 as described in table 2. If either mean Δp or v_{max} is greater than these values, the AS is classified as moderate.

2.2.2. Cardiac Catheterization

Hemodynamic measurements were performed during the cardiac catheterization, before implanting the aortic valve. Parameters mean Δp, AVA, and SV were obtained to determine the classification of AS.

The AS classification of hemodynamic parameters was performed without the values for v_{max} and EF.

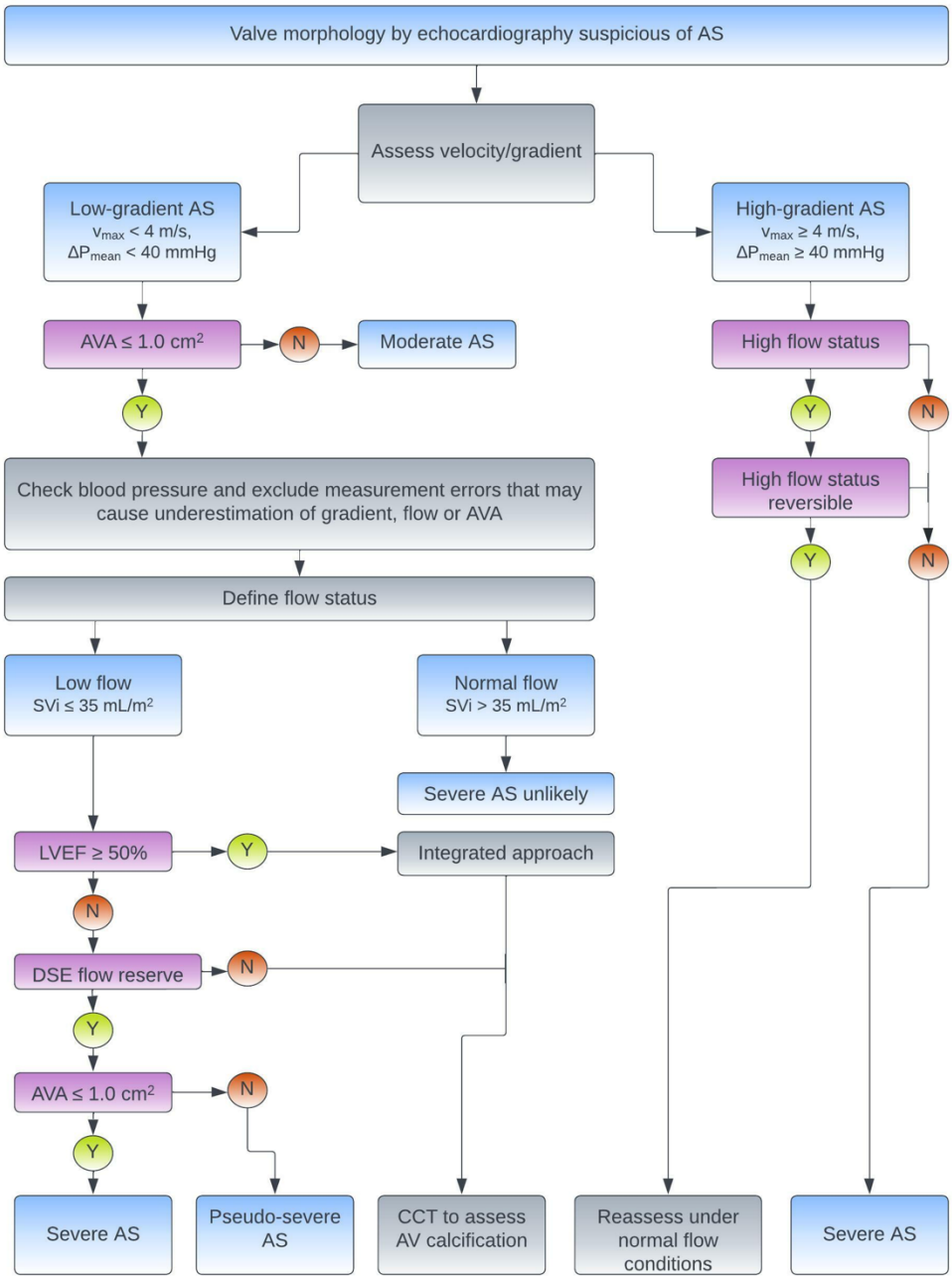

Figure 2: Assessment of AS severity adapted from the ESC/EACTS Guidelines 2021 (16)

2.3. Statistics

The statistical analysis was performed with IBM SPSS Statistics version 27 (38).

Descriptive analysis was carried out by presenting quantitative values with mean ± standard deviation (SD) in case of normal distribution, or with median and an interquartile range (IQR), labeled as Median [IQR] if parameters were not normally distributed. Qualitative values are described with absolute numbers and percentages (n (%)).

An independent sample t-test was performed to identify if there was a significant difference in mean age between men and women.

Kaplan-Meier curves were constructed to show the 30-days, 1-year, and 13.5-year mortality (the latter corresponds to the entire study period from 2007 to 2019) of the entire study population. Also, a 3-year mortality analysis in terms of echocardiographic and invasive hemodynamic AS classification was carried out. A log-rank test was performed to determine whether significant differences exist between the AS subtypes concerning all-cause mortality.

A p-value < 0.05 indicates statistical significance.

Figures have been created in IBM SPSS Statistics version 27 (38).

3. Results

3.1. Characterization of the Study Population

Of the 1156 patients included in this study, 691 (59.8%) were female and 465 (40.2%) were male (figure 3). This patient cohort comprised elderly patients with an average age of 81.5 ± 6.3 years. The mean age in female patients was slightly higher (82.1 ± 5.6 years) than in male patients (80.4 ± 7.1 years). There was a statistically significant difference between the mean age of men and women, with the mean age of male patients being 1.7 years (95% - CI [0.94, 2.74]) lower than female patients, $t(834.86) = 4.36$, $p < 0.001$. The age distribution is shown in figure 4. It is apparent that the age distribution is the same for both sexes.

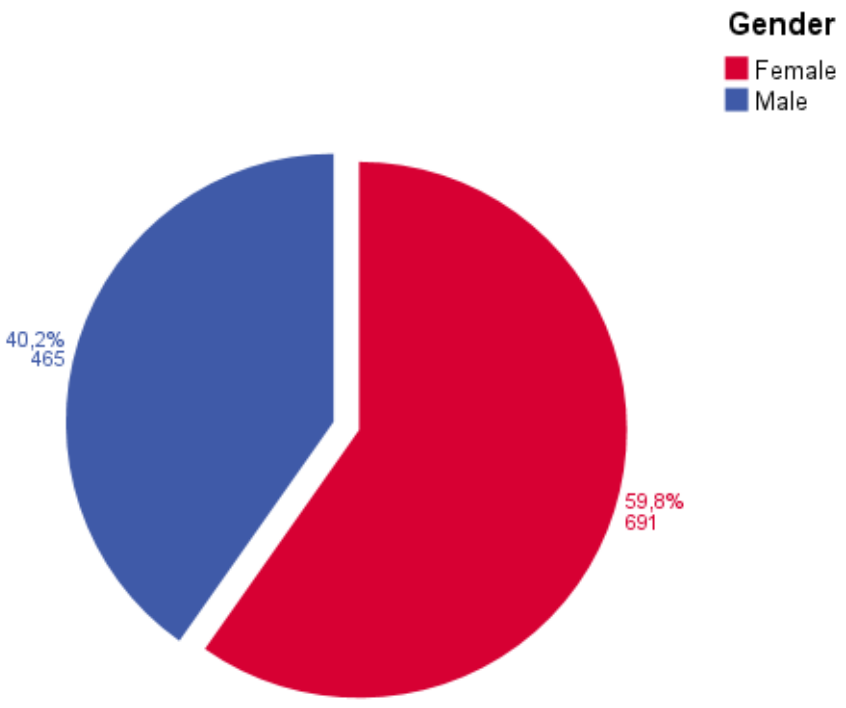

Figure 3: Gender Distribution

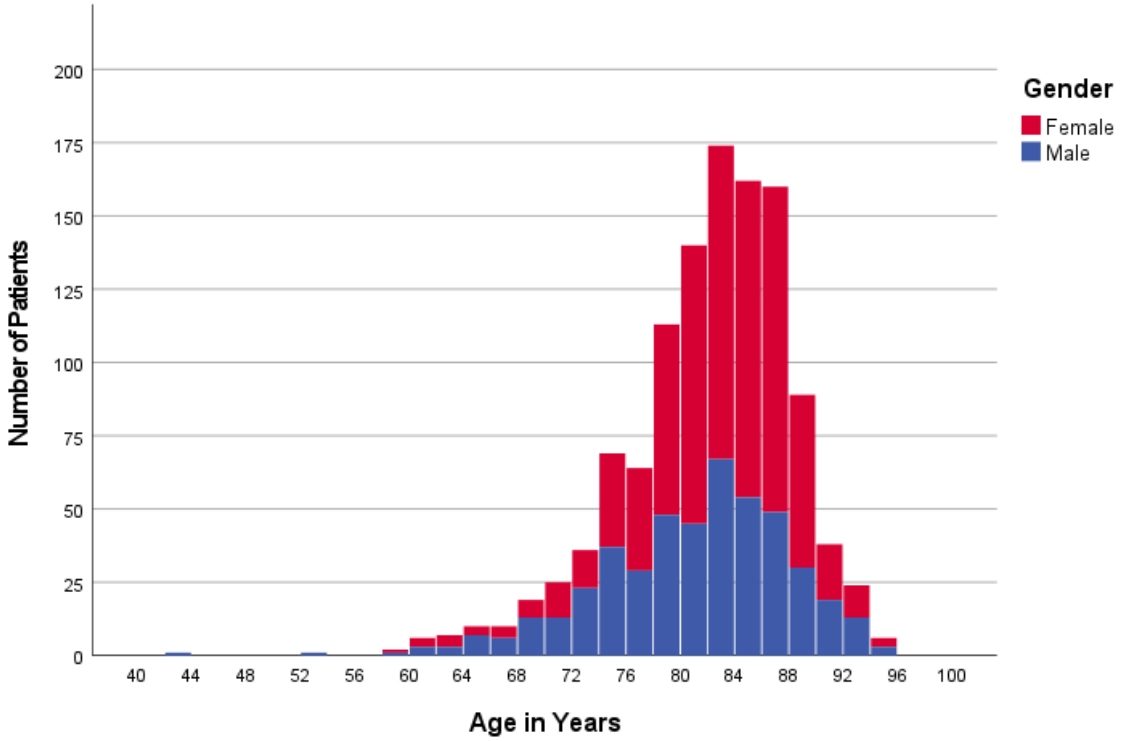

Figure 4: Age distribution based on gender showing both sexes had the same age distribution and were mainly between 80 and 88 years old.

Further characterization by the patients' comorbidities, in particular cardiovascular risk factors, medication intakes, and laboratory tests like hemoglobin, cardiac biomarkers, and renal function parameters at baseline are shown in tables 3, 4, and 5. Since not all data were available for all patients, the total number (n) of patients differs for each parameter.

Table 3 lists the baseline comorbidities and previous events/surgeries. The majority of the study population suffered from arterial hypertension (79.7%), coronary artery disease (64.0%), and heart failure. 21.5% indicated NYHA II, 58.9% NYHA III, and 10.9% NYHA IV. Regarding coronary artery disease (CAD), 25.4% of the patients had already undergone PCI, and 10.1% of the patients a coronary artery bypass graft (CABG) surgery. Other common comorbidities in this study were atrial fibrillation (37.1%), dyslipidemia (34.6%), and diabetes (27.6%).

Table 3: Baseline Patient Characteristics - Comorbidities

	Number of patients (n)	Mean ± SD n (%)
Age (years)	1156	81.5 ± 6.3
Age of female patients (years)	691	82.1 ± 5.6
Age of male patients (years)	465	80.4 ± 7.1
Gender (female)	1156	691 (59.8%)
Body mass index (kg/m^2)	1149	26.4 ± 5.0
Arterial hypertension	1011	806 (79.7%)
Diabetes	1012	279 (27.6%)
Dyslipidemia	376	130 (34.6%)
End-stage kidney disease (CKD V)	1011	15 (1.5%)
COPD IV	1011	61 (6.0%)
CAD (coronary artery disease)	1008	645 (64.0%)
CVD (cerebrovascular disease)	1010	177 (17.5%)
Stroke	1011	96 (9.5%)
Myocardial infarction <90 days	1011	24 (2.4%)
PCI (percutaneous coronary intervention)	1011	257 (25.4%)
CABG (coronary artery bypass graft surgery)	1012	102 (10.1%)
PAD (peripheral arterial disease)	1012	175 (17.3%)
NYHA - **I** - **II** - **III** - **IV**	749	 65 (8.7%) 161 (21.5%) 441 (58.9%) 82 (10.9%)
CCS - **0** - **I** - **II** - **III**	530	 278 (52.5%) 44 (8.3%) 86 (16.2%) 109 (20.6%)

- **IV**		13 (2.5%)
Atrial fibrillation (AF) - **paroxysmal AF** - **persistent AF**	1009	374 (37.1%) 116 (11.5%) 258 (25.6%)

As shown in table 4, the most frequent medication intake was heart failure medication, such as ACEi, ARB, or ARNI (62.9%), beta-blockers (67.1%), aldosterone-antagonists (21.2%), and high-ceiling diuretics (56.5%). However, also antiplatelet drugs like aspirin and P2Y12-receptor-antagonist (clopidogrel, ticagrelor, and prasugrel), were taken by more than half of the patients (52.9%).

Table 4: Baseline Patient Characteristics - Medication

	Number of patients (n)	**n (%)**
ACEi/ARB/ARNI	1101	692 (62.9%)
Beta-receptor blocker	1103	740 (67.1%)
Spironolactone/eplerenone	1099	233 (21.2%)
Antiarrhythmics class 1	1101	2 (0.2%)
Antiarrhythmics class 3	1101	21 (1.9%)
Digoxin/digitoxin	1100	107 (9.7%)
Coumarin derivative	1102	211 (19.1%)
NOAC	960	174 (18.1%)
Antiplatelet drugs - **Aspirin** - **P2Y12-receptor-antagonist**	1103 962 435	583 (52.9%) 491 (51.0%) 130 (29.9%)
Statin	964	528 (54.8%)

Anti-diabetic drugs
- **(Oral) antidiabetic drugs**
  ○ **Metformin**
  ○ **SGLT2i**
  ○ **DDP-4i**
	
	444
	965
	433
	434
		
		59 (13.3%)
		80 (8.3%)
		5 (1.2%)
		42 (9.7%)

○ **GLP1-receptor agonist**	433	3 (0.7%)
- **Insulin**	444	33 (7.4%)
High-ceiling diuretics	964	545 (56.5%)
PPI (proton pump inhibitor)	964	545 (56.5%)

Regarding the laboratory parameters (table 5), the average hemoglobin (hb) level was 11.2 ± 1.7 mg/dl. Overall, 75.7% of the patients were anemic with a hemoglobin level below 12 g/dl for women and below 13 g/dl for male patients.

In addition, the hs-troponin level and the NT-proBNP level were elevated for the majority of the patients. Median hs-troponin level amounted to 72.0 pg/ml with an interquartile range from 25.0 to 166.0 pg/ml. NT-proBNP was measured with a median value of 2186.0 pg/ml with an interquartile range from 844.0 to 4792.0 pg/ml.

In most patients, the renal function had been moderately impaired which was evaluated by the estimated glomerular filtration rate (eGFR). Chronic kidney disease (CKD) stage G2 (39.8%) and G3a (24.5%) were most frequently present.

Table 5: Baseline Patient Characteristics - Laboratory Parameters

	Number of patients (n)	**Mean ± SD Median [IQR] n (%)**
Hb (g/dl)	1152	11.2 ± 1.7
- **anemia (all patients)**	1152	872 (75.7%)
o **male < 13 g/dl**	465	350 (75.3%)
o **female < 12 g/dl**	687	522 (76.0%)
Calcium (mmol/l)	591	2.3 ± 0.1
Potassium (mmol/l)	1152	4.2 ± 0.5
Sodium (mmol/l)	596	139.0 ± 3.2
CK (U/l)	1152	78.5 [53.0 – 119.0]
CK-MB (U/l)	1108	17.0 [12.0 – 24.0]
hs-troponin (pg/ml)	986	72.0 [25.0 – 166.0]
NT-proBNP (pg/ml)	1105	2186.0 [844.5 – 4792.0]
Creatinine (mg/dl)	1153	1.1 ± 0.7
eGFR (ml/min/1.73m^2)	764	69.4 ± 25.4
CKD classification		
- ***stage G1:* ≥90**		155 (20.3%)
- ***stage G2:* 60 – 89**		304 (39.8%)
- ***stage G3a:* 45 – 59**		187 (24.5%)
- ***stage G3b:* 30 – 44**		94 (12.3%)
- ***stage G4:* 15 – 29**		23 (3.0%)
- ***stage G5:* <15**		1 (0.1%)

3.2. Classification of AS Subtypes

3.2.1. Echocardiography

275 patients met the inclusion criteria mentioned in section 2.1. and were classified as described in section 2.2. As shown in table 6, the average v_{max} was 4.3 ± 0.8 m/s, the average value of mean Δp was 46.9 ± 17.6 mmHg, the mean AVA was 0.7 ± 0.3 cm^2, and the mean SVi was 39.6 ± 13.4 ml/m^2. More than half of the patients (59.3%) had an EF greater than 50% and thus a normal ventricular function. 29.8% had a mildly to moderately reduced EF and only a small percentage had a severely (3.6%) and very severely reduced (7.3%) EF. 184 patients (66.9%) of the 275 patients were classified with high-gradient (HG) AS, 15 patients (5.5%) with low-flow, low-gradient (LF/LG) AS and preserved EF, 35 patients (12.7%) with low-flow, low-gradient (LF/LG) AS and reduced EF, and 25 patients (9.1%) with normal-flow, low-gradient (NF/LG) AS. There were 14 patients (5.1%) who had moderate AS and 2 patients (0.7%) who had mild AS according to the echocardiographic measurements (table 7).

Table 6: Descriptive Representation of Echocardiographic Measurements

Parameters n = 275	**Mean ± SD** **n (%)**
v_{max} (m/s)	4.3 ± 0.8
mean Δp (mmHg)	46.9 ± 17.6
AVA (cm^2)	0.7 ± 0.3
SVi (ml/m^2)	39.6 ± 13.4
EF (%)	
- **normal (> 50%):**	163 (59.3%)
- **mildly – moderately reduced (30 – 50%):**	82 (29.8%)
- **severely reduced (20 – 30%):**	10 (3.6%)
- **very severely reduced (< 20%):**	20 (7.3%)

Table 7: Echocardiographic Classification of AS

Classification of AS n = 275	**n (%)**
Mild AS	2 (0.7%)
Moderate AS (concordant constellation)	14 (5.1%)
- **NF/LG AS**	25 (9.1%)
Severe AS	
- **HG AS**	184 (66.9%)
- **LF/LG AS + preserved EF**	15 (5.5%)
- **LF/LG AS + reduced EF**	35 (12.7%)

3.2.2. Cardiac Catheterization

Regarding the invasive hemodynamic measurements, the average *mean Δp* was 46.6 ± 19.9 mmHg, the mean AVA was 0.7 ± 0.3 cm^2, and the mean SVi was 34.7 ± 11.4 ml/m^2 as indicated in table 8.

For the invasive hemodynamic classification of AS subtypes only the parameters AVA, mean *Δp* and SVi were used. Of the 275 patients, 153 (55.6%) were classified with high-gradient (HG) AS, 67 (24.4%) with low-flow, low-gradient (LF/LG) AS, and 35 (12.7%) with normal-flow, low-gradient (NF/LG) AS. Invasive measurements also identified one (0.4%) patient with mild AS, and 19 (6.9%) patients with moderate AS (table 9).

Table 8: Descriptive Representation of Invasive Hemodynamic Measurements

Parameters n = 275	**Mean ± SD**
mean Δp (mmHg)	46.6 ± 19.9
AVA (cm^2)	0.7 ± 0.3
SV (ml)	61.3 ± 20.9
SVi (ml/m^2)	34.7 ± 11.4

Table 9: Invasively Measured Classification of AS

Classification of AS n = 275	**n (%)**
Mild AS	1 (0.4%)
Moderate AS (concordant constellation)	19 (6.9%)
- **NF/LG AS**	35 (12.7%)
Severe AS	
- **HG AS**	153 (55.6%)
- **LF/LG AS**	67 (24.4%)

3.2.3. Accordance of Echocardiographic and Invasively Measured AS Classification

As demonstrated in table 10, there was no accordance in mild and moderate AS between the two measurement methods. 49.5% (136/275) of the patients with HG AS, 9.4% (26/275) with LF/LG AS (regardless of EF), and 2.2% (6/275) with NF/LG AS were consistent in their classification by echocardiography and cardiac catheterization (shown in green). 5.1% (24/275) of echocardiographically measured moderate AS were identified as severe AS (HG, LF/LG) or NF/LG AS in catheterization overall. 15.3% (42/275) of echocardiographically determined HG AS were identified invasively as LF/LG or NF/LG AS (shown in red). Conversely, 6.2% (17/275) of invasively measured moderate AS were found to have severe AS on echocardiography. 5.1% (14/275) of the patients classified as HG AS on cardiac catheterization were echocardiographically identified as LF/LG or NF/LG AS (shown in yellow).

Table 10: Accordance of Echocardiographic and Invasively Measured AS Classification

		Invasive hemodynamic classification					
Echocardiographic classification	**n = 275**	Mild AS	Moderate AS	HG AS	LF/LG AS	NF/LG AS	Total
	Mild AS	0.0%	0.7%	0.0%	0.0%	0.0%	**0.7%**
	Moderate AS	0.0%	0.0%	1.1%	1.8%	2.2%	**5.1%**
	HG AS	0.0%	2.2%	49.5%	8.4%	6.9%	**67.0%**
	LF/LG AS + preserved EF	0.0%	0.7%	2.2%	1.8%	0.7%	**5.4%**
	LF/LG AS + reduced EF	0.4%	1.5%	2.5%	7.6%	0.7%	**12.7%**
	NF/LG AS	0.0%	1.8%	0.4%	4.7%	2.2%	**9.1%**
	Total	**0.4%**	**6.9%**	**55.7%**	**24.3%**	**12.7%**	**100%**

Columns show invasively determined AS classifications, rows echocardiographically. The green fields represent the concordance of AS classification by both echocardiography and cardiac catheterization. The red fields indicate that echocardiographically determined AS were identified as more severe on cardiac catheterization. Conversely, the yellow fields indicate that invasively measured AS were identified as more severe on echocardiography.

3.3. Follow-Up

Figures 5, 6, and 7 show the all-cause mortality of 1153 patients 30 days, 365 days, and 13.5 years after TAVI. The 30-day mortality rate was 4.5%, i.e., 52 of the 1153 patients died within 30 days after the intervention indicating a cumulative survival of 95.5%. The 1-year mortality rate was 14.1%, i.e., 162 of the 1153 patients died within 365 days post-intervention, which corresponds to a cumulative survival of 85.9%.

During the observation period of 13.5 years, 582 patients (50.5%) died and 571 patients (49.5%) were censored.

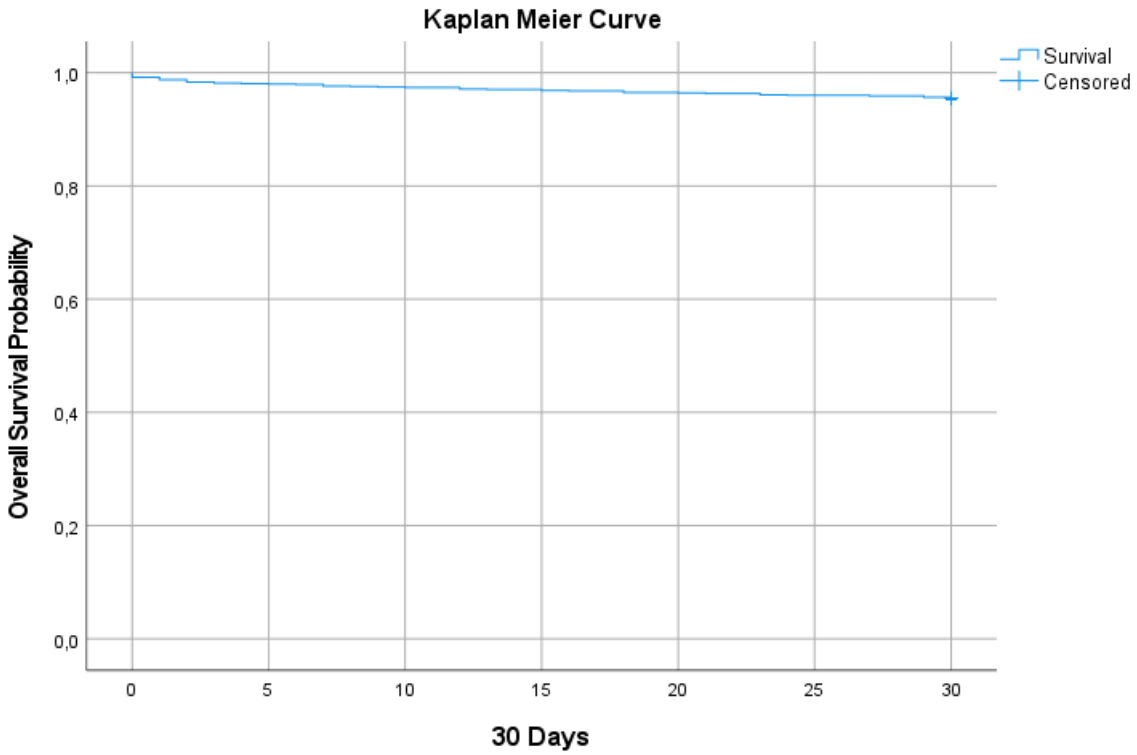

Figure 5: Kaplan Meier Estimator showing a cumulative survival of 95.5% of the entire study population 30 days after TAVI.

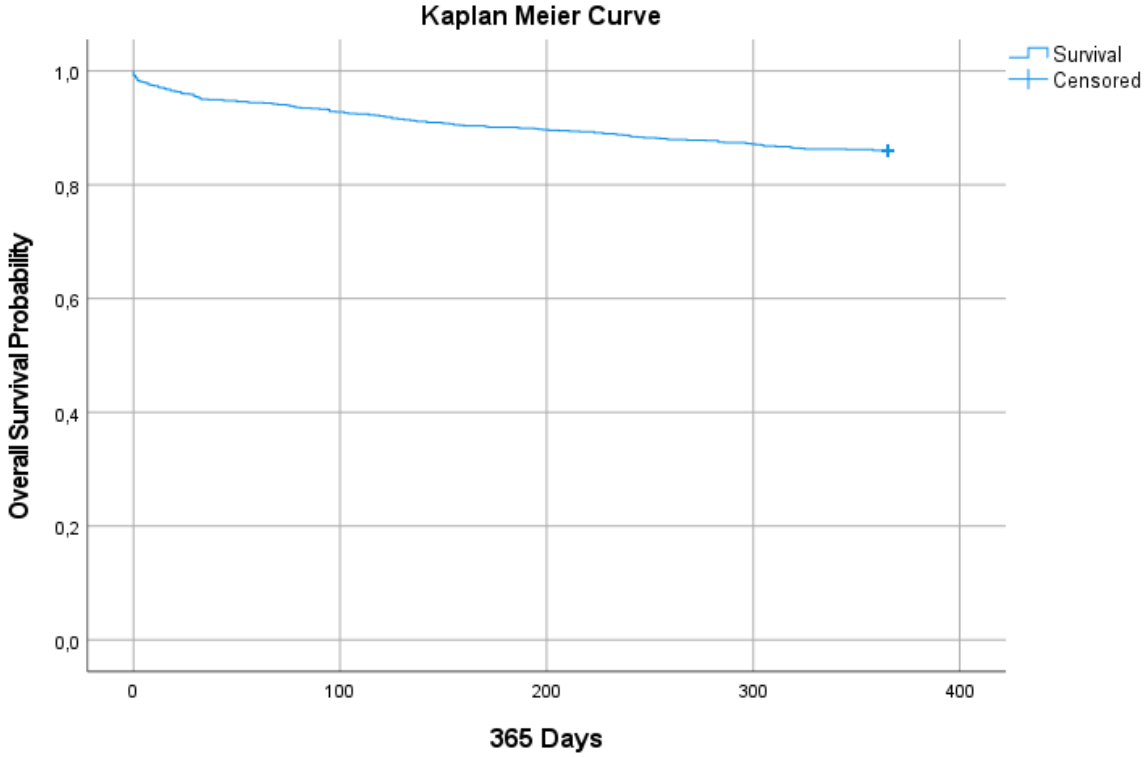

Figure 6: Kaplan Meier Estimator showing a cumulative survival of 85.9% of the entire study population one year after TAVI.

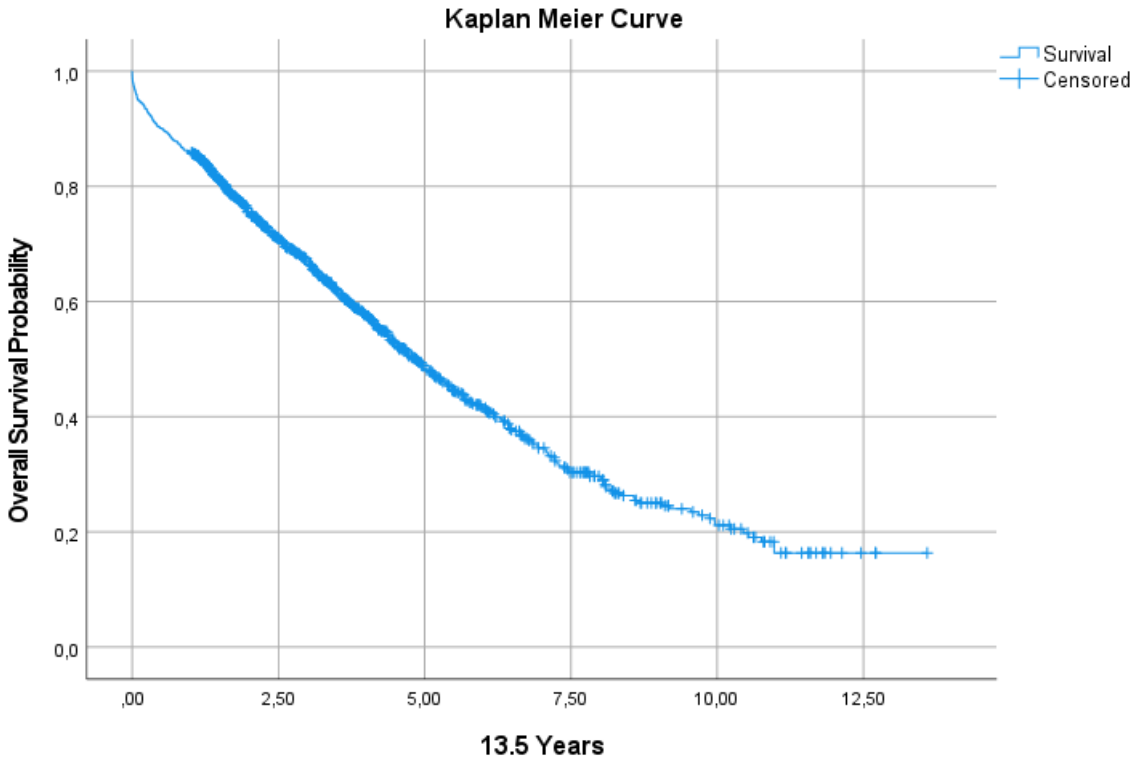

Figure 7: Kaplan Meier Estimator showing a cumulative survival of 49.5% of the entire study population after a follow-up of 13.5 years.

Figures 8 and 9 show the 3-year survival as a function of AS classification measured by echocardiography and invasively, respectively. AS subtypes were combined into 3 groups: Non-severe AS (including mild and moderate AS), high-gradient AS, and low-gradient AS (including LF/LG and NF/LG AS).

Based on the echocardiographic classification, the survival rate was 75.0% (12/16) in the non-severe AS group, 73.2% (134/183) in the HG AS group, and 62.7% (47/75) in the LG AS group.

On the basis of invasive hemodynamic classification, the survival rate was 50.0% (10/20) in the non-severe AS group, 76.5% (117/153) in the HG AS group, and 65.3% (66/101) in the LG AS group.

In the echocardiographic analysis (figure 8), it is noticeable that the survival of non-severe AS and HG AS is similar, and the survival of LG AS is lower three years after TAVI. However, the log-rank test of this curve showed that the survival distribution of these three groups does not differ significantly, $x^2(2) = 4.91$, $p = 0.086$. In the invasive analysis (figure 9), showing the highest survival in the HG AS group and the lowest in the non-severe AS group, the survival difference between the three groups is more evident and is statistically significant by the log-rank test, $x^2(2) = 10.03$, $p = 0.007$.

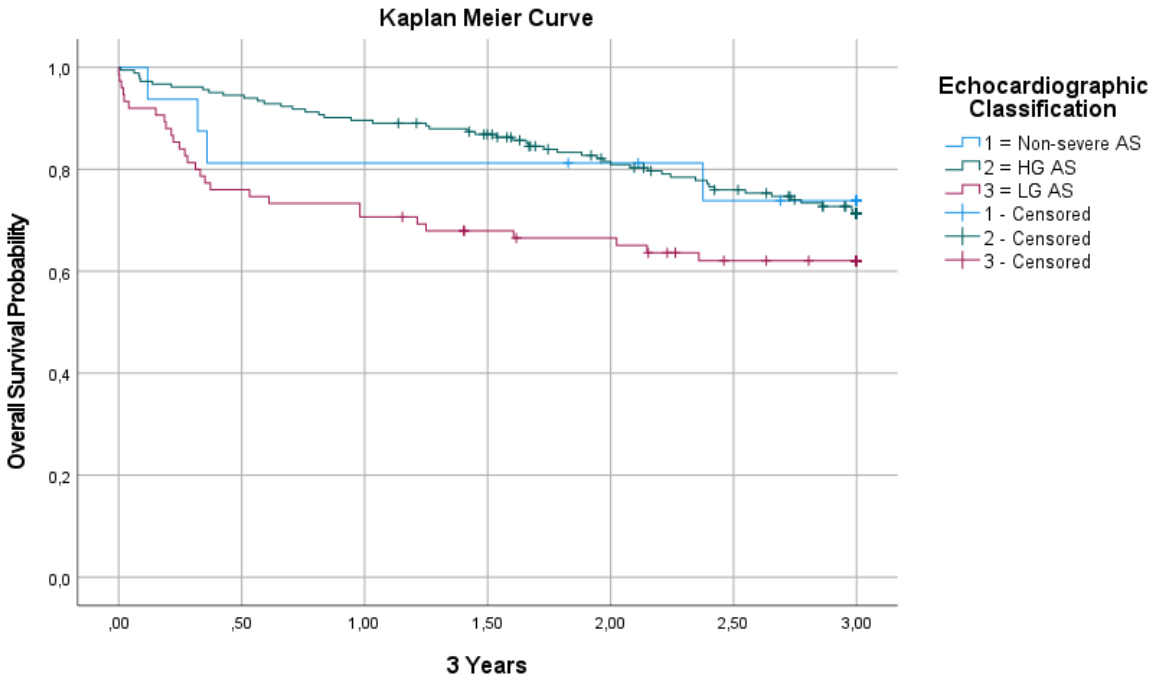

Figure 8: Kaplan Meier Estimator based on echocardiographic classification showing similar survival in non-severe and HG AS and lower survival in LG AS three years after TAVI.

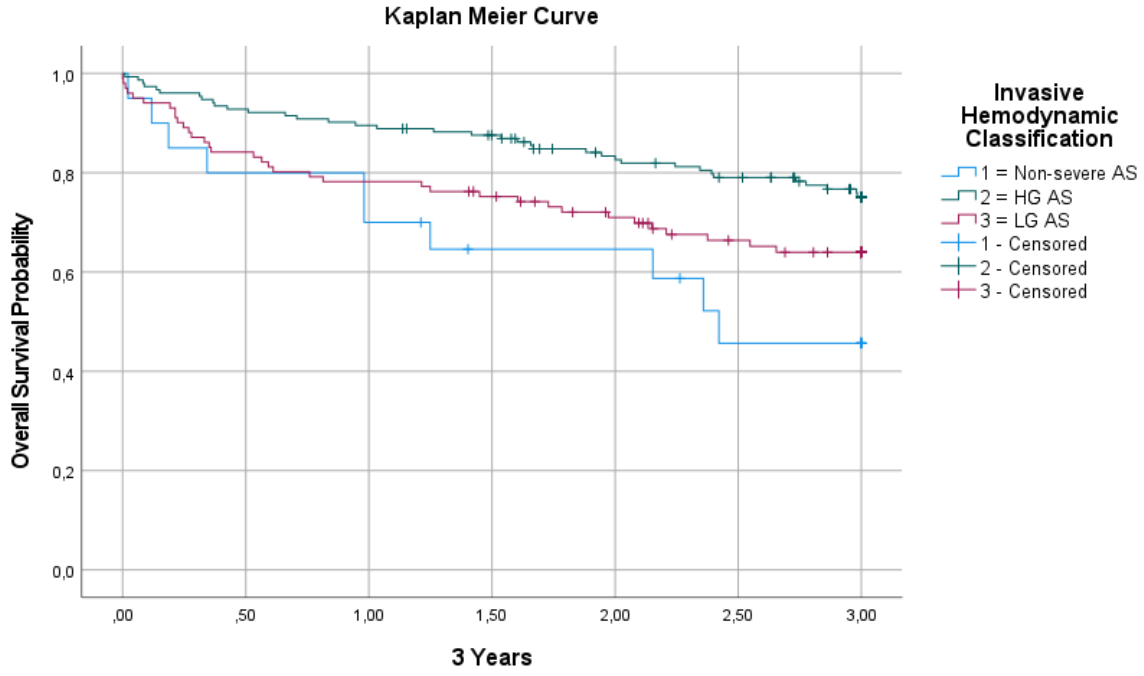

Figure 9: Kaplan Meier Estimator based on invasive hemodynamic classification showing highest survival in HG AS and lowest survival in non-severe AS three years after TAVI.

3.4. Time Period Analysis

Analyses were performed with respect to the evolution of the entire patient collective over time. For this purpose, all patients were divided into three time periods of approximately four years each. As shown in table 11, the number of patients who received TAVI has increased over time. In the third period, the number of patients has more than doubled compared to the first period. However, it is noticeable that the average age and the age distribution of the patients involved have not changed significantly over time (see figure 10).

Table 11: Time Period Analysis - Average Age

Time periods	Number of patients (n)	Mean ± SD
1. May 2007 - December 2011	208	81.1 ± 5.9
2. January 2012 – December 2015	349	81.8 ± 5.7
3. January 2016 – December 2019	599	81.4 ± 6.7

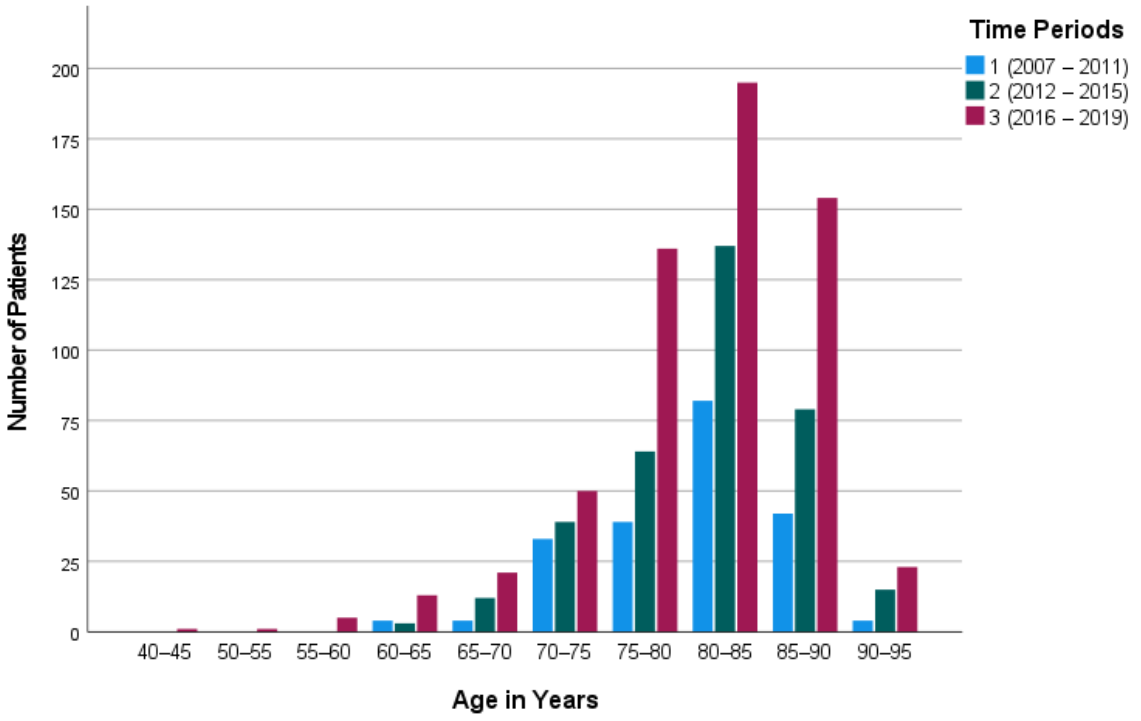

Figure 10: Age distribution based on time periods showing no significant changes in average age and age distribution over time.

Table 12 gives an overview of the AS subtypes obtained from echocardiography over these three time periods. In this analysis all patients with a complete set of echocardiographic parameters (v_{max}, *mean* Δp, AVA, SVi, and EF) were included regardless of whether hemodynamic parameters were present. This means a total of 452 patients were included. The percentage of HG AS has decreased from 77.0% to 63.7% whereas mild AS, moderate AS as well as LF/LG AS and NF/LG AS have slightly increased over time.

Table 12: Time Period Analysis - Echocardiographic AS Subtypes

		Time periods			
	n = 452	1. (2007 – 2011)	2. (2012 – 2015)	3. (2016 – 2019)	Total
Echocardiographic classification	Mild AS	0 (0.0%)	2 (1.2%)	2 (1.0%)	4
	Moderate AS	2 (2.3%)	9 (5.2%)	13 (6.7%)	24
	HG AS	67 (77.0%)	128 (74.4%)	123 (63.7%)	318
	LF/LG AS + preserved EF	5 (5.7%)	7 (4.1%)	12 (6.2%)	24
	LF/LG AS + reduced EF	7 (8.0%)	17 (9.9%)	21 (10.9%)	45
	NF/LG AS	6 (6.9%)	9 (5.2%)	22 (11.4%)	37
	All patients	**87 (100%)**	**172 (100%)**	**193 (100%)**	**452**

4. Discussion

The results of this study provide an insight into the patient population suffering from AS, the classification of AS by two different measurement methods, and the survival rate of these patients after receiving TAVI at the University Hospital of Graz.
Furthermore, the results show the evolution of TAVI patients between 2007 and 2019, particularly with regard to the AS subtypes.

4.1. Study Design

This present study is designed as a retrospective and single-center study. To analyze the concordance of the two measurement methods for the assessment of AS, we first classified AS on the basis of previously obtained echocardiographic and invasive hemodynamic parameters and then compared the classifications. This was done by contrasting them in a table. All patients who had a complete data set from echocardiography and cardiac catheterization were included in this analysis. No other inclusion criteria were set.
Comparable studies were also based on retrospective analyses, however, in contrast to the present study, they mainly compared the individual parameters (e.g., AVA, mean Δp) and reviewed for correlation. Patients, who had abnormal LV function (i.e., LVEF < 30%) and grade II or higher mitral regurgitation, were excluded from these analyses (39,40).
In this study, mortality analyses were performed using the Kaplan-Meier estimator. The focus was on 30-day and 1-year mortality, which was the same for comparable studies. Most of them were multi-center studies, which provided higher power and generalizability of the results (41–47).

4.2. Study Population

This study highlights the typical patient collective of severe AS. These patients are mostly octogenarians and suffer mainly from cardiovascular comorbidities, which are either clinical risk factors that contribute to AS development or arose as a result of AS.
Baseline comorbidities play an important role in the clinical outcomes of patients with AS, especially during and after aortic valve replacement. This is discussed in detail in section 4.4.

Another interesting aspect of this study population is that the number of female patients undergoing TAVI is higher, which was also noticeable in other studies (41,42,48). Kaier K. et al. analyzed the gender-specific differences between TAVI and SAVR (48). Firstly, they found that female patients with AS were on average older than male patients (82.02 versus 80.4 years), which was consistent with the present study (82.1 versus 80.4 years, with a statistical significance, $p < 0.001$). This can be explained by the fact that women often display fewer symptoms than men, resulting in a delayed diagnosis of AS. Secondly, the presence of higher surgical risk and the evidence of a higher mortality rate after SAVR in female patients lead to a more frequent treatment with TAVI in women (48). However, comparing male and female TAVI recipients, studies have reported a higher 1-year survival rate in women (49–51). In the meta-analysis by Saad M. et al. an even better long-term survival in women (3.28 ± 1.04 years) is reported, suggesting favorable baseline comorbidities and anatomical features as an explanation (52).

Another factor for this unequal gender distribution in TAVI patients could be that the average life expectancy in women is generally higher than in men and thus women have a higher risk of experiencing severe AS.

4.3. Classification of AS Subtypes – Echocardiography versus Cardiac Catheterization

The main objective of this study is the accuracy of AS severity assessment and the related inconsistency between echocardiographic and invasive hemodynamic AS classification.

Comparing the two measurement methods (table 10), it is apparent that there is no absolute agreement between the AS subtypes. Only 61.1% of the patients had the same classification invasively and non-invasively. Of note, 8.4% and 6.9% of the echocardiographically measured high-gradient (HG) AS were reclassified as low-flow, low-gradient (LF/LG) AS and normal-flow, low-gradient (NF/LG) AS, respectively, after invasive measurement.

One of the reasons for the poor agreement of AS classification between echocardiography and cardiac catheterization could be the different determination of key parameters such as aortic valve area (AVA) and pressure gradient (Δp).

Many authors described the “pressure recovery effect” as an important factor leading to the discrepancy between echocardiographic and invasive measurements (13,39,40).

After blood passes the stenotic valve area toward ascending aorta, its kinetic energy is converted into potential energy resulting in increased local pressure. This phenomenon is called “pressure recovery” (13). Since the precise positioning of the catheter at the vena contracta (the narrowest point where blood flow has its maximum velocity) is difficult, the measured pressure corresponds to the recovered pressure. This results in a lower Δp in the cardiac catheterization than in echocardiography ($\Delta p_{Echo} > \Delta p_{Catheter}$). In the latter, Δp is calculated using the Bernoulli equation and depends on the maximum transvalvular velocity (v_{max}) (13,53). Therefore, for the adequate assessment of AS subtypes, mean Δp is used, which is obtained by time averaging Δp across the entire systole and makes echocardiographic and invasive values comparable (13). This is also in agreement with a study by Yang C. et al., which analyzed a good correlation between echocardiographic and invasive mean Δp (39).

However, the determination of AVA gets critical. In echocardiography, AVA is calculated by means of the continuity equation, which is dependent on v_{max} and the correct measurement of LVOT diameter, assuming that the LVOT cross-section is circular shaped (13). Gaspar T. et al., however, revealed that LVOT is actually elliptical shaped, which leads to an underestimation of LVOT area and thus AVA on echocardiography by 17% (54). In contrast, AVA is determined in cardiac catheterization using the Gorlin formula. The Gorlin formula requires Δp ($\Delta p_{Catheter}$) and CO. The latter is normally determined by the thermodilution method, in which a cold saline solution is injected into the right atrium and causes a temperature change in the blood. By measuring this temperature change with a thermistor on the Swan-Ganz catheter, CO can be defined. This method is usually accurate except in patients with low-CO-states, significant tricuspid regurgitation, and irregular rhythms, which occurs frequently in patients with advanced heart diseases. This finally leads to $AVA_{Catheter} > AVA_{Echo}$ (13,55). Yang C. et al. have found a poor correlation (both Pearson’s and intraclass correlation) between echocardiographic and invasive AVA (39). Garcia D. et al. observed that especially patients with a small aortic diameter (≤ 3cm) have the greatest discrepancies between $AVA_{Catheter}$ and AVA_{Echo} (53).

The crucial question, however, is what clinical relevance these discrepancies between echocardiography and cardiac catheterization entail. In this study, we have found that the inconsistencies were mainly between the non-classical AS subtypes.

HG and LF/LG AS are considered severe AS and thus require the same treatment, namely valve replacement. However, according to the latest ESC/EACTS Guidelines, NF/LG AS may be considered moderate AS. The management of this AS subtype includes regular clinical and echocardiographic surveillance. Nevertheless, this is still dependent on the full picture of the patient's condition (16).

Another critical point of this study is that the assessment of AS severity was performed using only two examination methods – echocardiography and cardiac catheterization. Thus, the presence of mild and moderate AS should be questioned here. According to the echocardiographic classification, there have been two patients with mild AS and 14 with moderate AS. AS assessment with invasive parameters revealed one mild AS and 19 moderate AS. However, after comparing the AS classifications of both measurement methods (table 10), there was no consistency between the mild and moderate AS. Therefore, almost all of these patients were found to have severe AS by at least one of the two measurement methods, except for two patients who had echocardiographically mild AS and invasively moderate AS. In these discrepant cases, the inclusion of clinical presentation and further investigations is important, and ultimately the physician evaluates each patient individually and decides on the best treatment management.

Also, the fact that this retrospective study included only patients already diagnosed with severe AS and underwent TAVI at the University Hospital Graz should cast doubt on the presence of these mild and moderate AS. This reinforces the importance of looking at the full picture.

As mentioned earlier, the assessment of AS and the treatment decision do not depend on two examination modalities but require an overall assessment of the affected patient. This includes primarily the patient's clinical presentation, comorbidities, laboratory parameters, and transthoracic echocardiography, which is the current gold standard imaging modality in AS. In case of certain conditions or discrepancies between clinic and examination findings, there are further investigations such as stress testing, transesophageal echocardiography (TEE), CCT, and cardiac catheterization to determine the AS severity and the appropriate therapy (16).

Through this integrated analysis, severe AS was already judged in all patients in this study as an inclusion criterion for therapy.

4.4. Follow-Up

In this study, the 30-day and 1-year mortality rate after TAVI was at 4.5% and 14.1%, respectively, which was concordant with several other studies (41–47).

Comparable studies have shown a 30-day mortality rate of 2.6% to 10.4%. Most of these studies suggest that periprocedural factors and complications have a major impact on mortality within 30 days after TAVI (42–46).

Concerning the 1-year mortality, 15% mortality rate was reported by an Italian registry (42), 24% by the FRANCE 2 registry (44), 21.4% by the UK TAVI registry (45), 22.1% by a Canadian registry (46), 19.9% by Zahn R. et al. (41), and 19.7% by Kønjås D. et al. (47). A more recent study by Eftychiou C. et al. indicated an all-cause mortality rate of 15.1% in one year (43). Compared to these studies, the University Hospital Graz shows a lower mortality rate in TAVI patients. One of the factors that causes these differences in the mortality rate, is the patients' baseline characteristics. The more comorbidities at baseline, which carry higher surgical risk prior to intervention, the higher the mortality rate. According to several studies, the main impacts on patient's survival are the presence of COPD, renal failure (decreased eGFR), anemia, diabetes, history of myocardial infarction, low BMI, increased systolic pulmonary artery pressure (> 60 mmHg), pre-intervention moderate to severe mitral regurgitation, and post-intervention aortic regurgitation greater than grade I (41,43,47,56).

Because data were not collected on all of the above-mentioned comorbidities, it is not possible to draw a reasonable conclusion about the cause of the lower mortality rate in this study.

Another important factor leading to different survival outcomes is the presence of different AS subtypes. Although there was no significant difference in mortality between non-severe and HG AS groups in the 3-year mortality analysis with respect to echocardiographic AS classification (figure 8), higher mortality was evident in the LG AS group. However, in the 3-year mortality analysis with respect to invasive AS classification (figure 9), a more significant difference in mortality was found between all three groups. Patients with LG AS had a higher mortality rate than patients with HG AS. The highest mortality was seen in the non-severe AS group.

Concerning the severe AS subgroups, similar results were evident in the meta-analysis by Takagi H. et al. evaluating the impact of three AS subtypes (LF/LG AS with reduced EF, LF/LG AS with preserved EF, and normal-flow, high-gradient AS) on the patients' survival

after TAVI (53). It was observed that compared to normal-flow, high-gradient AS there was an association between LF/LG AS (with reduced/preserved EF) and increased midterm mortality (death one to seven years after TAVI) (57).
Another meta-analysis by Eleid M. et al. also concluded that low SVi, low gradient, and low EF are each associated with an increased 1-year mortality rate (58).

Looking at the outcome between the echocardiographic and invasive AS groups, the survival rates of HG (73.2% and 76.5%, respectively) and LG AS (62.7% and 65.3%, respectively) were each similar. However, there was a large discrepancy in the survival of non-severe AS (75.0% and 50.0%).
In general, non-severe AS shows a poorer 3-year survival outcome than expected in this study.
At this point, it has to be mentioned that, as aforesaid in section 4.3, no integrated analyses were performed in this study. Thus, the assumption that there are non-severe AS in this study population and that they have the highest mortality rate is unlikely. Although these patients were classified echocardiographically and invasively as non-severe AS, there still were other decisive factors that led to their poor outcomes. These included mostly anemia, diabetes, increased systolic and mean pulmonary artery pressure, pre-intervention moderate to severe mitral regurgitation, but also COPD IV, history of myocardial infarction, low BMI, liver cirrhosis, and advanced chronic kidney disease in individual cases.

4.5. Time Period Analysis

Since the advent of TAVI, data on this intervention and evidence of its efficacy as an AS treatment have accumulated, leading to an expansion of TAVI indications and thus increased TAVI interventions (59). Furthermore, the TOPAS-TAVI registry has shown that TAVI is a safe, even affirmative alternative to SAVR in patients with low-flow, low gradient AS because it is associated with a lower degree of myocardial injury during the procedure, rapid recovery of LV function, favorable 30-day mortality rate, and “acceptable 2-year outcomes” in comparison to surgery (56).

This study is consistent with these findings. Table 11 demonstrates that the number of TAVI procedures conducted at the University Hospital of Graz has increased continually in the period from 2007 to 2019. Table 12 shows that more patients with LF/LG AS have received TAVI in the last time period (2016-2019) than in the years before, which may represent the expansion of TAVI indications.

4.6. Limitations

Since this is a monocentric and retrospective analysis, we need to highlight the following limitations:

Data collection was carried out by different persons and its quality depends on the completeness of the data in the patient information system (MEDOCS). While in some patients all the necessary data and parameters were available, in many cases they were incomplete and thus caused a huge loss of information. 76.2% of the patients had to be excluded from this evaluation covering echocardiographic and hemodynamic classification of AS due to missing data.

Further limitations are that these two measurement methods (echocardiography and cardiac catheterization) were not executed simultaneously but days or weeks apart suggesting a possible change in the hemodynamic conditions in-between the measurement sets.

Additionally, there might be an interobserver bias: These measurements were carried out by different cardiologists, which means that different results or interpretations of the examinations are possible. Also, the study design was not prospective and not highly standardized regarding AS assessment, e.g., echocardiographic measurements. These limitations were also highlighted by other authors like Sakthi C. et al. (60).

5. Conclusion

This study highlighted an inconsistency between echocardiographic and invasive hemodynamic classification. It concerned the non-severe AS, i.e., mild and moderate AS, but also the non-classical AS subtypes, i.e., high-gradient (HG), low-flow, low-gradient (LF/LG), and normal-flow, low-gradient (NF/LG) AS. Both examination methods are important diagnostic tools for assessing AS severity and can complement one another. Indeed, this also depends on other contributors such as the patient's condition, clinical presentation, comorbidities, and other additional diagnostic tests. All these factors have to be considered when determining the individualized treatment plan and indication for valve replacement.

In addition, we could confirm that the AS subtypes have an impact on mortality. According to the mortality analysis, patients with LF/LG AS and NF/LG had statistically a significantly higher mortality rate three years after TAVI compared to patients with HG AS.

Furthermore, this study demonstrates that the use of TAVI has continuously risen over the past decades, and it has been established as an efficient and safe treatment of AS. In recent years, its use has also expanded to include higher-risk patients and more patients with low-gradient severe AS.

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