Diploma Thesis

Assessment of Quality of Life and Functional Status after Percutaneous Aortic Valve Replacement

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Declaration

I hereby declare that I, Amra Alickovic, have independently written this thesis. My research has been conducted without assistance from third parties, other than the sources recorded within the document. Furthermore, concepts and conclusions directly or indirectly acquired from existing publications are distinguished as such.

Graz, December 2010 …… *Signature*

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Hvala!

Abstract

Background: Aortic stenosis (AS) is a disease with high prevalence and severe prognosis. Percutaneous aortic valve replacement (PAVR) is an alternative therapeutic option for high-risk patients with severe symptomatic AS and significant co-morbidities which may preclude them from surgical valve replacement. This study was undertaken to primarly assess the impact of PAVR on the change in Quality of Life (QoL) in our study population. Additionally, biomarkers have become increasingly important for diagnosis, risk stratification and evaluation of response to therapy in various cardiovascular diseases. We therefore sought to determine alterations in functional parameters and cardiac biomarkers in the same study group before and after PAVR.

Materials and methods: From December 2009 to November 2010 30 consecutive patients with severe symptomatic aortic valve stenosis (mean age 80 ± 5 years; AVA 0.63 ± 0.21 cm^2) and the indication for PAVR were enrolled. Seven different tests were employed to assess various aspects of QoL: The SF-36-Health Survey, Minnesota Living with Heart Failure Questionnaire (MLHFQ), Hospital Anxiety and Depression Scale (HADS), General Self Efficacy (GSE), ENRICHD Social Support Instrument (ESSI), Physical Activity Scale and the Maastricht Questionnaire were completed at baseline, 30 days and 6 months following PAVR. Functional improvement was assessed using echocardiography. Biomarker-analysis included routine parameters (e.g. NT-pro BNP, C-reactive protein, creatinine, haemoglobin and troponin T (TnT)), as well as novel biomarkers such as homoarginine, asymmetric and symmetric dimethylarginine (ADMA and SDMA), myeloperoxydase (MPO) and the highly sensitive troponin T (hs-TnT).

Results: In all patients, PAVR resulted in an acute procedural success as indicated by a significant improvement in aortic valve area (AVA) and mean pressure gradient. This was associated with an improvement in the summarized physical health score, as assessed by the SF-36, 30 days and 6 months after PAVR, whereas the mental health summarized score remained nearly unchanged. Similarly, the physical MLHFQ subscale was characterized by a significant improvement in QoL while there was no significant change in emotional subscales of the MLHFQ. Interestingly, we did not observe any significant change in depression and anxiety according to the HADS. All patients reported positive general self efficacy and social support before the intervention and there was no further improvement after PAVR detectable by GSE and ESSI. PAVR resulted in a significant increase in easy physical activity after 30 days and in moderate physical activity after 6 months. Vital exhaustion as assessed by the

Maastricht Questionnaire was robustly increased in our study population before PAVR. However, despite a tendency for improvement at the 30 days follow up, there was no significant change found when comparing the baseline and the follow up scores. With respect to biomarkers, AS was found to be associated with significantly increased levels of MPO, hs-TnT, homoarginine and NT-proBNP. Changes in MPO (and TnT) appear to closely reflect myocardial injury and inflammation before, in response to PAVR, and during recovery.

Conclusion: PAVR leads to a significant improvement in various parameters of QoL, in particular physical QoL. Further studies are warranted to establish the role of MPO for risk stratification and prognosis in AS.

Zusammenfassung

Hintergrund: Die Aortenklappenstenose (AS) ist eine Erkrankung mit hoher Prävalenz und schlechter Prognose. Der perkutane Aortenklappenersatz (PAVR) stellt eine alternative Therapiemöglichkeit für Patienten mit hochgradiger symptomatischer AS, hohem Operationsrisiko und signifikanten Begleiterkrankungen dar. Das primäre Ziel dieser Studie war den Einfluss des PAVR auf die Lebensqualitäts (QoL) in unserer Studienpopulation zu quantifizieren. Im Rahmen verschiedener kardiovaskulärer Erkrankungen nehmen Biomarkern zunehmend eine Schlüsselrolle in der Diagnosestellung, der Risikostratifizierung und in der Evaluierung des Therapieerfolges ein. Daher war ein weiteres Ziel dieser Arbeit, die Veränderungen von funktionellen Parametern und kardialen Biomarkern in unserer Studiengruppe vor und nach PAVR zu bestimmen.

Materialien und Methoden: Im Zeitraum von Dezember 2009 bis November 2010 wurden 30 konsekutive Patienten (Alter: 80 ± 5 Jahre, AVA: 0.63 ± 0.21 cm^2) mit hochgradiger symptomatischer AS und der Indikation zur PAVR in die Studie eingeschlossen. Sieben verschiedene Fragebögen wurden eingesetzt, um diverse Aspekte der Lebensqualität zu evaluieren (vor PAVR, sowie 30 Tage und 6 Monate nach PAVR): Short Form-36 (SF-36), Minnesota Leben mit Herzinsuffizienz Fragebogen (MLHFQ), Hospital Anxiety and Depression Scale (HADS), General Self-Efficacy Scale (GSW), ENRICHD Social Support Instrument (ESSI), Körperliche Betätigungsskala (KöBet) und der Maastricht Fragebogen.
Die Verbesserung der Funktionsparameter wurde mittels der Echokardiografie ermittelt. Die Analyse der Biomarker inkludierte Routineparameter (z.B. NT-pro BNP, C-reaktives Protein, Kreatinin, Hämoglobin und Troponin T (TnT)) und auch neuere Biomarker wie Homoarginin, asymmetrisches und symmetrisches Dimethylarginin (ADMA und SDMA), Myeloperoxydase (MPO) und hoch sensitives Troponin T (hs-TnT).

Ergebnisse: Die PAVR resultierte bei allen Patienten in einem akutem prozeduralen Erfolg, gekennzeichnet durch eine signifikante Verbesserung der Aortenklappenöffnungsfläche (AVA) und eine Reduktion des mittleren Druckgradienten über die Aortenklappe. Dieses war mit einer signifikanten Verbesserung des Physical-Health-Summenscores im SF-36 nach 30 Tagen und 6 Monaten assoziiert., demgegenüber blieb der Summenscore für die mentale Gesunheit nahezu unverändert. In ähnlicher Weise wurde auch die physische Subskala des MLHFQ positiv beeinflusst, während PAVR keine signifikanten Einfluss auf die emotionale Subskala hatte. Interessanterweise konnte in der HADS-Auswertung keine signifikante Veränderung bei den Depressions- und Angstkomponenten gefunden werden. Alle Patienten

zeigten positives Selbswerteinschätzungsvermögen und soziale Unterstützung bereits vor der Intervention. Postinterventionell zeigte sich deshalb keine weitere Verbesserung in der GSW- und ESSI-Auswertung. PAVR führte zu einem signifikanten Anstieg von körperlichen Aktivitäten mit leichter Beanpsruchung nach 30 Tagen und von Aktivitäten mit stärkerer Beanspruchung nach 6 Monaten. Die vitale Erschöpfung, bewertet durch den Maastricht Fragebogen, war in unserer Studienpopulation präinterventionell stark verschlechtert.

Trotz Verbesserungstendenz (in der vitalen Erschöpfung), beim 30 Tage Follow up, konnte in der Folge im Vergleich zu den Ausgangsscores keine signifikante Veränderung beobachtet werden. Anhand der Biomarkerbestimmungen konnte eine Assoziation zwischen AS und erhöhten Werten von MPO, hs-TnT, Homoarginin und NT-pro BNP beobachtet werden. Veränderungen bei MPO (und TnT) scheinen die Schädigung des Myokards und die Inflammation vor, als unmittelbare Reaktion auf PAVR, und während der postinterventionellen Erholungsphase genauer wieder zu spiegeln.

Konklusion: Die PAVR führt zu einer signifikanten Verbesserung von verschiedenen Parametern der QoL, vor allem zu einer Steigerung der physichen Lebensqualität. Weitere Studien sind erforderlich, um die Rolle der MPO für Diagnose, Risikostratifizierung und Prognose von AS zu etablieren und validieren.

Contents

Glossary and abbreviations

α SMA	alpha-smooth muscle actin
ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ADMA	asymmetric dimethylarginine
AHA	American Heart Association
AKI	aortic kidney injury
ANOVA	analyses of variance
AO	aortic
AS	aortic stenosis
ASE	American Society of Echocardiography
AVA	aortic valve area
AVI	aortic valve implantation
aVICs	activated valve interstitial cells
AVR	aortic valve replacement
AV Vmax	aortic valve jet velocity
BAV	bicuspid aortic valve
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CD31	cluster of differentiation 31
CD34	cluster of differentiation 34
CE	Certified for Europe
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule1
CH	chamber
CRP	C-reactive protein
CSA	cross sectional area
CT	computed tomography
cTn	cardiac troponin T
CVD	cardiovascular disease
CWD	continuous wave Doppler
EAE	European Association of Echocardiography
ECG	Electrocardiogram
ECM	extracellular matrix
EDTA	ethylenediaminetetraacetic acid
EF	ejection fraction
ELISA	enzyme-linked immunosorbent assay

EQ-5D	Euro Quality of life-5D
ESSI	ENRICHD Social Support Instrument
Fr	French
FS	fractional shortening
HADS	Hospital Anxiety and Depression Scale
HDL	high-density lipoprotein
HRQL	health related quality of life
hs-TnT	highly sensitive troponin T
GABR	global arginine bioavailability ratio
GFR	glomerular filtration rate
GSE	General Self-Efficacy
iPTH	intact parathormone
IVS	interventricular septum
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrium
LAD	left anterior descending coronary artery
LDL	low-density lipoprotein
LV	left ventricular
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MACE	Major Adverse Cardiovascular Events
MCS	Mental Component Summary
MI	myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MMPs	matrix metaloproteinases
MPG	mean pressure gradient
MPO	myeloperoxydase
MRI	magnetic resonance imaging
NO	nitric oxide
NT-pro BNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
obVICs	osteoblastic valve interstitial cells
PAD	peripheral artery disease
PAP	pulmonary artery pressure
PAVR	percutaneous aortic valve replacement
PCI	percutaneous coronary intervention
PCS	Physical Component Summary
PCT	procalcitonin

PMN	polymorphonuclear neutrophils
PPG	peak pressure gradient
pVICs	progenitor valve interstitial cells
PW	posterior wall
PWD	pulsed wave Doppler
QoL	Quality of Life
qVICs	quiescent valve interstitial cells
RBC	red blood cells
RV	right ventricular
SAVR	surgical aortic valve replacement
SD	standard deviation
SDMA	symmetric dimethylarginine
SF-36	Short Form-36
SPARC	secreted protein, acidic and rich in cysteine/osteonectin
SPSS	Statistical Package for Social Sciences
STS	Society of Thoracic Surgeons
TEE	transoesophageal echocardiography
TGF ß1	transforming growth factor β1
TIA	transient ischaemic attack
TIMPs	tissue inhibitors of matrix metaloproteinases
TnT	troponin T
TTE	transthoracal echocardiography
Tx	transplant
VECs	vascular endothelial cells
VEGF	vascular endothelial growth factor
VHD	valvular heart disease
VICs	valvular interstitial cells
WHO	World Health Organization

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1 Introduction

Aortic stenosis (AS) is reported to be the third most common cardiovascular disease, only outnumbered by arterial hypertension and coronary artery disease (CAD). (1)
Historically, the earliest descriptions of calcific aortic valve stenosis refer to the 17th century when Riverius firstly described the condition. (2) Later reports on calcific AS were presented by Stockes in 1845 and by Mönckeberg in 1904. (1) At the present time, degenerative (senile) AS is the most common acquired valvular heart disease (VHD) amongst the elderly in developed countries. In its origin, it is linked to demographic changes and improved life style modalities in the population as well as the decline in the incidence of rheumatic fever over the past decades. (3, 4) The prevalence of calcific AS increases with higher life expectancy in the population. (5)

Since the turn of the 20th century to our times, remarkable improvements in diagnosis and treatment of VHD have been achieved. (6) Surgical replacement is an effective and safe therapy and remains the gold standard for the treatment of AS even in the elderly. (7) Despite these encouraging data, it has previously been estimated that about 31% of patients presented with severe and symptomatic, single VHD, do not receive surgical treatment. (3, 8) A possible explanation for this short-coming might be that a high surgical risk in these patients is often associated with concomitant diseases, older age and short life expectancy. (3)
In order to provide an alternative treatment option for these patients, new, less-invasive, catheter-assisted techniques for aortic valve implantation (AVI) have been developed. (7, 8) A break through in the field of interventional cardiology was the first percutaneous implantation of the aortic valve prosthesis in a 57-year old man with severe symptomatic AS. (9) Improvements in Quality of Life (QoL) after surgical aortic valve replacement were determined in the majority of patients at ≥ 75 years of age whereas the long term survival was not affected in this patient group. (155)
On the other hand, recent studies imply that, despite the high risk profile of this patient population, percutaneous aortic valve replacement (PAVR) was associated with excellent procedural success (97%) and low procedural and post-interventional mortality rates. (11)
Since the majority of patients undergoing PAVR is older and suffers from multiple co-morbidities, classical “hard” clinical endpoints like mortality and morbidity may not be

sufficient and appropriate to evaluate the benefit of such therapeutic interventions. In terms of mortality and morbidity measurements after surgical or percutanoues aortic valve replacements it is not possible to gain fulfilled information covering patient´s physical, functional, emotional, and mental well-being at the same time. To date, few data concerning developed quality of life changes in patients undergoing surgical aortic valve replacement (SAVR) are available in the literature. (13)

Taking into account the high aged and frail population currently presenting for PAVR, functional and quality of life improvements might be limited despite the haemodynamically effectiveness of this novel AS treatment option. (7) Therefore, QoL is considered to be a key parameter not only in patient-centered clinical decision-making for PAVR but also in assessing the efficacy of this novel treatment option. Up to now, quality of life assessment before and after PAVR has been ill-defined and only a few studies have addressed this issue. (7) Results of previous studies imply that improvements in hemodynamic parameters and markers of neurohumoral activation may be associated with short term beneficial effect on quality of life after PAVR. (8, 12-17) Furthermore, various tests assessing QoL are available and have been used in these studies. Most tests have been evaluated for heart failure patients. It remains unclear, which of these tests has the capacity and is the most appropriate to evaluate this particular group of patients suffering from severe AS.

1.1 Definition and classification of AS

The term AS refers to restricted opening of the aortic valve leaflets during systole producing an obstruction to the left ventricular outflow tract (LVOT) at the level of the aortic valve. (18) Congenital subvalvular and supravalvular forms of AS are not included in the previous definition but present potential causes of the leftventricular outflow obstruction. (20)

In accordance with the ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease, the severity of AS can be classified on the basis of hemodynamic and natural history data obtained in patients.

Hemodynamic parameter	Mild	Moderate	Severe
Jet velocity (m/s)	< 3	3.0 – 4.0	> 4
Mean gradient (mm Hg)	< 25	25 - 40	> 40
Valve area (cm²)	> 1.5	1.0 – 1.5	< 1.0

Table 1: Classification of AS severity (ACC/AHA Guidelines) (20)

Doppler echocardiography has become the key tool in assessing the severity of AS. Combining the measured aortic valve area (AVA) with flow rate, pressure gradient and ventricular function may be of help in classifying the severity. The European Society of Cardiology defines severe grade of AS considering the AVA as < 1.0 cm^2 and indexing it to the body surface area (BSA) with a cut-off value of 0.6 cm^2/ m^2. If the cardiac output is normal and the mean pressure gradient is lower than 50 mmHg, a severe AS is unlikely (21). On the other hand, the presence of low flow, low pressure gradients may be encountered in patients despite severe AS. (21) This is usually due to significantly impaired systolic LV-function. Furthermore, even a calculated small valve area does not definitely confirm severe AS if the mean gradient is < 40 mmHg, since mild-to-moderately diseased valves may not open fully, resulting in a 'functionally small valve area (pseudosevere AS). (21) Stress echocardiography using low-dose dobutamine may be helpful in this setting to distinguish truly severe AS from the rare cases of pseudosevere AS. (153, 154)

1.2 Epidemiology and Aetiology

Data from The Euro Heart Survey on Valvular Heart Diseases demonstrate AS being the most frequent (43.1 %) of all acquired VHD, followed by mitral regurgitation (31.5 %), aortic regurgitation (13.3 %) and mitral stenosis (12.1%). (3)

It primarily presents as calcific AS in adults of advanced age. Lindroos and colleagues evaluated the prevalence of AS in an unselected elderly population in Finnland using two-dimensional and Doppler echocardiography. Mild calcification forms of the aortic valves were found in 40 % while severe forms were present in 13%. Critical native valve stenosis (AVA ≤ 1.2 cm²) was present in 2.9 % in the enrolled group, aged from 75 to 86 years. (5)

Frank AS was reported in the Cardiovascular Health Study affecting 1.3 % of patients aged 65-75 years, 2.4 % of those aged 75-85 years, and 4 % of patients aged over 85 years. (22, 26)

The second most frequent aetiology, which dominates in the younger age group, is congenital (23, 25) whereas rheumatic AS has become rare. Roberts et al. examined operatively excised, stenotic aortic valves in their study including 932 patients aged 26 to 91 years. Congenitally malformed valves were originated in 54 % of the study population while 45 % had tricuspid valves. Furthermore, the study underlined a higher prevalence of bicuspid compared to tricuspid aortic valves in patients aged < 70 years. Both types of congenitally affected aortic valves were more prevalent in men. (24)

Decreased incidence of rheumatic fever, developed living standards, better access to medical care as well as wider use of antibiotics and natural changes in the streptococcal strains have lead to expressive changes in the etiology of AS through the last decades.

Being once the main cause of rheumatic VHD in the last century, rheumatic fever seems to be disappeared in the industrialized world in our times. (28, 29)

Accordingly, AS is degenerative in its origin nowadays and it may affect both normal tricuspid and congenitally deformed aortic valves. (24)

Among the 1197 patients observed in the Euro Heart Survey on VHD, degenerative AS existed in 81.9 % of the subjects, rheumatic AS in 11.2 % and congenital in 5.4 %. Other causes named for AS were endocarditis (0.8 %), inflammation (0.1 %) and ischemia (0 %) while other reasons for AS were assessed in 0.6 % of the included study population. (3)

1.2.1 Pathobiological mechanisms in degenerative (sclerocalcific) AS

Age, hypertension and body mass index were calculated as independent predictors of aortic valve calcification. (26, 32)

Despite the high prevalence of aortic valve disease in advanced age, it has been evidenced that degenerative aortic valve disease is not simply a consequence of ageing. (26) The mechanism underlying the degeneration of normal as well as bioprosthetic aortic valves resemble to that in atherosclerosis. (30)

Some risk factors, including hypercholesterolemia, cigarette smoking, hypertension, diabetes and male gender are involved in both AS and atherosclerosis. Taking the calcification process into account the similarities differ here. (31, 34, 35)

The pathobiological processes in aortic valve stenosis appear to be similar in both tricuspid and congenitally affected bicuspid aortic valves despite the earlier manifestation of the disease in bicuspid valves. (31)

Recent studies have shown that the pathogenesis of AS is rather an active process sharing similarities with arteriosclerosis of the arterial wall. (31, 33, 34) These comparable lesions include disruption of the basement membrane, subendothelial accumulation of intracellular lipids and lipoproteins as well as infiltration of foam cell and nonfoam cell macrophages, and T lymphocytes, resulting in local and systemic activation of inflammation. (27)

Other histological changes of calcific AS besides inflammation include extracellular matrix remodelling with increasing fibrosis, valve thickening, as well as angiogenesis, and calcification. In a possible pathogenetic concept the high mechanical force on aortic valves, together with atherosclerotic risk factors, leads to valvular endothelial dysfunction / leakage, followed by deposition of low-density lipoprotein (LDL) particles as well as other compounds that trigger inflammation. This pathway in turn activates valvular interstitial cells (VICs) resulting in their osteoblastic transformation. (36)

1.2.1.1 Endothelial function and lipid metabolism

In addition to related mechanism shared between AS and artherosclerosis, endothelial damage in patients with severe calcific aortic valve disease is further supported by the demonstration of increased E-selectin plasma levels which return to normal after surgery. Furthermore, diseased aortic valves express more markedly several endothelial markers such as CD31, CD34, von Willebrand factor, and carcinoembryonic antigen-related cell adhesion molecule (CEACAM1). These, however support the association between endothelial dysfunction and the progression of calcific aortic valve disease.

Abnormalities in lipid metabolism have been frequently associated with calcific aortic valve disease. (27) Lipid accumulation is presented in the early lesions of the aortic valve and continues to accumulate during the further progress of the lesions. (31)

Metabolic syndrome seems to be involved in the progression of aortic stenosis over time, explaining that patients affected by AS had greater LDL cholesterol levels than controls (124 mg/dl vs. 85mg/dl). High total cholesterol levels, low high-density lipoprotein (HDL),

and a higher total cholesterol/HDL ratio are besides LDL independently associated with higher progression rates of AS. (28)

1.2.1.2 Valve interstitial cell transformation

The most prevalent cells contained in the heart valves are valve interstitial cells (VICs). They are part of all three layers of the valve: the fibrosa, the spongiosa, and the ventricularis. The response of the valvular tissue to disease is characterized by a marked accumulation of VICs associated with inflammatory cells, neovascularization, increased matrix, and eventually fibrosis and calcification. Five identifiable phenotypes of VICs have been described so far, including embryonic progenitor endothelial/mesenchymal cells, quiescent VICs (qVICs), activated VICs (aVICs), progenitor VICs (pVICs), and osteoblastic VICs (obVICs). These cells may exhibit plasticity and may convert from one form to another. The qVICs are contained in adult valves and maintain normal valve physiology. qVICs become aVICs under conditions underlining pathological injury or abnormal hemodynamic/mechanical stress. Activation of qVICs is stimulated by appearance of activated valve interstitial cells (VECs) and macrophages (foam cells), as well as by chemokines and growth factors. Accordingly, aVICs increase secretion of cytokines, one of the most important being TGF-ß, which has important autocrine functions. Thus, aVICs are responsible for the regulation of pathobiological responses of the valve in disease and injury.

Activation of VICs results in increased extracellular matrix (ECM) secretion and degradation, expression of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs), as well as increased proliferation and migration. Furthermore, the pVICs consist of a heterogeneous population of progenitor cells that may play an important role in repair. (36, 37)

1.2.1.3 Inflammation

The stenotic valve is characterized by accumulation of macrophages and T lymphocytes. Early lesions of aortic valve stenosis contain inflammatory cell infiltrates composed of macrophages, macrophage foam cells, and sporadic T lymphocytes. The initiating event of aortic valve stenosis is considered to be an endothelial injury, which occurs primarily on the aortic side of the leaflet in response to increased mechanical or decreased shear stress across the endothelium: Inflammatory cells and plasma lipoproteins cause early lesions by infiltrating the valve leaflet at sites where the endothelial layer is disrupted .(31)

The accumulation of inflammatory cells into valves is supported by adhesion molecules, such as intracellular cell adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin, which are expressed in the endothelium of stenotic but not normal aortic valves. Serum levels of soluble E-selectin have been found to be elevated in patients with aortic valve stenosis and to decrease after valve replacement. This fact may support the idea that aortic valve stenosis represents a systemic inflammatory condition. Taking this into consideration, other signs of systemic inflammation, such as elevated plasma concentrations of C-reactive protein, have been described in patients with AS. Therefore, C-reactive protein is present in stenotic aortic valves and is included in valve calcification. Interestingly, Chlamydia pneumoniae has been found in both stenotic and normal aortic valves, but there is no evidence confirming the association between this agent and development of AS. (31)

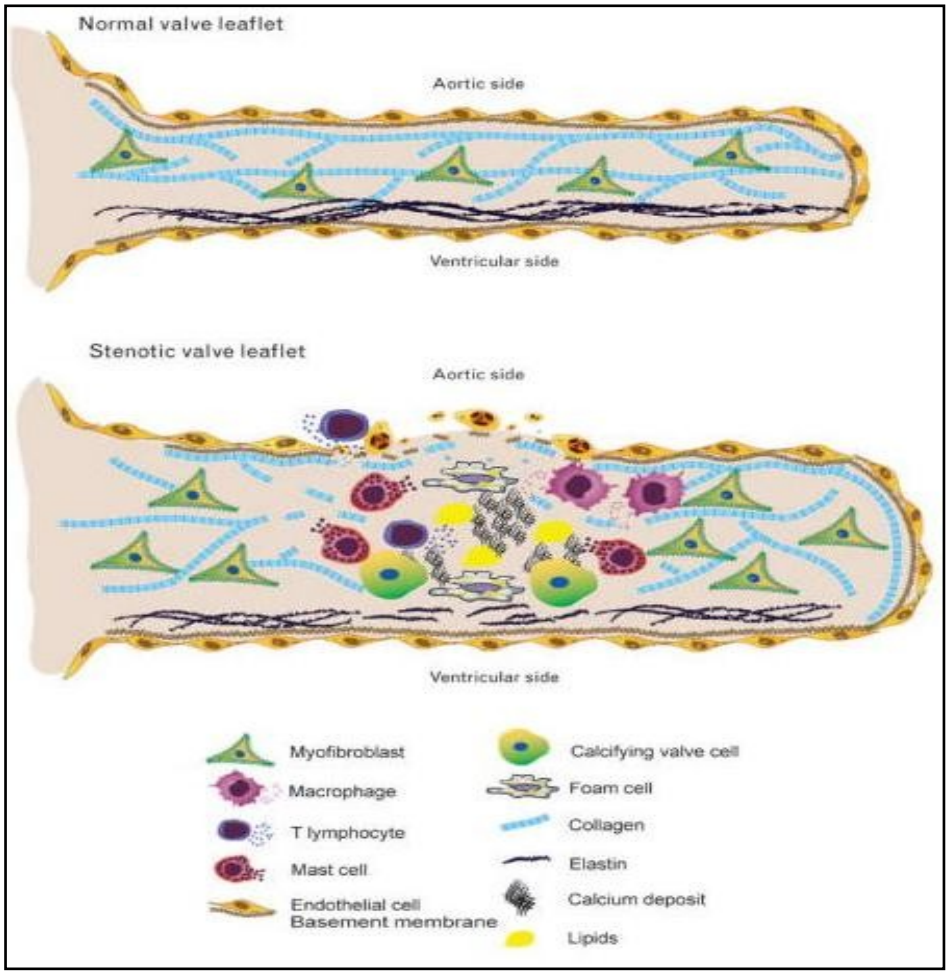

Figure 1: Schematic cross-sections of a normal and stenotic aortic valve leaflet (31)

1.2.1.4 Angiogenesis

Recent data resulting in immunohistochemistry analysis on stenotic aortic valves have shown that stenotic aortic valves contain 3 types of neovessels: small microvessels, medium microvessels, and organized arterioles. The density of the neovessels was significantly higher in stenotic valves than in control valves and correlated positively with the degree of valvular calcification and mast cell density. In the neovascularized areas of stenotic aortic valves active degranulated mast cells all contained the vascular endothelial growth factor (VEGF) that otherwise was secreted by myofibroblasts. Accordingly, the degradation of the antiangiogenic molecule endostatin was achievable in vitro utilizing the mast cell triptase. In summary, this data show that both mast cells and myofibroblasts may influence the progression of AS modifying the balance between angiogenic and antiangiogenic factors in the aortic valve. (39) Similar results were obtained by Charest et al., additionally showing the correlation between neovascularization in AS and the

expression of SPARC (secreted protein, acidic and rich in cysteine/osteonectin). As a matricellular protein SPARC is implicated in ossification, the modulation of angiogenesis and the production of metalloproteinases. (40)

Angiogenesis occurring in AS is related to the expression of angiogenesis-promoting factors such as VEGF, its receptors Flk-1 and Flt-1, but also the NO-synthesizing enzymes. (38)

1.2.1.5 Calcification and bone metabolism

Another important feature involved in the progression of AS considers calcification. Early detected mechanism in the development of aortic valve calcification may be connected to genetic factors, such as vitamin D receptor genotypes or mutations found in the NOTCH gene. (31)
Patients affected by AS presented significantly higher serum levels of calcium and phosphate, increased calcium-phosphorus products and elevated osteoprotegerin status. Consequently, no statistically significant variances were notable in vitamin-D or intact parathormone (iPTH) levels. The ratios of calcium, phosphate and vitamin D to iPTH were significantly elevated in patients with AS. (31, 41)

Furthermore, calcific valves are characterized by elevated levels of several osteoblast markers such as osteopontin (27, 31, 42, 45, 47), osteocalcin (27, 31, 42, 47), osteoprotegerin (29, 31, 43), bone sialoprotein (31, 42, 47), and by the osteoblast-specific transcription factor Cbfa 1. (27, 31, 42, 47)
Additionally to calcification, active osteoblastic bone formation and osteoclastic bone resorption appear in stenotic aortic valves. In accordance, mature lamellar bone with hematopoietic components (27, 31, 44, 46) and microfractures, and healing may be found in these valves. (31)

1.2.1.6 Extracellular matrix remodeling

An increase in cell proliferation, matrix synthesis as well as expression and activation of metalloproteinases (MMPs) lead to intense valve thickening and extracellular matrix remodelling in advanced stage of AS. Increased expression of MMPs, a family of 23 zinc-

dependent endoproteases, is involved in extracellular matrix degradation in AS. Interestingly, this MMP effect was not found in control valves. (27, 36)
Activated MMPs are able to increase space for cell migration, activate or deactivate free signalling molecules and degrade cell-adhesion molecules as well as basement membranes. (37) The MMPs are located in VICs, monocytes-macrophages, lymphocytes and endothelial cells. Tissue inhibitors of metelloproteinases (TIMPs) consider endogenous inhibitors of MMPs. (36)

1.3 Pathophysiology of AS

In patients with AS the obstruction of the left ventricular outflow may be present at birth and/or progress gradually, over the course of many years. Consequently, obstruction to the LV outflow produces a systolic pressure gradient between the LV and aorta. (19)
The left-ventricular pressure overload progresses with advanced decrease in AVA inducing concentric hypertrophy of the left ventricle as a compensatory mechanism. (22)
Pressure overload by itself further increases the left-ventricular afterload (wall stress), impairing ejection performance. (22, 48)
In order to maintain the LV output the systolic stress developed by the myocardium must be reduced to normal. This mechanism is predicted by the Laplace law (19, 22, 49) as follows:

$$\mathbf{S = p\ r\ /\ h}$$

where S is systolic wall stress, p is left-ventricular pressure, r is left-ventricular radius, and h is left ventricular wall thickness. (19, 22, 49)
The wall stress is directly proportional to the left-ventricular pressure but there is an inverse proportion between wall stress and left-ventricular wall thickness. Tending to keep the wall stress normal the left-ventricular wall thickness must rise with increasing pressure. (22)
During systole myocardial fibers undergo an increased tension. This results in fiber thickening just sufficient to return the systolic stress to normal. In AS chronic LV pressure overload results primarily in wall thickening and concentric hypertrophy. On the contrary, an increased resting or diastolic tension, like in aortic insufficiency appears to result in

gradual fiber elongation or lengthening. Therefore, chronic LV volume overload is characterized by chamber enlargement and an eccentric pattern of hypertrophy. (50)

Hence, while LV pressure overload is associated with concentric hypertrophy, characterized by an increased value for the ratio of LV wall thickness to its radius and a normal cavity shape (51), LV volume overload is, in contrast related to eccentric hypertrophy and a normal or decreased wall thickness to radius ratio. This fact supports the hypothesis that hypertrophy develops to normalize systolic but not diastolic wall stress. (50)

As long as the product of (r/h) and LV systolic pressure remains constant, hypertrophy has been postulated to be appropriate. An increase in the product of (r/h) and the LV pressure represents an elevation in wall stress and indicates inadequate LV hypertrophy. (51)

According to the study conducted by Hess and associates, the LV myocardial stiffness increased significantly in patients with AS but remained unchanged in those with AI observed after surgery. The changes in myocardial structure following aortic valve replacement (AVR) were characterized by an increase in interstitial fibrosis and a decreased fiber diameter in muscles. (52)

Since afterload is a key determinant of ejection performance, its normalization accompanied by LV concentric hypertrophy development is of importance in maintaining a normal ejection fraction and stroke volume. (22)

Gunther et al. came to the conclusion that poor cardiac performance may be caused due to inadequate hypertrophy (or inadequate LV geometry) rather than to depression of LV myocardial contractility. (53)

Others, however, disagreed with results obtained by Gunther and Grossman, presenting evidence that the ejection performance was also determined by the actual inotropic state and not only by the extent of afterload in AS. (54)

Gender seems to play an additional role in LV geometry and function. Aurigemma et al. observed that women in comparison to men had smaller LV end-diastolic dimensions, higher relative wall thickness, higher peak LV pressures and finally higher ejection fractions. (55)

Although the development of hypertrophy appears to serve as a beneficial compensatory mechanism of the heart to preserve ejection performance, it may on the other hand impair coronary blood-flow and has been shown to be associated with increased postoperative mortality (56). (22)

The heart is unique among all organs in that its blood flow is regulated mainly during diastole and the oxygen extraction from hemoglobin is always close to maximum. The only way for the myocardium to match enhanced oxygen demand with increased supply is by boosting coronary blood flow. Healthy individuals show a blood flow reserve by 500–800 % over resting flow. Under conditions of concentric hypertrophy the blood flow reserve is diminished to about 200–300 %. (22)

Experimental evidence suggest that subendocardial ischemia may be triggered in hypertrophied LVs despite normal coronary anatomy under conditions such as atrial tachycardia, systolic hypertension, diastolic hypotension, and exercise in both animal models and patients suffering form aortic stenosis. (57, 58, 59, 60)

1.4 Clinical course and natural history of AS

1.4.1 The clinical picture of patients with AS

Although considered a progressive chronic disease, patients with AS stay asymptomatic during a long latent period. The duration of the asymptomatic phase varies widely among individuals. (21)

The obstruction of the aortic valve orifice progresses gradually for decades. Tough, most patients develop symptoms relatively late, in the seventh to eight decade of age. (61) Patients with congenitally affected bicuspid valves evolve symptoms at an earlier age, usually two decades before in comparison to patients with tricuspid aortic valves. (24, 61) Patients with rheumatic AS present symptoms at a wider age range, from second to fifth life decade. (61)

The three cardinal symptoms of AS involve exertional dyspnea, angina pectoris, and syncope. Heart failure occurs when the compensatory mechanisms fail to maintain the hemodynamic demands for an appropriate systolic and diastolic function. (22)

One of the initial symptoms of AS is reduced exercise tolerance manifested as exertional dyspnea or fatigue. The mechanism of this symptom is explainable considering the elevated LV end-diastolic pressure due to a LV systolic dysfunction or coronary artery

disease (CAD). An increase of the pulmonary capillary pressure accompanies this underlying mechanism. (19, 61)

Exertional dyspnea may progress to frank heart failure with symptoms typical for a long-standing severe valvular obstruction. In some cases asymptomatic patients may develop acute heart failure or pulmonary edema mostly in relation to an infectious process, anemia or other hemodynamic stress conditions. (61)

Angina pectoris reflects the imbalance between increased myocardial oxygen demands and reduced oxygen availability The onset of angina pectoris may be established by accompanying CAD (seen in 50 % of patients (61)) or by a compression of the coronary vessels by an hypertrophied myocardium. (19)

Syncope demonstrates the third classic symptom appearing in AS. Ventricular arrhythmias, systolic dysfunction, as well as an acute drop in blood pressure caused by an inappropriate LV baroreceptor response are discussed as potential mechanisms predisposing to syncope. (61)

Putting syncope in relation to sudden death, Schwartz et al. reported that sudden death in such patients was found to be caused by ventricular standstill, ventricular flutter or ventricular fibrillation, or a combination of these. Moreover, they concluded that syncope and sudden death in patients with AS expresses a decrease of coronary arterial blood induced by acute LV failure and diminished cardiac output. (67)

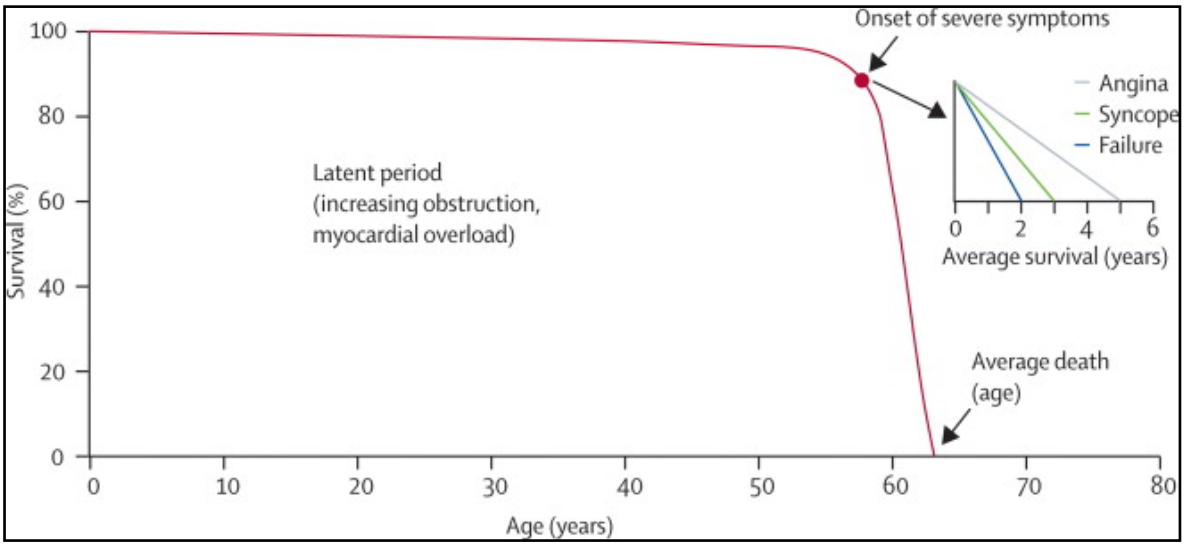

Figure 2: Survival of patients with AS over time (22)

1.4.2 Asymptomatic patients with AS

The symptom onset in initially asymptomatic patients with AS depends on predictors such as older age, male gender, AS severity as well as the functional status. The rate of symptom onset varies individually. (61)

According to multivariate analysis in the study of Rosenhek and co-workers, the only independent predictor of outcome in asymptomatic patients was the degree of aortic-valve calcification, whereas age, sex, and the presence or absence of coronary artery disease, hypertension, diabetes, and hypercholesterolemia were not. (66)

Nevertheless, if even moderate stenosis is present (jet velocity > 3.0 m/s), the average rate of progression measures an increase in jet velocity of 0.3 m/s per year, an augmentation in mean pressure gradient (MPG) of 7 mm Hg per year (61), and a decrease in valve area of 0.1 cm^2 per year. (8)

The probability of remaining alive without valve replacement at 2 years was only 21±18% for a jet velocity at baseline >4.0 m/s, compared with 66±13% for a velocity of 3.0 to 4.0 m/s and 84±16% for a jet velocity <3.0 m/s ($p<.0001$). (62)

Asymptomatic patients with AS require frequent monitoring for development of symptoms and progression of the disease. Interestingly, these patients show outcomes similar to age-matched adults in general population. (8)

Despite agreements that the prognosis of asymptomatic patients with AS is affirmative, and favoring watchful waiting approach as a safe therapeutic strategy, it has been assumed that these patients might rather benefit from early elective surgery.

Rosenhek and colleagues recently confirmed this assumption. AV jet velocity but not AVA was shown to independently affect event-free survival. Event free survival was higher in patients with lower AV jet velocities and decreased with longer follow up period. (63)

Pellikka et al. came to the concluded that asymptomatic patients may develop symptoms within a period of 5 years whereas sudden death occurrence was seen in about 1% of cases per year. Independent predictors of all-cause mortality were age, chronic renal failure, inactivity, and aortic valve. (64)

1.4.3 Symptomatic patients with AS

As soon as symptoms occur, the prognosis of untreated AS is poor and mortality is high. This is complicated by the fact, that onset of symptoms is often not promptly reported by patients. 2 years survival rates in patients with severe symptomatic AS and without surgical intervention have been reported to vary between 20 to 50%. (61)

For example, Chizner and colleagues followed 32 symptomatic patients (23 with moderate or severe AS) from catheterisation until death or for an average observational period of 64.4 months. Documented mortality rates from onset of symptoms were 26% at 1 year, 48% at 2 years, and 57% at 3 years. Sudden death cases occurred in 56%, and within hours of new symptoms. (65)

An overall poor prognosis had been observed in patients with haemodynamically severe stenosis who had refused the recommended surgical intervention (n= 55). Mean survival averaged 23±5 months while the five-year likelihood of survival was 18±7%. Mean survival after the onset of angina pectoris, after syncope, and after first appearance of left heart failure was 45±13, 27±15 and 11±10 months, respectively. (68)

1.5 Diagnostic issues in AS

1.5.1 Physical examination

The physical examination of AS is focused on cardiac auscultation including assessment of the carotid impulse and signs of heart failure.

Palpation of the carotid pulse contour and amplitude should provide information about the central aortic pressure. In severe AS the peak aortic pressure occurs later in systole (pulsus tardus) and is accompanied by decreased pulse amplitude (pulsus parvus). The pulse contour may be influenced by AS severity or low cardiac output. In coexisting atherosclerosis the timing and amplitude of carotid pulse contour seem to be normal due to the high and rapid pressure development in the stiff vessels. (61)

Characteristic for AS is a crescendo-decrescendo systolic ejection murmur, often heard best at the second right intercostal space and radiating to the carotid arteries (22, 69). The murmur commences shortly after the first heart sound, S1, gaining in intensity towards midsystole and ending just before aortic valve closure. It is low-pitched, rough and rasping

in character. (19) With progressing AS severity the murmur may lessen in intensity but reaches its maximum later in systole. (22)
A paradoxic splitting of the second heart sound (S2) usually appears when the synchrony in aortic and pulmonic valve closure becomes impaired due to the progression of AS severity and prolonged LV systole. (19)
Additionally, the LV impulse is vigorous and slightly enlarged. (22) In patients in sinus rhythm S4 might be audible at the apex due to LV hypertrophy and an elevated LV end-diastolic pressure. (19, 22) It has a musical quality and may be confused with the murmur of mitral regurgitation (Gallavardin phenomenon). (19, 69) S3 usually occurs late in the disease course when LV dilates. (19)
In children and adolescents affected by congenital noncalcific AS it is possible to auscultate an early systolic ejection sound which disappears in the later course of the disease, when the valve becomes calcified and rigid. (19)

1.5.2 Echocardiography

To date, echocardiography has become the key diagnostic tool for diagnosis and assessment of AS. (69) The basic hemodynamic parameters recommended for the determination of AS severity are:

- AS jet velocity
- Mean transaortic pressure gradient (MPG)
- AVA estimated by continuity equation.

Aortic jet velocity defines the maximal antegrade velocity across the narrowed aortic valve during systole and its highest values may be measured using the continuous-wave Doppler (CWD) ultrasound in transcapical, suprasternal, or right parasternal window. (70)
Characteristic for laminar flow patterns is the equal velocity of all fluid particles. In the course of AS, the blood flow undergoes movements through the obstructive valve, forming a jet area in which all particles have the highest velocities and where the flow is laminar. (71) The echocardiographic examination should provide a continuous velocity curve with a dense outer edge and clear maximum velocity.

As the maximum velocity in AS occurs later in systole the curve is more rounded in shape with more severe obstruction. In patients with mild obstruction, the peak comes in early systole, demonstrating a triangular shape of the velocity curve.
The transvalvular pressure gradient indicates the difference in pressure between the LV and aorta in systole. Mean pressure gradient is the average gradient across the aortic valve occurring during the entire systole. (70)

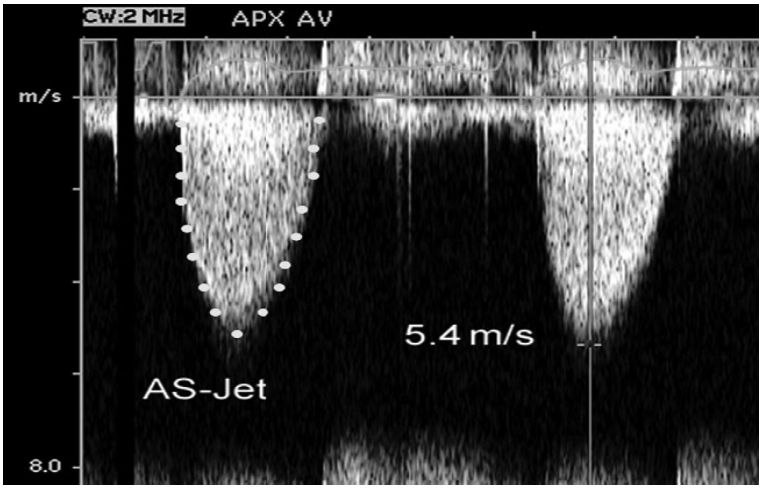

Figure 3: Continuous-wave Doppler of severe AS jet (70)

Hatle applied the Bernoulli equation to Doppler velocity measurements to calculate the transaortic gradient. The Bernoulli law states that a pressure drop across a stenotic orifice may be determined as:

$$P_1 - P_2 = \tfrac{1}{2}\, p\, (V_2^2 - V_1^2)$$

(P_1 is the pressure proximal to the obstruction; P_2 is the pressure distal to the obstruction; V_1 is velocity proximal to the obstruction; V_2 is the velocity distal to the obstruction; P is the mass density of blood.)

In patients with very severe AS and with no subaortic obstruction or enormous regurgitation, the proximal velocities may be ignored in the Doppler equation. Therefore, the final pressure drop may be obtained using the following simplified formula: (71)

$$P_1 - P_2 = 4\, V_2^2 \rightarrow \Delta P = 4\, V_2^2$$

The maximum gradient is calculated considering the maximal velocity (V_{max}) while the determination of the mean gradient requires the average of instantaneous gradients over ejection time:

$$\Delta P = 4\ V_{max}^{2}.$$

If proximal velocity is lower than 1m/s, it is acceptable to avoid its value in the Bernoulli equation, whereas proximal velocities over 1.5 m/s or aortic velocities of 3.0 m/s should be considered. The maximum pressure gradient is then: (70)

$$\Delta P = 4\ (V_{max}^{2} - V^{2}_{\ proximal}).$$

AVA calculation evolves the continuity equation (72), which postulates flow on both sides of the valve is equal ($A_1 = A_2$) (70)
The AVA can be calculated using peak aortic jet velocities or velocity time integrals:

$$AVA \bullet V_{AS\ jet} = CSA_{LVOT} \bullet V_{AS\ jet} \rightarrow AVA = CSA_{LVOT} \bullet V_{LVOT} / V_{AS\ jet}$$

$V_{AS\ jet}$ is jet velocity at the level of the stenotic aortic valve; V_{LVOT} is the velocity in the LV outflow tract (LVOT) and CSA_{LVOT} is the cross sectional area of LVOT.

To calculate the CSA of the LVOT, the LVOT diameter should be measured from a 2D long axis parasternal view, parallel and close to the aortic valve plane in mid-systole. The LVOT flow velocity is measured in pulsed Doppler ultrasound and from the apical window. (73)

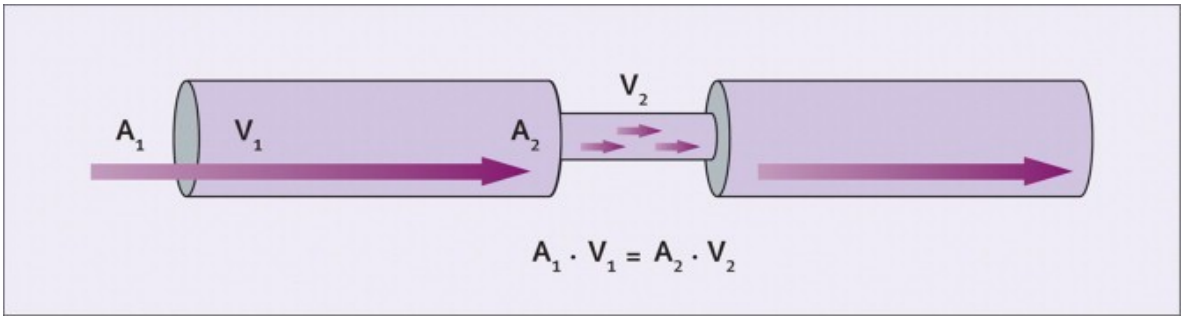

Figure 4: Schematic illustration of the continuity equation (22)

As illustrated above, if flow (F) is defined as area (A) multiplied by velocity (V) the continuity equation can be expressed as follows:

$$\mathbf{F_1 = F_2 \rightarrow A_1 \bullet V_1 = A_2 \bullet V_2}$$

In this formula flow is set as equal to stroke volume, where V is the velocity time integral (instead of peak velocity). Reaching the stenotic valve, velocity must increase for flow to stay constant. (22)

AVA planimetry provides an alternative way to estimate the AVA by 2D or 3D transthoracal echocardiography (TTE) or transoesophageal echocardiography (TEE). This method offers a direct visualization of the aortic valve orifice. (70)

TEE is rarely indicated in AS severity assessment but may provide useful hemodynamic data in cases where TTE can not be adequately performed. (69)

1.5.3 Cardiac catheterization

According to the Guidelines of the European Society of Cardiology, cardiac catheterization is no longer recommended as the first choice procedure for assessing the hemodynamic conditions due to the valve. (8, 70) However, if a discrepancy between clinical and echocardiographic diagnosis is present, the invasive measurement may be useful. Coronary arteriography is usually performed preinterventionally considering that 50 % of patients presented for AVR also require a bypass grafting. (19, 22)

The essential parameters for an adequate invasively evaluated diagnosis of AS include the measurement of the transvalvular gradient as well as a precise cardiac-output quantification. To invasively estimate the AVA, the noted parameters must be applied to the Gorlin formula (22):

$$\mathbf{A_2 = Q / (44.3 \bullet m \bullet \sqrt{\Delta P}) \rightarrow A_2 = Q / (\alpha \bullet m \bullet \sqrt{\Delta P})}$$

where Q is mean transaortic flow in ml/s, $m \bullet \sqrt{\Delta P}$ is the mean pressure drop in mmHg and the value of 44.3 is constant, but might not be universally applicable. Therefore, 44.3 can be replaced by α. (74)

1.5.4 Electrocardiogram and chest X-Ray

In patients with AS the electrocardiogram is usually characterized by LV hypertrophy, by left atrial abnormality, as well as by ST-wave and T-wave changes (typically by ST segment depression and T-inversion). However, the electrocardiogram is not a reliable diagnostic feature as LV hypertrophy must not be present in all patients with AS. (19, 22)
The findings diagnosed in the chest X-Ray are neither sensitive nor specific in the course of AS. (69) These findings may include cardiomegaly, aortic calcification or an enlargement of the left atrium. (19)

1.5.5 Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and cardiac MRI are useful diagnostic features for evaluation of the aorta as AS might be associated with an aortic aneurysm or coarctation of the aorta. (69)
Hence, the high sensitivity and specificity of MRI in assessing the thoracic aorta may exceed those of CT or TEE. Its advantages refer to identification of aortic variants, involving the imaging of the branch arteries, the pathological diagnostic of the aortic valve and the detection of LV dysfunction. The patients are also less exposed to radiation or iodinated contrast mediums. Nevertheless, there are also several disadvantages of this diagnostic method such as: prolonged investigational duration, inability to use gadolinium contrast medium in patients with renal insufficiency, but also the contraindication in patients with metal implants or pace makers, claustrophobia, etc. (75)

1.5.6 Stress testing

Stress testing is used in patients with severe AS in order to provide a fair assessment of existing functional impairment. It is recommended for asymptomatic patients with a remarkably reduced physical activity. Thus, stress testing is usually contraindicated in symptomatic patients with AS. The stress testing might be performed as exercise testing or as testing with dobutamine application.
The most common exercise tests are treadmill or upright bicycle ergometry. It is of importance to record the total exercise time, maximum workload, peak blood pressure and heart rate value, and the reasons for ending the exercise.

Dobutamine testing is used in patients with low flow/ low gradient AS to distinguish truly severe AS from the rare cases of pseudosevere AS. (154) Truly severe AS shows only small changes in valve area (increase 0.2 cm^2) with increasing flow rate but significant increase in gradients (maximum value of mean gradient 50 mmHg), whereas pseudosevere AS shows marked increase in valve area but only minor changes in gradients (21, 153, 154) In addition, this test may detect the presence of contractile reserve, which has prognostic implications. (21, 153, 154)

1.5.7 Biomarkers

Brain natriuretic peptide (BNP) has been extensively studied in patients with AS and it has become an objective prognostic variable in establishing symptomatic status as well as predicting outcomes in these individuals. It has been estimated that patients with symptomatic AS have higher levels of BNP or pro-BNP than those without symptoms. Accordingly, elevated BNP levels were present in patients shortly before symptom development. In conclusion, it may be announced that BNP associates symptom onset and adverse outcome in patients with AS. Relating to this, it can be accepted as an important prognostic marker and it is of help for decision making in asymptomatic patients. (22, 76)
Further, NT pro-BNP has been determined as an independent predictor of symptom-free survival in AS suggesting that the preoperative values of NT pro-BNP independently predict the postoperative outcomes, regarding survival, symptomatic status and LV function. (77)
Correlations between NT pro-BNP levels in patients with severe symptomatic AS and PAVR have already been observed in previous studies and will be circumstantially discussed later in this thesis.

1.6 Treatment options in AS

1.6.1 Medical therapy

Currently there is no evidence-based medical treatment available to improve survival in patients with AS. The current medical management of asymptomatic patients with AS considers reduction of cardiovascular risk factors, patient education, therapy of comorbitant diseases, and regular clinical and echocardiographic observation. (69)

Recognizing the similarities in the pathobiological course between AS and those in atherosclerosis, efforts have been taken to investigate in how far medical treatment options of CAD can influence similar processes in AS. (22)
Thus, several studies have observed the impact of statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) and ACE inhibitors on the progression of AS. (69)

Initially, Rosenhek and colleagues reported a significant reduction in hemodynamic progression of mild to moderate AS but also in individuals with severe AS in response to treatment with statins. This effect was not related to cholesterol lowering. ACE inhibitors had no effect on reduction of AS progression in this study. (78)
Similar findings with respect to statin treatment in AS were presented by Bellamy et al. (79) However, these preliminary findings in smaller studies could not be confirmed in the ASTRONOMER Trial: Chan and co-workers did not observe a significant effect of Rosuvastatin treatment on disease progression in patient with mild to moderate AS. (80)
Testing different cholesterol lowering drugs (Simvastatin, Atorvastatin or Rosuvastatin), several studies were unable to detect a significant effect on disease progression of AS, (81, 82, 83)
Vasodilators such as sodium nitroprusside have been reported to rapidly and markedly improve symptoms and cardiac function in patients with decompensated heart failure due to aortic stenosis. This therapeutic strategy may be used as a bridging therapy to valve replacement. (84)
Despite assumptions that ACE-inhibitors would further decrease afterload, under conditions of low cardiac output, and that this may lead to hypotension or adverse disease outcomes in patients with severe AS, these drugs are well tolerated, if applied appropriately.
Associated systemic hypertension should preferably be treated by vasodilators or ACE inhibitors. The use of ß-blockers or diuretics should be considered carefully. (69)
According to the ACC/AHA update on endocarditis prophylaxis, the antibiotic prophylaxis before dental or other procedures is no longer recommended for patients with BAV or AS unless related to the presence of intracardial prosthetic material, congenital defects, mucosal injuries or previous endocarditis. (69, 85)

1.6.2 Surgical treatment strategies

The presence of severe symptomatic AS is a clear indication for urgent surgical valve replacement. Patients with an asymptomatic severe AS and a reduced LV ejection fraction (EF) also benefit from surgical aortic valve replacement. In case of a moderate AS but a co-existing indication for other cardiac surgery (e.g. CABG), the indication for a valve replacement has to be made individually. (69) So far, surgical AVR is the only survival and symptom improving effective treatment in patients with symptomatic AS.

In symptomatic patients with AS, AVR should be performed soon after the onset of symptoms because the average survival in these patients is only 2 to 3 years, combined with a high risk of sudden death.

Furthermore, surgical AVR is associated with low perioperative mortality and morbidity. The average perioperative mortality in the Society of Thoracic Surgeons (STS) database was estimated at 3.0% to 4.0% for isolated AVR and 5.5% to 6.8% for AVR and coronary artery bypass grafting (CABG). (8) A recently published study summed this data up as follows: the major adverse event rate was 17% for isolated AVR, whereas the mortality rates varied from 6% to 26% with concomitant CABG. (69)

Importantly, centers with higher frequency of surgical treatment have lower perioperative mortality rates than those with low surgical volume. The overall in-hospital mortality rate was reported as 8.8% in patients elder than 65 years. (8)

Risk factors in patients undergoing valve surgery are incorporated into different risk scores and may include older age, female gender, comorbid conditions such as pulmonary hypertension, chronic pulmonary disease or extracardiac arteriopathy, LV dysfunction, emergency operation, active endocarditis, recent myocardial infarction, etc. (21)

The most significant risk factors in patients with low-flow, low-gradient aortic stenosis were determined in a study conducted by Clavel et al. A poor outcome in these patients was associated with impaired functional capacity, more severe valve stenosis and reduced peak stress left ventricular ejection fraction. (86)

Nevertheless, Connolly and co-workers were able to show that patients with severe AS, reduced LV function, a low mean gradient and reported increased risk of operative mortality should not be denied surgical AVR due to the given substantial potential clinical benefit (87) and the improvement in survival. (88)

Accordingly, Vaguette and colleagues presented data of a good long term survival among patients who underwent surgical AVR, accompanied by a significant improvement in LV function and an augmented functional status. (89)

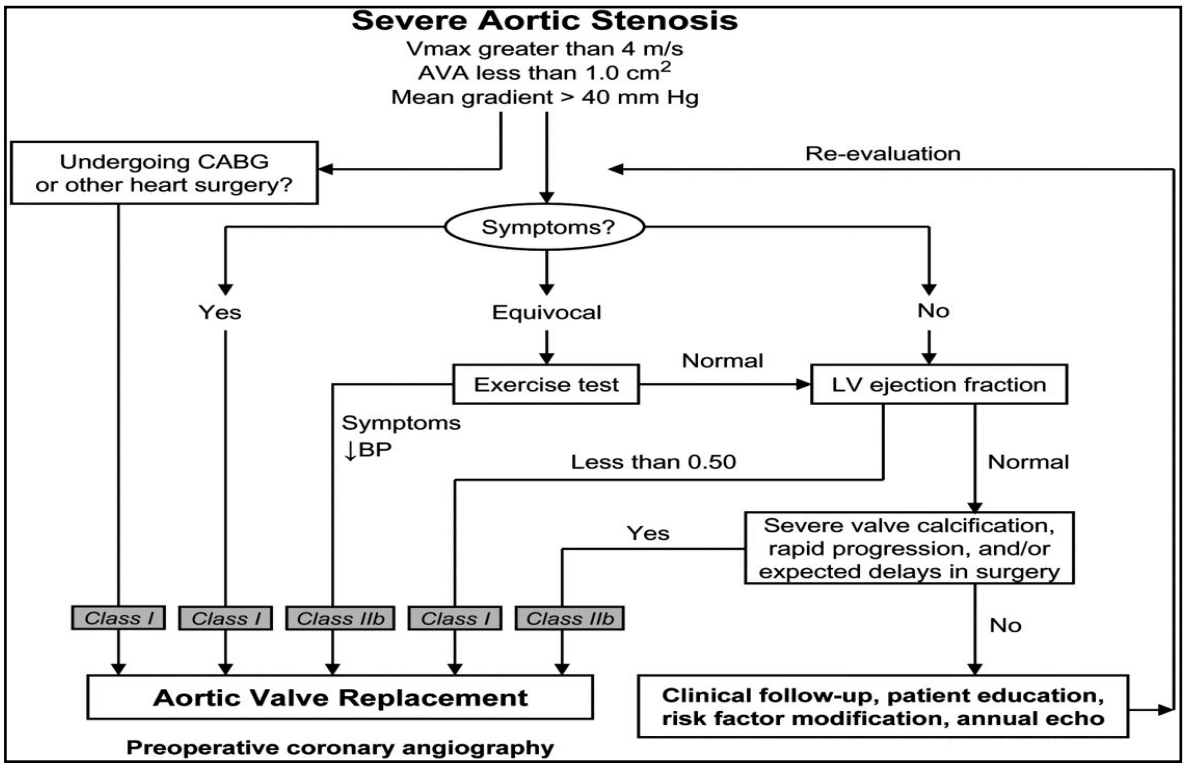

Figure 5: Management strategies for patients with severe AS (8)

1.6.3 Balloon valvuloplasty

Despite its important role in therapy of adolescents and children with AS, balloon valvuloplasty cannot be recommended as an alternative to AVR in adults. Although balloon valvuloplasty results regularly in a significant acute reduction of the transvalvular pressure gradient, the achieved valve area rarely exceeds 1.0 cm^2. Despite the modest change in valve area, an early symptomatic improvement is usually seen. However, balloon valvuloplasty may lead in more than 10% to acute symptomatic complications (e.g. worsening of aortic regurgitation, embolic stroke, LV-perforation, myocardial infarction). Furthermore, progressive restenosis and clinical deterioration frequently occur within 6 to 12 months in most patients. Therefore, balloon valvuloplasty may mainly be indicated as a bridge to surgical treatment in haemodynamically unstable or pregnant patients. Additionally, aortic balloon valvotomy might be a reasonable palliative treatment option in

adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions. (8, 21, 69)

1.6.4 Novel treatment modalities in AS

According to the official guidelines for the treatment of patients with valvular heart disease, patients with severe symptomatic AS have a Class I indication for AVR. (8,90) Furthermore, surgical AVR may improve survival of elderly patients and of those aged over 80 years, and the benefits of AVR among these population were similar to those in younger patients. (91, 93)

Despite these assumptions, it has been estimated that surgery is not always offered to patients who might benefit from it. (91) Older age, high surgical risk scores, depressed LVEF, the presence of comorbidities, and/or patient´s wish to refuse surgery are the most commonly reported reasons for denied surgical treatment. (91, 94)

The findings presented by Iung and colleagues, suggest that 33% of elderly patients with severe, symptomatic AS did not undergo surgery. The most striking characteristics for this decision-making were older age and LV dysfunction whereas comorbidity played a less important role. The only comorbidity significantly linked to surgical refusal in elderly was neurological dysfunction. (92)

Taking all these facts into account and relying on device and technical improvements in the field of interventional cardiology over the last years, PAVR has been introduced as a novel alternative treatment for this subgroup of patients.

1.6.4.1 Early experience in percutaneous valve interventions

The first artificial heart valve implantation as a treatment option for patients with heart valve disease dates back to Hufnagel in the year 1952. With the development of extracorporal circulation the first subcoronary heart valve implantation was achieved by Harken et al. Since then open heart surgery has become the treatment option in valvular heart disease. (95)

Various efforts to modify catheter mounted valves for clinical and temporary use have been made in interventional cardiology but all implantation procedures were carried out in

animal models and remained a matter of further requirements for device and technical development. (95, 96)

The new treatment modality gained a huge public attention over the years. In 2000, Bonhoeffer et al. performed the first percutaneous human implantation in pulmonary position. (10) Two years later this landmark achievement was followed by Cribier and collegues accomplishing the first antegrade implantation of a balloon expandable valve in aortic position in a 57-year old man with severe calcific aortic stenosis. (9)

Due to the technical complexity and associated risks during implantation, the antegrade, transvenous approach was limited in its applications and the new less complicated and more promising transfemoral transarterial retrograde approach has become the standard in percutaneous valve interventions. (97)

1.6.4.2 The currently available devices for PAVR

To date, multiple valve prototypes for PAVR have been investigated and are in different stages of development. The currently most available and implanted valves worldwide are the Edwards SAPIEN valve (Edwards Lifescience, Irvine, California) and the CoreValve ReValving system (CoreValve Inc., Irvine, California).

The Edwards SAPIEN valve achieved the CE (certified for Europe) markin the European community in September 2007, and the CE mark for the Core Valve was proven in the same year. (98) The CoreValve system is still not available for clinical trials in the USA. (103)

1.6.4.2.1 The Edwards SAPIEN valve

The Edwards SAPIEN valve is constituted from a tubular, slotted, stainless steel stent with an attached equine pericardial trileaflet valve. A covered fabric cuff wraps the left ventricular portion of the prosthesis. Before implantation, the prosthesis must be attached onto a specially constructed valvuloplasty balloon catheter using a mechanical crimping system. The valve is adequate for an antegrade, retrograde but also for a transapical approach and is placed in subcoronary position. (97, 98)

An annulus diameter of 18 to 22 mm requires a 23-mm-diameter prosthesis whereas a 21 to 25 mm annulus diameter is adequate for the 26-mm prosthesis. The femoral arterial sheaths

(Edwards Lifesciences Inc) with internal diameter of 22Fr (8 mm external diameter) are used for delivery of the 23-mm prosthetic valve and 24Fr (9 mm external diameter) for the 26-mm valve. (97) A recently published study describes the currently available SAPIEN XT valve mounted on a low profile NovaFlex delivery system of 18-19Fr. (105)

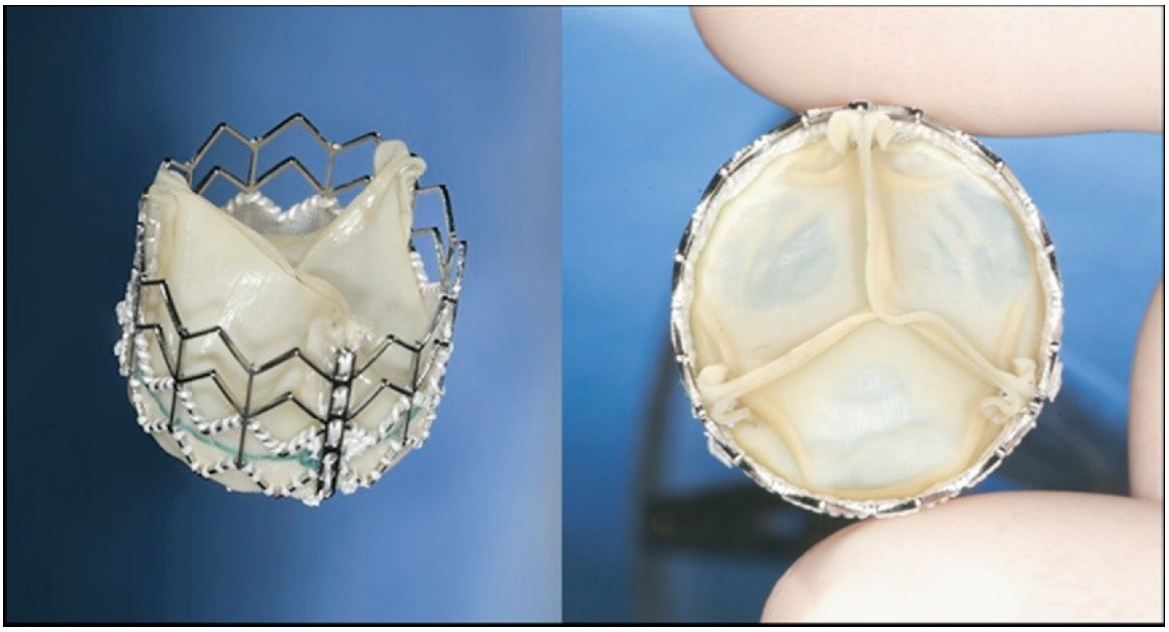

Figure 6: The Edwards SAPIEN prosthetic valve (98)

1.6.4.2.2 The CoreValve Prosthesis

The CoreValve prosthesis for PAVR is composed of a trileaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured in a self-expanding nitinol frame. The nitinol frame is manufactured by laser cutting and measures 50 mm in length. It extends from the left ventricular outflow tract into the aortic root. Three assigned functional areas characterize the frame allowing proper orientation, anchoring and valve placement. (100)

The lower part of the frame has a high radial force to expand and press the calcified leaflets to the side avoiding recoil. The middle portion carries the valve and is constrained in order to avoid coronary arteries, whereas the upper part fixes the valve in the ascending aorta matching longitudinal stability. (100-102)

The first generation of the CoreValve device was made of bovine pericardial tissue and required a 24 Fr delivery sheath while the second generation devices introduced the porcine pericardial tissue valves and were suitable for a 21 Fr sheath. (102)

Currently available and used third generation devices allow a more secure fixation in the ascending aorta supported by a broader upper segment and may also be suitable for patients with an ascending aortic diameter up to 43 mm.

This device demands an 18 Fr delivery system and the, to date, available valves are characterized by a 26-mm or 29-mm diameter. (99, 101, 104)

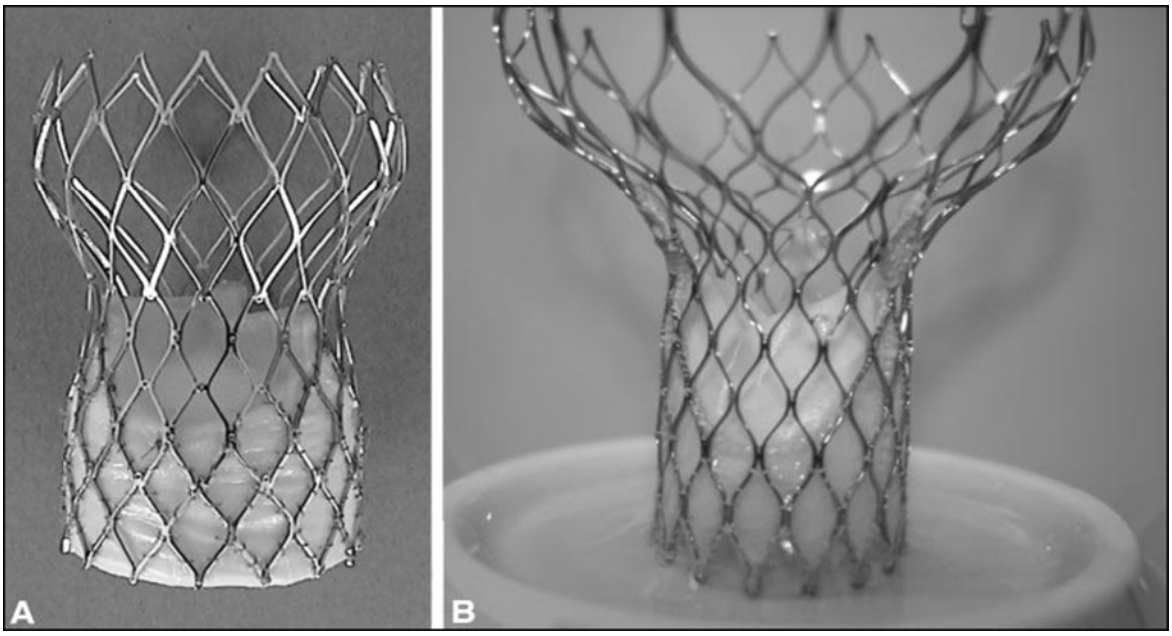

Figure 7: The CoreValve System – (A) first generation, (B) second generation (102)

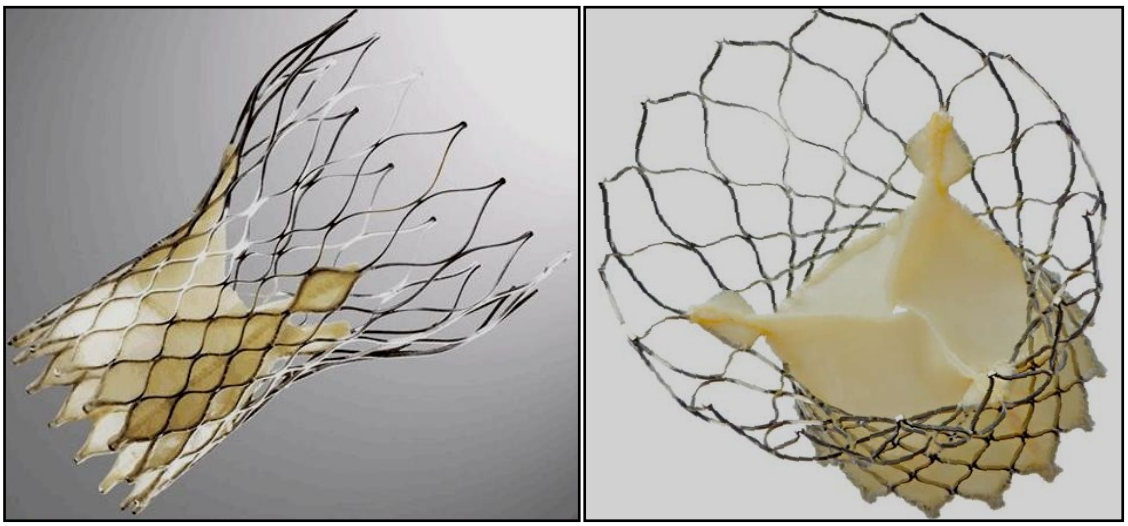

Figure 8: The third generation of the CoreValve prosthesis (103, 104)

The CoreValve prosthesis can be delivered using the retrograde or, under specific conditions, the subclavian approach.

1.6.4.2.3 An overview of the main percutaneous approaches

As noted above, the currently described percutaneous approaches refer to the antegrade, retrograde or the transapical valve implantation.

The antegrade approach was firstly described by Cribier and collegues, and was performed during the first human percutaneous valve implantation, in 2002. The right femoral vein was used for the antegrade device insertion, including prior guide wire advancement to the right atrium, followed by a transseptal catheterization, left atrium and mitral valve passage, to finally reach the stenotic aortic valve and the descending aorta. The guide wire was exchanged by another long guide wire, which was snared from the left femoral arterial site and externalized via the arterial sheath. The left femoral arterial access was previously ensured, and a 5Fr catheter was advanced for continuous blood pressure monitoring.

	Edwards-SAPIEN™	**CoreValve™**
	Stainless steel	Nitinol frame
Material	Bovine pericardium	Porcine pericardium
Valve positioning	Balloon-expandable	Self-expandable
Aortic annulus diameter	18 – 25 mm	20 – 27 mm
Valve diameter	23 and 26 mm	26 and 29 mm
Delivery system	22 and 24 French	18 French
Approach	Anterograde, retrograde and transapical	Retrograde or subclavian

Table 2: Main differences between the two currently available PAVR devices

The interatrial septum was balloon dilated so that the device carrying balloon catheter could be passed further.

After delivering and placing the device in the midposition of the aortic valve the balloon was maximally inflated, then rapidly deflated and withdrawn. Rapid right ventricular pacing (200-220 beats/min) was carried out to enable precious valve positioning, decrease transaortic blood flow and to avoid adverse procedural complications. (9, 106)

In order to facilitate the procedural steps and avoid damage to the heart or excessive mitral regurgitation the antegrade approach was followed by alternative ways of valve implantation. The retrograde approach requires insertion of percutaneous sheaths in both femoral arteries and one femoral vein. The device is delivered using one of the femoral arteries. The Edwards SAPIEN valve is mounted on a balloon expandable catheter and is released immediately after balloon valvuloplasty, and during right ventricular pacing, whereas the CoreValve is a self-expandable device and it can be delivered without a balloon catheter. However, a balloon valvuloplasty must be performed prior to the CoreValve releasing procedure. (97, 107)

The originally required surgical cut down for femoral sheath insertion has been replaced by percutaneous puncture and specific percutaneous suture closure techniques. Alternatively the vascular access may be performed through the axillary/subclavian artery, retroperitoneal iliac artery, ascending aorta or left ventricular apex. The subclavian approach is favourable for the CoreValve system while the transapical implantation necessities the Edward SAPIEN device. (105) The retrograde approach with the Edwards SAPIEN or CoreValve is usually performed in local or general anaesthesia while the transapical access is carried out in general anaesthesia. (97, 99, 108)

Premedication includes Aspirin and Clopidogrel as well as periprocedural antibiotic prophylaxes with Vancomycin or Cefazolin. Furthermore, heparin is administered during the procedure. (97, 108)

Another alternative to retrograde implantation is the transcapical access which uses the Edward SAPIEN valve and is undertaken under general anaesthesia. One of the major advantages of this approach is the possibility to perform the valve implantation even in those patients who are not eligible for femoral or subclavian approach.

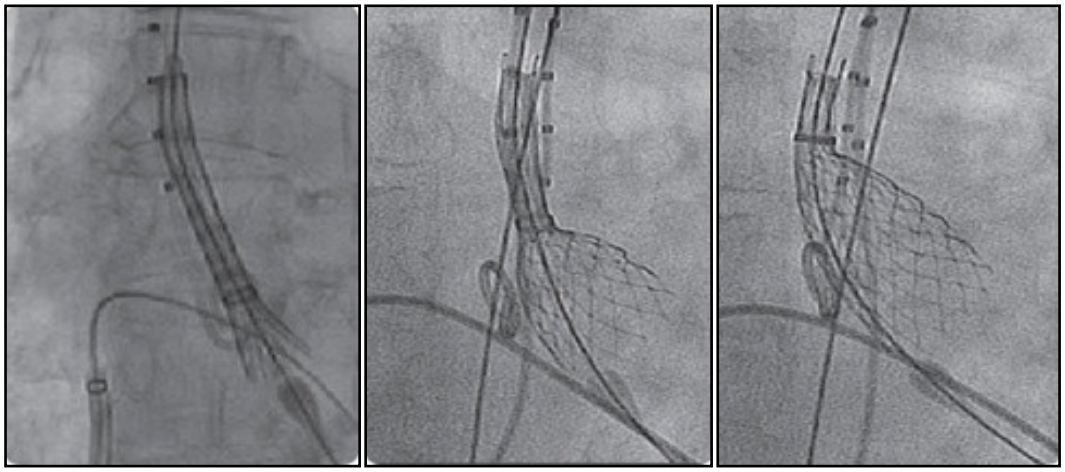

Figure 10: Deployment and positioning of the CoreValve system under fluoroscopic guidance. Not expanded valves are fully repositionable; partially expanded valves are partially repositionable. (109)

The CoreValve system deployment might be performed without right ventricular rapid pacing due to the nitinol frame ability to self-expand.

The LV transapical access is characterized by a minimally invasive anterolateral thoracotomy (5-8 cm), usually in the sixth intercostal space, under general anaesthesia and using rapid epipericardial LV pacing. Rapid pacing is used during the procedure to decrease the systemic systolic arterial pressure, transaortic blood flow and cardiac motion for proper positioning of the valve. (108)

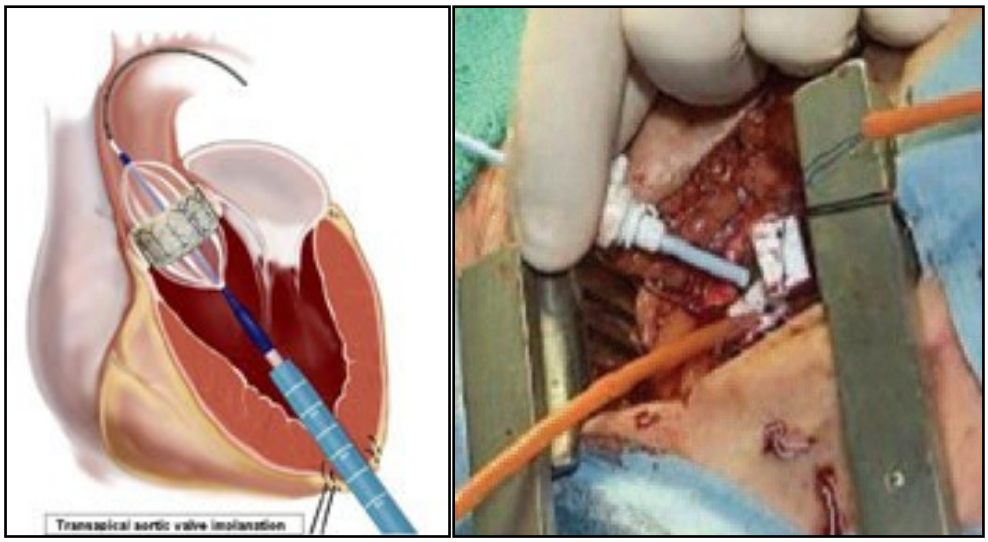

Figure 11: Transapical aortic valve implantation (108, 110)

1.6.4.2.4 Patients outcomes after PAVR

The procedural success rates of PAVR have improved to over 95% through the last years. (105) Recently published data from the multi-center European registry (PARTNER EU) have shown the success rate of transapical and transfemoral implantation of the Edwards SAPIENS valve in 95.4 and 96.4% of the 130 enrolled patients, respectively. (14) Piazza and colleagues demonstrated a procedural success of 97% after the implantation of the CoreValve third generation 18Fr device system. (11)

According to the data of different reviews, including 2356 patients who received the Edwards Lifesciences and the Medtronic aortic valve prosthesis, the survival rate at 30 days was documented at 89% and was similar for both systems. Other reports present 30 day survivals at 93-95%. (105)

Piazza and co-workers noted procedural mortality rate of 1.5%, whereas the 30 days, all-cause mortality was 8% (including procedural mortality). The combined rate of death, stroke and myocardial infarction was 9.3%. (11) Low 30-day mortality of 6.4% amongst patients undergoing PAVR was agreeable, as compared to the Society of Thoracic Surgeons (STS) surgical risk estimate of 11.6%. Moreover, according to the STS National Cardiac Database, the overall mortality among 46 397 patients undergoing SAVR in the USA was also 6.4%. (105) The PARTNER EU has estimated 30-day survival of 81.2% for the transapical access and 91.8% for the transfemoral. (14)

Reported survival rates at 1 year after PAVR vary from 69 to 85%. These unfavorable late survival rates rather refer to various comorbidities than to the aortic valve itself. The most commonly detected predictors of late mortality following PAVR are the logistic EuroSCORE, STS score, age, liver disease, severe mitral regurgitation, anaemia, prior stroke, pulmonary disease, and renal failure. (105) The PARTNER Study has demonstrated six month survival after transapical and transfemoral PAVR at 58.0% and 90.2%, respectively. (14) These results show an dramatic 20% absolute survival improvement at 1 year after PAVR as compared to the standard therapy group with a dismal survival rate <50% at 1 year. The combined rate of mortality and stroke decreased to 18.3% in the PARTNER 1B study. (105)

Several studies have, furthermore reported improvements in functional status in patients undergoing PAVR. (105) Most recent published data of haemodynamic and functional

improvements at 12 months relate to the PARTNER Study where 78.1 and 84.8% of patients undergoing transapical and transfemoral PAVR, experienced significant improvement in New York Heart Association (NYHA) class respectively. These patients achieved also improved cardiomyopathy questionnaire scores. (14)

Stroke rates range from 0-10% after PAVR. The SOURCE self-reported registry published stroke rates of 2.4% while the recently findings in the PARTNER B trial show a major stroke (permanent disability) rate of 5.0%. New cerebral lesions, as assessed by diffusion-weighted magnetic resonance imaging, have been detected in 58–91% of patients undergoing PAVR. (105)

Valve durability has been predicted to excess 10 years. Late valve functioning has been reported 2, 3 and 5 years after PAVR including both the Edward SAPIENS and the CoreValve. Interestingly, the longest surviving patient at 6.5 years with the original Cribier series still has a normal functioning valve. (105)

1.6.5 Hypothesis and Objectives

1.6.5.1 Hypothesis

Most experts describe QoL as a multidimensional concept that involves multiple domains (health, psychological, social and environmental dimensions), including subjective and objective components. Over the last years, QoL has more often been linked to subjective evaluations, to health or to subjective psychological aspects such as well-being, happiness and life satisfaction. (126)

The key components that may frequently affect QoL in older age include person-related psychological variables, health and functional status, social relations, support and activity, economic circumstances and independence, environmental conditions, and relaxing activities and mobility. (127)

Summing up, the health related quality of life (HRQL) in older population is widely defined as *"the value assigned to the duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy."* (128)

Therefore, one of the major issues in management and decision making for PAVR in elderly patients suffering from severe symptomatic AS and undergoing PAVR, considers

not only a longer life expectancy, mortality and morbidity outcomes, or haemodynamic valve performance but more the determination of quality of life in this patient group ("Not only to add years to the life, but to add life to the years.")

Pre-interventional QoL may be affected by multiple factors, such as physical symptoms, psychological impairment, adverse treatment effects, and social limitations. With pre-interventional symptoms worsening either resulting from AS or heart failure, these factors may lead individuals to neglect activities or previous social life, losing social relations or social support. (7)

Despite haemodynamical developments and high effectiveness of PAVR, the presence of concomitant diseases may often restrict functional and QoL improvements in this patient group.

The assessment of QoL in this particular patient population should gain relevance investigating if despite various co-existing diseases a post-interventional improvement in QoL still can be accomplished. Therefore, developments in QoL should become one of the most important endpoints in decision making for this novel treatment modality.

To date, only a few assessed QoL changes in patients undergoing PAVR. (7, 13-17) The majority of these studies evaluated the QoL changes mostly applying only one QoL questionnaire (e.g. SF-36, SF-12 v2, MLHFQ, KCCQ, EQ-5D UK-TTO rating scale). Thus, it still remains unclear which of these self-evaluating batteries is the most appropriate for the assessment of QoL in this particular patient group.

1.6.5.2 Objectives

1.) To determine the influences of PAVR on QoL changes in dependence on the applied questionnaire.
2.) To investigate, which of the administered instruments is the most appropriate for this patient group and which questionnaires do not seem to fulfill these expectations?
3.) To evaluate the effects of PAVR on established functional parameters
4.) To investigate the effects of PAVR on established biomarkers.
5.) To verify new biomarkers, which are potentially relevant to represent acute effects of PAVR.

2 Materials and Methods

This study was undertaken as a pilot study in order to investigate three different (quality of life-related and functional) endpoints among the included patients at baseline and after PAVR.

The primary objective of the present study was to assess the changes in quality of life among the included patients before, thirty days and six months after the intervention. Furthermore, we analyzed the acute hemodynamic response by retrospectively collecting available and performed pre- and post-interventional echocardiographic data of these patients.

In order to observe the impact of PAVR on heart failure specific and correlating parameters, we sought to obtain blood plasma analyzes in a subgroup of 15 patients.

2.1 Study population

From December 2009 to November 2010, thirty-one consecutive patients with severe, symptomatic AS (11 male and 20 female, mean age (80 ± 5 years), AVA (0.63 ± 0.21 cm^2), who underwent PAVR at the Department of Cardiology (University Hospital of Graz), were enrolled in the present study. Due to post-procedural death occurrence, 24 hours after the intervention, a patient had died and was therefore excluded from this study.

All patients suffered from severe symptomatic AS and had been evaluated for AVR undergoing all required examinations and investigations such as medical history assessment, laboratory analyzes, physical examination, 12-lead surface ECG, TTE, aortography and coronary angiography.

After interdisciplinary consultations including cardiac surgeons and cardiologists, all patients were selected for PAVR due to their advanced age, high surgical risk, comorbidities, previous cardiac surgery or their own wish not to undergo conventional surgical treatment.

Inclusion criteria for participation were the patient ability to understand, read and write German but more importantly the patients wish to participate. Furthermore, only patients who were physically and mentally able to complete the questionnaire by themselves, or with minimal assistance, were enrolled in the present study.

Exclusion criteria included dementia, and insufficient capacity to consent, understand or read German.

The study was approved by the local ethical committee and all patients signed an informed consent for further investigations exceeding those incorporated into routine clinical evaluations.

2.2 Device and procedure description

PAVR was performed in the catheter laboratory or the hybrid operating theatre. In all 30 patients, the procedure was carried out using the femoral approach technique, under local anaesthesia and analgesic sedation without surgical cut-down.

Balloon valvuloplasty was performed immediately before the implantation of the self-expanding CoreValve prosthesis (26 or 29 mm diameter) and an 18 Fr delivery system was used for the valve advancement. The procedure was supported by haemodynamic monitoring, measuring the pressure gradient over the aortic valve. A special vascular closure system (Prostar^{TM}) was available for the femoral artery access after the valve implantation. 15 patients received the 29 mm diameter prosthesis while the 26 mm device was implanted in other 15 patients.

After the procedure all patients were routinely referred to the cardiac care unit for at least 48 hours.

A dual antiplatelet therapy with Aspirin (100 mg/d lifelong) and Clopidogrel (300 mg loading dose, 75 mg/d for 6 months) as initiated before the intervention, and accompanied by a periprocedural antibiotic prophylaxis.

2.3 Quality of life assessment

As noted above, the primary target of the present study was to evaluate QoL changes in patients with sever, symptomatic AS and multiple concomitant diseases, undergoing PAVR at our institution.

In order to determine the most sensitive, and for our study group most appropriate health related QoL instrument, we combined several reliable, validated and well established batteries commonly used for self-administration in cardiac care population.

The standardized instruments used in our study population are the following:

- Medical Outcomes Study Short-Form health survey 36 (SF-36)
- Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Hospital Anxiety and Depression Scale (HADS)
- General Self-Efficacy Scale (GSE), ENRICHD Social Support Instrument (ESSI), Physical Activity Scale, and the
- Maastricht Questionnaire.

Patients were asked to complete currently available and adapted German versions of all selected questionnaires, at baseline (day of admission: 2-3 days before PAVR), 30 days and 6 months post-procedural. The baseline questionnaires were equal to the follow-up instruments and were all answered before the intervention. Reading help was offered to patients who were not physically able to accomplish the questionnaire but did understand the read text. At baseline 16 patients completed the self-evaluating batteries with our or with the help of their relatives, whereas 14 patients were able to finish the assessment without any help.
To obtain the QoL changes 30 days and 6 month after the valve implantation all questionnaires were mailed to the patients. We kindly asked all patients to repeat participation on the study and return the instruments within one week after completion.

2.3.1 Short-Form 36 (SF-36)

The SF-36 questionnaire is self-administered, standardized, validated and reliable generic health survey that has been established in the QoL assessment among cardiac patients. It consists of 36 items grouped into 8 domains, assessing the QoL status over the last 4 weeks, and a single item which evaluates the health change over the past year. The eight subscales are listed as follows: (112-114)

1. **Physical functioning** (10 items)
2. **Role-physical** (4 items)
3. **Bodily pain** (2 items)
4. **General health** (6 items)
5. **Vitality** (4 items)

6. **Social functioning** (2 items)
7. **Role-emotional** (3 items)
8. **Mental health** (5 items)

Physical functioning:	limitations in lifting, bending, kneeling, walking, or running
Role-physical:	degree of physical health to perform activities typical for age and social status (job, community activities, volunteer work)
Bodily pain:	intensity, frequency, and duration of bodily pain and limitations in normal activities due to pain
General health:	beliefs and evaluations of overall health, including past and present health
Vitality feeling:	feelings of energy, fatigue and tiredness
Social functioning:	ability to develop and maintain mature social relationships
Role-emotional:	personal feelings about job performance, work, or other activities
Mental health:	emotional, cognitive, and intellectual status of the patient

Table 3: The SF-36 (7, 113)

Each item relates to different aspects of daily life measuring the patient´s performance. Additionally, it is possible to represent the overall physical and mental functioning by combining all multi-item domains into a Mental Component Summary (MCS) and a Physical Component Summary (PCS) that can be calculated as 2 metascores. (17)
The number of possible answers per item varies from 2 to 6 and all 8 subscales score from 0 to 100 points, with higher scores indicating better perceived QoL. The completion time is about 10 to 15 minutes. (7, 112, 113) (Please see Appendix LQ-1, 2)

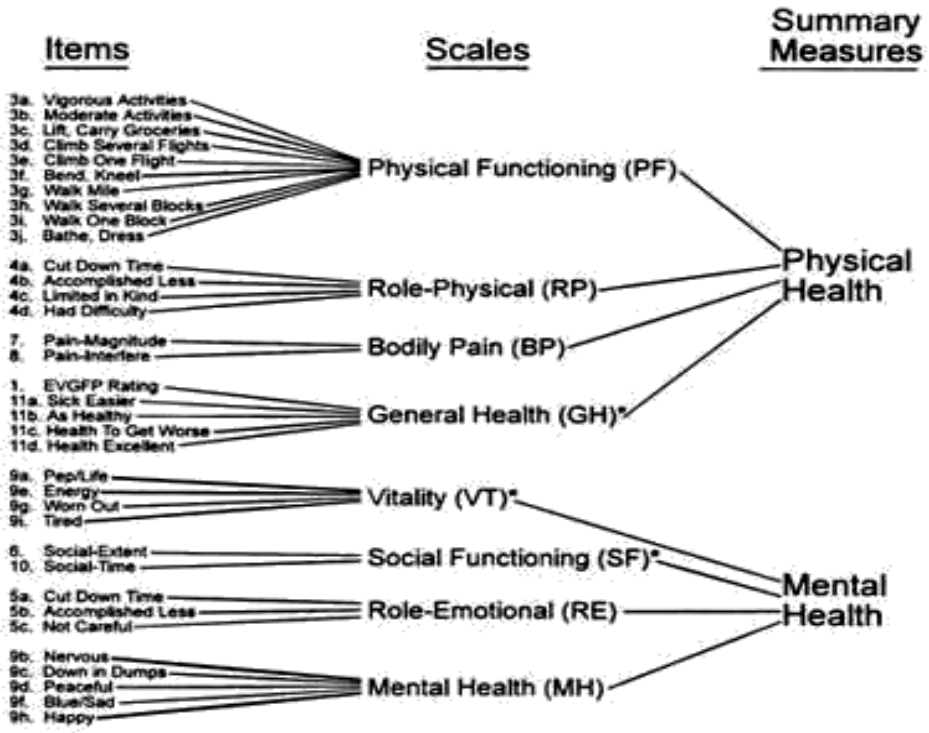

Figure 12: Schematic illustration of the SF-36 (115)

2.3.2 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The MLHFQ was developed to determine the influence of heart failure related conditions and the heart failure treatment on QoL, specifically, the physical, mental, emotional, and social components of QoL. (116) This disease specific tool measures patient perceptions concerning the effects of heart failure on their lives in the last 4 weeks using 21 items. The items refer to three different domains: physical and symptoms (11 items), psychological (7 items) and socio-economic subscale (3 items). Each item is introduced by the question: "Did your heart failure prevent you from?" (117)

A 6 point Likert scale (0 = not at all to 5 = very much) is accorded to each item. Maximum score measures 105 points, whereas higher scores indicate poorer QoL. (116) (Please see Appendix LQ-3)

2.3.3 Hospital Anxiety and Depression Scale (HADS)

HADS has been established as a reliable, dimension specific questionnaire that performs well in screening for the separate dimensions of anxiety and depression. (119, 120) It consists of 14 items, 7 items contributing to the anxiety and 7 items rating depression.
All items incorporate a 4 point Likert scale ranging from 0 to 3 (score range 0-21 points). Zigmond and Snaith reported that each patient may subsequently be adjusted to one of three anxiety and depression category groups, and based on the individual final scores (0–7 = non-case; 8–10 = borderline case and >11 definite cases). (118-120)
As valid and responsive self-administered instrument, HADS has been designed as a screening test for depression and anxiety giving an indication of their clinical severity. (119) (Please see Appendix LQ-4)

2.3.4 General Self-Efficacy Scale (GSE), ENRICHD Social Support Instrument (ESSI) and Physical Activity Scale

The General Self-Efficacy Scale is a psychometric, unidimensional instrument designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life. The original version of the instrument was published in German by Matthias Jerusalem and Ralf Schwarzer in 1981 and has since been used in studies counting hundred thousands of participants. It aims to evaluate a general sense of perceived self-efficacy to cope with daily troubles and to adapt after experiencing stressful life events. Furthermore, the scale was designed for general adult population and consists of 10 items each responding on a 4 point scale (1 = Not at all true; 2 = Hardly true, 3 = Moderately true; 4 = Exactly true). The completion time is 4 minutes on average. The final composite score ranges from 10 to 40 points. According to samples from 23 nations the Cronbach´s alpha ranged from 76 to 90, including majority in the high 80s. Currently, the scale is available in 33 languages.

GSE can be applied in before and following cardiac surgery to determine changes in quality of life, but also among patients with chronic pain conditions or those within a rehabilitation program.

Criterion-documented validity has already been documented for GSE in various correlation studies. Positive coefficient was related to favorable emotions, optimism or work satisfaction while negative coefficients were found with depression, anxiety, stress, burnout or health complaints. (121)

The ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) Social Support Instrument was estimated as a valid and reliable measure of social support in patients who underwent treatment for CAD. However, social support plays an important role in the outcomes of patients treated for ischemic heart disease, and in controlling patient variability in those studies, where the results depend on social support. Higher morbidity and mortality were furthermore observed among patients with ischaemic heart disease due to the lack of social support.

ESSI is a self-report survey composed of 7 items that assess four defining characteristics of social support: emotional, instrumental, informational, and appraisal. It has shown agreeable internal consistence and positive correlation with other social support tools. Nonetheless, there was a negative correlation between ESSI and depression scales.

Individual items are summed for a total score indicating that higher scores present greater social support. The Completion time required for ESSI was reported as 2-3 minutes. (122)

In conclusion, it is of importance to note that not all items of the previous two questionnaires were included in assessment of QoL in our study. Of the 10 GSE items 6 were adapted in our study. Furthermore, 5 out of 7 items incorporated into the ESSI tool were selected here.

The Physical Activity instrument evolved in our study aimed to measure the total amount of time in hours spent on physical activity during a usual week. Three domains of physical activity provide information about time spent on walking, moderate or vigorous activities. (Please see Appendix LQ-5)

2.3.5 The Maastricht-Questionnaire

To estimate the status of excessive mental fatigue, loss of energy, feelings of demoralization, and increased irritability in our study population, we adapted a 24 item self-evaluating Maastricht Questionnaire on Vital Exhaustion. Others reported about modified Maastricht Questionnaires, either containing 21 or 23 items. (118, 123,124)

Each of the 21 items incorporated into the questionnaire is rated on a 3-point scale (No = 0; Don´t know (?) = 1; Yes = 2 points). (119, 124)

The total scale score is determined by summing the answers to an overall vital exhaustion score, ranging from a minimum of 0 and the maximum of 48 points. High score indicates a severe level of vital exhaustion with a good reliability among cardiac patients, and a Cronbach´s alpha of > 0.89. (118, 123, 125) The duration of the interview is 15 minutes approximately. (Please see Appendix LQ-6)

2.4 Echocardiography

Standard TTE examinations were routinely performed before intervention, at hospital discharge, and 1, 3 and 6 months after PAVR using a commercially accessible ultrasound system. In order to observe acute and mid-term haemodynamic response to valve implantation in our study group, we retrospectively collected available echocardiographic data of these patients. The accessible data were gathered either from patient medical history archives or using computer installed echocardiography programs.

The TTE examinations were carried out using a standardized echocardiography protocol. On the basis of parasternal and apical views 2D, M-Mode, Color and CW-Doppler measures were accomplished.

The aortic valve anatomy and echogenicity, right ventricular (RV) and LV diameters, interventricular septum (IVS) thickness, left atrial (LA) and aortic measurements (AO) were obtained in the 2D long axis and 4-chamber (4 CH) views at end-diastole, while the LVOT diameter determination was taken in mid-systole. Furthermore, 2D-guided M-Mode measurements of the LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), IVS thickness in diastole and systole (IVS diast. and syst.), diastolic and systolic posterior wall thickness (PW diast. and syst.), as well as LA and AO diameter were taken according to the leading-edge convention of the American Society of Echocardiography (ASE).

Ejection fraction was calculated in 2D images in apical two- (2CH) or four chamber-views (4CH) using the apical biplane Simpson method and was classified according to the current EAE/ASE recommendations for chamber quantification (EF ≥55% normal, EF = 45–54% mildly abnormal, EF = 30 – 44 % moderately abnormal, EF < 30 severely abnormal). (129) Fractional shortening (FS) was automatically calculated from M-Mode measurements.

Furthermore, systolic pump function and regional wall motion were evaluated visually from parasternal long and short axis, as well as apical 2CH and 4CH views.
The peak aortic and LVOT jet velocities were taken from CW-Doppler and pulsed wave (PW) recordings obtained from an optimized apical 5 CH view.
Peak and mean pressure gradients above the aortic valve were calculated using the Bernoulli law and the AVA was established using the continuity equation as previously described in this thesis.
Mitral, tricuspid or aortic valve regurgitation was assessed using color flow imaging and was graded as mild, moderate or severe.
The value of the pulmonary systolic pressure was entered into the standard examination protocol and was calculated by adding the central venous pressure value to the tricuspid valve peak pressure gradient. Filling and respiratory alterations of the vena cava were observed from a subcostal view.

2.5 Blood sample analyzes

The third goal of the present study was to evaluate and observe acute postprocedural changes in blood plasma concentration of N-terminal brain natriuretic peptide (NT-pro BNP), CRP, creatinine and haemoglobin. These parameters were included into routinely performed clinical investigations and were immediately analyzed in the local laboratory. Therefore we retrospectively collected the obtained values of these parameters using concentrations measured 1 day before and 1 day after the intervention, as well as at hospital discharge. NT-pro BNP, CRP and creatinine were determined from venous blood samples previously collected in lithium-heparinate tubes with separating gel, while haemoglobin was detected from blood samples mixed up with ethylenediaminetetraacetic acid (EDTA) tubes.
In a subgroup of 15 patients, we furthermore set the goal to analyze the correlation between acute haemodynamic response following PAVR and blood plasma concentration of novel biomarkers such as homoarginine, myeloperoxydase (MPO) and the high sensitive troponin T. The venous blood samples were collected 1 day before, 1 day after and exactly 7 days postprocedural, and were drawn into lithium-heparinate tubes (8ml) with separating gel. We immediately centrifuged the samples for 15 minutes and pipetted the supernatant

into plastic tubes (5 ml). The tubes were stored at minus 20 °C until further proceeding in a specialized laboratory.

Preceding laboratory analyzes, the samples were defrosted at room temperature under standardized conditions and were then divided into aliquots (each containing 200 µl).

For determination of homoarginine, MPO and high sensitive troponine T at 1 day before, 1 and 7 days after PAVR we prepared 3 times 200 µl aliquots pro each time point and biomarker for all 15 patients and counted 135 aliquots before analyzes.

Further determinations of the three previously listed biomarkers were carried out at the Clinical Institute of Medical and Chemical Laboratory Diagnostics (Medical University of Graz).

2.5.1 Determination of NT-pro BNP

Under haemodynamic stress conditions such as hypetrophy, increased wall tension or volume overload of the ventricles, the pre-prohormone BNP is transformed into a 108 amino acids containing prohormone BNP. The prohormone BNP is cleaved by a circulating endoprotease, the corin into a bioactive form, the BNP (32 amino acids in length) and the inactive NT-pro BNP (76 amino acids). (130-132)

NT-pro BNP has a longer circulating time (half-life time: 60-120 minutes) and fluctuates slowly in circulation. (132)

Both natriuretic peptides are cleared by the kidneys. Hypervolaemia and hypertension as caused by the renal failure increase the secretion and elevate BNP levels, especially the NT-pro BNP portion. Besides conditions implicated in chronic heart failure, enhanced circulating BNP levels are reported in older age and pulmonary hypertension. (130)

The NT-pro BNP analyzes are implicated into standard laboratory investigations in our institute and the local laboratory considers NT-pro BNP values < 150 pg/ml as normal. Venous blood samples are routinely drawn into lithium-heparin tubes with separating gel and undergo a 10 minutes centrifugation process immediately after collection.

The NT-pro BNP values are determined using the Elecsys proBNP II assay from Cobas®, Roche Diagnostics, Mannheim Germany) following manufacturer´s recommendations.

2.5.2 Haemoglobin

Haemoglobin was analyzed from EDTA-containing venous blood. The reference values for the local laboratory were between 12.0 and 15.3 g/dl.
Patients were classified anaemic according to the World Health Organization (WHO) definition (< 12 g/dl for women, and < 13 g/dl for men). (136)

2.5.3 C-reactive protein

CRP is detectable in blood serum due to various inflammatory conditions and its increased levels were linked to heart failure patients in the early 1956. As an acute phase reactant, CRP is formed by hepatocytes in response to interleukin-6, a proinflammatory cytokine. Elevated CRP concentrations were related to adverse outcomes in patients with acute or chronic heart failure and served to identify asymptomatic subjects at high risk for developing heart failure. (130)
Local reference value for CRP analyzed from lithium-heparinated venous blood and being < 8 mg/l is considered normal. Retrospective collection of CRP values determined at 1 day before, 1 day following PAVR, and at hospital discharge, was obtained.

2.5.4 Creatinine

Serum creatinine levels are the key points in diagnosing acute renal failure. This Conventional renal biomarker is elevated when the serum glomerular filtration rate reaches values <50 % of normal values. (133)
According to the Valve Academic Research Consortium definitions, acute kidney injury is currently defined as an absolute increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.4 μmol/L), or a percentage enhancement of ≥ 50% within 72 hours following PAVR.

To investigate if PAVR led to acute kidney injury or permanent haemodialysis in our study population we retrospectively observed creatinine concentrations estimated 1 day before, 1 day after PAVR and at hospital discharge. Creatinine was included into standard blood analyzes during hospital stay, evaluated from venous blood samples and collected into

lithium-heparin tubes with separating gel following standard laboratory procedures. The local laboratory sets a reference value for creatinine ranging from 0.50 to 1.00 mg/dl.

2.5.5 Homoarginine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and global arginine bioavailability ratio (GABR)

Homoarginine is a cationic amino acid originated from lysine. It may increase the availability of nitric oxide and advance endothelial function. Accordingly, homoarginine serves as a precursor of nitric oxide (NO) and enhances the intracellular concentration of L-arginine, which serves as a main substrate for NO synthase. Hereby, it inhibits the enzyme arginase, which is the competitive enzyme of NO-synthase in the course for the key substrate L-arginine. (137) Concentration of endogenous homoarginine ranges from 0.90 to 6.2 μM, in other publications. (138)

Asymmetric dimethylarginine (ADMA) and its inactive stereoisomer symmetric dimethylarginine (SDMA) are generated in hydrolysation processes of proteins with methylated arginine residues.They are formed through the transfer of methyl groups from S-adenosyl-methionine. ADMA inhibits the conversion of the amino acid L-arginine into L-citrulline and nitric oxide (NO). (138)

The synthesis steps of ADMA and SDMA are similar but the degradation routes differ. SDMA is eliminated renally while ADMA shows a renal and a metabolic pathway. Over 90% of ADMA is metabolized via dimethylarginine dimethylaminohydrolase. (138) The present study aimed to determine the association of PAVR and its influence on homoarginine, ADMA and SDMA concentrations in blood plasma samples drawn as described before in this thesis.

The exact step-by-step procedure for homoarginine, ADMA and SDMA estimation in plasma using the HPLC method with pre-column derivatization and fluorescence detection have been previously described by Meinitzer et al. (138)

In addition, plasma levels of free arginine, ornithine and citrulline were measured with liquid chromatography combined with tandem mass spectrometry. We furthermore estimated the global arginine bioavailability ratio (GABR) which is defined as arginine/(ornithine + citrulline). (157)

2.5.6 Myeloperoxydase (MPO)

Myeloperoxidase (MPO) is a biomarker of inflammation and oxidative stress, produced by activated leukocytes (mostly polymorphonuclear neutrophils (PMN)), monocytes and endothelial cells (139, 140). It catalyzes the production of hypochlorous acid and increases antimicrobial activity serving as a defender of the organism.

MPO is furthermore considered as a bactericidal agent but also as a potential marker of cardiovascular disease (CVD) and may play an important role in the progression of CVD.

MPO has been identified in human plaques expressing potent proatherogenic effects such as the oxidation of LDL and oxidative modification of apolipoprotein (apo) AI. Besides, MPO activity decreases bioavailability of nitric oxide, promoting endothelial dysfunction. Considering these effects, MPO may serve as an active mediator in the process of atherosclerosis and the transition to unstable plaque. (139-141)

Moreover, the hypochlorus acid which is induced by myeloperoxydase is involved in apoptosis and separation of endothelial cells, leading to superficial erosions.

Higher levels of MPO have been found in patients with CAD predicting future cardiovascular events in these patients or patients with chest pain.

Elevated MPO levels were detected among liver and heart transplant (Tx) patients before any signs of infection or rejection, and the appearance of increased MPO levels was notable earlier in those transplant patients infected by cytomegalovirus. (158)

To measure MPO plasma concentrations in patients undergoing PAVR we used a new MPO assay, the Architect MPO (Abbott Laboratories Diagnostics, Abbott Park, IL, USA)). This assay has been evaluated to be a precise and convenient automated method for the determination of MPO in plasma, lasting only 15 minutes, and may be of interest in selecting patients at risk for adverse cardiac events. (139)

The concentration of MPO is detected relative to a standard curve achieved by calibrators of known MPO concentration. The detection limit is 2.9µg/l. Therefore, the automated Architect MPO assay is superior for routine analyzes than immune-enzymatic methods, and it shows good correlation to the reference enzyme-linked immunosorbent assay (ELISA) method. (139)

2.5.7 Highly sensitive troponin

The local cut-off value for cardiac troponin T is 14 pg/ml. To detect the concentration of highly sensitive troponin T in our study population and the changes of troponin T

influenced by PAVR we used a new Cobas® 8000 electrochemiluminescence immunoassay. Highly sensitive troponin levels were assessed from lithium-heparinated plasma drawn 1 day before and after PAVR as well as exactly 7 days post-procedural.

2.6 Statistical analyzes

Numerical values were presented as mean ± SD. The QoL scores were illustrated including mean values, as well as SDs. The Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, USA), Version 18 was used to calculate the QoL scores. For further statistical analysis of the QoL scores, echocardiographic parameters or biomarkers in blood plasma, the Sigmastat version 3.5 Software Package was chosen. Paired t-test was applied for comparison between baseline variables and short term outcome values (for example, baseline vs. 1 day post-procedural, etc). To test the statistical significance in changes of QoL or plasma biomarkers between groups at different time points, an ANOVA (Analyzes of Variance) for repeated measurements was used with a Tukey's post hoc test. Graphical illustrations were performed using the Microsoft Excel 2007 Software. Data were considered as statistically significant with a two-sided-P-value of less than 0.05 ($p < 0.05$).

3 Results

Initially, 31 consecutive patients undergoing PAVR at the Department of Cardiology, University Hospital of Graz were included in the current study

3.1 Baseline characteristics

Table 4 summarizes baseline demographic and clinical characteristics of the study population.

Parameter	**N (%)**
Patients	30
Age, y	
Mean ± SD	80 ± 5
Median (range)	81.5 (70-89)
Male	11 (36.7)
Female	19 (63.33)
Marital status (widowed/married)	(15/11) (50/36)
Basic /advanced school education	15/8 (50/26)
Retired / part-time employment	25/1 (83.33/3)
Diabetes mellitus	9 (30)
Chronic obstructive pulmonary disease	5 (16.66)
Prior cerebrovascular event (TIA/stroke)	10 (33.33)
Chronic renal failure	13 (43.33)
Cancer	5 (16.66)
Neurological disorder	7 (23.33)
Musculoskeletal disorder	12 (40)
Peripheral artery disease (PAD)	4 (13.33)
Prior permanent pacemaker	2 (6.66)
Prior PCI/stent implantation	11 (36.66)
Prior cardiac surgery	8 (26.66)
Prior SAVR	3 (10)
Coronary artery disease (CAD)	19 (63.33)

NYHA Class	
NYHA I	1 (3.3)
NYHA II – III	6 (20)
NYHA III	14 (46.7)
NYHA III – IV	6 (20)
NYHA IV	3 (10)

Table 4: Study group characteristics at baseline – Data are presented as number of patients and percentage of the enrolled study group. CAD – coronary artery disease, NYHA Class – New York Hearth Association Class, PAD – peripheral artery disease, SAVR – surgical valve replacement, TIA – transient ischaemic attack

3.2 Procedural outcomes

Immediate procedural success was obtained in 100% of patients. All procedures were accomplished by means of a transfemoral approach. 1 patient died from acute haemodynamic failure within 24 hours post-procedurally and was therefore excluded from further analysis.

Major access site complication was observed in one patient requiring iliaco-femoral bypass operation immediately after valve implantation. Permanent pacemaker implantation was necessary in 7 of 30 patients (23.3%)

3.3 Quality of life

31 patients received combined QoL questionnaires at the day of admission (2 to 3 days before PAVR). The same QoL questionnaires were mailed to the remaining 30 patients 30 days after PAVR. Of these 30 contacted patients, 24 returned the completed questionnaires to the Department of Cardiology, University Hospital of Graz 6 patients did not reply to the 30-days follow up.

According to information received from patients´ general practitioners or from recently obtained medical histories 2 of the 6 patients who were lost to follow up had died. The cause of death was not linked to cardiac or device function. One patient died on excessive subarachnoidal bleeding (3.5 months after) whereas the other patient died by suicide (2 months after PAVR). Thus, 4 patients were still lost to the 30 days follow up.

In order to obtain the 6 months QoL follow up assessment, we mailed the same questionnaires again to the enrolled patients. From December 2009 to December 2010, 12 patients replied to follow up. A summary of these results is shown in Figure 13.

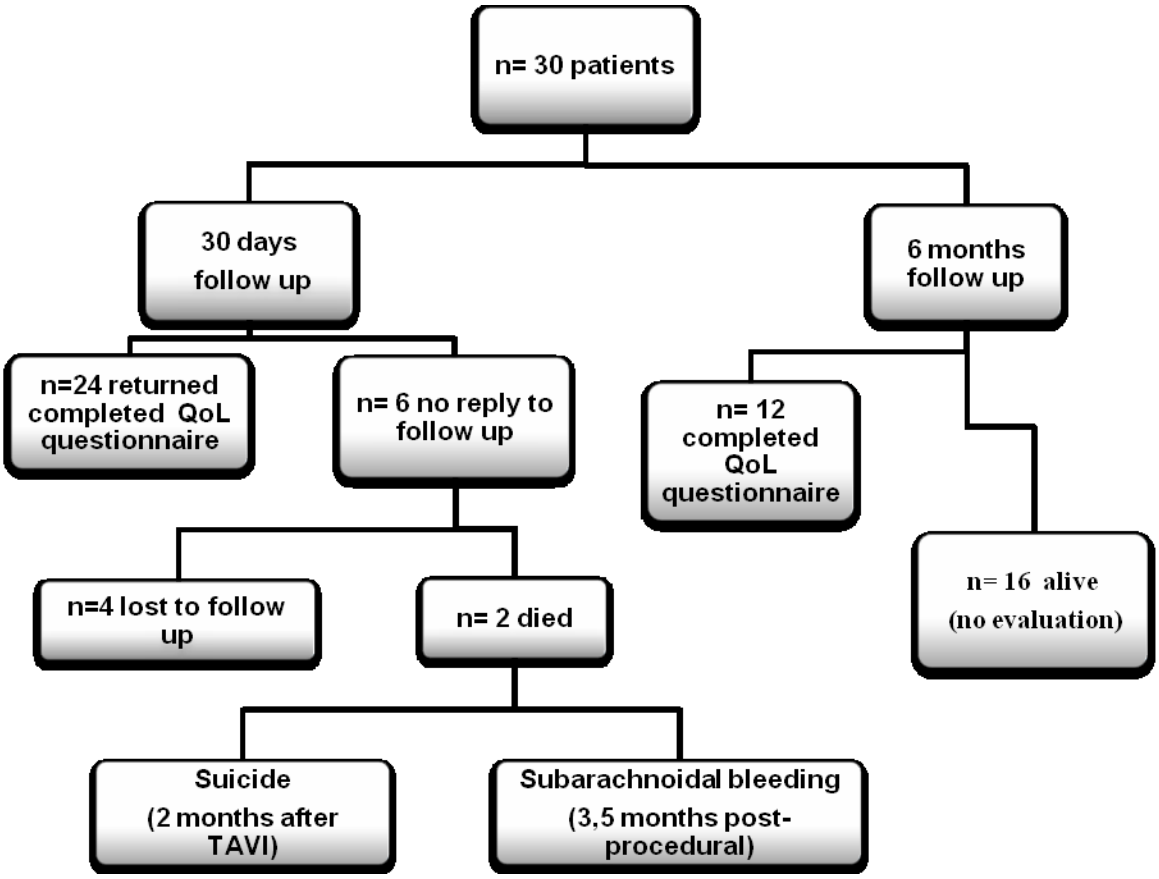

Figure 13: A summary of the follow up responses

3.3.1 Quality of life as assessed by the SF-36

The data are presented as mean ± SD and refer to 30 patients who completed the QoL questionnaires at baseline, 24 patients at 30 days follow up and 12 patients included into the 6 months follow up evaluation.

Scores matched by the SF-36 at baseline, 30 days and 6 months post-procedurally are schematized in Figure 14. The summarized score for physical health showed a significant improvement between the perceived baseline QoL and at 30 days follow up (26.0 ± 7.2 vs. 34.5 ± 9.4, $p = 0.001$) as well as at baseline compared to the 6 months follow up (26.0 ± 7.2 vs. 41.7 ± 7.8 $p < 0.001$). No significant changes were found in the summarized scores

of physical health measured evaluated between 30 days and 6 months follow ups (34.5 ± 9.4 vs. 41.7 ± 7.8, $p > 0.05$).

The mental health summarized score remained nearly unchanged expressing no significant overall improvement at 30 days follow up (48.5 ± 11.8 vs. 48.1 ± 13.1, $p > 0.05$) as well as 6 month post-procedural (48.5 ± 11.8 vs. 44.9 ± 11.2, $p > 0.05$).

With regard to the physical health scales patients experienced a significant improvement in physical functioning (22.8 ± 17.1 vs. 45.0 ± 25.1, $p = 0.002$ and 22.8 ± 17.1 vs. 55.0 ± 23.5, $p < 0.001$). Advanced results 30 days after PAVR were notable in general health (42.9 ± 60.6, $p = 0.002$). Six months but not 30 days post-interventional improvement was achieved in bodily pain (50.7 ± 34.4 vs. 82.4 ± 19.4, $p = 0.009$). No significant changes were found in role physical scores at baseline and post-interventional (4.2 ± 14.1 vs. 8.7 ± 23.4 and 4.2 ± 14.1 vs. 22.9 ± 39.1, $p > 0.05$).

Significant gain related to the mental health components was distinguished in vitality 27.9 ± 18.9 vs. 43.8 ± 18.4, $p = 0.004$ and 27.9 ± 18.9 vs. 48.5 ± 13.9, $p = 0.002$) comparing initial to 30 days and 6 months follow up results. Thus, no significant changes were present in social functioning, role emotional and mental health (66.3 ± 28.2 vs. 75.0 ± 21.5, 66.3 ± 28.2 vs. 77.1 ± 17.5, 54.2 ± 48.0 vs.37.9 ± 45.2, 54.2 ± 48.0 vs. 33.3 ± 40.2 and 63.8 ± 20.8 vs. 73.2 ± 19.7, 63.8 ± 20.8 vs. 67.8 ± 19.4, $p > 0.05$).

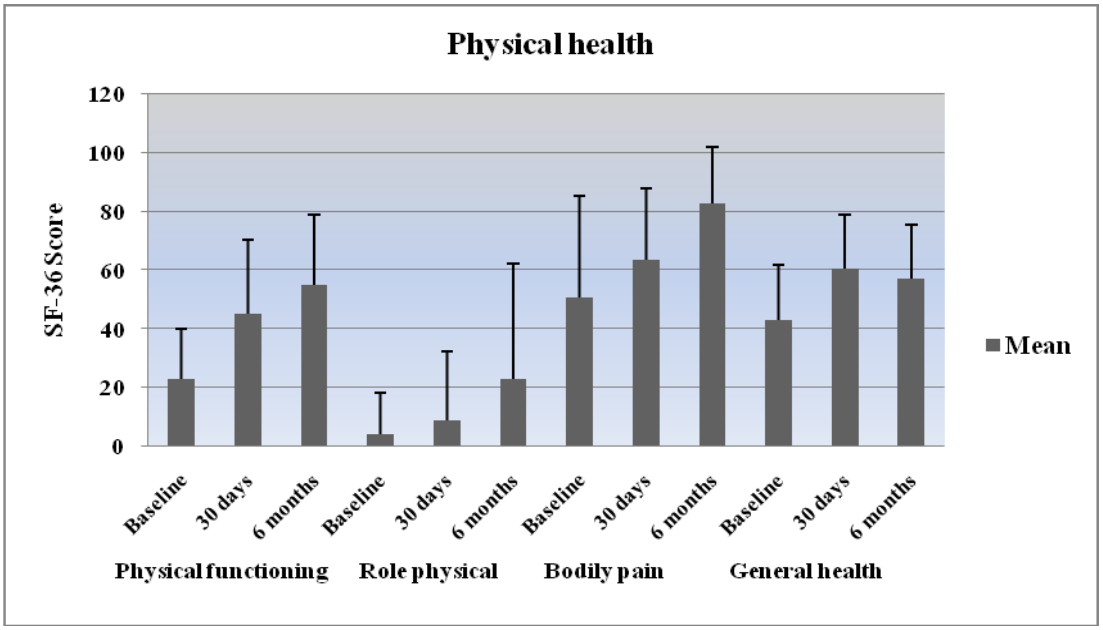

Figure 14: The SF-36 Physical Health Score (0-100) – Data are presented as mean value ± SD. Higher scores indicate better quality of life. Significant improvements were found in physical functioning at 30 days and 6 months, general health at 30 days and bodily pain at 6 months after PAVR.

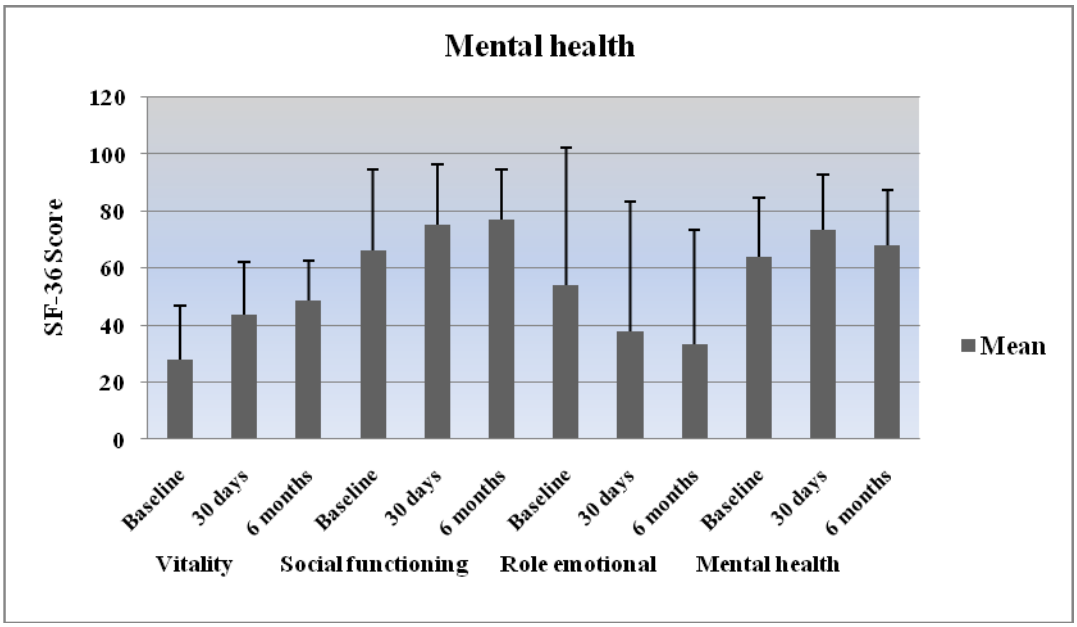

Figure 15: The SF-36 Mental Health Score (0-100) – Data are presented as mean value ± SD. Higher scores indicate better quality of life. Vitality was significantly improved comparing baseline to follow up scores. Other mental health components remained significantly unchanged.

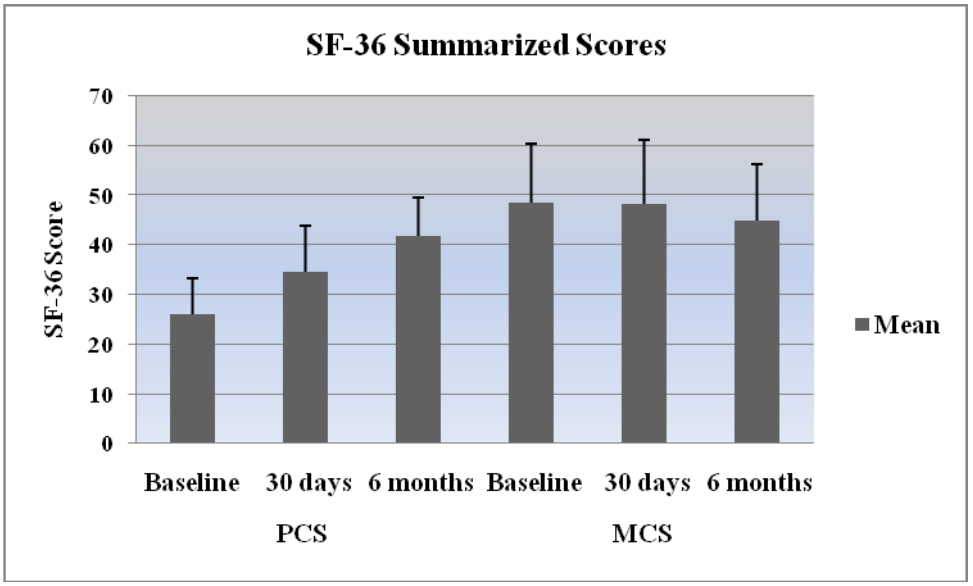

Figure 16: The SF-36 Physical and Mental Health Summary Scores (0-100) - Data are presented as mean value ± SD. Higher scores indicate better quality of life. PCS (Physical Component Summary) was significantly improved at 30 days and at 6 months follow up. No significant changes were detectable in MCS (Mental Component Summary).

3.3.2 The MLHFQ evaluation

The MLHFQ summarized score showed a significant change 30 days and 6 months after PAVR as compared to the baseline scores (50.0 ± 16.9 vs. 38.1 ± 22.4, p = 0.004, 50.0 ± 16.9 vs. 26.8 ± 12.0, p = 0.012).

The physical MLHFQ subscale was characterized by a significant improvement in QoL at 30 days and 6 months follow ups and in comparison to the scores matched at baseline (27.5 ± 6.4 vs. 20.1 ± 10.2, p = 0.005, 27.5 ± 6.4 vs. 17.8 ± 10.0, p = 0.003). There was no significant change in the compared emotional subscales of the MLHFQ (8.2 ± 5.5 vs. 6.9 ± 6.3, 8.2 ± 5.5 vs. 4.6 ± 4.1, p > 0.05).

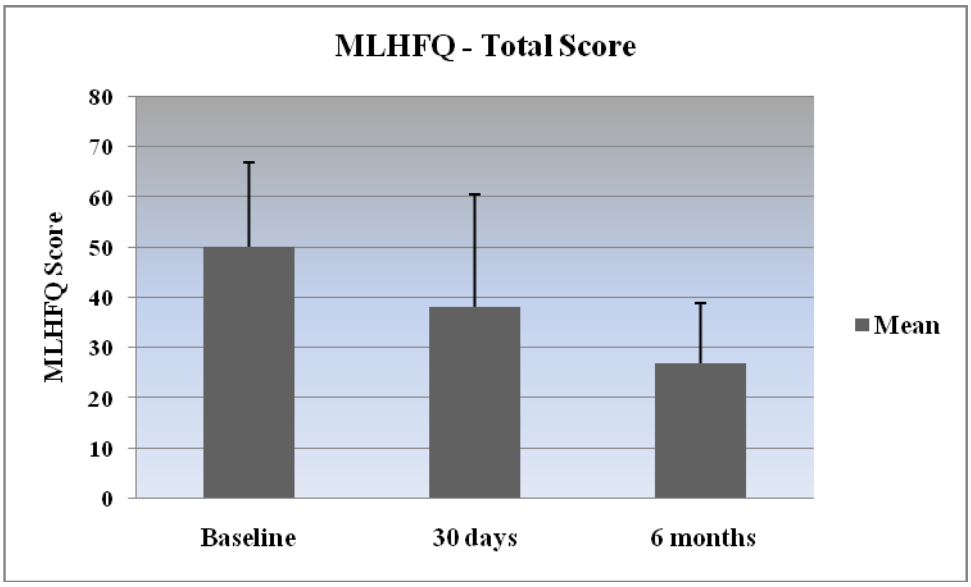

Figure 17: The MLHFQ - Total Score (0-105) - Data are presented as mean value ± SD. Higher scores indicate poorer quality of life. There was a significant improvement found 30 days and 6 month following PAVR.

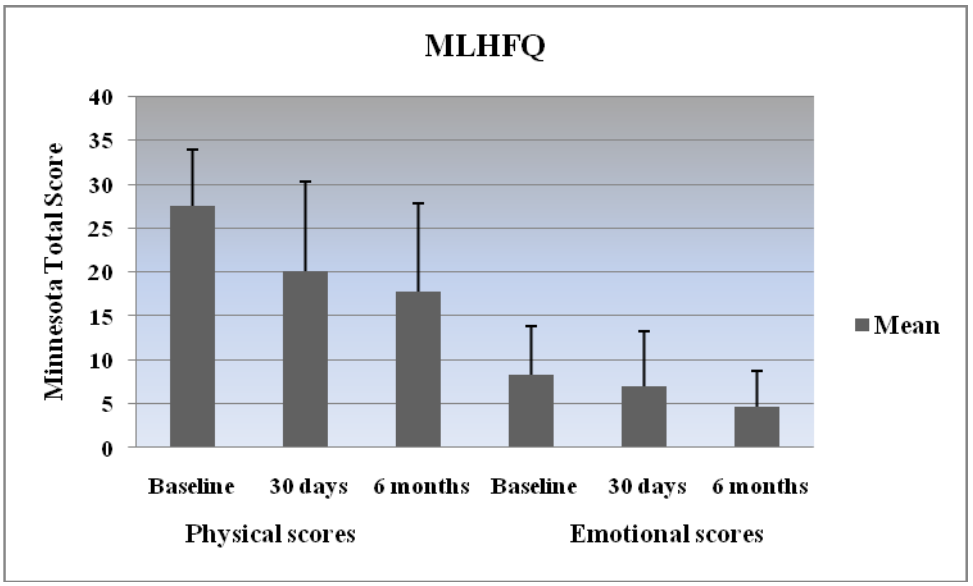

Figure 18: MLHFQ - Physical and Emotional Scores - Data are presented as mean value ± SD. Higher scores indicate poorer quality of life. Physical health was a significantly improved at 30 days and 6 month follow up whereas the emotional scores remained unchanged.

3.3.3 The HADS

Taking the cut-off mean value of 8 (148)into account, 7 of the 30 included patients were depressive at baseline, whereas 6 of the 24 patients and 4 of the 12 patients were evaluated as depressive at the 30 days and 6 months follow up. Comparing the mean values there was no statistically significant difference found between the values at baseline and follow ups. Anxiety was evaluated as positive (cut-off value 10) (148) in 2 of the 30 patients at baseline, while only 1 patient had a positive mean value for anxiety 30 days after PAVR. No positive anxiety scores were found 6 months after the intervention.

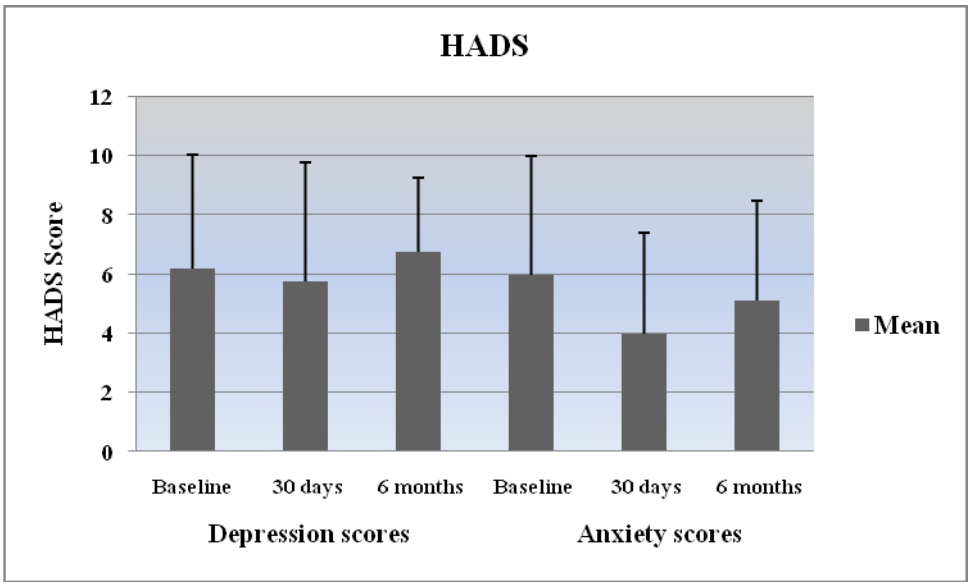

Figure 19: HADS (Hospital Anxiety and Depression Scale): Data are presented as mean value ± SD. Individual scores < 8 refer to absence of depressive symptoms. Individual scores > 11 are related to the presence of anxiety. The mean value of all pre- and post-interventional individual anxiety and depression scores is given here. There was no significant change in depression and anxiety according to the general mean value comparisons.

3.3.4 GSE, ESSI and physical activity

The patients self efficacy evaluation might be interpreted as positive at baseline and has remained significantly unchanged 30 days and 6 months after PAVR (11.3 ± 4.5 vs. 10.5 ± 4.6 and 11.3 ± 4.5 vs. 9.7 ± 6.3, $p > 0.05$).

Additionally, according to the scores matched by the ESSI and adapting a cut-off value of ≤ 18 (151), the positive social support was present at baseline as well as after PAVR (22.2 ± 3.4 vs. 22.9 ± 3.1 and 22.2 ± 3.4 vs. 22.9 ± 2.4, $p > 0.05$).

Easily physical activity as expressed in total hours per week was significantly improved 30 days after the intervention (2.1 ± 3.4 vs. 6.3 ± 9.4, $p = 0.037$). The extent of moderate physical activity was increased 6 months after PAVR in comparison to the baseline and 30 days results (0.4 ± 0.9 at baseline vs. 1.8 ± 2.3 6 months after PAVR, $p = 0.009$, and 0.5 ± 1.2 30 days post-procedural vs. 1.8 ± 2.3 at the 6 months follow up, $p = 0.019$).

No changes were detected in vigorous activity scores at all three time points (0.2 ± 0.7 vs. 0.0 ± 0.2 and 0.2 ± 0.7 vs. 0.2 ± 0.6, $p > 0.05$).

The total hours of physical activity per week at baseline were 69 and have risen to 163 (n=24) 30 days after PAVR. Twelve patients reported 82 as the total amount of hours 6 months post-interventional.

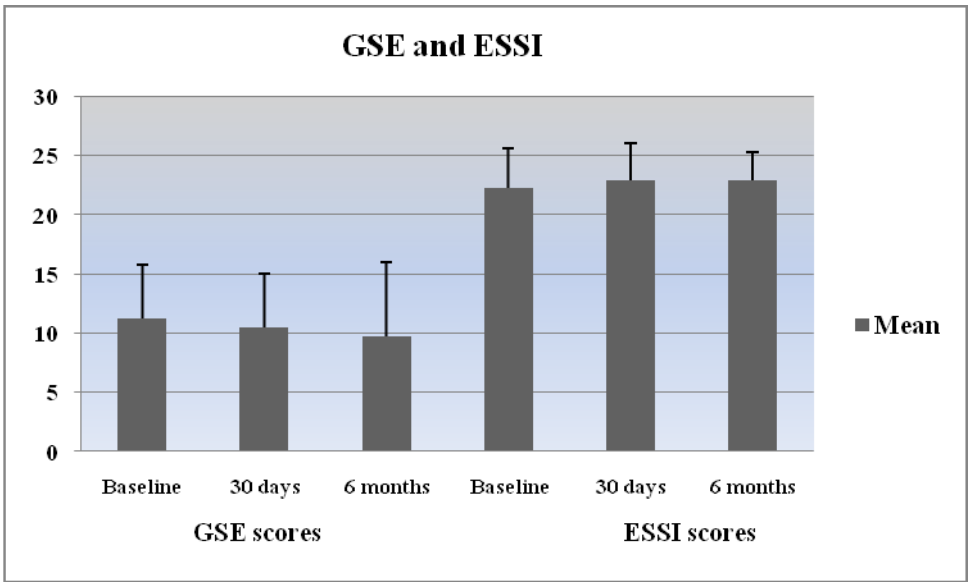

Figure 20: GSE and ESSI (General Self Efficacy and ENRICHD Social Support Instrument) - Data are presented as mean value ± SD. All patients reported positive general self efficacy and social support. There was no significant change after the intervention.

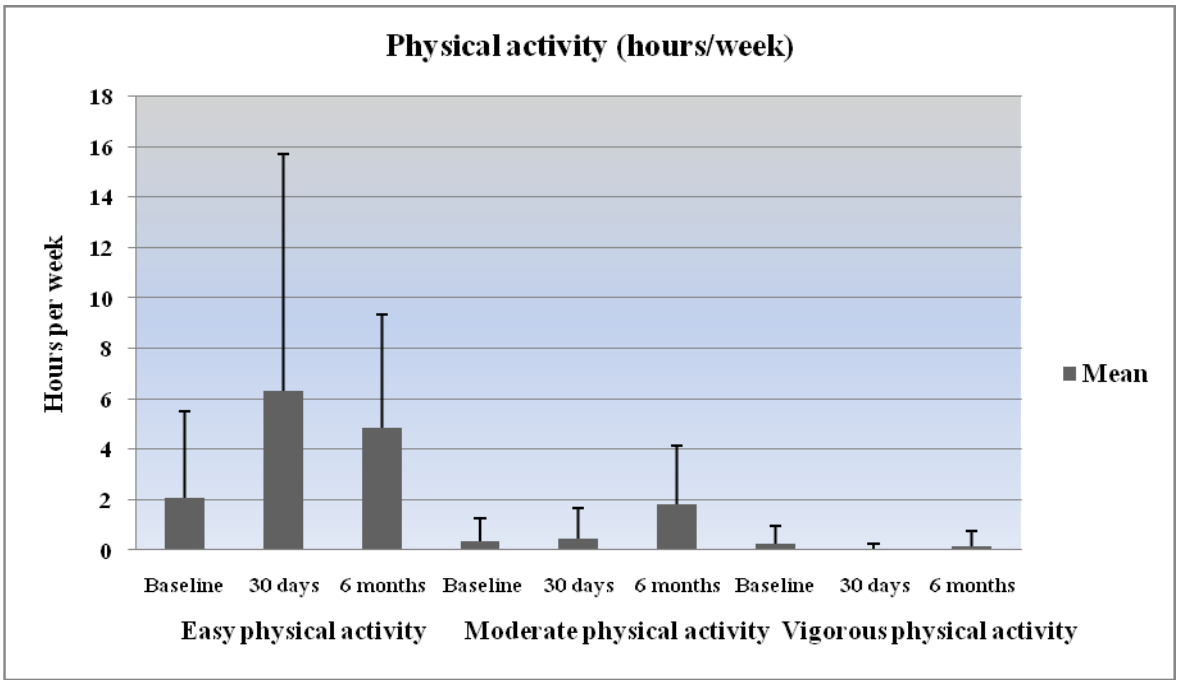

Figure 21: The Physical Activity Scale - Data are presented as mean value ± SD. Easy, moderate and vigorous physical activity is expressed in total hours per week. There was a significant change in easy physical activity 30 days and in moderate physical activity 30 days and 6 months after PAVR. No significant changes were shown in vigorous physical activity.

Physical activity	Baseline	30 days	6 months
Total hours per week	69 (n = 30)	163 (n = 24)	82 (n = 12)

Table 5: The Physical Activity Scale – Data are shown as total hours per week including easy, moderate and vigorous physical activity.

3.3.5 Vital exhaustion as assessed by the Maastricht Questionnaire

The mean score of the Maastricht Questionnaire in a healthy population is 8.8 ± 8.7, as previously reported. (146) Higher scores indicate higher levels of vital exhaustion (147). The mean baseline score of 22.0 ± 8.5 was achieved in our study population and was followed by a decrease of 17.5 ± 7.9 at 30 days and again by an increase of 19.7 ± 9.6 at 6 months after the intervention. Despite the improvement tendency at the 30 days follow up, there was no significant change found while comparing the baseline and the follow up scores ($p > 0.05$).

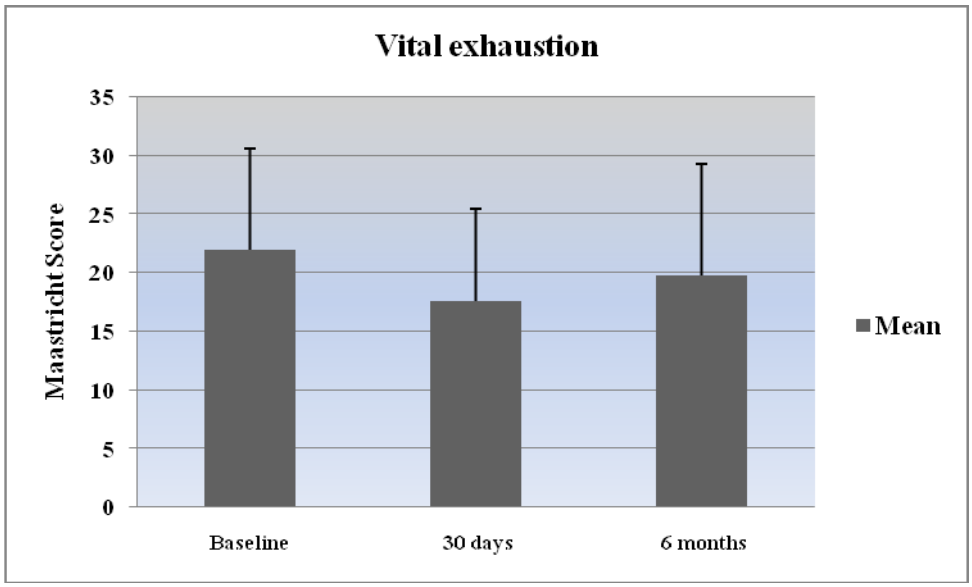

Figure 22: Vital exhaustion as assessed by the Maastricht Questionnaire – Data are presented as mean value ± SD. Higher scores indicate an increase in vital exhaustion. The mean cut off value in healthy population group is 8.8 ± 8.7 (146)

3.4 Echocardiography

Echocardiographic parameters were assessed in routinely performed clinical echocardiographic controls before and immediately after PAVR but also 1, 3 and 6 months post-procedural.

PAVR resulted in an acute improvement of hemodynamic parameters (AV Vmax, MPG and PPG) and aortic valve area. At baseline, mean AVA (n=30); AV Vmax (n=26), MPG (n=28) and PPG (n=27) were 0.63 ± 0.21 cm^2, 4.47 ± 0.95 m/s, 51.21 ± 22.98 mmHg, and 81.96 ± 37.54 mmHg, respectively. After PAVR AVA (n=15) was 1.68 ± 0.38 cm^2, AV Vmax (n=29) 2.09 ± 0.49 m/s, MPG (n=29) 9.95 ± 5.31 mmHg, and PPG (n=30) was 17.92 ± 8.8 mmHg at a median follow up of 60 days (range 7 to 180 days). All mentioned parameters showed a highly significant change ($p < 0.001$) post-interventionally. Graphical illustration of these parameters is given in Figures 23 – 26.

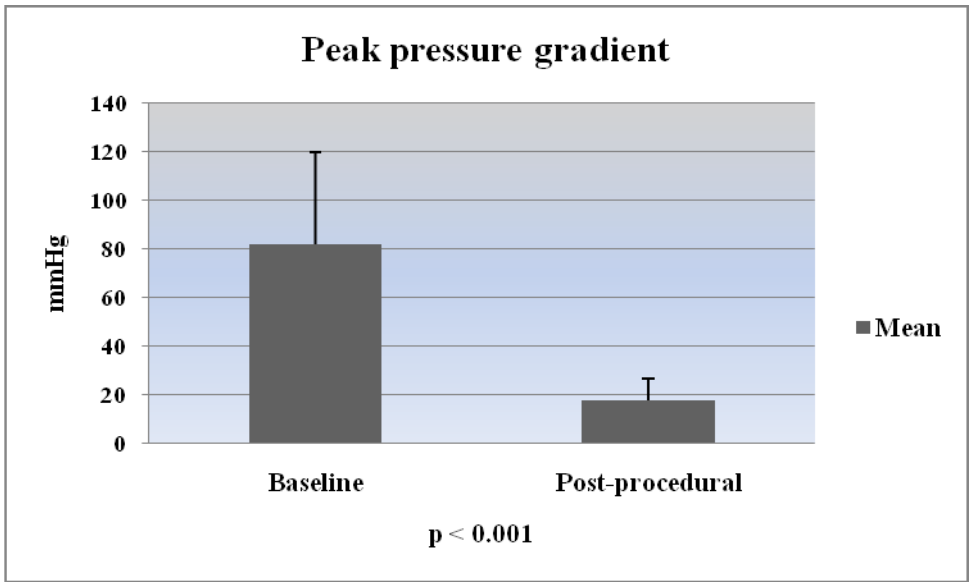

Figure 23: Peak pressure gradient (mm Hg) – Data are presented as mean value ± SD. Acute and midterm haemodynamic response to PAVR. There was a highly significant post-interventional decrease in peak pressure gradient values ($p < 0.001$) – The results refer to a clinical control period from 7 to 180 days.

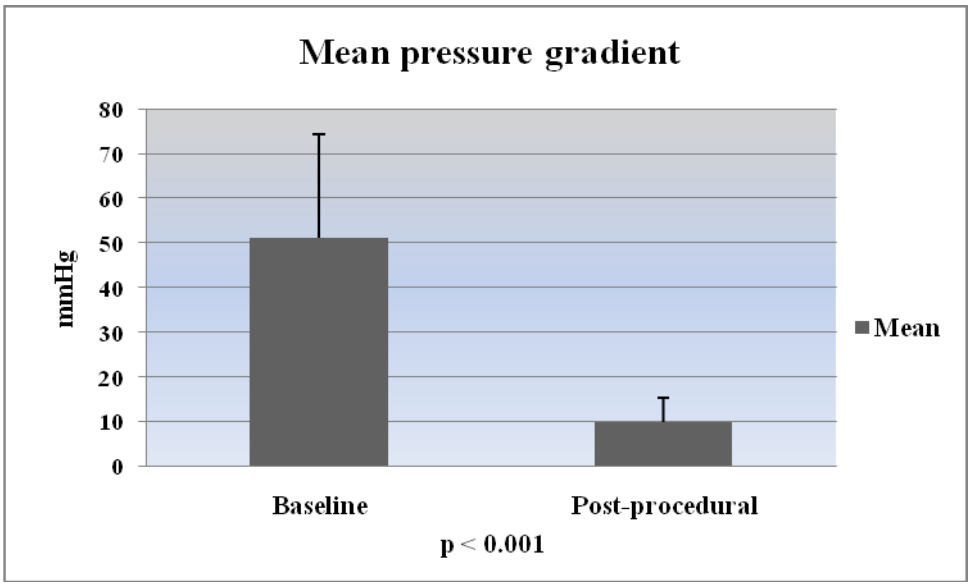

Figure 24: Mean pressure gradient (mm Hg) - Data are presented as mean value ± SD. Acute and midterm haemodynamic response to PAVR. A highly significant post-interventional decline in mean pressure gradient values ($p < 0.001$) was observable. – The results refer to a clinical control period from 7 to 180 days.

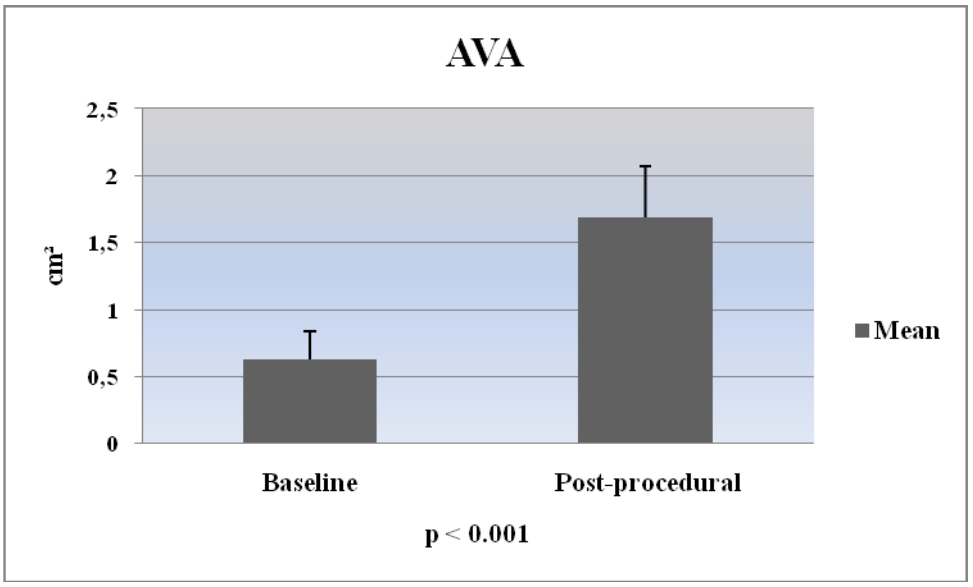

Figure 25: Aortic Valve Area (cm^2) - Data are presented as mean value ± SD. PAVR resulted in a highly significant improvement ($p < 0.001$) in AVA (aortic valve area). The period of observation ranged from 7 to 180 days.

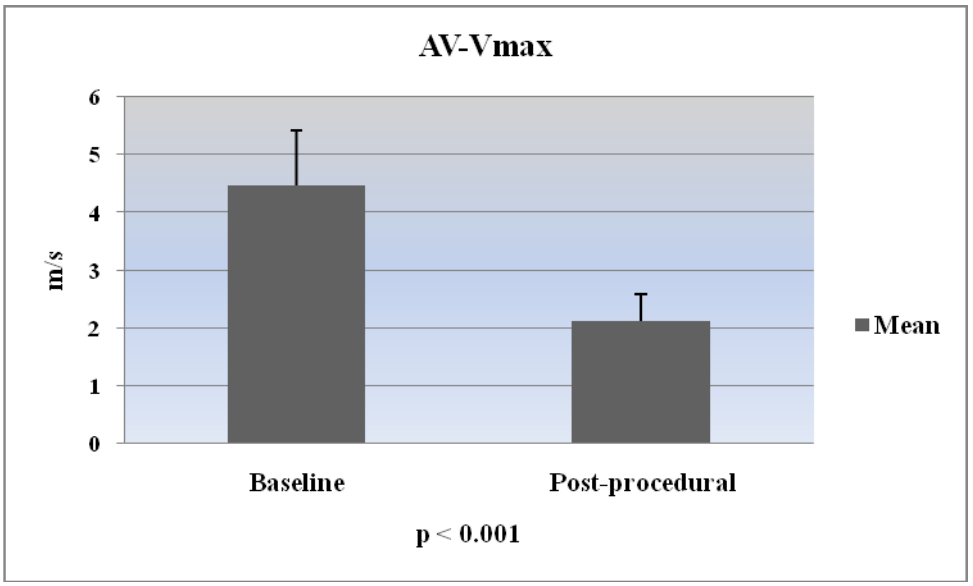

Figure 26: AV – Vmax - Aortic jet velocity (m/s) - Data are presented as mean value ± SD. Highly significant decrease ($p < 0.001$) in jet velocity was detectable throughout a period from 7 to 180 days post-interventionally.

In contrast to haemodynamic improvement, PAVR did not significantly affect left ventricular, left atrial and aortic dimensions and geometry. Table 6 summarizes these parameters.

M –Mode Parameter (mean ± SD)	Pre-interventional	Post-interventional	Probability
AO	30.1 ± 4.9	29.6 ± 5.8	n. s.
LA	47.7 ± 6.8	49.3 ± 5.6	n. s.
LVEDD	49.1 ± 6.9	49.3 ± 8.2	n. s.

Table 6: An overview of the echocardiographic parameters (M-Mode measurements): AO – aortic diameter, LA – left atrial diameter, LVEDD – left ventricular enddiastolic diameter. Data are presented as mean value ± SD. No significant midterm changes of these parameters were observable after PAVR.

Furthermore, PAVR seemed to have a positive effect on systolic function, as indicated by a higher number of patients with normal ejection fraction fraction. However, there was no significant effect on mean systolic pulmonary artery pressure (PAP sys) (50.47 ± 14.09 mmHg (n=19) at baseline vs. 45.88 ± 13.38 mmHg (n= 26) post-procedurally ($p > 0.05$)). Valvular regurgitation (aortic, mitral, tricuspid) was not significantly influenced by PAVR. A summary of the echocardiographic outcomes are given below in Table 7.

Ejection fraction	Baseline n (%)	Post-procedural n (%)
Normal	13 (43.3)	19 (63.3)
Mild	10 (33.3)	3 (10)
Moderate	3 (10)	5 (16.7)
Severe	4 (13.3)	3 (10)

Aortic regurgitation	Baseline n (%)	Post-procedural n (%) (Paravalvular leakage)
No	5 (16.7)	6 (20)
Minimal	10 (33.3)	7 (23.3)
Mild	12 (40)	13 (43.3)
Mild-moderate	1 (3.3)	3 (10)
Moderate	2 (6.7)	1 (3.3)
Severe	No	0

Mitral regurgitation	Baseline n (%)	Post-procedural n (%)
Mild	14 (46.7)	14(46.7)
Mild-moderate	7 (23.3)	8 (26.7)
Moderate	3 (10)	7 (23.3)
Moderate-severe	1(3.3)	0
No value	5 (16.7)	1 (3.3)

Tricuspid regurgitation	Baseline n (%)	Post-procedural n (%)
Mild	15 (50)	19(63.3)
Mild-moderate	3 (10)	2 (6.7)
Moderate	2 (6.7)	3(10)
Moderate-severe	2 (6.7)	1 (3.3)
No value	8 (26.7)	5 (16.7)

Table 7: An overview: Ejection fraction; Aortic, mitral and tricuspid regurgitation. – Data are presented as number and percentage of the study population. Baseline values in comparison to post-procedural.

3.5 Biomarkers

NT-pro BNP, haemoglobin, CRP and creatinine values were measured 1 day before, 1 day after PAVR and at discharge. A summary of the mean values is presented in Table 8.

:

3.5.1 Biomarkers in heart failure (NT-pro BNP)

NT-pro BNP is an established diagnostic and prognostic marker of heart failure. Mean NT-pro BNP levels were considerably elevated in all patients of our study group at baseline and showed a tendency to steadily decrease 1 day after PAVR and at discharge. However, due to the small sample size these changes were more variable and did not reach statistical significance.

3.5.2 Haemoglobin

Measurement of haemoglobin concentration, a potent prognostic factor, is incorporated into standard laboratory analyzes of the total blood cell count. In our study, PAVR resulted in an acute and significant decrease of haemoglobin levels at day 1. The concentrations remained stabile thereafter but did not reach the reference values and were still under the baseline concentrations.

3.5.3 C-reactive protein (CRP): A marker of inflammation

Increased CRP levels are found in patients with various inflammatory conditions and have furthermore been reported in patients suffering from acute or chronic heart failure. Mean CRP levels were elevated in our study group at baseline increased nearly three fold after PAVR to slightly decrease at discharge.

3.5.4 Creatinine

Creatinine levels, the key biomarker for the diagnosis of renal failure, were increased at baseline which may explain conditions of chronic renal failure among the patients. A significant drop could be detected in creatinine levels on the day immediately after the procedure. Interestingly, we observed a stabile state in creatinine concentrations between day 1 and discharge.

The summary of the listed values including the statistical significance levels of the compared groups is illustrated in Table 8.

Parameter (mean ± SD)	1 day pre-interventional	Day of intervention	1 day post-interventional	Discharge	30 days	6 months
NT-pro BNP (pg/ml)	5257.7 ±7143.4	-	3847.8 ±3400.9	3171.6± 2416.9	3862.9± 8358.3	2973.2± 3569.2
HB (g/dl)	12.3 ± 1.3	-	10.7 ± 1.3	10.9 ±1.2	-	-
CRP (mg/l)	12.8 ± 19.7	-	34.8 ± 31.1	28.8 ± 20.9	-	-
Creatinine (mg/dl)	1.2 ±0.3	1.1±0.3	1.1 ±0.3	1.1 ±0.3	-	-
Probability	1 day pre- vs. 1 day post-interventional	1 day pre-interventional vs. discharge	1 day pre-interventional vs. day of intervention	1 day post-interventional vs. discharge	1 day pre-vs.30 days post-interv.	1 day pre-interventional vs. 6 months postinterv.
NT-pro BNP	n. s.	n. s.	-	n. s.	n. s.	n. s.
HB	$p < 0.001$	$p < 0.001$	-	n. s.	-	-
CRP	$p < 0.001$	$p < 0.05$	-	n. s.	-	-
Creatinine	n. s.	n. s.	$p = 0.004$	-	-	-

Table 8: A summary of the blood sample analyzes - Data are presented as mean value ± SD. NT-pro BNP – N-terminal pro brain natriuretic peptide, HB – haemoglobin, CRP – C reactive protein, n. s. – not significant, P – probability (p – value), - no comparisons performed.

As described previously in this thesis, we furthermore observed the changes in blood plasma levels of homoarginine, ADMA, SDMA, GABI, MPO, TnT, hs-TnT and the amino acids, arginine, citrulline and ornithine, in a subgroup of 15 patients 1 day before PAVR as well as 1 and 7 days post-interventionally.

3.5.5 Markers of NO metabolism and oxidative stress

3.5.5.1 Homoarginine

Low homoarginine levels, as a marker of endothelial function and NO metabolism, have previously been associated with severe heart failure and higher cardiovascular mortality. (137) In our study group pathological homoarginine concentrations were measured at baseline, but also post-procedurally. PAVR resulted in a decline of homoarginine levels. A significant change among the concentrations was only detectable comparing the results at day 1 to those at day 7 after the intervention.

3.5.5.2 Asymmetric and symmetric dimethyarginine (ADMA and SDMA)

Levels of ADMA, a strong predictor of cardiovascular morbidity and mortality were significantly decreased at day 1 after PAVR and showed a tendency to steadily increase thereafter.

On the contrary, SDMA, a stereoisomer of ADMA and a reliable marker of renal function, was elevated at day 1 after the intervention. At day 7 after PAVR SDMA values decreased bellow baseline concentrations but we did not find a significant change

3.5.5.3 Global Arginine Bioavailability Ratio (GABR), arginine, ornithin and citrulline

Diminished global arginine bioavailability ratio (GABR), estimated as arginine/(ornithine + citrulline) has been associated with presence of CAD and increased risk for major adverse cardiovascular events. (157) In our study group GABR was steadily increased after PAVR. We found significant changes comparing baseline values to those estimated at day 7 post-interventionally but also between the values at day 1 and day 7 after PAVR.

Furthermore, we noticed low levels of arginine, ornithin and citrulline. The amino acid status was found to be extremely low at day1 post-interventionally. While arginine status was improved at day 7 after PAVR, and reached levels above those at baseline, ornithin and citrulline had remained steadily elevated but did not reach the baseline values.

3.5.6 Myeloperoxydase (MPO): A marker of endothelial inflammation and oxidative stress

MPO, a marker of endothelial inflammation and a sensitive indicator of graft rejection in heart transplant patients, was found to be robustly elevated in patients with AS before PAVR (normal range 88.0 - 165.4 ng/ml. (161) Thus, PAVR resulted in a pronounced increase in MPO at d1 followed by a significant drop below baseline values at d7.

3.5.7 Highly sensitive troponin T (hs-TnT): A marker of myocardial injury

Pathologically increased levels of highly sensitive troponin T (hs-TnT), as a marker of myocardial injury were found in our study population before PAVR. At day 1 post-

interventionally hs-TnT levels were further markedly elevated, before they significantly decreased to levels above those before PAVR at day 7.

The results and statistical significance between the compared time points are given bellow (Tables 9 – 10).

Parameter (mean ± SD)	1 day pre-interventional	1 day post-interventional	7 days post-interventional
Homo-arginine (µM/L)	1.5 ± 0.8	1.4 ± 0.8	1.2 ± 0.8
ADMA (µM/L)	0.9 ± 0.2	0.7 ± 0.2	0.9 ± 0.2
SDMA (µM/L)	1.3 ± 0.6	1.5 ± 0.8	1.0 ± 0.4
GABR	0.5 ± 0.1	0.5 ± 0.2	0.8 ± 0.3
Arginine (µM/L)	55.2 ± 12.8	37.6± 21.1	83.2 ± 34.3
Citrulline (µM/L)	25.3 ± 12.3	18.5 ± 6.8	21.1 ± 8.4
Ornithine (µM/L)	88.5 ± 22.3	62.5 ± 14.8	83.5± 26.0

Probability	1 day pre- vs. 1 day post-interventional	1 day pre- vs. 7 days post-interventional	1 vs. 7 days post-interventional
Homo-arginine	n. s.	n. s.	p = 0.011
ADMA	p = 0.004	n. s.	n. s.
SDMA	n. s.	n. s.	n. s.
GABR	n. s.	p = 0.003	p < 0.001
Arginine	p = 0.032	p = 0.011	p < 0.001
Citrulline	p = 0.041	n. s.	n. s.
Ornithine	p = 0.007	n. s.	p = 0.029

Table 9: An overview of the blood sample analyzes - Data are presented as mean value ± SD. ADMA - asymmetric dimethylarginine, SDMA – symmetric dimethylarginine, GABR – global arginine bioavailability ratio, n. s. – not significant, P – probability (p – value).

Parameter (mean ± SD)	1 day pre-interventional	1 day post-interventional	7 days post-interventional
MPO (ng/ml)	141.3 ± 74.3	194.1 ± 80.8	124.6 ± 63.0
hs-TnT (pg/ml)	53.5 ± 70.7	172.5 ± 136.6	60.8 ± 34.9
TnT (ng/ml)	0.1 ± 0.1	0.2 ± 0.2	0.1 ± 0.1

Probability	1 day pre- vs. 1 day post-interventional	1 day pre- vs. 7 days post-interventional	1 vs. 7 days post-interventional
MPO	n. s.	n. s.	p = 0.033
hs-TnT	p = 0.002	n. s.	p = 0.005
TnT	p = 0.015	n. s.	n. s.

Table 10: A summary of the MPO, hs-TnT and TnT analyzes - Data are presented as mean value ± SD. MPO – myeloperoxidase, hs – TnT – highly sensitive troponin T, TnT – tropnin T, n. s. – not significant, P – probability (p – value).

4 Discussion

4.1 Quality of life

The present study was undertaken as a prospective single-centre, pilot study in order to primarily determine the impact of PAVR on QoL changes in the selected study group at our institution at baseline, 30 days and 6 months.

Furthermore, we tended to characterize the acute haemodynamic response to PAVR in patients with severe symptomatic AS by assessing alterations of major echocardiographic parameters shortly after the intervention.

The third goal of this study was to examine blood plasma levels of heart failure specific and related biomarkers pre- and post-interventional.

Previously, up to 33% of patients with severe symptomatic AS did not undergo cardiac surgery (92) and therefore were excluded from adequate medical treatment. With the development of a less-invasive technique of aortic valve replacement, PAVR, a potential therapeutic offer can be made for many of these patients. However, it is important to

evaluate how this novel treatment modality may affect a key outcome parameter of this population: quality of life.
Besides existing co-morbidities it is of high importance to consider various other factors in decision-making and treatment of elderly patients. These factors are mostly linked to low-life expectancy, fragile general constitution, degree of disability as well as perceived cognitive functions or impaired psychological conditions.
Significant clinical benefits, improvements in QoL, hemodynamic parameters and neurohumoral activation have already been reported in previous works. (7, 13-17)

In terms of comparing baseline to post-interventional QoL scores we used different self-evaluating and widely accepted QoL instruments designed for cardiac population (SF-36, MLHFQ, HADS, GSE, ESSI, Physical Activity Scale and the Maastricht Questionnaire).

4.1.1 Short Form-36 (SF-36)

In accordance with the SF-36 summarized score results (PCS and MCS) we were able to demonstrate a significant improvement in the physical component summary (PCS) 30 days and 6 months following PAVR while the MCS (mental component summary) remained unchanged and with no remarkable impairment at baseline.
Interpreting the single physical and mental health subscales, significant changes were notable in physical functioning (limitations in lifting, bending, kneeling, walking, or running) both 30 days and 6 months after the intervention.
General health scale, evaluating overall health by including past and present health, was improved 30 days and bodily pain 6 months post-interventional. Bodily pain was expressed in its intensity, frequency, duration, and its limitations on normal activities.
Thus, no significant changes were found in role physical, indicating no measurable effect of PAVR on .the degree of physical health to perform activities typical for age and social status (job, community activities or volunteer work).
Vitality (feelings of energy, fatigue and tiredness) was the only mental health related subscale that significantly improved in the SF-36-Item Health Survey.
In summary, analyzing the results of single SF-36 subscales we were able to note significant changes in two out of four physical health subscales (physical functioning and general health) and in one out of four mental health subscales (vitality) 30 days after

PAVR. Six month post-procedurally, we found significant improvements in two subscales related to physical health (physical functioning and bodily pain) and in one subscale considering changes in mental health (vitality). The only physical health subscale, which remained unaffected by PAVR was role physical. Three out of four mental health subscales (social functioning, role emotional and mental health) did not seem to be impaired at baseline but did also not show changes after PAVR.

With respect to the results assessed by the SF-36 instrument and the compliance among patients in our study group, we came to the conclusion that this test is reliable for determination of QoL changes in patients with severe symptomatic AS and evaluated for PAVR.

4.1.2 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Similar results were obtained from the quantitative analysis of the MLHFQ scores. PAVR had a significant positive impact on the total MLHFQ as well as the physical subscale of the questionnaire 30 days and 6 months after the intervention, while emotional health did not seem to be affected. Analyzing the final scores of this test and the missing answers related to physical and mental status of our study group, we could conclude that this test was not suitable enough for this patient group.

4.1.3 Hospital Anxiety and Depression Scale (HADS)

Observing the anxiety and depression results 7 of the 30 enrolled patients were evaluated as “depressive” (23.3%) and 2 out of 30 patients as “anxious” (6.6%) at baseline. Thirty days after PAVR, 6 of 24 patients had positive depression scores (25.0%) while 4 of the 12 evaluated patients (33.3%) matched positive depression scores 6 months post-interventional. Only one patient was assessed as anxious 30 days following the intervention (4.0%). There was no positive anxiety score 6 months post-interventional. Therefore, one may conclude that PAVR had no influence on depression or anxiety, in our study population or that the used tests were not capable of measuring these changes despite the high compliance in answering the questions. More importantly, this might be explainable by the small sample size evaluated at 30 days and 6 months (24 vs. 12), and the short follow up periods.

4.1.4 General Self-Efficacy Scale (GSE), ENRICHD Social Support Instrument (ESSI) and Physical Activity Scale

All patients who underwent PAVR at our institution were able to describe themselves as competent enough to deal with every day´s troubles and received positive social support from their family members or relatives (GSE and ESSI). Both tests were easy to understand and complete. Furthermore, both tests were capable for patients to express their self-efficacy and experienced social support.

The physical activity was determined by the Physical Activity Scale, and was expressed in total hours per week. Significant advancement 30 days after PAVR was shown in easy and moderate activities. Moderate activity was further improved 6 months post-interventionally. This test has additionally been useful to confirm improvements in physical health after PAVR.

The vital exhaustion scores were decreased at the 30 days follow up and increased again 6 months after the intervention, but there was no significant change detectable between the chosen time points. This could mean that the patients subjectively felt the relief of symptoms related to dyspnea and heart failure after PAVR but were still exhausted due to their objective health status and associated comorbidities. All in all, we could conclude that this test may be usefully applied for assessing vital exhaustion in this patient group as it was easy for understanding and completion and showed a high compliance among the patients.

In summary, this study clearly confirmed the hypothesis that PAVR leads to a significant short-term improvement in physical health components. The results of the current study are in line with recently published studies. (13-17).

Ussia et al. published the first results of short term QoL changes in patients undergoing PAVR. At the 5 months follow up they observed remarkable improvements in both physical and mental scores matched by the SF-12v2 questionnaire, a short adapted version of the SF-36, comparing them to the general Italian population over the age of 75 years. Furthermore, significant improvements were noted in all of the 8 subscales of the SF-12v2 questionnaire. These improvements were in conjunction with significantly improved NYHA class and hemodynamic parameters. (13)

Another Study undertaken by Gotzmann and colleagues proved significant clinical benefits, a reduction of neurohormonal activation and a considerable development in QoL as measured by the MLHFQ in 44 consecutive patients with severe and symptomatic AS. The MLHFQ scores improved from 44 ± 19 at baseline to 28 ± 17.5, $p< 0.001$ at the 30 days follow up but did not reach normal values. Furthermore, they demonstrated an improved perfomance in the 6-minute walk test and reduced natriuretic peptide levels. (15)

Similar results were obtained in the REVIVAL II feasibility study. Six months after PAVR the QoL was comparable to the age-based population norms with large and clinically significant enhancement in both physical and mental QoL, as well as the Kansas City Cardiomyopathy Questionnaire (KCCQ) (16)

Similarly, Krane et al. determined a considerably increased SF-36 physical health summarized score in 99 patients 3 months after PAVR compared to preoperative values whereas the mental health summarized score remained unchanged. Interestingly, observing all of the eight SF-36 subscales, they came to the conclusion that only four out of eight subscale scores were significantly increased 3 month post-procedural (physical functioning, bodily pain, general health, and vitality) while the scores for role-physical, social functioning, mental health showed no significant changes as compared to baseline scores. The only post-procedurally decreased score was notable for the role-emotional subscale.

Importantly, 85% of the patients who underwent PAVR reaffirmed their decision to undergo the procedure at the 3 months follow-up and more than 80 % of the patients declared themselves to be able to live independently or with minor help at home. (7)

Lefévre and co-workers reported a considerable QoL advancement in 73.2 % of the enrolled patients. The KCCQ scores developed in 73.9 % of the patients in the transapical group and 72.7 % of those in the transfemoral group at a follow up of 12 months. (14)

Bekeredjian and colleagues presented significant improvements in both physical and mental component summary scores achieved using the SF-36 questionnaire in 80 consecutive patients (average age 86 ± 2.9 years). A development in the average scores of all 8 subscales was seen 6 months after PAVR. The highest increase in physical components was noticed in the physical functioning subscale score whereas the lowest gain included the bodily pain. The mental components were characterized by the greatest improvement in vitality scores and by the lowest in mental health scores. The changes in assessed QoL were associated with a significant reduction in brain natriuretic peptide levels 6 months post-procedurally compared to baseline.

In contrast to these studies, our study population was not characterized by impaired mental health components at baseline. Consequently, PAVR was less likely to significantly improve mental health. Krane et al. observed similar results related to the mental health in patients undergoing PAVR, 3 months post-interventionally. (7) In our study this fact might be further influenced by the small sample size and the short follow up periods.
Short-term developments in physical health, physical activity or vital exhaustion might be explained by the acute symptom relief resulting after the intervention. Increased scores in vital exhaustion or missing ability to vigorous physical activities refer to considerable concomitant diseases in our study population.
The lower number of depressive and anxious patients after PAVR might be due to the small sample size at the follow ups. It might be reasonable to speculate that depressive or anxious patients were more likely not to participate in the follow up assessments.
Furthermore, positive social support and self-efficacy evaluation might be related to the help provided to some patients from sides of their family members or relatives.

It must be considered that our study was designed as a single-centre pilot study with a small study population and with a short term follow up. It would be of importance to conduct further studies with a larger study population and a longer follow-up period.
In terms of QoL assessment in patients undergoing PAVR, our study differs to previous works as it is, to our knowledge, the first trial evaluating the changes in QoL by a comprehensive approach employing a variety of approved, standardized, and specific self-evaluating instruments for cardiac patients groups. This enabled us to draw a more complete picture of QoL in our study population, considering concurrently physical, mental, emotional and social components in patients´ daily life.

4.2 Echocardiography

The second goal of this study was to evaluate the acute and midterm haemodynamic response in our study cohort. We retrospectively collected and analyzed the routinely performed echocardiographic data and accomplished highly significant improvements in the main AS specific parameters, which on the other hand reflects the acute impact of the prosthetic valve implantation on haemodynamics. In the first place the fast drop of the high pressure gradient over the aortic valve is notable.

Our results demonstrated highly significant improvements ($p < 0.001$) in PPG, MPG, AV-Vmax and AVA. Short and long term results of echocardiographic parameters in a large patient group who underwent PAVR, have previously been published by our institution.(150) Our data confirm these short term findings with the exception that our study cohort is smaller and that our data are linked to a median follow up period of 60 days. Haemodynamic short and long term improvements, efficacy and durability of this novel treatment have furthermore been demonstrated by others. (7, 13-15,105, 151, 152)
We were not able to present significant changes in LVEDD, AO or LA in such a short period of observation and decreased LV wall stress post-interventionally. Therefore, the evaluation of these parameters would be of interest in a larger study group and within a longer follow up period.

4.3 Biomarkers

4.3.1 NT-pro BNP

Decreases in NT-pro BNP levels in patients with severe symptomatic AS who underwent PAVR were demonstrated in previous works. (15, 17, 151, 152) Similarly, in our study NT-pro BNP levels were markedly elevated in patients suffering from AS before PAVR. PAVR resulted in a decrease in NT-pro BNP levels 1 day after the intervention in most patients but not all. In some patients, an acute increase of NT-pro BNP levels could be observed despite a good technical success. This fact might be explained by various comorbidities, e.g. renal insufficiency, in this advanced age patient group. At discharge, a good tendency for a decrease of NT-pro BNP levels could be observed, but again, this did not reach statistical significance. In conclusion, more patients are needed to reach the statistical power needed to confirm previous studies.

4.3.2 Haemoglobin

Haemoglobin levels were significantly declined 1 day after the intervention and at discharge and refer to the peri-interventional blood loss. Access site complications requiring surgical intervention occurred in only 3 patients, bleeding with need of transfusion affected 3 patients.

4.3.3 C-reactive protein

Elevated CRP levels in our study group, 1 day post-interventionally and at discharge were linked to peri-interventional stress. Usually, CRP is detectable in blood serum due to various inflammatory conditions and increased levels were linked to heart failure patients in the early 1956. As an acute phase reactant, CRP is formed by hepatocytes in response to interleukin-6, a proinflammatory cytokine. Elevated CRP concentrations were related to adverse outcomes in patients with acute or chronic heart failure and served to identify asymptomatic subjects at high risk for developing heart failure. (129) Moreover, CRP is detectable in patients affected by various active inflammatory conditions, acute and chronic infections, acute coronary syndrome or cigarette smoking. (129) Although we don`t know the exact mechanism of this isolated CRP elevation (PCT and leukocytes were not significantly elevated), from a pathophysiological point of view, it might be reasonable to speculate that the displacement of the original calcified aortic valve by the new implanted Core Valve may cause a relevant local inflammatory response.

4.3.4 Creatinine

Interestingly, creatinine levels decreased within days after the interventions despite the use of nephrotoxic contrast agents. This change might be related to improved heamodynamics and enhanced renal perfusion after PAVR. According to the literature, acute kidney injury (AKI) occurs in 4% to 30% of patients undergoing cardiac surgery. The severity of AKI is proportional to the increased mortality rate in these patients. Taking into account that PAVR patients often have impaired renal function, an increased risk for AKI may be considered after PAVR. (134)

The risk of AKI may independently be associated with periprocedural red blood cell (RBC) transfusions during cardiac surgery and PAVR. According to the results presented by Burg and colleagues, PAVR was associated with a significant reduction of AKI as compared to SAVR. (135)

Nuis and co-workers reported occurrence of AKI in 19% of the patients after PAVR of whom 2% needed temporary haemodialysis. Patients with AKI had a higher frequency of previous myocardial infarction, coronary bypass surgery, low-flow low-gradient aortic stenosis and thrombocytopenia and showed higher mean serum creatinine levels and a higher logistic Euro SCORE. (134, 135)

To our knowledge our study has been the first to analyze biomarkers such as homoarginine, ADMA, SDMA, MPO and highly sensitive TnT in patients undergoing PAVR.

4.3.5 Homoarginine

With respect to homoarginine plasma levels we could observe pathological values at all three time points and a statistically significant decrease 7 days post-interventionally. Decreased pre-interventional homoarginine concentrations might be explained by the presence of severe symptomatic heart failure. Despite improvement in heart failure symptoms after PAVR, an unpredictable drop in homoarginine levels appeared. This might be associated with the malnutrition of our old multimorbid patients.

Results of a recently published study have shown an independent association between homoarginine, and cardiovascular and all-cause mortality. Lowest homoarginine levels were characteristic for subjects at older age, lower levels of albumin, lower body mass index, lower glomerular filtration rate, and a higher percentage of congestive heart failure.

In subjects referred for angiography, low homoarginine levels were linked to a 3.6-fold higher cardiovascular mortality and 2.7-fold higher all-cause mortality. (138)

Haemodialysis patients with low homoarginine levels had a 5-fold higher mortality rate than patients referred for coronary angiography. (137)

A positive association was marked between serum homoarginine and lysine concentrations. In accordance, the ratio of arginine to ornithine, applied as an indirect measure of arginase activity and relative arginine bioavailability, showed a significant correlation with homoarginine concentrations. Negative association was found between homoarginine and endothelial adhesion molecules. (137)

4.3.6 Asymmetric and symmetric dimethyarginine (ADMA and SDMA)

ADMA levels declined while SDMA levels were elevated 1 day after the intervention. The raised SDMA levels may be linked to a decreased creatinine concentration immediately after the intervention. This relation is of interest as it may support the observation that the application of the contrast medium did not lead to elevated creatinine levels as one would have been expected pre-interventionally.

Elevated ADMA levels are associated with various cardiovascular risk factors such as hypertension, diabetes, insulin resistance, hypercholesterolaemia, hypertriglyceridaemia and hyperhomocysteinaemia.(138) Augmented circulating ADMA concentrations may serve as strong predictor of cardiovascular morbidity and mortality as well as the risk of acute vascular events. ADMA reflects the summary effect of various risk factors on endothelial health and may predict total mortality in patients with angiographically established CAD. Furthermore, ADMA represents a marker of progression of various chronical renal diseases while SDMA has been considered a reliable marker of renal function. (138) Plasma SDMA levels correlate highly with GFR as assessed by creatinine or inulin clearance. (156)

Under conditions of chronic renal failure, SDMA concentrations increase tenfold, while ADMA concentrations double whereas SDMA shows a better correlation to creatinine than ADMA. (138)

4.3.7 Global Arginine Bioavailability Ratio, arginine, ornithin and citrulline

Additionally to these measurements we analyzed the amino acid status in all 15 patients and were able to demonstrate a low level of amino acids, especially on the first day after PAVR. It would be of interest to further discuss this appearance in a larger patient cohort and to investigate if this was linked to the low nutritional status of the study population at that time point.

It is known that arginine serves as the sole nitrogen source for NO synthesis while the major catabolic products of arginine are ornithine and citrulline.

According to the study of Thang et al. significantly lower GABR and arginine but higher citrulline and ornithin levels were found in patients with significantly obstructive CAD as compared to those without the condition. They concluded that GABR might express a reduced NO synthetic capacity more comprehensively than systemic arginine levels.

Adjusting for Framingham risk score, C-reactive protein, and renal function, diminished GABR (but not arginine levels) and higher citrulline levels were still significantly associated with incidence of obstructive atherosclerotic CAD and increased long term risk for Major Adverse Cardiovascular Events (MACE). (157)

According to the literature, a relative arginine deficiency was reported in subjects with hypertension or heart failure as a result of abnormal transport mechanisms across vascular

cellular membranes. Several arginine catabolic pathways, including its augmented degradation, might lead to relative NO deficiency and subsequently to progression of cardiovascular disease. (157)

4.3.8 Myeloperoxydase

MPO has been proposed to be a marker of endothelial inflammation and a sensitive indicator of graft rejection in heart transplant patients. So far, no one has evaluated its role as a marker in AS. In patients with AS in our study group, MPO plasma concentrations were markedly elevated as compared to its reference values, which have been previously reported by Zelzer et al. (139) We have noted an increase 1 day after PAVR and significant reduction under the baseline values 7 days following the intervention.

In our study population AS was associated with significantly increased levels of MPO. Changes in MPO (and troponin T) appear to closely reflect myocardial injury and inflammation before, in response to PAVR, and during recovery.

Summing up, besides troponin T and hs-TnT, MPO additionally serves as a non dependent predictor of cardio-vascular risk. While troponin presents a heart specific biomarker, MPO is related to other pathophysiological processes such as inflammatory vascular alterations. (159, 160) It is included into formation and progression of plaques as well as into the peroxidation of lipids by producing atherogenic lipoproteins. Furthermore, MPO plays a role in the formation of foam cells but assists also the activation of proteases. (159, 160)

The significant decrease in MPO concentration 7 days post-interventionally confirms the fact that myeloperoxydase improves the risk stratification of cardiac events and might be included into interpretation of other clinical events and the produced effects.

In conclusion, further studies are warranted to establish the role of MPO for risk stratification and prognosis in AS.

4.3.9 Highly sensitive troponin T (hs-TnT)

Patients with AS who were included in our study appeared to suffer from permanent myocardial cell injury, as indicated by pathologically increased levels of highly sensitive troponin T (hs-TnT) before PAVR. Both TnT and highly sensitive TnT showed a markedly augmented concentration at day 1 after PAVR and a decrease at day 7 post-interventionally. This status might be related to the interventional stress effects.

It is known that cardiac troponins T (cTnT) and I are the key biomarkers used in the diagnosis of acute myocardial infarction (MI). (142, 143) Besides, increased troponin levels may be linked to other conditions related to acute myocardial injury, CAD, heart failure and chronic kidney disease.

Standard troponin assays seldom enable detection of troponins T and I in individuals from the general population, but are strongly associated with structural heart disease, increased risk of death and adverse cardiovascular events. It has been hypothesized that the plasma troponin level in healthy subjects ranges from 0.1 to 0.2 ng/l because of the continuous microscopic loss of cardiomyocytes during normal life. (146)

Recently, a highly sensitive assay for cTnT has been introduced and it may distinguish levels roughly 10-fold lower than those detectable with the standard assay. (143, 144) This novel assay enhances accuracy for the diagnosis of MI in patients with questionable acute coronary syndromes as compared with the standard cTnT assay. It furthermore allows the detection of circulating cTnT in almost all individuals suffering from CHF and chronic CAD. Higher levels of cTnT estimated by the highly sensitive assay correlate strongly with increased cardiovascular mortality. (143)

4.4 Limitations

There are several limitations of the present study. Firstly to note is its relatively small sample size, its monocentric character and the short follow up period. However, one has to take into accoount that the study was primarily planned as a pilot study for hypothesis generating. Furthermore, the advanced age of our study group as well as their pre-interventional physical and mental health status limited the patients in completing the QoL questionnaires fully on their own. In justified cases, patients received support by the study team or their family members. Furthermore, not all of our patients were able to attend all postinteventional outpatient-visits and therefore were lost for follow up evaluation.

Additionally, the retrospective nature of data collection for the echocardiographic evaluation and routine blood sample analyzes led to limited data availability, as the data were not specifically obtained for our study but for daily clinical routine.

4.5 Conclusion

In conclusion, we are able to demonstrate that PAVR leads to a significantly improvement in physical quality of life, non significant depressive or anxious symptoms relief as well as a better functional status in patients with severe symptomatic AS. PAVR was performed with an excellent technical success rate as indicated by an acute improvement in hemodynamic parameters. Functional alterations were closely associated with changes in established and novel biomarkers of neurohumoral and inflammatory activation as well as markers of cardiac injury and function.

Further prospective studies with a larger sample size are warranted to confirm our preliminary data.

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6 Appendix

The Quality of Life Questionnaires (Currently available German form

	Fragebogen zur Lebensqualität		
pAVR	**Center - ID** _ _ _ _	**Stud - PID** _ _ - _ _ _ _ - _	LEBENSQ
Anlass: ❍ **Baseline** ❍ **F 1** (1 Mon.) ❍ **F 6** (6 Mon.)		**Datum der Befragung**	_ _ / _ _ / 2 0 _ _ (T T M M J J J J)

Sehr geehrter Patient, sehr geehrte Patientin,

hiermit überreichen wir Ihnen einige Fragebögen zu Ihrem Gesundheitszustand, Ihrem persönlichen Lebensgefühl und Ihrem seelischen Empfinden, um den Zusammenhang zwischen Herzfunktion und allgemeinem Befinden zu untersuchen.

Selbstverständlich ist die Beantwortung freiwillig und ohne Einfluss auf Ihre Behandlung. Alle Ihre Angaben unterliegen der **ärztlichen Schweigepflicht** und werden nach den Bestimmungen des Datenschutzgesetzes anonym ausgewertet. Eine Weitergabe an Dritte ist ausgeschlossen.

Bitte beachten Sie beim Ausfüllen:

- Bei den vorliegenden Bögen handelt es sich um abgeschlossene Fragenkomplexe, so dass es sich nicht vermeiden ließ, dass sich einige Fragen ähneln oder wiederholen. Wir bitten Sie dennoch, alle Fragen vollständig mit jeweils einem Kreuz zu beantworten. Sollten Sie bei einer Frage Zweifel haben, kreuzen Sie bitte die Antwort an, die noch am ehesten für Sie zutrifft.
- Bei der Beantwortung können Sie sich ruhig Zeit lassen. Allerdings sollten Sie nicht ins Grübeln geraten, sondern eher spontan antworten.
- Selbstverständlich ist es unbedingt notwendig, dass Sie die Fragen selbst beantworten und sich dabei z.B. nicht „helfen“ oder gar „vertreten“ lassen. Hilfe ist auch gar nicht möglich, da es bei den Fragen um Ihre ganz persönlichen Empfindungen geht, die nur Sie allein kennen.

Wir bedanken uns herzlich für Ihre Mitarbeit!

Ihr Studienteam

Im ersten Teil dieses Fragebogens geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

---

1. Wie würden Sie Ihren Gesundheitszustand im allgemeinen beschreiben ? Bitte kreuzen Sie nur eine Antwort an.

Ausgezeichnet	Sehr gut	Gut	Weniger gut	schlecht
❍	❍	❍	❍	❍

2. Im **Vergleich zum vergangenen Jahr**, wie würden Sie Ihren **derzeitigen** Gesundheitszustand beschreiben? Bitte kreuzen Sie nur eine Antwort an.

Viel besser	Etwas besser	Etwa gleich	Etwas schlechter	Viel schlechter
❍	❍	❍	❍	❍

7. Wie stark waren Ihre Schmerzen in den **vergangenen 4 Wochen**?

Nicht vorhanden	Sehr leicht	leicht	mäßig	stark
❍	❍	❍	❍	❍

8. Inwieweit haben die Schmerzen Sie in den **vergangenen 4 Wochen** bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?

Überhaupt nicht	etwas	mäßig	ziemlich	sehr
❍	❍	❍	❍	❍

9. In diesen Fragen geht es darum wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. Bitte kreuzen Sie in jeder Zeile nur die Antwort an, die Ihrem Befinden am ehesten entspricht. Wie oft waren Sie in den **vergangenen 4 Wochen**:

	immer	meistens	oft	manchmal	selten	nie
. . . voller Schwung ?	❍	❍	❍	❍	❍	❍
. . . sehr nervös ?	❍	❍	❍	❍	❍	❍
. . . so niedergeschlagen, dass nichts Sie aufheitern konnte ?	❍	❍	❍	❍	❍	❍
. . . ruhig und gelassen ?	❍	❍	❍	❍	❍	❍
. . . voller Energie ?	❍	❍	❍	❍	❍	❍
. . . entmutigt und traurig ?	❍	❍	❍	❍	❍	❍
. . . erschöpft ?	❍	❍	❍	❍	❍	❍
. . . glücklich ?	❍	❍	❍	❍	❍	❍
. . . müde ?	❍	❍	❍	❍	❍	❍

10. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den **vergangenen 4 Wochen** Ihre normalen Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?

immer	meistens	manchmal	selten	nie
❍	❍	❍	❍	❍

11. Inwieweit trifft jede der folgenden Aussagen auf Sie zu ? Bitte kreuzen Sie in jeder Zeile nur eine Antwort an.

	trifft ganz zu	trifft weitgehend zu	weiß nicht	trifft weitgehend nicht zu	trifft gar nicht zu
Ich scheine etwas leichter als andere krank zu werden	❍	❍	❍	❍	❍
Ich bin genauso gesund wie alle anderen, die ich kenne	❍	❍	❍	❍	❍
Ich erwarte, dass meine Gesundheit nachlässt	❍	❍	❍	❍	❍
Ich erfreue mich ausgezeichneter Gesundheit	❍	❍	❍	❍	❍

pAVR	**Leben mit Herzinsuffizienz**	**LQ-3** LEBENSQ

Die Fragen dieses Bogens sollen darüber Aufschluss geben, wie Ihre Herzinsuffizienz (der Zustand Ihres Herzens) Sie im vergangenen Monat an der von Ihnen gewünschten Lebensweise gehindert hat. Die unten aufgelisteten Punkte beschreiben verschiedene Arten der Beeinträchtigung. Wenn Sie sicher sind, dass ein Punkt auf Sie nicht zutrifft oder in keinem Zusammenhang mit Ihrer Herzinsuffizienz steht, kreuzen Sie die ‚0' (=Nein) an und gehen zur nächsten Frage über. Wenn ein Punkt Sie betrifft, kreuzen Sie die Zahl an, die widerspiegelt, wie stark Sie an der von Ihnen gewünschten Lebensweise gehindert wurden. Bitte beachten Sie, dass nur nach dem vergangenem Monat gefragt ist !

Wurde Ihre gewünschte Lebensweise durch Ihre Herzinsuffizienz im vergangenen Monat eingeschränkt, dadurch dass...

	Nein	Sehr wenig				Sehr stark
Schwellungen Ihrer Knöchel, Beine, etc. auftraten ?	0	1	2	3	4	5
Sie sich tagsüber hinlegen oder hinsetzen mussten, um auszuruhen?	0	1	2	3	4	5
Sie beim Gehen oder Treppensteigen Schwierigkeiten hatten ?	0	1	2	3	4	5
Sie bei der Haus- oder Gartenarbeit Schwierigkeiten hatten ?	0	1	2	3	4	5
Sie Schwierigkeiten hatten, außer Haus zu gehen ?	0	1	2	3	4	5
Sie nachts Schwierigkeiten beim Schlafen hatten ?	0	1	2	3	4	5
Sie Schwierigkeiten hatten, mit Familie und Freunden Kontakte und gemeinsame Unternehmungen zu pflegen ?	0	1	2	3	4	5
Sie Schwierigkeiten hatten, Ihren Lebensunterhalt zu verdienen ?	0	1	2	3	4	5
Sie bei Freizeit, Sport und Hobby Schwierigkeiten hatten ?	0	1	2	3	4	5
Sie in Ihrer Sexualität beeinträchtigt waren	0	1	2	3	4	5
Sie weniger Appetit auf Speisen hatten, die Sie gern essen ?	0	1	2	3	4	5
Sie unter Atemnot litten ?	0	1	2	3	4	5
Sie müde, erschöpft und ohne Energie waren ?	0	1	2	3	4	5
Sie ins Krankenhaus gehen mussten ?	0	1	2	3	4	5
Sie für Ihre medizinische Versorgung Geld bezahlen mussten ?	0	1	2	3	4	5
Sie unter unerwünschten Nebenwirkungen Ihrer Medikamente litten ?	0	1	2	3	4	5
Sie Sich als Belastung für Ihre Familie empfanden ?	0	1	2	3	4	5
Sie das Gefühl hatten, die Kontrolle über Ihr Leben verloren zu haben ?	0	1	2	3	4	5
Sie Ihnen Sorgen bereitete ?	0	1	2	3	4	5
Sie Schwierigkeiten hatten, Sich an etwas zu erinnern ?	0	1	2	3	4	5
Sie Sich depressiv fühlten ?	0	1	2	3	4	5
Schwellungen Ihrer Knöchel, Beine, etc. auftraten ?	0	1	2	3	4	5

pAVR	HADS	LQ-4 LEBENSQ

Bitte beantworten Sie jede der folgenden Fragen so, wie es für Sie persönlich **in der letzten Woche** am ehesten zutraf. Machen Sie bitte nur **ein Kreuz** pro Frage und lassen Sie bitte keine Frage aus! Überlegen Sie bitte nicht lange, sondern wählen Sie die Antwort aus, die Ihnen auf Anhieb am zutreffendsten erscheint!

1. Ich fühle mich angespannt oder überreizt

❍ meist ❍ oft ❍ von Zeit zu Zeit / gelegentlich ❍ überhaupt nicht

2. Ich kann mich heute noch so freuen wie früher

❍ ganz genau so ❍ nicht ganz so sehr ❍ nur noch wenig ❍ kaum oder gar nicht

3. Mich überkommt eine ängstliche Vorahnung, dass etwas Schreckliches passieren könnte

❍ ja, sehr stark ❍ ja, aber nicht allzu stark ❍ etwas, aber es macht mir keine Sorgen ❍ überhaupt nicht

4. Ich kann lachen und die lustige Seite der Dinge sehen

❍ ja, so viel wie immer ❍ nicht mehr ganz so viel ❍ inzwischen viel weniger ❍ überhaupt nicht

5. Mir gehen beunruhigende Gedanken durch den Kopf

❍ einen Großteil der Zeit ❍ verhältnismäßig oft ❍ von Zeit zu Zeit, aber nicht allzu oft ❍ nur gelegentlich / nie

6. Ich fühle mich glücklich

❍ überhaupt nicht ❍ selten ❍ manchmal ❍ meistens

7. Ich kann behaglich dasitzen und mich entspannen

❍ ja, natürlich ❍ gewöhnlich schon ❍ nicht oft ❍ überhaupt nicht

8. Ich fühle mich in meinen Aktivitäten gebremst

❍ fast immer ❍ sehr oft ❍ manchmal ❍ überhaupt nicht

9. Ich habe manchmal ein ängstliches Gefühl in der Magengegend

❍ überhaupt nicht ❍ gelegentlich ❍ ziemlich oft ❍ sehr oft

10. Ich habe das Interesse an meiner äußeren Erscheinung verloren

❍ ja, stimmt genau ❍ ich kümmere mich nicht so sehr darum, wie ich sollte ❍ möglicherweise kümmere ich mich zu wenig darum ❍ ich kümmere mich soviel darum wie immer

11. Ich fühle mich rastlos, muss immer in Bewegung sein

❍ ja, tatsächlich sehr ❍ ziemlich ❍ nicht sehr ❍ überhaupt nicht

12. Ich blicke mit Freude in die Zukunft

❍ ja, sehr ❍ eher weniger als früher ❍ viel weniger als früher ❍ kaum bis gar nicht

13. Mich überkommt plötzlich ein panikartiger Zustand

❍ ja, tatsächlich sehr oft ❍ ziemlich oft ❍ nicht sehr oft ❍ überhaupt nicht

14. Ich kann mich an einem guten Buch, einer Radio- oder Fernsehsendung freuen

❍ oft ❍ manchmal ❍ eher selten ❍ sehr selten

pAVR	GSW/ ESSI/ KöBet	LQ-5 LEBENSQ

Bitte geben Sie an,
inwieweit folgende Einschätzungen auf Sie zutreffen.

	trifft gar nicht zu	trifft kaum zu	trifft eher zu	trifft voll und ganz zu
1. Die Lösung schwieriger Probleme gelingt mir immer, wenn ich mich darum bemühe.	❍	❍	❍	❍
2. Es bereitet mir keine Schwierigkeiten, meine Absichten und Ziele zu verwirklichen.	❍	❍	❍	❍
3. Auch bei überraschenden Ereignissen glaube ich, dass ich gut damit zurechtkommen werde.	❍	❍	❍	❍
4. Was auch immer passiert, ich werde schon klarkommen.	❍	❍	❍	❍
5. Wenn ich mit einer neuen Sache konfrontiert werde, weiß ich, wie ich damit umgehe.	❍	❍	❍	❍
6. Wenn ich mit einem Problem konfrontiert werde, habe ich meist mehrere Ideen, wie ich damit fertig werde.	❍	❍	❍	❍

Der folgende Fragebogenteil beschäftigt sich mit Ihrem sozialen Umfeld. Bitte kreuzen Sie zu jeder Frage die Antwort an, die Ihre derzeitige Situation am besten beschreibt.

	nie	selten	manchmal	meistens	immer
1. Ist jemand für Sie erreichbar, auf den Sie sich verlassen können, dass er Ihnen mit Gewissheit zuhört, wenn Sie sich aussprechen möchten?	❍	❍	❍	❍	❍
2. Ist jemand für Sie erreichbar, der Ihnen bei Problemen mit guten Ratschlägen beisteht?	❍	❍	❍	❍	❍
3. Ist jemand für Sie erreichbar, der Ihnen Liebe und Zuneigung zeigt?	❍	❍	❍	❍	❍
4. Können Sie sich darauf verlassen, dass jemand Sie gefühlsmäßig unterstützt (z.B. Probleme besprechen oder Hilfestellung bei schwierigen Entscheidungen geben)?	❍	❍	❍	❍	❍
5. Haben Sie soviel Kontakt wie Sie wünschen mit einer Ihnen nahestehenden Person, die Ihr Vertrauen besitzt?	❍	❍	❍	❍	❍

Mit den nächsten Fragen möchten wir den Umfang ihrer körperlichen Betätigung erfassen. Wie viele Stunden <u>in der Woche</u> verbringen sie üblicherweise mit

Mäßig beanspruchenden Betätigungen (z.b. spazieren gehen, Fahrrad fahren, einkaufen gehen, putzen)	_____ Stunden
Stärker beanspruchenden Betätigungen (z.B. jogging, walking, schwimmen, moderates Fitnesstraining, Wasserkisten tragen, Gartenarbeit)	_____ Stunden
Stark beanspruchenden Betätigungen (z.B. Ausdauer/ Zirkeltraining, Aerobic, Leistungsorientiertes Fitnesstraining, Holz hacken, schwere körperliche Arbeit)	_____ Stunden

pAVR	**Maastricht-Fragebogen**	**LQ-6** LEBENSQ

Dieser Teil des Fragebogens erfasst, wie Sie sich in **letzter Zeit** fühlen. Dabei gibt es keine „richtigen“ oder „falschen“ Antworten. Bitte kreuzen Sie die für Sie zutreffenden Antworten an. Falls Sie sich bei einer Frage nicht sicher oder unentschieden sind, kreuzen Sie bitte das „ ? “ an.

		ja	**?**	**nein**
1.	Fühlen Sie sich oft müde?	❍	❍	❍
2.	Haben Sie häufig Schwierigkeiten mit dem Einschlafen ?	❍	❍	❍
3.	Wachen Sie nachts wiederholt auf ?	❍	❍	❍
4.	Fühlen Sie sich insgesamt schwach ?	❍	❍	❍
5.	Haben Sie das Gefühl, dass Sie in der letzten Zeit wenig schaffen ?	❍	❍	❍
6.	Haben Sie das Gefühl, dass Sie mit den alltäglichen Problemen nicht mehr so gut fertig werden ?	❍	❍	❍
7.	Glauben Sie, in eine Sackgasse geraten zu sein ?	❍	❍	❍
8.	Fühlen Sie sich in letzter Zeit lustloser als früher ?	❍	❍	❍
9.	Sex macht mir genauso viel Spaß wie sonst !	❍	❍	❍
10.	Haben Sie in letzter Zeit ein Gefühl der Hoffnungslosigkeit verspürt ?	❍	❍	❍
11.	Brauchen Sie inzwischen mehr Zeit dazu, ein schwieriges Problem in den Griff zu bekommen als vor einem Jahr ?	❍	❍	❍
12.	Bringen Kleinigkeiten Sie jetzt schneller aus der Fassung als früher?	❍	❍	❍
13.	Möchten Sie manchmal einfach aufgeben ?	❍	❍	❍
14.	Ich fühle mich gut !	❍	❍	❍
15.	Haben Sie manchmal das Gefühl, dass Ihr Körper wie ein Akku ist, dessen Energie zur Neige geht ?	❍	❍	❍
16.	Wünschen Sie sich manchmal, tot zu sein ?	❍	❍	❍
17.	Haben Sie gegenwärtig das Gefühl, Ihren Anforderungen einfach nicht mehr gewachsen zu sein ?	❍	❍	❍
18.	Fühlen Sie sich niedergeschlagen ?	❍	❍	❍
19.	Ist Ihnen manchmal zum Weinen zumute ?	❍	❍	❍
20.	Wachen Sie manchmal erschöpft und müde auf ?	❍	❍	❍
21.	Haben Sie zunehmend Schwierigkeiten, sich für längere Zeit auf eine bestimmte Sache zu konzentrieren ?	❍	❍	❍
22.	Haben Sie in letzter Zeit ungewohnte körperliche Empfindungen ?	❍	❍	❍
23.	Haben Sie einen Widerwillen gegen übliche Arbeiten entwickelt ?	❍	❍	❍
24.	Ich rege mich in letzter Zeit leicht auf.	❍	❍	❍

pAVR	**Zusatzangaben zur Person**	**LQ-7** LEBENSQ

1. Wann sind Sie geboren?

Monat :___ ; Jahr: 19___

2. Welches Geschlecht haben Sie?

❍ männlich ❍ weiblich

3. Welcher Familienstand trifft auf Sie zu?

❍ verheiratet, mit Ehepartner(in) zusammen lebend
❍ verheiratet, von Ehepartner(in) getrennt lebend
❍ ledig
❍ geschieden
❍ verwitwet

falls hier angekreuzt: **Leben Sie mit einem Partner / einer Partnerin zusammen?**

❍ ja ❍ nein

4. Welchen höchsten allgemeinbildenden Schulabschluss haben Sie?
(Bitte nur den höchsten Abschluss ankreuzen.)

❍ ohne Schulabschluss
❍ Hauptschule / Volksschule
❍ Realschule (Mittlere Reife)
❍ Polytechnische Oberschule
(vor 1965: Abschluss nach 8.Klasse, ab 1965: Abschluss mit 10. Klasse)
❍ Fachhochschulreife
❍ Hochschulreife / Abitur (Gymnasium oder EOS)
❍ anderer Schulabschluss: _____

5. Welchen beruflichen Ausbildungsabschluss haben Sie?
(Bitte alle zutreffenden Abschlüsse ankreuzen.)

❑ keine und nicht in beruflicher Ausbildung
❑ noch in beruflicher Ausbildung
❑ beruflich-betriebliche Ausbildung (Lehre)
❑ beruflich-schulische Ausbildung (Berufsfach-/Handelsschule)
❑ Fach-/Meister-/Technikerschule/Berufs-Fachakademie
❑ Fachhochschule
❑ Hochschule
❑ anderer Berufabschluss: _____

6. Sind Sie zur Zeit erwerbstätig? Was auf dieser Liste trifft auf Sie zu?

❍ Vollzeit ≥35 h / Woche
❍ Teilzeit 15...<35 h / Woche
❍ Teilzeit (auch stundenweise) <15 h / Woche
❍ nicht erwerbstätig

Bitte überprüfen Sie noch einmal, ob Sie alle Fragen beantwortet haben!

Vielen Dank für Ihre Mitarbeit!

Echokardiographie – Datenblatt
AST – Evaluation der Lebensqualität und des funktionellen Status nach perkutanem Aortenklappenersatz bei hochgradiger Aortenstenose

Echokardiographie (2D-Echo, transthorakal)
(aktuell; keine historischen Angaben)

Datum des Echo __/__/20__ (T T / M M / J J J J)

Dimensionen (Lange Achse: M-Mode parasternal)

Aorta (in Klappenebene) ⌊⌋⌊⌋ mm ❑ nicht gemessen

LVD_{ED} * ⌊⌋⌊⌋ mm LVD_{ES} * ⌊⌋⌊⌋ mm $LA_{ES\ (quer)}$ * ⌊⌋⌊⌋ mm

IVS_{ED} * ⌊⌋⌊⌋ mm PW_{ED} * ⌊⌋⌊⌋ mm ❑ parasternal nicht anlotbar

Volumina (4CH apikal)

LVEF * (nach Simpson oder visuell) ⌊⌋⌊⌋ % → Methode: ❍ Simpson biplan ❍ Simpson monoplan ❍ visuell

LVV_{ED} * ⌊⌋⌊⌋⌊⌋ ml LVV_{ES} * ⌊⌋⌊⌋⌊⌋ ml ❑ nicht gemessen

$LA_{ES\ (ap.\ längs)}$ * ⌊⌋⌊⌋ mm $LA_{ES\ (ap.\ quer)}$ * ⌊⌋⌊⌋ mm ❑ nicht gemessen

Wandbewegungsstörung	❍ ja	❍ nein
RV Dilatation	❍ ja	❍ nein
Perikarderguss	❍ ja	❍ nein
Vena cava inferior gestaut	❍ ja	❍ nein

Diastolische Funktion ❑ nicht beurteilt

Mitralisdoppler

E-Welle ⌊⌋⌊⌋⌊⌋ cm/s A-Welle ⌊⌋⌊⌋⌊⌋ cm/s Dezelerationszeit ⌊⌋⌊⌋⌊⌋ ms IVRT ⌊⌋⌊⌋⌊⌋ ms

Bestimmung von TEI

a = ⌊⌋⌊⌋⌊⌋ ms (Abstand Ende A-Welle, Anfang E-Welle) b = ⌊⌋⌊⌋⌊⌋ ms (Ejektionszeit Aorta)

Gewebe-Doppler (lateraler Mitralanulus)

e´-Welle ⌊⌋⌊⌋, ⌊⌋ cm/s a´-Welle ⌊⌋⌊⌋, ⌊⌋ cm/s ❑ keine Aussage möglich

Gewebe-Doppler (medialer Mitralanulus)

e´-Welle ⌊⌋⌊⌋, ⌊⌋ cm/s a´-Welle ⌊⌋⌊⌋, ⌊⌋ cm/s ❑ keine Aussage möglich

Pulmonalvenöser Fluss

Systolischer Fluss ⌊⌋⌊⌋⌊⌋ cm/s Diastolischer Fluss ⌊⌋⌊⌋⌊⌋ cm/s ❑ keine Aussage möglich

Atrialer Rückfluss ⌊⌋⌊⌋⌊⌋ cm/s ❑ keine Aussage möglich

Flow-propagation-time (Vp) ⌊⌋⌊⌋⌊⌋ cm/s

Grad der diastolischen Funktionsstörung nach ASE ⌊⌋

Klappenstatus

Mitralklappe	❍ nativ	❍ operiert		
Mitralinsuffizienz	❍ keine	❍ leicht	❍ mittel	❍ schwer
Mitralstenose	❍ keine	❍ leicht	❍ mittel	❍ schwer
Aortenklappe	❍ nativ	❍ operiert		
Aorteninsuffizienz	❍ keine	❍ leicht	❍ mittel	❍ schwer
Aortenstenose	❍ keine	❍ leicht	❍ mittel	❍ schwer
Pulmonalklappe	❍ nativ	❍ operiert		
Pulmonalinsuffizienz	❍ keine	❍ leicht	❍ mittel	❍ schwer
Pulmonalstenose	❍ keine	❍ leicht	❍ mittel	❍ schwer
Trikuspidalklappe	❍ nativ	❍ operiert		
Trikuspidalinsuffizienz	❍ keine	❍ leicht	❍ mittel	❍ schwer

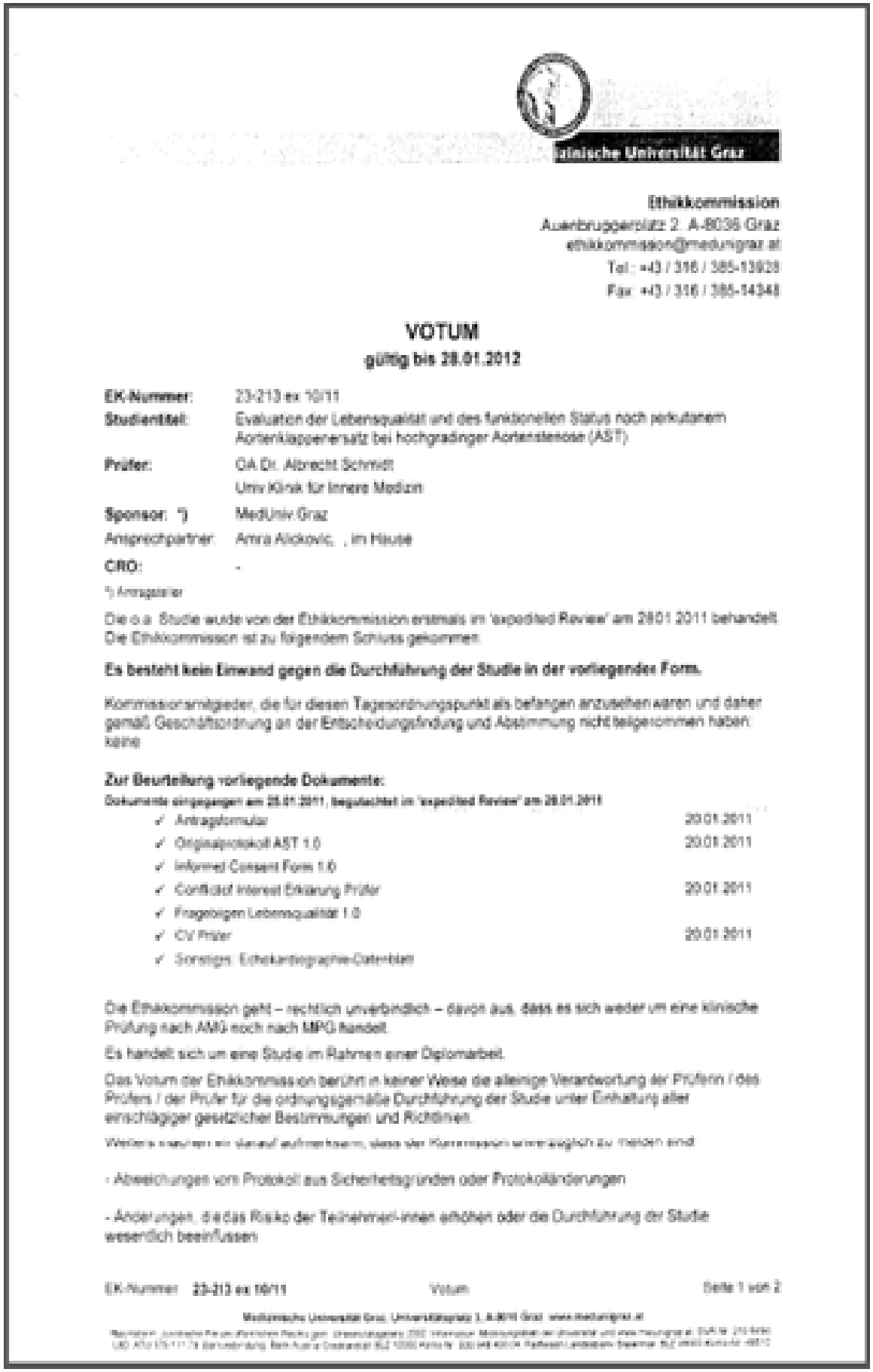
Gemessener Gradient über Trikuspidalklappe ⌊⌋⌊⌋ mmHg

Bitte Video bzw. CD an Referenzeinrichtung schicken (per Post o. Mail) !!!
→ Nicht mit Patientennamen versenden! (Stud-PID-Aufkleber verwenden bzw. Dateibezeichnung beachten); → siehe Handling Guideline im Prüferordner

*Abkürzungen:

LVD_{ED}	linksventrikulärer enddiastol. Ventrikeldurchmesser
LVD_{ES}	linksventrikulärer endsystol. Ventrikeldurchmesser
$LA_{ES\ (quer)}$	linksatrialer endsystolischer Durchmesser (parasternal/LAX)
IVS_{ED}	enddiastolische interventrikuläre Septumdicke
PW_{ED}	enddiastolische Hinterwanddicke
LVEF	Ejektionsfraktion
LVV_{ED}	linksventrikuläres enddiastolisches Volumen
LVV_{ES}	linksventrikuläres endsystolisches Volumen
$LA_{ES\ (ap.,\ quer)}$	linksatrialer endsystolischer Durchmesser (apikal, quer)
$LA_{ES\ (ap.,\ längs)}$	linksatrialer endsystolischer Durchmesser (apikal, längs)

Ethical Committee Approval



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VOTUM

gültig bis 28.01.2012

EK-Nummer:	23-213 ex 10/11
Studientitel:	Evaluation der Lebensqualität und des funktionellen Status nach perkutanem Aortenklappenersatz bei hochgradiger Aortenstenose (AST)
Prüfer:	OA Dr. Albrecht Schmidt Univ Klinik für Innere Medizin
Sponsor: *)	MedUniv Graz
Ansprechpartner:	Amra Alickovic, , Im Haute
CRO:	-

*) Antragsteller

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 28.01.2011 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegender Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 28.01.2011, begutachtet im 'expedited Review' am 28.01.2011

✓ Antragformular	20.01.2011
✓ Originalprotokoll AST 1.0	20.01.2011
✓ Informed Consent Form 1.0	
✓ Conflict of Interest Erklärung Prüfer	20.01.2011
✓ Fragebogen Lebensqualität 1.0	
✓ CV Prüfer	20.01.2011
✓ Sonstiges: Echokardiographie-Datenblatt	

Die Ethikkommission geht – rechtlich unverbindlich – davon aus, dass es sich weder um eine klinische Prüfung nach AMG noch nach MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters ersuchen wir darauf aufmerksam zu machen, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 28. Jänner 2011

Univ.Prof.DI Dr.Peter H. Rehak
Vorsitzender

Univ.Prof.DDr.Hans-Peter Kapfhammer
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!