Diplomarbeit

Predictive value of invasively determined hemodynamic parameters regarding post-procedural prognosis in patients undergoing transcatheter aortic valve implantation

eingereicht von

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zur Erlangung des akademischen Grades

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an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Innere Medizin an der klinischen Abteilung für Kardiologie

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Graz, am 08.11.2019

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 08.11.2019 Dominik Hatz eh.

Credits

Regarding this study, I would like to thank my two academic advisors, Assoz. Prof. Priv.-Doz. Dr.med. D.Med.Sci Peter Rainer and Dr.med.univ. David Zweiker, without whom this project would not have been feasible. Luckily for me the word “perseverance” was mentioned in their bidding, yet not knowing that then, their perseverance had been tested with me, due to my chronic postponements.

Reflecting on my academic career and pathways chosen up to this point, I am thankful for all the friendships I have made during my years at high school, university and in general. These have broadened my horizons all along and even to this day the wonderful thoughts and experiences still bring a bright smile to my face. This and more, also accounts for my girlfriend, Julia, whom I met on my very first day of university. She always has my back, loves, inspires and supports me and (most of) my decisions. For that I am blessed.

However, most importantly I would like to thank my family. I am grateful for my mother (Muxxi) and father (Fonso), not just for enabling and financing my studies, but also for teaching me manners, independence, thoughtfulness, respect and patience (the latter we are still working on). My grandparents’, who helped to form and build my character, no matter whether they were near by or miles away.

Last but not least my brother, Kevin, who has proven to be a messy roommate at times, but has never let me down. In times, when my fragile patience was and is at its limits, he remains settled and has the ability to calm me down. Thank you.

Zusammenfassung

Einführung

Da TAVI in ganz Europa an Beliebtheit gewinnt wird sie in letzter Zeit nicht nur bei Hochrisikopatientinnen und Patienten, sondern auch bei Menschen welche ein mittleres Risiko aufweisen eingesetzt, weswegen die Dringlichkeit besteht neue diagnostische Werkzeuge zu erforschen, um eine individuelle Risikostratifizierung zu kreieren. Das Ziel ist es einen hämodynamischen Parameter zu finden, welcher das Potenzial beinhält einen prädiktiven Wert in Bezug auf die 1-Jahres Mortalität zu repräsentieren.

Methoden

In einer retrospektiven Studie wurden die Daten von 554 Probandinnen und Probanden, die einer TAVI unterzogen wurden überprüft und in Bezug auf Bevölkerungsdemographie, Komorbiditäten und hämodynamische Parameter deskriptiv und mittels Regressionsanalysen statistisch aufgearbeitet. 375 Probandinnen und Probanden erfüllten die notwendigen Einschlusskriterien um in einem multivariablen COX-Regressionsmodell untersucht zu werden, welches sich auf die Signifikanz der hämodynamischen Parameter und der 1-Jahres Mortalität bezieht.

Ergebnisse

Die 1-Jahres Mortalität der gesamten Studienpopulation betrug 11.6 %. Die univariablen, mittels COX-Regression analysierten hämodynamischen Werte zeigten eine statistische Signifikanz des aortalen Mitteldruckgradienten ($p = 0,005$), des diastolischen Lungenarteriendrucks ($p = 0,029$), sowie des rechten Vorhofdrucks ($p = 0,002$). Die periphere arterielle Verschlusskrankheit ($p < 0,001$), chronisch obstruktive Lungenerkrankung ($p = 0,028$), glomeruläre Filtrationsrate ($p = 0,037$) sowie der rechte Vorhofdruck ($p = 0,007$) zeigten in der univariablen Analyse sowie in der multivariablen Analyse signifikante Resultate.

Schlussfolgerung

Insgesamt konnte diese Studie einen signifikanten Zusammenhang zwischen einem erhöhten rechten Vorhofdruck und erhöhter 1-Jahres Mortalität nach TAVI nachweisen. Daher könnte der rechte Vorhofdruck als prädiktiver Wert bei TAVI dienen. In Anbetracht

der Limitationen der Studie muss jedoch die Genauigkeit der Messung selbst, sowie die Tatsache, dass sie die erste Studie ist welche dieses Ergebnis erzielt, berücksichtigt werden. Die Rechtsherzkatheterisierung und die dabei erhobenen pulmonalen Drücke konnten keine weiteren signifikanten Ergebnisse in Bezug auf das Überleben liefern. Die Ergebnisse jedoch stimmen teilweise mit statistisch signifikanten Resultaten aus anderen Studien überein und bestätigen, dass die chronisch obstruktive Lungenerkrankung, periphere arterielle Verschlusskrankheit sowie die Nierenfunktionen als Prädiktor für die 1-Jahres Mortalität fungieren. Allerdings müssen weitere Forschungsarbeiten durchgeführt werden um festzustellen, ob der rechte Vorhofdruck auch in anderen TAVI-Populationen als prädikativer Wert genutzt werden kann.

Abstract

Introduction

With TAVI becoming popular throughout Europe it has been applied not only in high-risk but also in intermediate-risk patients. It now bears the necessity to find diagnostic tools to create individual patient risk stratification towards the outcome. The aim of this study is to find a hemodynamic parameter, which is predictive in regards to the 1-year mortality.

Methods

In a retrospective study, data from originally 554 subjects, who have undergone a TAVI, have been reviewed and analyzed descriptively and with regression analysis, in terms of population demographics, comorbidities and hemodynamic parameters. 375 subjects meeting the inclusion criteria were analyzed in a multivariable COX-regression model, focusing on significance in parameters regarding the 1-year-mortality.

Results

The all-cause 1-year mortality rate of the entire study population was 11.6 %. Hemodynamic values analyzed univariably showed a statistical significance (aortic mean pressure gradient ($p = 0.005$), diastolic pulmonary artery pressure ($p = 0.029$), right atrial pressure ($p = 0.002$). Peripheral vascular disease ($p < 0.001$), chronic obstructive pulmonary disease ($p = 0.028$) and estimated glomerular filtration rate ($p = 0.037$) as well as right atrial pressure ($p = 0.007$) showed to be strongly significant in univariable analysis as well as in multivariable analysis.

Conclusion

Overall, this study was able to show a significant association between the right atrial pressure and the 1-year mortality rate after TAVI. Therefore, the RAP could act as predictive value in TAVI outcome. However, considering the study's limitations, the accuracy of the measurement itself, as well as being the first study to accomplish this finding, needs to be considered. According to the outcome of the study, besides right atrial pressure, right heart catheterization could not establish any further significant results in regards to survival, since values pulmonary pressures have shown no statistical evidence. The results were partially concordant with findings from previous studies, confirming that

chronic obstructive pulmonary disease, peripheral vascular disease and kidney function act as predictor regarding 1-year mortality. Further research needs to be committed in order to determine whether RAP can be used as predictive value in TAVI patients.

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Abbreviations

AF	Atrial fibrillation
AMG	Aortic mean pressure gradient
AP	Angina pectoris
APG	Aortic peak gradient
AS	Aortic stenosis
ASA	Acetylsalicylic acid
AVA	Aortic valve orifice area
CAD	Coronary artery disease
CI	Confidence interval
CO	Cardiac output
COPD IV	Chronic obstructive pulmonary disease IV
CT	Computer tomography
CVD	Cerebral vascular disease
CVRF	Cardiovascular risk factors
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EuroSCORE	European System of Cardiac Operative Risk Evaluation
F	French
LBB	Left bundle branch
LIMA	Left internal mammary artery
LV	Left ventricle
LVEDP	Left ventricular enddiastolic pressure
LVEF	Left ventricle ejection fraction
ICU	Intensive care unit
ICS	Intercostal space
ml	Milliliter
ml/min	Milliliter/Minute
mm	Millimetre
mmHg	Millimetre of mercury
mPAP	mean pulmonary artery pressure
m/s	Meter per second

mV	Millivolts
OR	Odds ratio
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVD	Peripheral vascular disease
PVR	Peripheral vascular resistance
RAP	Right atrial pressure
RIMA	Right internal mammary artery
SAVR	Surgical aortic valve replacement
sPAP	Systolic pulmonary artery pressure
SV	Stroke volume
TAVI	Transcatheter aortic valve implantation
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VARC	Valve Academic Research Consortium

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1 Introduction

Aortic stenosis

1.1 Definition

Aortic stenosis (AS) is defined as being the pathological narrowing of the aortic valve. AS is the most common primary valve disease leading to surgery or catheter intervention in Europe and North America, with a growing prevalence due to the ageing population. (1)

1.2 Aetiology

There are four main mechanisms to develop an AS in adulthood. First and most common is the degenerative process where a calcification on the aortic cuspids occurs. (2)

The calcification of the aortic valve is similar to atherosclerosis, where endothelial dysfunction, lipid accumulation, release of cytokines and activation of inflammatory cells play a key role. Additionally, proinflammatory signal transduction makes valvular myofibroblasts differentiate to phenotypically osteoblasts, which produce active bone-matrix-proteins that support the debris of calcium hydroxyapatite crystals. Furthermore, risk factors such as low-density-lipoprotein-cholesterol, lipoprotein a, diabetes mellitus, smoking, chronic kidney disease and metabolic syndrome are closely associated with the development and progression of AS. (2)

The bicuspid aortic valve is the most common congenital heart valve disease. This type of valve can be found within 0.5 – 1.4 % of the population. The likelihood for men is 3 times higher than for women. (2,51)

Due to consequent treatment of streptococcal infections with antibiotics, the rheumatic AS has decreased tremendously in countries with a modern health system. In rheumatic AS the commissures of the aortic valve thicken and start to become attached to each other. Tricuspid valves may seem as bicuspid at this point, making the valve vulnerable for micro trauma, which leads to fibrosis and calcification over time. The rheumatic AS is known to show signs of regurgitation and often also the mitral valve exhibits rheumatic alterations. (2,3)

1.3 Pathophysiology

If the stenosis were to be acute, the left ventricle would have no time to adapt to the increasing systolic pressure gradient between the aorta and the left ventricle (LV). This would lead to a dilation of the ventricle and a reduced stroke volume (SV). However, patients with AS acquire the obstruction over time, making it possible for the heart to create a coping mechanism. Normally the orifice of the aortic valve in adults is 2.6 – 3.5 cm^2. To even get a hindrance and cause hemodynamic effects, the area has to be below 1.5 cm^2. In order to overcome the obstruction the LV develops a concentric hypertrophy, following the law of Laplace (S = P x r/h; s= systolic ventricular wall tension, r = radius, P = pressure and h = ventricular wall thickness). By increasing the wall thickness, the systolic wall tension of each muscle segment is reduced. This mechanism can work for years, without reducing the cardiac output (CO), or causing LV dilation. As soon as the adaptive hypertrophy becomes a maladaptive hypertrophy, the functionality of the LV decreases, the diastolic dysfunction increases and the fibrosis of the myocardium can continue irreversibly. Clinically this can be noted as dyspnea and reduced performance. The hypertrophy comes with a price: There is an increased amount of oxygen needed to supply the myocardial tissue, such as the increased wall tension compromise the endothelial blood flow causing angina pectoris (AP) even though no coronary stenosis is present. AP, however, does not enable an objective say on how far advanced the hypertrophy is. In cases of severe AS the left ventricle end-diastolic pressure (LVEDP) rises, limiting the coronary perfusion pressure making the coronary reserve decline. The CO in most patients with severe AS is normal. However, during exercise, syncope and dizziness can occur, which are signs of insufficient cerebral perfusion, and a scanty ejection fraction. LV baroreceptors induce a peripheral vasodilation, causing the blood pressure to decline and resulting in syncope. Another possibility are arrhythmias, such as atrial fibrillation (AF) leading to an insufficient filling of the ventricle and reduced SV. (2–4)

1.4 Symptoms

Symptoms tend to appear late in the disease, but usually concur with the following three physiological occurrences: cardiac ischemia, increased LVEDP and a diminished CO. These mechanisms lead to the typical AS symptom, which is AP, syncope and heart

failure, in any given order. Angina for one, is a result of many different mechanisms including elevated LVEDP, the LV hypertrophy and its increased demand of oxygen, diastolic dysfunction and additionally coronary sclerosis is a contributor to the AP-symptoms. Syncope evolves after an insufficient cerebral perfusion. With AS this can be found after exercise or with a decreased preload due to diuretics or many other factors. Another theory is that the LV-baroreceptor reflex might be causing an inadequate reaction by creating a vasodilation after detecting an elevated intracavitary pressure leading to an insufficient blood pressure. (5)

1.5 Natural progression

Depending on the beginning of symptoms, the majority of patients with severe AS die between the 7th and 8th decade of life. Retrospective analyses suggest that with the onset of AP, dyspnea, syncope and heart insufficiency the patients pass away within 3 and 1.5 - 2 years. Once symptoms begin, more than 80 % of patients die within 4 years. AS is a progressive disease with a decline of aortic valve orifice area (AVA) of 0.1 mm^2, an increase of valvular flow velocity of 0.3 m/s and a rise of the valve gradient of about 7 mmHg each year. (2)
Predictors of symptom development as mentioned below, can shorten the latency time or favour the onset of symptoms: (6)

- Clinical characteristics: age, cardiovascular risk factors (CVRF)
- Echocardiographic parameters: Degree of valve calcification, maximum velocity over the aortic valve, percentage of left ventricular ejection fraction (LVEF) and LV hypertrophy
- Stress testing: symptoms occur during exercise, unusual blood pressure reaction and ST-depression in an electrocardiogram (ECG)
- Biomarkers: increased plasma levels of NT-pro BNP

1.6 Diagnosis

The clinical presentation of the patient is often difficult to assess due to the variety of symptoms. For example, patients can have an aortic valve sclerosis, where the prevalence is 30 % in patients older than 65 years of age, without signs of hemodynamic limitation or having a hemodynamic effective AS. Normally, a patient with symptoms appears in the clinic when the AVA becomes less than 1 cm^2 and the mean systolic pressure gradient rises above 40 mmHg. (3)

1.6.1 Clinical examination

At the beginning of the examination of suspected AS, a thorough medical history is required. Information is gathered with questions specifically designed to determine if typical symptoms of AS are present and if everyday life situations have been affected in anyway to determine the progression of the illness. In chronically ill, the adaption of the patient due to the disease has to be taken in consideration as symptoms are often described less limiting as they truly are. The degree of the symptoms gives insight on how to intervene. Patients who deny questions about specific symptoms, but are treated medically for a heart disease are to be classified as symptomatic. (6)

1.6.2 Inspection and auscultation

The auscultation plays a key role in finding pathological heart murmurs, especially in asymptomatic patient as they have no awareness of the disease and do not claim to experience any symptoms. In patients with implanted mechanic heart valves an alteration in the prosthetic heart murmur is the first sign of a disorder. For this reason, the auscultation is a basic diagnostic tool in follow-ups with patients of implanted heart valves. When auscultating the patient, a crescendo-decrescendo rough systolic murmur can be heard, typically located with the punctum maximum above the second intercostal space (ICS) right parasternal. The murmur is separated from the first heart sound and is radiating into the carotid arteries. The more distinctive the AS becomes, the less blood flows through the valve leading to a prolonged ejection time and delayed development of a peak gradient. Hence shifting the maximum of the murmur to a later point in the systole and additionally reducing the aortic component of the second heart sound. Also, a protosystolic

ejection-click is missing due to the decreased mobility of the valve. If an aortic regurgitation is also present furthermore a diastolic murmur can be found. (3,5,6)

1.6.3 Electrocardiogram

Typical changes in severe AS are an electrical horizontal heart axis deviation, LV hypertrophy signs regarding the Sokolow-Lyon-Index for LV hypertrophy ($S_{V1} + R_{V5} >$ 3.5 mV (30)) and as a sign of the pressure hypertrophy there can be T-negativity in left precordial leads (V_{4-6}). Important to note is that even in severe AS the ECG can present itself as ordinary and hypertrophy signs can be absent. (3)

1.6.4 X-ray

In the compensated stage the heart appears with its normal size. Other signs are: (3)

- Poststenotic dilation of the ascending aorta
- Valve calcification
- Pulmonary vascular congestion if cardiac decompensation is reached

Clinically, the X-ray plays no role in the diagnosis of AS but may depict lung edema.

1.6.5 Echocardiography

Typical findings are thickened calcified leaflets with reduced systolic opening movement and a hypertrophy of the LV. In presence of a congenital bicuspid aortic valve the closure of the leaflets are often eccentric. Although, this is not the routine diagnostic tool, because the obstruction is best seen in a transesophageal echocardiography. The Doppler-derived mean pressure gradient over the valve as well as the AVA can be calculated by using the Doppler-ultrasound to determine the transvalvular velocity. Patients continue asymptomatic as long as the peak transvalvular velocity is less then 4.0 meters per second (m/s), or is below 4 times the normal velocity. In patients with a discretely elevated transaortic velocity, but an AVA below 1.0 cm^2, the stenosis is more difficult to classify and therefore is often underestimated. The classification of the AS can be seen in Table 1. The echocardiography can also be used to differentiate between a valvular AS or another outflow tract obstruction such as hypertrophic obstructive cardiomyopathy. Additionally, the diameter of the aortic root as well as the ascending aorta can be determined,

which is important information if a congenital bicuspid valve is present. The dobutamine-stress echocardiography is useful in an existing low-flow-low-gradient AS with compromised ejection fraction (EF), because in this case assessing the severity can be challenging. (2,7)

1.6.6 Stress testing

Stress testing is indicated in asymptomatic patients to measure exercise capability. The objective of the test is to reveal hidden symptoms in order to design a correct risk evaluation for the asymptomatic patient with severe AS. Particularly in elderly patients or in people who do not participate in sport at all, a stress-induced dyspnea is hard to diagnose or interpret.

Furthermore, it helps to distinguish between low-flow low-gradient severe AS and a pseudo severe AS, which is important since the therapies differ. In patients diagnosed with pseudo severe AS, the aortic valve, although not severely stenotic, only opens inappropriately at rest, due to impaired LV function, resulting in an AVA < 1 cm^2. In the case of a pseudo severe AS and a LV with contractile reserve, the AVA will increase > 1 cm^2, and the AMG will only rise minimally, during a dobutamine stress test. Therefore, it can be differentiated from true severe AS where the AMG will rise > 40 mmHg and the AVA remains below 1 cm^2.

Stress testing is only done with the supervision of medical staff. An ECG and blood pressure monitoring are used to diagnose potential symptoms early. During every stress test, emergency medical equipment including a defibrillator has to be present and a resuscitation team on call. (6,52)

1.6.7 Cardiac catheterization

Despite the ESC guidelines describing that, “retrograde LV catheterization to assess the severity of AS is no longer routinely performed” (1), in specific circumstances left and right heart cardiac catheterization is still practised and indicated, for example in the preparation for a catheterized valve replacement. Right heart catheterization displays information about pulmonary pressures and resistance, as well as invasive characterization of the valve stenosis, which may help in discrepant non-invasive measurements. (2)

Further details about cardiac catheterization prior to the TAVI, including coronary angiography, are described in section 1.8.2.

1.6.8 Classification of AS

	Flow rate	AVA	AMG
Mild AS	2.6 – 2.9 m/s	≥1.5 cm^2	<20 mmHg
Moderate AS	3.0 – 4.0 m/s	1.5 – 1.0 cm^2	20 - 40 mmHg
Severe AS	>4.0 m/s	<1.0 cm^2	>40 mmHg

Table 1: Echocardiographic parameters (50)

Echocardiographic measurements are used to determine the severity of the AS. The main parameters are, AVA, aortic mean pressure gradient (AMG), EF and aortic velocity. Nevertheless measurements such as wall size and thickness, ventricle functionality, valve calcification, blood pressure and the functional status have to be included in prior made clinical decisions. (1)

Forms of severe AS include:

- High gradient AS – is found with an AVA < 1 cm^2 and an AMG > 40 mmHg. These findings are described as a severe AS regardless if LVEF or flow rate is normal or decreased. (1)
- Low-flow, low-gradient AS with reduced EF – same rules apply as for high gradient AS except for an EF < 50 %, a SV ≤ 35 ml/m^2 and a AMG < 40 mmHg. In this case, a low-dose dobutamine echocardiography is needed in order to establish an objective distinction between an actual severe AS and a pseudo-severe AS. While a low-flow, low-gradient AS remains the same, a pseudo-severe AS will increase its AVA to > 1.0 cm^2 as the flow rates normalizes itself. (1)
- Low-flow, low-gradient AS with preserved EF – in this scenario also the AVA is < 1 cm^2 and the AMG is < 40 mmHg, however the EF remains ≥ 50 %. This is usually the result of a hypertrophic LV, a small ventricle size and hypertension and is found within elderly patients. (1)
- Normal-flow, low-gradient AS with preserved EF – AVA < 1 cm^2, a mean gradient of < 40 mmHg and an EF of ≥ 50 % is considered a moderate AS and therefore should be diagnosed as such. (1)

1.7 Therapy

1.7.1 Medical management in asymptomatic patients

Guidelines state that no medication has shown significant evidence to improve the natural progression of the disease. Patients not eligible for surgery or awaiting transcatheter aortic valve implantation (TAVI) should be treated following the heart failure guidelines. The often co-persisting hypertension should be managed accordingly and re-evaluated frequently in order to avoid hypotension. (1)

However, a lot of research has been put into the medical management of patients suffering from AS. Although no medication is known to improve AS, Cary and Pearce suggest treatment of asymptomatic patients should focus on CVRF. If deemed necessary establishing or improving the medical therapy of hypertension, diabetes mellitus and hypercholesterolaemia as well as avoiding tobacco smoking and taming obesity should be considered. Patients should be taught about AS and its upcoming symptoms in order to be alert and additionally be assigned to follow-up appointments dependent on the severity of the AS. Regarding the progression of mild, moderate and severe AS, follow-ups including echocardiography should be done every 3-5 years, 1-2 years or 6-12 months. (8,9)

Surgical intervention is discussed controversial for asymptomatic patients even if the AS is very severe the evidence is not conclusive. Early elective surgery has to be considered very thoughtfully regarding benefits and risks. Whereas TAVI is not an option for asymptomatic patients, surgical aortic valve replacement (SAVR) is solemnly indicated when LV function is decreased for no other reason and symptoms occur in patients while exercise testing. If asymptomatic patients lack signs of predictors for symptom developments such as described in the section 1.5, watchful waiting is considered the right therapy while early surgery seems unrewarding. (1)

1.7.2 Balloon aortic valvuloplasty

Balloon aortic valvuloplasty is used for palliative patients or to bridge patients in order to receive SAVR or TAVI. Using the femoral artery as entry point, a balloon catheter is inserted and positioned within the aortic valve. Once inflated, the balloon's aim is to fracture calcified aortic leaflets to improve their mobility, discreetly enlarging the AVA and separating the joined commissures. The effects seen after this intervention are an improvement in CO, pulmonary hypertension (PH) and hemodynamic stability.

Unfortunately, the separation results only last for 3 to 6 months. Therefore this procedure is strictly used as symptom relief or in patients awaiting a TAVI or SAVR in the near future. The procedures main complications are aortic regurgitation, annulus rupture and cerebrovascular accidents and the mortality rate itself is fairly high as well. (9–11,31)

1.7.3 Surgical aortic valve replacement

This intervention is the gold standard for over 50 years and is usually made via median sternotomy. The heart is arrest while full cardiopulmonary bypass upkeeps the circulation. The surgeon removes the calcified valve as well as the aortic annulus and implements a prosthetic valve. Most mechanical valves are made of pyrolytic carbon and function with a bileaflet or a tilting-disk, which shows great results regarding durability and hemodynamic profile. However, their disadvantage is a lifelong oral anticoagulation. Usually, these types of valves are implemented in patients of young age (< 65 years). One reason being, bleeding is 7 times more likely in patients above 60 years of age and second, due to the long durability, a second operation can be spared. A repeated surgery despite the younger age of the patient leads to an increased surgical mortality as well as the risk of needing a pacemaker and aortic regurgitation after the surgery.

In older patients, biological valves designed from porcine valves and roots, or bovine pericardiums are used. Xenografts have a tendency to last between 10-20 years and have the advantage of not needing anticoagulation. This type of valve can be found with a stent supporting the valve or without. Important to note is that stentless biological valves result in a greater AVA than mechanical or stented biological valves. If the aortic annulus is small, hemodynamics of stentless valves have been superior and data implies longer durability as well.

A newer approach is the minimally invasive SAVR. With this procedure, only a partial median sternotomy is needed resulting in less pain, lower risk of postoperative AF, and a briefer hospital stay. Additionally full daily activities can be taken up sooner. (9,11–13)

Data from Europe and the USA show a low 30-day mortality rate with minimally invasive SAVR between 2-3 %. (14–16)

1.8 TAVI

1.8.1 Indications

Treatment for patients with symptomatic severe AS is best done as early as possible due to the progression of the disease. Except cases in which comorbidities overweigh too heavily, leading to an estimated survival less than 1 year and in patients where an intervention is unlikely to improve neither survival nor quality of life. (1)
Is the AMG > 40 mmHg, surgery or TAVI are advisable. More challenging are low-gradient AS patients where the therapy is as followed: (1)

- Low-flow, low-gradient AS and reduced LVEF: Is the EF reduced due to a heavy afterload, an intervention usually improves the LV function and the EF increases. A distinction between severe AS and pseudo-severe AS has to be made, because of different therapy plans. An intervention is needed in severe AS, whereas in pseudo-severe AS conventional treatment for heart failure is recommended.
  In patients with limited or no flow reserve, surgery or TAVI is still advised because of an improvement in the clinical status and the EF in the patient, even though a higher operative mortality rate is found.
  When reaching a decision regarding the therapy all factors including comorbidities, the clinical condition, valve calcification, the extent of coronary artery disease (CAD) as well as the feasibility to re-vascularize the artery should be taken into consideration. (1)
- Low-flow, low-gradient AS and preserved EF: This is the most controversial discussed and challenging subgroup of all. Data on the natural progression and on the outcome after an intervention has not led to a clear pathway. In patients like this, an intervention is recommended when symptoms are present and the evaluation of the patient shows a significant aortic valve obstruction. (1)
- Normal-flow, low gradient AS and preserved EF: If this data is found, the patient should be re-evaluated. If normal-flow and low-gradient remains the patient is likely to not have severe AS and an intervention is not beneficial or necessary. (1)

1.8.2 Pre-interventional testing

Access route

Most of the time the transfemoral route (75 %) is used, but if it is not accessible, the subclavian, axillary or transapical approach, remain an option. Besides an obligatory CT scan to check for tortuosity, calcification and size of the access site, an invasive angiography is necessary to find the perfect entry site and to examine how the vasculature reacts to the catheter manipulation.

For the iliofemoral angiography a 5 French (F) metric (graded) pigtail catheter is used to detect the vessel calibres. Particularly interesting is the area of the femoral bifurcation over the femoral head because it is used for the transfemoral approach. Calcification and tortuosity are graded from 0-3 (none, mild, moderate and severe). Patients unsuitable for the femoral access have a vessel diameter less than 6mm, significant obstructive atherosclerotic disease or ulcerated plaques and severe calcification and tortuosity. For those, an alternative route, such as the axillary or subclavian route has to be considered.

In this case the left subclavian artery supplies a better angle for a TAVI, yet the right subclavian artery is advised if the ascending aorta is orientated very vertically. The angiography of the subclavian artery is also used to exclude stenosis or tortuosity. (17)

Coronary angiography

In order to evaluate and objectivize CAD a coronary angiography is recommended prior to the TAVI. Usually this is conducted via the transfemoral approach in regards of needing to evaluate the transfemoral route and additionally needing a right heart catheterization. In elderly high-risk patients concomitant CAD is observed frequently. Therefore a percutaneous coronary intervention (PCI) is indicated prior to TAVI or at the same time of the intervention. Also the angiography can be used to determine the location and height of the coronary ostia and then they are compared with the CT results. (17)

Aortogram

The same is with the peripheral vasculature evaluation. The aorta is observed and compared with a CT scan to reduced vascular complications. Once again tortuosity, calcification, aneurysmal dilation and obstructive atherosclerosis, which would contradict a TAVI are excluded. Also, the aortic calcification and aortic regurgitation can be looked at. Fluoroscopic projections in LAO 10 and CAUD 10 deliver the best view orthogonally to

the aortic valve and the alignment of the coronary cusps, after inserting a 5 F graded pigtail catheter into the non-coronary cusp and injecting 20 milliliters (ml) contrast at 20 ml/sec. (17)

Aortic valve cross over

The main reason of this procedure is to show the feasibility to cross the aortic valve, detect the valve area and its gradient. A failure in crossing the valve, having difficulties or a lack of operator experience demonstrates no contradiction to a TAVI. However the risk of an embolic stroke from protracted manipulation within the valve should be taken into consideration and therefore a time limit of less than ten minutes from Zaman et. al is suggested.

The procedure works as follows:

"An AL1 catheter is placed into the aorta and an exchange length straight tip glide wire crossed across the aortic valve into the left ventricle. The AL1 catheter is then prolapsed into the LV and the glide wire replaced with an exchange length J wire with an exaggerated curve fashioned on the tip to increase the amount of wire within the ventricle and improve support. The AL1 can the be exchanged for the 5 F-graded pigtail." (17)

Hemodynamic assessment

In some centres use a 5 F pigtail catheter, which is pushed into the LV where the systolic and diastolic pressures can be measured. While retrieving the catheter also the transaortic gradient can be measured and compared to echocardiographic findings. (17)

However, at the university hospital in Graz a 6 F double lumen catheter is used, which is able to measure pressure gradients instantaneously.

Left ventriculogram

The LV functionality is always detected before a TAVI is committed. While the LVEF is a strong predictor for a SAVR there is not enough evidence to make a similar statement for a TAVI. Better prognostic tools to determine the myocardial function are CO and SV, which both can be detected with a right heart catheterization. The LVEDP is measured, once again using a 5 F graded pigtail catheter localized in the LV. The followed LV angiography can also show if a mitral regurgitation is present. (17)

Right heart catheterization

In order to diagnose PH or to calculate pulmonary vascular resistance a right heart catheterization has to be made. Already known is that PH, particularly if combined with an increased peripheral vascular resistance (PVR) mortality rates after SAVR incline. Data suggest that this also applies for TAVI. Severe PH is reflected in an increased LVEDP and an increased atrial pressure. Both are known to improve after implanting a new valve and removing the stenosis. Right heart catheterization is done using a 7 F femoral venous sheath and using a 7 F Swanz-Ganz catheter. Using this catheter, the pulmonary capillary wedge pressure (PCWP), right-sided cardiac pressures, and pulmonary pressures can be measured, whereas the CO is calculated using the standard thermodilution method. If the patient has cardiac-shunts or a valvular regurgitation the CO can be undependable. If the obtained CO is correct the AVA can be calculated using the Gorlin formula or the simplified Gorlin formula. Furthermore, the SV and especially the SV-index can be determined. The latter is an independent predictor of mortality when the pre-TAVI SV-index is $< 35 mL/m^2$. (17)

Measuring the aortic annulus

Measuring of the aortic annulus is crucial for the decision which size of valve to implant. Knowing the valves diameter can lower the risk of paravalvular leakage and device migration. The dimension of the prosthetic valve has to extend the measured annulus diameter a little bit in order to diminish a paravalvular aortic leakage. The following diagnostic tools are available to determine the aortic annulus: (19)

- Transthoracic echocardiography (TTE): Although it should not be the solemn diagnostic tool to determine the diameter due to examiner-depending measurement results, it is the primary one.
- Transesophageal echocardiography (TEE): This tool can be used when TTE measurements are borderline and further imaging is required. Additionally the TEE is used if TTE quality is not satisfying.
- Computer tomography (CT): In a CT the dimension of the annulus as well as cardiac anatomic structures can be seen. In many cases the aortic valve is not circular but oval. In these cases the smallest diameter can be determined using the sagittal axis of the scan in order to choose the right prosthesis size. Furthermore, the CT offers information about the distance between the annulus and the coronary ostia, as well as to which degree the valve is calcified. (21)

1.8.2.1 Choosing the right approach

Which approach will finally be used for the intervention is decided by the consensus of the heart team. However, information about the cardiac anatomy and the condition of the peripheral vessels has to be assessed carefully, as they are crucial for the decision. If the transfemoral method is planned but the approach is not possible, a transaxillary route is an option. All three options bare their contraindications mentioned in section 1.8.2.2. (19)

Heart Team

Finding the right medical, surgical or interventional therapy for each individual patient is a decision made by many. Therefore, the heart team is designed, combining several specialties including interventional cardiologists, cardiac surgeons, anaesthesiologists and radiologists.

Additionally, geriatricians, general practitioners, and specialists in the field of heart failure or electrophysiology can be part of the heart team or involved in the individual decision finding of a patient. (1)

Cardiac anatomy

In order to pursue a TAVI not only the aortic annulus has to be examined, but other structures as well. A combination of TTE, TEE, CT, angiography and cardiac magnet resonance imaging (MRI) is used to determine all of the following parameters: (19)

- If the diameter of the left ventricle outflow tract lies within 18 and 21 mm, the 23 mm Edwars SAPIEN or Edwards SAPIEN XT ® prosthesis is used. If dimensions above 21 mm occur the 26 mm Edwards SAPIEN®, Edwards SAPIEN XT® or Medtronic CoreValve® can be implanted. (22)
- Bicuspid aortic valves with an ellipsoidal orifice can cause paravalvular leakage if a cylindrical prosthesis is implanted. Therefore bicuspid valves are considered a relative contraindication. (23)
- A wide angle between the aorta and the heart can make an exact implantation very difficult. Especially if a horizontal aortic root has a vertical annulus. (19)
- A strongly calcified aortic wall (porcelain aorta) in combination with a horizontal aortic root states a strong risk of an aortic dissection if the transfemoral approach is used. In this cases the transapical implantation, or the use of self-expanding valves such as the CoreValve-System, would be preferred. (19)

- Ventricular thrombi can cause thromboembolic complications if manipulated by a guide wire or a catheter. (19)
- Between the coronary ostia and the base of the cuspids, a distance above 10 mm is needed in order to avoid an iatrogenic coronary occlusion. (21) Is the space less than described, a lower implantation of the Medtronic CoreValve® (1-2 mm lower than usual) is possible to evade the problem. This lower implantation often causes disorders in the atrioventricular transition, hence requires a permanent pacemaker therapy. (19)
- Calcified lumps on the valve can be a contraindication for a TAVI. Severe calcified lumps are able to lead to a coronary occlusion or a paravalvular leakage. (24)

Peripheral artery system

Every type of prosthetic valve needs a different intravascular diameter in order to apply the valve. Therefore, the luminal diameters of the aorta, the iliac and femoral arteries are gathered. Additionally calcification or torsion are looked at using the following diagnostic tools: (19)

- Angiography: Information about the intravascular diameters as well as the pathways of the vessels is looked at.
- Contrast-CT: High-resolution images are created to objectivize the pathways, calcifications and the intravascular diameters.
- Contrast-MRI: Here also high-resolution images are collected.

For these types of imaging a contrast agent needs to be injected. Therefore the renal and thyroid function has to be viewed and checked beforehand. In patients with severely calcified or tortuous arteries the TAVI should be done rather using the transapical, transaortic or transaxilliar approach rather than the transfemoral method. However the decision should be made by the consensus of the heart team, consisting of an interventional cardiologist, a heart surgeon and a heart-anaesthetist. (19)

1.8.2.2 Contraindication for the implantation methods

Transfemoral approach:

Depending which valve type is used during the intervention, the luminal iliac artery diameter has to be < 6 mm for the Medtronic CoreValve® and the Edwards SAPIEN XT® valve, where as for the Edwards SAPIEN® valve a diameter < 7 mm is needed. Also contraindicated are heavily calcified iliac and femoral arteries, as well as severely tortuous arteries. Aortic pathologies, such as severe atheroma in the aortic arch or an abdominal aortic aneurysm including a thrombus as well as a wormed pathway of the aorta itself are taken into consideration. (19)

Transapical approach:

This method is unfeasible for several reasons including a calcified pericardium, prior surgical interventions involving the LV or surgical difficulties in approaching the pericardium due to chest deformities. Further contraindications are the inability for endotracheal intubation as well as severe pulmonary disease. (19)

Transaxillary approach:

Similar to the transfemoral approach, a too small diameter and a heavily tortuous pathway of the subclavian artery represent a contraindication. Additionally, a precarious angiography of the carotid and vertebral artery, patients with a left or right internal mammary artery (LIMA/RIMA) bypass graft, or patients with a circumferential calcified subclavian artery proximal of the LIMA/RIMA are not able to receive a TAVI using this approach. (19)

1.8.3 Euro-SCORE I/II

The EuroSCORE (European System of Cardiac Operative Risk Evaluation) was designed to assess the mortality risk in percentage after a cardiac surgery. For the calculation numerous factors have been included. At this time two scores were available, for one the additive EuroSCORE and since 2011 the EuroSCORE II. (28)

In order to calculate a percentage each risk factor is given a different number and summed up afterwards. This calculations' approach is simple and easily feasible at the patients' bedside. The downside is that the mortality rate is rather imprecise. Particularly in high-risk patients with multiple comorbidities the mortality rate is underestimated. (28)

Therefore a newer and more complex score, the EuroSCORE II was established in 2011. This model uses a certain algorithm and a calculator found at www.euroscore.org, thus cannot be simply calculated next to the patient. (28)

1.8.4 Contraindications for TAVI

There are certain absolute and relative contraindications for TAVI:

Absolute contraindications: (6)

- For organisational or technical reasons
    - No heart surgery team on site
    - No operating room considered acceptable for a surgical heart intervention (Missing heart-lung machine or other operating room resources)
- For clinical reasons
    - Life expectancy < 1 year
    - An improvement in the quality of life is post TAVI unlikely due to the comorbidities of the patient
    - Severe disease of other heart valves causative for the symptoms of the patient and can only be repaired by surgery
- For anatomical reasons
    - Inadequate diameter of the aortic annulus (< 18 mm or > 29mm)
    - Thrombus found in the left ventricle
    - Active endocarditis
    - Expected obstruction of the coronary ostia due to asymmetric valve calcification, little distance between the annulus and the coronary ostia or small aortic sinuses
    - Access thru the femoral or subclavian artery: inappropriate size, calcification of the artery or the vessel itself is too tortuous

Relative contraindications: (6)

- Bicuspid or not calcified aortic valve
- Untreated CAD in need of revascularisation
- Hemodynamic instability
- LVEF < 20 %

- Transapical: severe pulmonary disease or no surgical accessibility to intervene through the LV.

1.8.5 Procedure

1.8.5.1 Transapical approach

The antegrade approach of a catheter-based implantation through the cardiac apex is usually done with an endotracheal anaesthesia. In high-risk patients the intervention can also be done with a special anaesthesia where the patient remains awake throughout the procedure (1).

An anterolateral thoracotomy is made near the apex of the heart in the 5th or 6th ICS. After proper preparation, the pericardium is reached and incised longitudinally. Prior to the puncture of the apex, two purse-string sutures are made and a pericardial pacemaker is implemented. After the perforation is fulfilled, an arterial guide wire is inserted and a 14 F catheter is pushed antegrade through the LV into the ascending aorta. Via Seldinger technique a balloon catheter is guided over a guide wire and positioned at the aortic valve to complete a balloonvalvuloplasty. In order to place the balloon catheter on its exact position the aortic valve is hindered in its up and downward motion and the LV is disabled to eject blood during the systole via rapid ventricular transvenous pacing. This is the reason why the temporary transvenous pacemaker is installed beforehand. As soon as the catheter is placed, the balloonvalvuloplasty can be achieved. The balloon catheter is then removed and the guide wire is used to insert the TAVI delivery system containing the new heart valve and placed in the right position. Once again rapid ventricular pacing is applied and the valve can be placed and expanded using again a balloon catheter. Directly after placing the valve, its position and function are assessed either via transesophageal echocardiography or aortography. The catheter as well as the guide wire can be removed and the myocardium of the ventricle is occluded with the already placed purse-string sutures. A chest drainage is applied and the wound is closed. (18)

1.8.5.2 Transfemoral approach

With the transfemoral approach the femoral artery is accessed after surgical preparation or percutaneously. The entry point should be below the inguinal ligament and at the height of the capitis femoris. A vascular closure system is induced in order to seal the artery properly after the completed intervention. Next, the contralateral femoral vein is punctured and a guide wire is pushed forward until the right atrium is reached. This is for safety reasons if severe complications occur. If an extracorporeal circulation is needed, a tube connected to the heart-lung machine can be inserted and applied quickly using the venous catheter as guidance. (18)

Same as in the section (1.8.5.1) above, a balloonvalvuloplasty is undertaken. In this scenario the balloon catheter is induced retrograde into the area of the aortic valve. Using rapid ventricular transvenous pacing the balloon is expanded crushing the calcified structures of the original aortic valve. After the catheter is withdrawn, the new valve is positioned onto the guide wire. Depending on the valve manufacturer, different types of valves and expanding systems are created. Some are applied with an inflating balloon whereas others have a self-expanding stent, once the stent reaches body temperature. The Medtronic CoreValve® for example is covered in a mantle to maintain its size, while the exact location is searched for. Once found, the mantle is removed and the valve extends to its original size. For this very type of valve no rapid pacing of the ventricle is needed, for different valves this may not apply. After the valve is in place, an aortography or transesophageal echocardiography is made to ensure the functionality and a suitable position. In case a paravalvular leakage occurs to be too great, the new valve can be expanded once more using balloonvalvuloplasty in order to fixate the valve deeper into the tissue surrounding it. After the new prosthetic valve is implanted, the guide wire is rejected and the femoral artery is sutured. (18)

1.8.5.3 Valve types and diameters

In Europe there are three producers of valves which are available and used.

The Edwards SAPIEN® valve for one, is a balloon expandable stainless steel-stent with three cuspids designed from bovine pericardium. It may be implanted via the transapical approach, using the Ascenda Delivery System®, or via the transfemoral method where the Retroflex 3 Delivery System® is in use. The Edwards SAPIEN XT® valve is a newer

generations issue and is made with a cobalt-chrome alloy. Both Edwards® valves are available in the sizes 23 mm and 26 mm. (19)

The Medtronic CoreValve® uses self-expanding Nitinol stents where three porcine semilunar cuspids are attached. This valve is only applicable via the transfemoral approach and is available in the sizes 26 mm and 29 mm. (19)

The Direct Flow Medical® valve is available in two sizes, 25 mm and 27 mm. It is a valve made from bovine pericardial tissue, which contains of two polyester rings that are first inflated with air until the final position is found, and after filled with a polymer solution 90 minutes is needed to dry solid. The valve itself is repositionable and fully retrievable via the introducer even after the final deployment. A benefit of the valve is that rapid ventricular pacing is not required and blood flow is never interrupted. (20)

Patients who have an aortic annulus diameter extending 27 mm or less than18 mm are not suitable for TAVI. Detecting the exact diameter prior to the intervention is very important information, regarding the appropriate prosthesis size and functionality. (19)

1.8.6 Post-interventional care

The post interventional care is usually looked after by the intensive care unit (ICU). Having no complications, the stay usually lasts only a day. The invasive blood pressure measurement used at the intervention is continued at the ICU in order to react to hemodynamic alterations. Particularly when using the Medtronic CoreValve® severe atrioventricular transition disorders can be seen. Thus the external pacemaker is mandatory after the intervention for 24 - 48 hours.

Functionality and behaviour of the new valve is assessed via TTE and during clinical examination.

If the SAPIEN® valve is implanted a combined platelet aggregation inhibition therapy is indicated, using 100 mg acetylsalicylic acid (ASA) and 75 mg Clopidogrel for 4 weeks. When the Medtronic CoreValve® is applied a dual platelet aggregation inhibition is advised lasting 6 months. After the described timeframes are over, a single therapy with 100 mg ASA is continued. (25)

1.8.7 Indications for a post interventional pacemaker therapy

A temporary pacemaker therapy is needed regardless which approach was used to perform the TAVI. For one, the pacemaker is needed to trigger the rapid ventricular pacing during the balloonvalvuloplasty and valve implantation. Secondly, due to a very close anatomical relation between the atrioventricular node and the left bundle branch (LBB) the risk for a post interventional atrioventricular block is increased. (26)

The highest risk regarding a transition disorder is given using the Medtronic CoreValve®. (27).

1.9 Aim of the study

Since the TAVI has proven itself to be equally successful as SAVR in in regards to patients' outcome in high- and intermediate risk patients new methods of risk stratification need to be developed. Therefore, this study's aim is to assess predictive value in invasively measured hemodynamic parameters. Firstly, this would become truly useful in patient selection. Secondly right heart catheterization as practised in Graz would show its significance in regards to TAVI.

2 Methods

2.1 Hypothesis

Invasive hemodynamic characteristics predict outcome after TAVI.

2.2 TAVI procedure at the university hospital of Graz

2.2.1 Screening before TAVI

Any patient with severe AS, in whom a TAVI is feasible, are scheduled for a stay prior to the intervention to conduct all pre-evaluation exams. These include, a thorough echocardiography, left and right heart catheterization, CT of the aortic valve and the whole aorta assessment of frailty, electrocardiogram and lab tests.

Left heart catheterization is done to 1) diagnose or exclude CAD, 2) check the vascular access and 3) measure pressures in the aortic valve. Diagnosing CAD before TAVI is important because it significantly alters the all-cause 1-year mortality (49). The vascular access is checked by direct fluoroscopy and by CT angiography to evaluate if the femoral artery can be punctured and if there are any stenosis, which would hinder large vascular sheets, which are necessary for TAVI. In such cases, alternative approaches have to be discussed. Lastly, LV pressures and the gradient at the aortic valve are measured. During the measurement of the CO, by right heart catheterization, the AVA is calculated.

To confirm right-ventricular pressures from echocardiography, every patient evaluated for TAVI undergoes right heart catheterization. This includes the measurements of the systolic, mean and diastolic pulmonary artery pressure (sPAP, mPAP, dPAP), mean right atrial pressure (RAP) as well as systolic, diastolic and mean ventricle pressure, PCWP and SV. Further tests are important to adequately calculate surgical risk.

2.2.2 Heart team at the university hospital of Graz

As proposed by guidelines, the heart team plays a fundamental part in the decision to perform TAVI in patients in Graz (1). After the discharge of the patient, all exam results are reviewed by, cardiologists, cardiac surgeons and cardiac anaesthesiologists. Based on risk scores, such as EuroSCORE, Score of thoracic Surgeons Score (STS-Score) or the

German Aortic Valve Score II, the individual risk is calculated (47,48). These risk scores and other individual factors, such as suitability of femoral access, are included into the final decision how to proceed with the individual patient. Patients may be scheduled for SAVR, TAVI, balloon angioplasty or no interventional therapy at all, due to a futile intervention. After the decision, the patient is contacted and an appointment for the final procedure is set.

2.2.3 TAVI at the university hospital of Graz

Approximately two days before the procedure, the patient is admitted to the normal ward and is prepared for the procedure. An interventional cardiologist performs the TAVI in a hybrid heart surgery/heart catheterization room during continuous availability of a heart surgery team. After the TAVI, the patient is monitored at the ICU for 24 hours, and afterwards at the normal ward for 72 hours. After post-procedural exams, including, echocardiography and ultrasound of the femoral artery (depending on access site), the patient is released within 7-10 days. If other access sites require further narcosis after the intervention is done, the patient will be monitored at the ICU for additional two to three days before the transfer to the normal ward.

2.3 Study design

In this retrospective study, 554 people received a TAVI between the years 2007 and 2015 and gave their consent to provide data for research purposes. A focus was set on finding a predictive value in hemodynamic parameters in regards to the 1-year mortality rate.

2.3.1 Data collection

Information about routinely done pre- and post-procedural tests (including blood draws, electrocardiograms, echocardiography and invasively measured hemodynamic parameters), comorbidities (i.e. chronic obstructive pulmonary disease IV (COPD IV), diabetes mellitus, AF, CAD, peripheral vascular disease (PVD), cerebral vascular disease (CVD)) as well as data of the procedure itself was collected via a hospital information system (MEDOCS) and added to the pre-existing TAVI Registry of Graz.

In the same method, information about the procedure itself was obtained (valve types, access route and successful implantation).
In regards to the hypothesis, a special focus was set on the hemodynamic parameters gathered during a cardiac catheterization prior to the intervention. These parameters included right atrial and left and right ventricle pressures, the PCWP, CO, SV, LVEDP as well as aortic pressures and gradients (AMG, aortic peak gradient (APG), systolic and diastolic aorta pressure).
Information about possible deaths of subjects after the procedure was gathered by carrying out a comparison between our data set and the death registry of Statistik Austria (29).

Subjects diagnosed with end stage kidney failure have been excluded from further analysis since their mortality may be driven by different factors and due two their small number.

The ethics committee of the Medical University of Graz has certified the study (**27-114 ex 14/15**).

2.3.2 Inclusion criteria

- Male and female patients who received a TAVI between 2007 and 2015 and have given their consent
- Complete set of hemodynamic parameters including: sPAP, mPAP, PCWP, LVEDP, AMG, APG

2.3.3 Exclusion criteria

- Incomplete set of hemodynamic parameters
- Incomplete set of demographic parameters
- Incomplete set of comorbidities

2.4 Statistics

The statistical analysis has been carried out with IBM STATISTICS SPSS Version 25. All figures have been created with Microsoft® Excel® for Mac 2011 and IBM STATISTICS SPSS Version 25.

The descriptive analysis of the entire study population as well as the analysis only regarding subjects with a complete set of hemodynamic parameters has been carried out. The focus was set on the post interventional mortality after 365 days.

Focusing on the Kolmogorow-Smirnow test either the median or the arithmetic mean of the gathered parameters will be demonstrated. In the descriptive analysis the student's t-test was used to compare sex throughout numerous categories. Out of all data collected the chosen hemodynamic parameters were set to be the sPAP, dPAP, mPAP, PCWP, RAP, and AMG. In addition, all of these have been looked at individually and combined in COX-regression models. Also included into the regression analyses were sex, age, estimated glomerular filtration rate (eGFR), EF and comorbidities such as COPD IV, PVD, CVD, CAD, stroke, diabetes type 2, arterial hypertension and AF.

While creating the regression analysis, multiple models have been tested in order to examine the hemodynamic parameters most thoroughly. The final COX-regression model was calculated using the "Forward: conditional" method. Additionally, the confidence interval (CI) of the odds ratio (OR) was calculated.

Two Kaplan-Meier estimators were created to show survival outcomes in the overall and based on gender. In regards to calculate the equality of the survival distribution the Wilcoxon test was used.

3 Results

3.1 Study population

Of the 554 subjects looked at in this study, 346 were female, representing 62.5 % of the total, and 208 were male with 38 % of the total (see Figure 1). At the time of the intervention the average age was 83 years, with the youngest being a 62-year-old and the oldest being 94 years, both female. In regards to the interquartile range the majority of the subjects were between 79 and 85 years of age. Both genders are displayed separately in Figure 2.

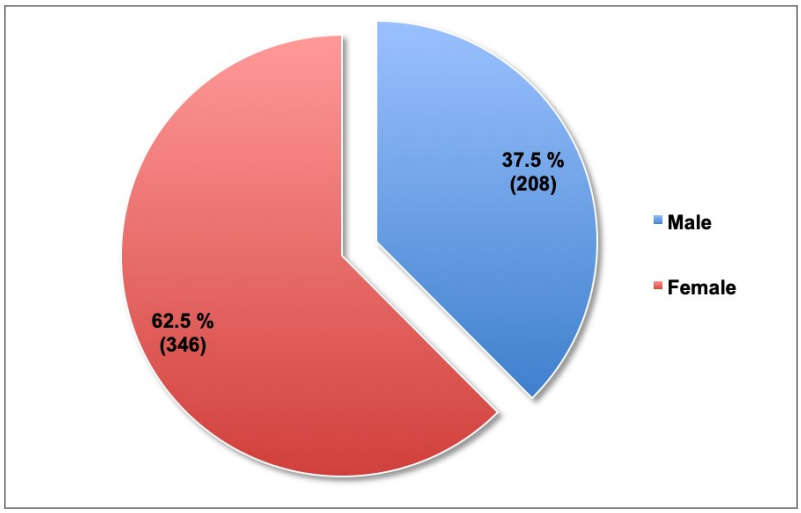

Figure 1: Gender distribution

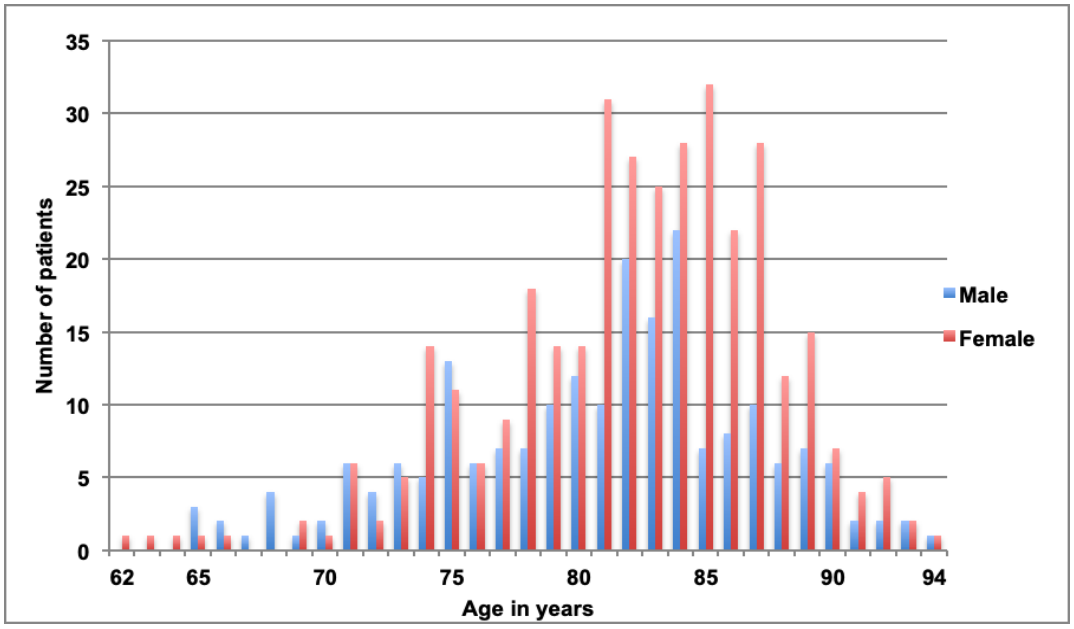

Figure 2: Age distribution based on gender

In the study univariable COX regression analyses have been carried out in all subjects, with the number of patients varying (see section 3.5). However, in the multivariable COX regression analysis only subjects with complete data sets have been used, which can be seen in section 3.6. A flow chart of the study is shown in Figure 3.

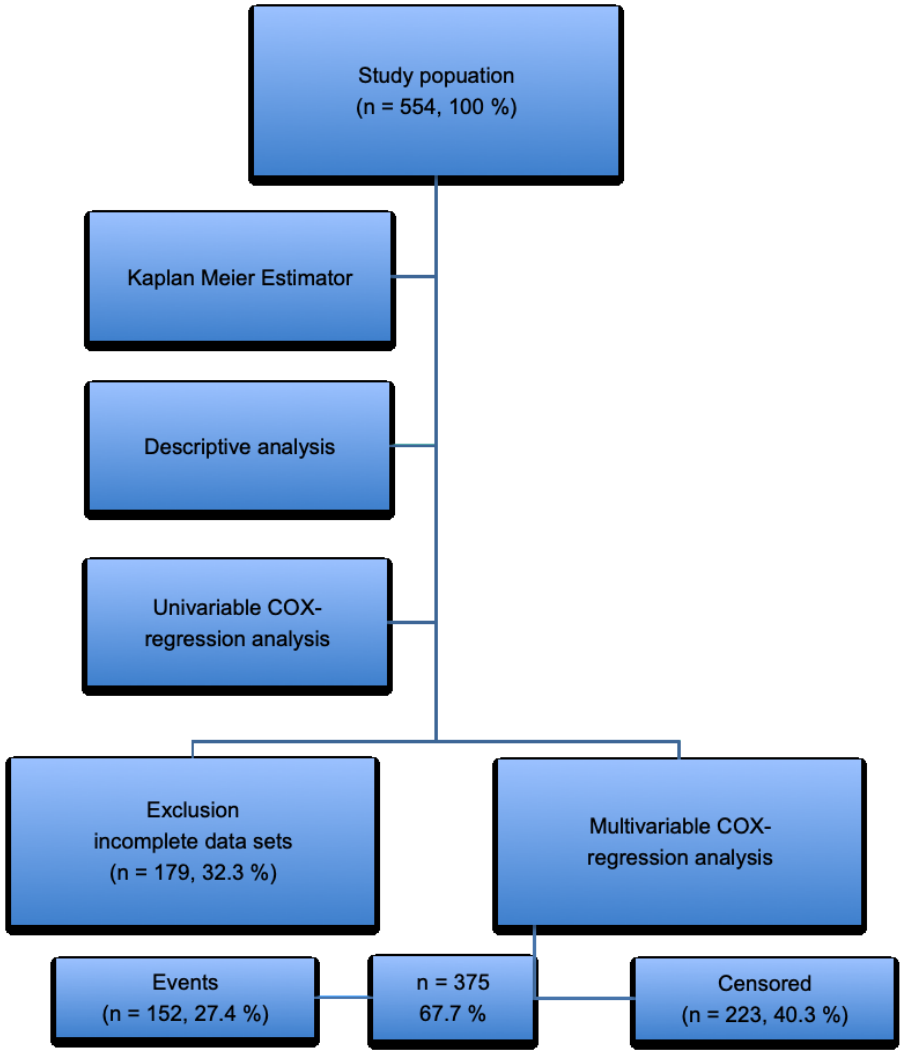

Figure 3: Study population flow chart

3.2 Comorbidities and hemodynamic parameters

During the time of the study the most common comorbidity in the entire study population was arterial hypertension with 79.1 % followed closely by CAD with 65.9 %. In Figure 4 comorbidities are demonstrated separately for gender.

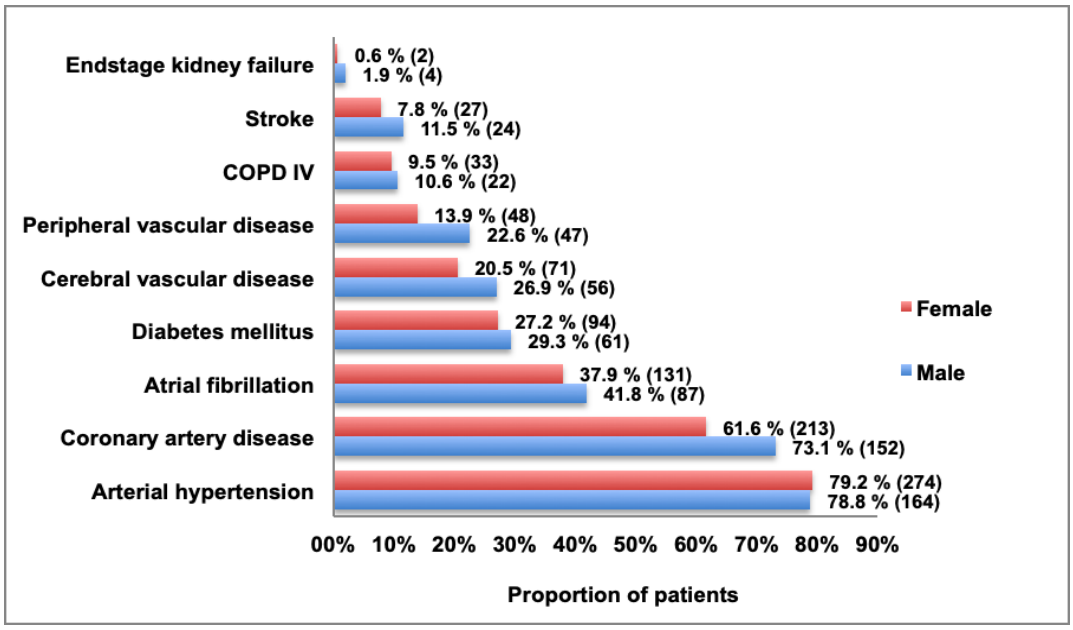

Figure 4: Comorbidities by gender

In Table 2 the measurements of invasively measured pulmonary pressures for each gender can be seen. If comparing the medians of males and females a statistical significance can be seen among all four pressures. In both groups, whether surviving 365 days after TAVI or dying within 365 days after the procedure, it can be seen that the sPAP (45 mmHg) was higher than its normal value (cut off value 30 mmHg) (30). Additionally to this finding, the mPAP was elevated as well with values above 25 mmHg (32). Parameters such as PCWP and dPAP where elevated too (32).

Parameter	n available	Male	n available	Female	p-value
sPAP	156 (75.0 %)	45 (32 - 62) mmHg	262 (75.7 %)	44 (33 - 58) mmHg	< 0.001
mPAP	156 (75.0 %)	28 (19 - 37) mmHg	262 (75.7 %)	29 (21 - 37) mmHg	< 0.001
dPAP	148 (71.2 %)	16 (11 - 23) mmHg	249 (72.0 %)	17.4 (± 7.7) mmHg	< 0.001
PCWP	155 (74.5 %)	17 (12 - 24) mmHg	261 (75.4 %)	17 (11 - 24) mmHg	< 0.001

Table 2: Invasive pulmonary pressures based on gender
(* p-value < 0.05)

Figure 5 shows the different types of PH based on gender prior to the intervention. 135 (39 %) of all female, and 78 (37.5 %) of all male subjects had post-capillary PH, of which 130 (37.6 %) women and 71 (34.1 %) men showed to have a combined form of PH.

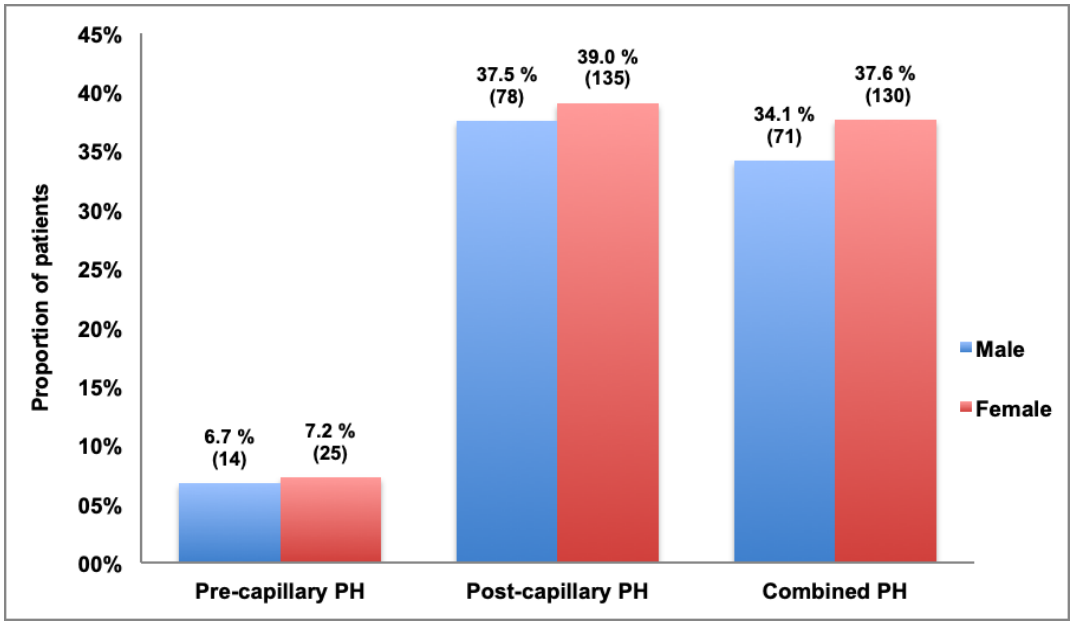

Figure 5: Types of PH based on gender (32)

In Table 3 other baseline characteristics such as age, AVA, AMG, estimated Glomerular Filtration Rate (eGFR) as well as the EuroSCORE 2 and STS-Score are demonstrated. When stratified by gender, a statistically significant difference among all groups can be seen. Additionally the AMG has been tested if low-flow low-gradient AS is present in the data set, showing that 154 (27.8 %) subjects, have an AVA less than 1 cm^2 and an AMG below 40 mmHg. This accounts for 59 (28.4 %) of all men, and 95 (27.5 %) women.

Parameter	n available	Male	n available	Female	p-value
AMG	170 (81.7 %)	44 (34 - 56) mmHg	280 (80.9 %)	47 (33 - 61) mmHg	< 0.001
AVA	148 (71.2 %)	0.6 (0.5 - 0.8) cm^2	256 (74.0 %)	0.5 (0.4 - 0.6) cm^2	< 0.001
eGFR	208 (100 %)	72 (57- 89) ml/min	342 (98.9 %)	62 (49 – 84) ml/min	< 0.001
Age	208 (100 %)	82 (76 - 84) years	346 (100 %)	83 (79 - 86) years	< 0.001
ES	208 (100 %)	4.82 (2.82 – 8.67)	342 (98.9 %)	5.21 (3.37 – 8.41)	< 0.001
STS-Sc	208 (100 %)	3.13 (2 – 4.44)	342 (98.9 %)	3.84 (2.74 – 5.91)	< 0.001

Table 3: Baseline characteristics based on gender
(ES = EuroSCORE 2, STS-Sc = STS-Score)
(* p-value < 0.05)

Figure 6 objectivizes the EF between male and female and depicts four categories, "< 20 %", "20 – 30 %", "30 – 50 %" and "> 50 %". Most of the females (233 (67.3 %)) and 98 (47.1 %) males can be seen in category "> 50 %".

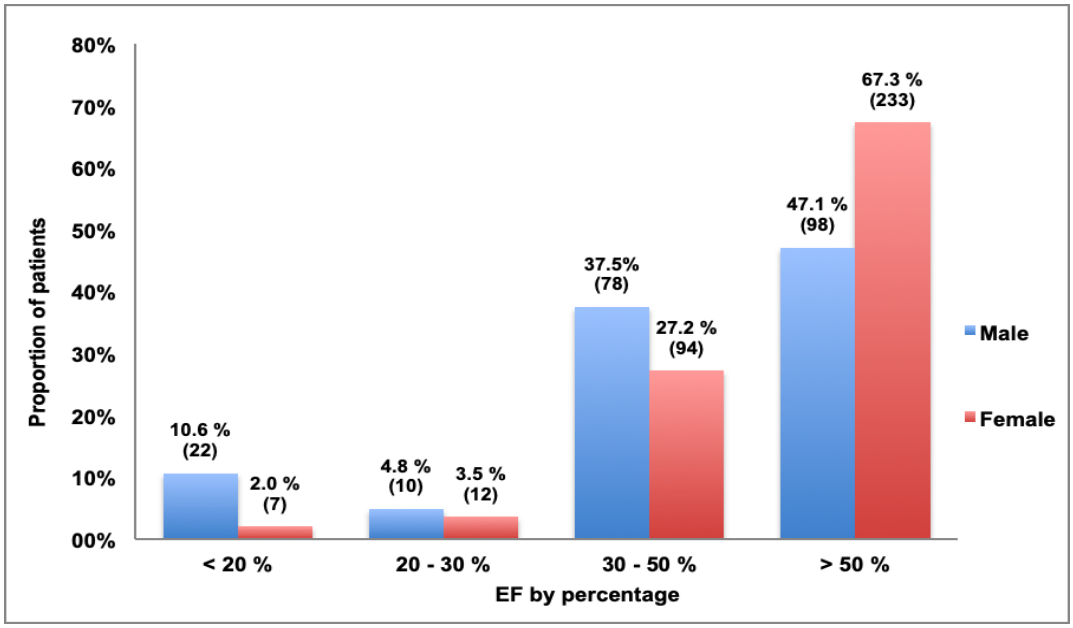

Figure 6: Ejection fraction based on gender

3.3 Procedure

Table 4 shows, that the Medtronic CoreValve® with 508 (91.7 %) applications, out of 550 implantations, was mostly used. The Direct Flow Medical® was used 38 (6.9 %) times and St. Judes Portico as well as the BS Lotus only twice.

N=550	CoreValve	Direct Flow	BS Lotus	St. Judes Portico
Applications	508 (91.7 %)	38 (6.9 %)	2 (< 0.1 %)	2 (< 0.1 %)

Table 4: Valve types applied

The most frequently used access route was the transfemoral approach with 527 (95.1 %) accesses. The transaortal approach was chosen 22 (6.9 %) times, where as the subclavian access was only used 2 (0.4 %) demonstrated in Table 5.

N=551	Transfemoral	Transaortal	Subclavian
Accesses	527 (95.1 %)	22 (6.9 %)	2 (< 0.1 %)

Table 5: Access routes used

Depending on the Valve Academic Research Consortium (VARC) guidelines to determine if an intervention was successful or not, 512 patients (92.4 %) have been implanted successfully, where as 38 (6.9 %) were not (see Table 6). (37)

N=550	Success	Failure
Implantations	512 (92.4 %)	38 (6.9 %)

Table 6: Implantation success depending on VARC guidelines

3.4 Follow up

Figure 7 shows the difference in mortality after 365 days in regards to gender of the entire study population. 13.5 % of male participants died after a year, whereas only 10.4 % of all female subjects passed away. In other words 28 male subjects and 36 female subjects have died during this time period, showing a statistical significant (p = 0.021). EuroSCORE 2 and STS-Score medians in regards to gender can be seen in Table 3.

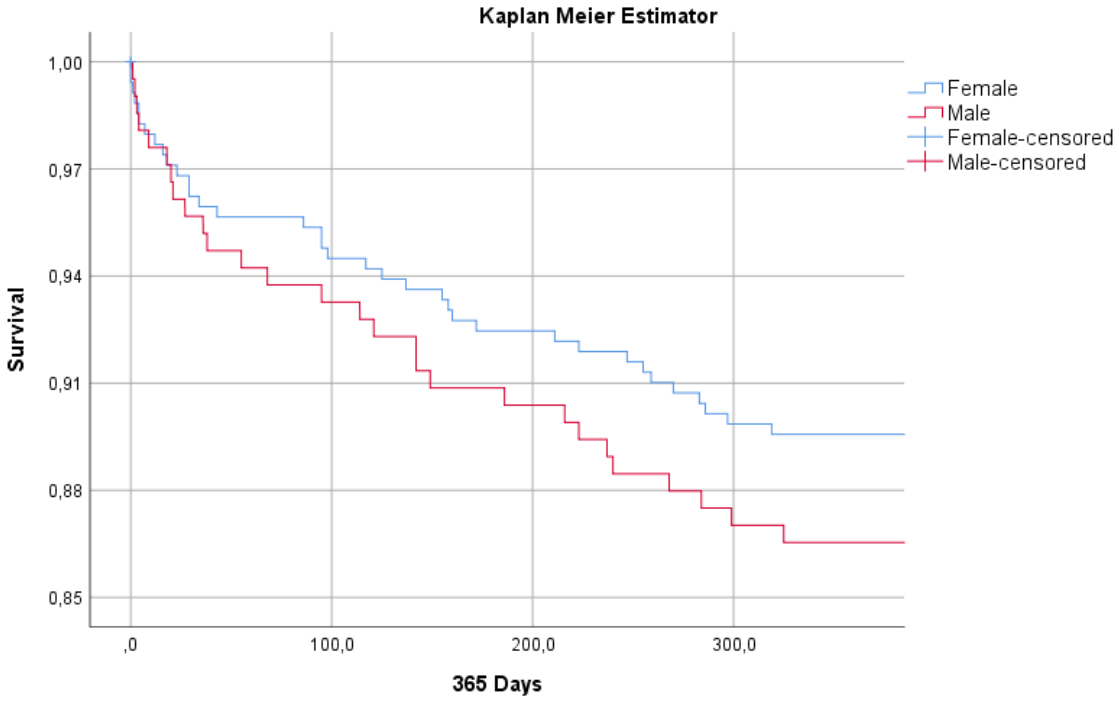

Figure 7: Kaplan Meier Estimator based on gender

In Figure 8 a Kaplan Meier Estimator has been created showing all 554 subjects included in the study. After 365 days 64 subjects have passed away, which represents a 1-year mortality rate of 11.6 % of the study population. The EuroSCORE 2 median of the study population was 5.12 (3.14 – 8.56) and the STS-SCORE median was 3.55 (5.32 – 2.47).

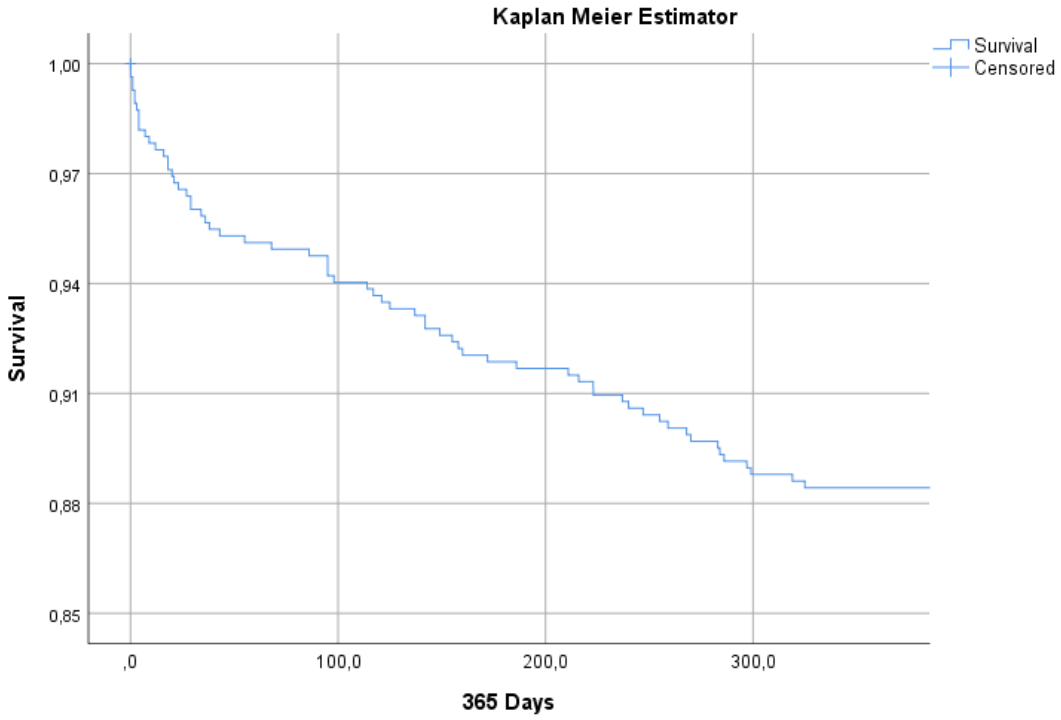

Figure 8: Kaplan Meier Estimator 1-year morality

In Table 7, the medians between subjects surviving at least 365 days and those who did not are compared showing statistical significance. It can be seen that subjects who have passed way were slightly older, had higher pulmonary pressures and risk scores, a smaller AVA and AMG, and a worse kidney function.

Parameter	n available	survived 365 days	n available	died	p-value
Age	490 (100 %)	82 (78 – 85) years	64 (100 %)	83 (79 – 87) years	< 0.001
sPAP	362 (73.9 %)	44 (33 – 57) mmHg	56 (87.5 %)	51 (35 – 64) mmHg	< 0.001
dPAP	364 (74.3 %)	16 (11 – 22) mmHg	51 (79.7 %)	18 (14 – 25) mmHg	< 0.001
mPAP	362 (73.9 %)	28 (20 – 37) mmHg	56 (87.5 %)	33 (22 – 38) mmHg	< 0.001
PCWP	362 (73.9 %)	17 (11 – 24) mmHg	54 (84.4 %)	18 (13 – 24) mmHg	< 0.001
RAP	348 (71.0 %)	6 (4 – 10) mmHg	51 (79.7%)	8 (5 – 11) mmHg	< 0.001
AMG	390 (79.6 %)	46 (34 – 61) mmHg	60 (93.8 %)	41 (28 – 52) mmHg	< 0.001
AVA	358 (73.1 %)	0.57 (0.45 – 0.70) cm^2	56 (87.5 %)	0.51 (0.38 – 0.77) cm^2	< 0.001
eGFR	490 (100 %)	66 (52 – 86) ml/min	64 (100 %)	59 (47 – 89) ml/min	< 0.001
ES	485 (99.0 %)	5 (3.10 – 8.20)	64 (100 %)	6.29 (4.37 – 10.65)	< 0.001
STS-Sc	485 (99.0 %)	3.46 (2.41 – 5.24)	64 (100 %)	4.40 (2.94 – 6.42)	< 0.001

Table 7: Median differences based on 1-year mortality
(ES = EuroSCORE 2, STS-Sc = STS-Score)
(* p-value < 0.05)

3.5 Univariable analysis

Depicted in Table 8 are numerous univariable COX-regression analyses. Depending on the data sets, "n" varies among the categories. Variables, such as the dPAP (p = 0.029), the RAP (p = 0.002) and the AMG (p = 0.005), as well as in the eGFR (p = 0.008), show to be statistically significant.

Parameter	n available	median	p-value*	OR + 95 % CI
sPAP	418 (75.5 %)	44.0 (33 – 59) mmHg	0.064	1.008 (1.000 – 1.017)
dPAP	397 (71.7 %)	17 (12 – 22) mmHg	0.029*	1.022 (1.002 – 1.042)
mPAP	418 (75.5 %)	29 (20 – 37) mmHg	0.052	1.013 (1.000 – 1.026)
PCWP	416 (75.1 %)	17 (11 – 24) mmHg	0.164	1.012 (0.995 – 1.030)
RAP	399 (72.0 %)	7 (4 – 10) mmHg	0.002*	1.051 (1.019 – 1.084)
AMG	450 (81.2 %)	46 (33 – 60) mmHg	0.005*	0.989 (0.981 – 0.997)
AVA	414 (74.7 %)	0.57 (0.44 – 0.70) cm^2	0.472	1.343 (0.601 – 3.002)
eGFR	550 (99.3 %)	70 (51 – 87) ml/min	0.008*	0.992 (0.987 – 0.998)
Age	554 (100 %)	82 (78 – 86) years	0.449	0.991 (0.969 – 1.014)
Sex	554 (100 %)		0.066	1.286 (0.983 – 1.683)

Table 8: Univariable COX regression of hemodynamic measurements and baseline characteristics (* p-value < 0.05)

In addition, an univariable COX-regression of all comorbidities has been completed, where OR above 1.7 for PVD and COPD IV can be seen. Other factors, except AF, do not show any significance (see Table 9).

Parameter	n available	p-value	OR + 95 % CI
COPD IV	554 (100 %)	0.003*	1.706 (1.192 – 2.440)
PVD	554 (100 %)	<0.001*	1.777 (1.310 – 2.411)
CVD	554 (100 %)	0.856	0.972 (0.716 – 1.320)
CAD	554 (100 %)	0.411	1.128 (0.847 – 1.501)
Stroke	554 (100 %)	0.458	0.833 (0.514 – 1.350)
Diabetes mellitus	554 (100 %)	0.350	1.146 (0.861 – 1.525)
Art. hypertension	554 (100 %)	0.148	1.301 (0.910 – 1.860)
AF	554 (100 %)	<0.001*	1.334 (1.155 – 1.541)

Table 9: Univariable COX-regression of the comorbidities (* p-value < 0.05)

3.6 Multivariable analysis

In the multivariable COX-regression 179 subjects have been excluded due to missing values. Of the remaining 375 participants, 223 have been censored. At the beginning of the equation already nine factors were excluded because they exceeded the exclusion criteria of $p > 0.10$ (AVA, EF, Age, Sex, CVD, stroke, diabetes mellitus, CAD, arterial hypertension). In the first step of the calculation PVD, being the most significant was added. After three more steps introducing RAP, COPD IV and eGFR to the equation, no more variables could be added, due to losing their significance with every stage of the COX-regression model. The significance values of all variables after four phases of the COX equation can be seen in Table 10, as well as the OR of those parameters, which met the criteria until the last step.

Parameter	n = 375	events = 152	censored: 223	p-value	OR + 95 % CI
PVD				<0.001*	2.023 (1.400 – 2.922)
RAP				0.007*	1.046 (1.012 – 1.082)
COPD IV				0.028*	1.646 (1.057 – 2.565)
eGFR				0.037*	0.993 (0.986 – 1.000)
AF				0.169	
Age				0.230	
Art. hypertension				0.232	
AMG				0.397	
Diabetes mellitus				0.428	
CVD				0.440	
PCWP				0.531	
Sex				0.553	
Stroke				0.735	
mPAP				0.757	
EF				0.839	
CAD				0.916	
sPAP				0.930	
dPAP				0.975	

Table 10: Final model of the multivariable COX-regression and the p-values of excluded variables (* p-value < 0.05)

4 Discussion

The findings of this study suggest that invasively measured hemodynamic parameters might have the potential to become a predictive value in regards to the 1-year mortality of all patients receiving a TAVI.
Statistically speaking, the collected data was able to produce evidence indicating that the invasively measured RAP is significant in regards to the 1-year mortality. Furthermore, it is shown that comorbidities such as PVD, eGFR and COPD IV have a statistical significance in patient outcome and therefore have a predictive value.

In this study the median age was 83 years and comorbidities such as arterial hypertension (79.1 %), CAD (65.9 %) and AF (39.4 %) were most dominant. Even though, COPD IV was only diagnosed 55 (9.9 %) and PVD 51 (9.2 %) times in total, these factors show to be statistically significant as a predictive value for the 1-year mortality after TAVI (see Table 10).

Similar to the above-mentioned comorbidities, the RAP remains significant in the univariable ($p = 0.002$) as well as in the multivariable ($p = 0.007$) analysis with an OR of 1.046 (1.012 – 1.082). By comparing the median within both groups in Table 7, in regards to 1-year mortality, RAP is lower in patients surviving 365 days. However, other pressures obtained from right heart catheterization do not show significance. Since literature is rare on RAP being a predictive value, further research needs to be done to detect its possible value.

According to Table 2, elevated values of sPAP, dPAP, mPAP and PCWP, including the interquartile range, were found indicating PH. Based on the PH guidelines classification, a total of 39 (7 %) subjects had pre-capillary PH and 213 (38.4 %) had post-capillary PH of which 201 (36.3 %) subjects can be classified as having combined PH (32).
Comparing the medians of the pulmonary pressures in the two categories seen in Table 7, it can be noted that within the “died” group pressures are significantly higher.
A high prevalence of PH in combination with severe AS is not a new finding since it had already been postulated in 1993, when a prevalence up to 29 % was described (40). However, elevated values of sPAP have been under research before. In the research paper by Lucon A, Oger E, Bedossa M, et al., the prognostic implication of PH was under

investigation by measuring the sPAP via echocardiography. They created three groups (sPAP < 40 mmHg, sPAP 40 to 59 mmHg and sPAP > 60 mmHg) showing a statistical significance in regards to 1-year mortality for the latter two (41). However, in this study neither the sPAP, nor other invasively measured parameters, used to classify PH, could show significance as a predictive value for the 1-year mortality in the multivariable analysis.

Reviewing the results of the AMG, univariable (p = 0.005) but not multivariable, significance was shown. However, the AMG is very helpful in classifying severe AS into its subgroups (see section 1.6.8) and is described for the entire study population in section 3.2. Therefore, it can determine if low-flow low-gradient AS is present, which is associated with a higher operative mortality, especially if comorbidities are present (1).

In Figure 8, the 1-year mortality rate (11.6 %) of the entire study population is illustrated. Compared to the gender based 1-year mortality rate seen in Figure 7, a worse outcome in men with 13.5 % deaths versus 10.4 % deaths in women is depicted with a statistical significant difference (p = 0.021). In regards to the procedure, the Medtronic CoreValve® was used 508 (92.4 %) times and the implantation success rate following the VARC guidelines was 93.1 %. As access route, the transfemoral approach was used 527 (95.1 %) times in comparison to the transaortal route which was chosen 22 (6.9 %) times. These procedural facts make the study comparable to the Italian registry from Tamburino et al. in 2011, where 663 patients underwent TAVI using the transfemoral approach and a Medtronic CoreValve® resulting in a 1-year mortality rate of 15.0 % (35).
However, the German Aortic Valve Registry combines data from 78 sites leading to a total of 2694 transvascular aortic valve implantations, having a worse 1-year mortality rate of 20.7 % (42). Furthermore, keeping an eye on the results seen in Table 10 in regards to COPD and PVD, it needs to be stated that the collective in the Italian registry shows 21.3 % diagnoses of COPD and 19.2 % diagnoses of PVD, by far more than seen in Figure 4; hence making a higher 1-year mortality rate more likely (35).

Referring to COPD IV (9.9 %) in the COX-regression model, a significance of p = 0.028 and an OR of 1.646 (1.057 – 2.565) (see Table 10) can be observed. These results are consistent with previous studies. Brown, James M. et al. has found COPD prevalences within TAVI patients ranging from 14.2 % to 43.4 % (43). In studies such as from Mok M,

Nombela-Franco L and Dumont E et al., patients undergoing TAVI without COPD had an 84.5 % expectancy of survival in comparison to subjects with COPD, who had a 70.6 % survival chance (p = 0.008) (44). Additionally, the study shows that COPD could act as a marker in regards to TAVI futility, with a third of the COPD patients included in the study, having no signs of benefit, in regards to a six minute walk test (44).

Almost similar to the COPD findings, high 1-year mortality rates for PVD patients undergoing TAVI, are described by the systematic review of Ueshima, Barioli, and Fovino, L, et al. They pointed out that the all-cause mortality rate amongst the mid-term follow up category, including 12.127 (2.931 with PVD) subjects, was worse with PVD than without PVD, having a hazard ratio of 1.18, 95 % CI 1.08–1.30, (p = 0.0005) thus being statistically significant (45). Conclusively, the statistical significance in this study (p > 0.001) and the OR (2.023 (1.400 – 2.922)) is rather not surprising.

In this multivariable COX-regression model, eGFR shows to be statistically significant as a predictive value for the 1-year mortality with a p-value of 0.037, (OR 0.993 (0.986 – 1.000)). The data of the entire study population, if analyzed univariably, shows a median of 70 (51 – 87) ml/min and also a statistical significance (p = 0.008). Comparing the medians of both groups (“died” and “survived 365 days”) in Table 7, also proves to be significant. Thus, these results consilience with the ones found by Voigtländer L, Schewel J, Martin J et at., who have conducted a study, finding that eGFR has a significant impact on 1-year morality. Furthermore, they could establish that if kidney function improves post TAVI, the mortality rate does as well (46).

4.1 Limitations

First of all, the monocentric study population needs to be seen as a limiting factor itself. Due to its inhomogeneity, the comparability within the study, as well as in regards to other studies is challenging. Furthermore, 32.3 % of all subjects, as well as potential information were lost because of an incomplete data set, limiting the power of the study.
Secondly, a comparison between different valve types or access routes in regards to the 1-year mortality would be ignorant, since the transfemoral approach, as well as the Medtronic CoreValve® was almost used exclusively.
Thirdly, right heart catheterization results often vary due to measurement errors and physiologic variations (38), which limits the statistical power.

5 Conclusion

Overall this study was able to show a significant association between the right atrial pressure and the 1-year mortality rate after TAVI. Therefore, the RAP could act as predictive value in the TAVI outcome. However, considering the above-mentioned limitations, the accuracy of the measurement itself, as well as its value, need to be treated carefully since this is the first study to accomplish this finding. According to the outcome of the study, right heart catheterization, could not establish any further significant results in regards to survival, since values such as sPAP, dPAP, mPAP or PCWP have shown no statistical evidence. The results were partially concordant with statistically significant findings from previous studies, confirming that comorbidities such as COPD, PVD and kidney function are associated with a higher mortality and therefore need to be considered in regards to patient selection and possible futility of a TAVI. Further research needs to be committed in order to determine whether RAP can be used as predictive value in TAVI patients.

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