Cardiovascular risk markers in aortic valve stenosis

Insights in peak systolic left ventricular function, ejection dynamics and obesity

Eigir Einarsen

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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“The height of sophistication is simplicity.”
Clare Boothe Luce

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2. Scientific environment

The present research project was performed within the *Bergen Hypertension and Cardiac Dynamics group* at the Department for Clinical Science, University of Bergen, Norway, through the years 2014-2020. The first part was conducted through the Medical Student Research Program at The Faculty of Medicine, and continued through the Ph.D. program at the University of Bergen from 2018-2020.

The Bergen Hypertension and Cardiac Dynamics Group is chaired by Professor Eva Gerdts. The group consists of two additional Professors, one post-doctoral fellow, six PhD-fellows, one research medical student, technicians, study nurses and several consultants in cardiology employed at the Department of Heart Disease, Haukeland University Hospital, who also work closely with the group. The *Bergen Hypertension and Cardiac Dynamics Group* is focused on non-invasive cardiac imaging methods in clinical and experimental studies, with echocardiography as the main scientific tool. The group is responsible for the *Echocardiography Research Laboratory*, which is a state-of-the-art laboratory for echocardiographic image analysis. The core fields of interest are valvular heart disease, hypertensive heart disease and sex differences in cardiovascular disease. The group has a large collaborating network that extends both nationally and internationally.

A collaboration with the Department of Clinical Pharmacology, British Heart Foundation Centre of Research Excellence, King's College London, through Professor Phillip J. Chowienczyk, Professor John B. Chambers and senior researcher Gu Haotian was established during the work with Study 1 in this thesis.

3. Acknowledgements

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The work in the present thesis was first started through the Medical Student Research program at the University of Bergen. Starting at the Medical Student Research program provided a basis in scientific thinking which eased the transition to the PhD program. I am forever grateful for this experience. I would like to especially thank its leader Anne Berit Guttormsen, one of the most enthusiastic and inspiring people I have ever met. Dana Cramariuc, who was my co-supervisor during these years deserves a special mention. Thank you for your supportive and motivating help. I will be forever grateful to Sahrai Saeed, who although he was not my official supervisor, took me under his wings and tutored me during several research projects. If it had not been for you, I would never have been introduced to our colleagues in London and the concept of peak systolic function. I would like to thank PhD Haotian Gu and Professor Phillip Chowienzyck for welcoming me during my research trips to London. May they continue in the future.

This journey would not have been the same without my fellow PhD-candidates Ingeborg Eskerud, Hilde Halland, Johannes Hjertaas, Arleen Aune, Ester Kringeland and Lisa Grymyr. Ingeborg Eskerud was my office mate during most of my PhD-years, and our friendship and daily talk has been crucial for motivation and happiness. Johannes Hjertaas deserved a special mentioning; your technical insight has been an invaluable asset during this project. To my co-authors , Helga Midtbøe

and Professor John Chambers, thank you for your creative and intelligent feedback. I hope our scientific discussion may continue in the future. A special thanks needs to be directed to Vegard Lysne, who introduced me to R, and has come to my rescue many times when things get difficult. None of this would have been possible if it had not been for my parents. Thank you for your continuous love and support. My father showed me early on what academic life was all about. As a true scientist, when I told him I wanted to apply for the Medical Student Research Program, he thoroughly analyzed the different research groups and found out that joining the group of Eva Gerdts would be the best choice. You were right. Last, but definitely not least, I need to thank Marte for her love, support, patience and simply her existence. You remind me every day the greatest mysteries in life has its origin in the heart. In the midst of writing this thesis, our daughter Ada arrived. I can truly say that I discovered a new joy of writing with Ada sleeping on my chest. This process would not have been the same without my two girls.

Eigir Einarsen
Bergen, August 2020

4. Abbreviations

AS	Aortic valve stenosis
AT/ET	Acceleration /ejection time
AVA	Aortic valve area
AVR	Aortic valve replacement
β	Standardized beta coefficient
BMI	Body mass index
CI	Confidence interval
CV	Cardiovascular
EF	Ejection fraction
EF1	First phase ejection fraction
GAM	Generalized additive model
HF	Heart failure
HR	Hazard ratio
LV	Left ventricular/Left ventricle
NRI	Net reclassification index
OR	Odds ratio
PLGAS	Paradoxical low gradient severe aortic stenosis
PP/SVi	Pulse pressure/stroke volume index
RWT	Relative wall thickness
S`	Peak systolic annular velocity
SEAS	Simvastatin Ezetimibe in Aortic Stenosis
Zva	Valvulo-arterial impedance

5. Abstract

Background: Aortic valve stenosis (AS) is the most prevalent valvular heart disease requiring valvular intervention. With no pharmacological treatment available, optimal management requires detection of early left ventricular (LV) systolic dysfunction, accurate grading of AS severity and identification of risk factors associated with residual cardiac damage after aortic valve replacement (AVR). This thesis aimed to address these concerns.

Material and methods: This thesis include three papers based upon two different cohorts. In Study 1, we prospectively included 120 patients with mild, moderate and severe AS in a cross-sectional study to investigate the covariates of the first-phase ejection fraction (EF1), a novel marker of peak systolic function in AS. In Study 2 we included 1530 patients with asymptomatic non-severe AS from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study to evaluate the prognostic impact of increased acceleration ejection time (AT/ET) ratio on cardiovascular (CV) outcome during progression of AS. In study 3, we explored the association between preoperative obesity and persistent LV hypertrophy after AVR in 399 patients who developed severe AS during follow-up in the SEAS study.

Results: In Study 1, EF1 was associated with lower strain rate, a marker of myocardial contractility, and higher pulse pressure/stroke volume index, a surrogate of arterial stiffness, independent of AS severity. EF1 declined from mild to severe AS, while EF remained similar across groups. In Study 2, higher AT/ET ratio was an independent predictor of poor outcome in the total study population and among patients with discordantly graded AS. An AT/ET ratio >0.32 was found to be the best cut-off to predict CV death and heart failure (HF) hospitalization among patients with discordantly graded AS. In Study 3, preoperative obesity was strongly associated with persistent LV hypertrophy after median a 6 months follow-up 6 after AVR. In multivariable analysis, this association was independent of lower myocardial function and higher systolic blood pressure pre-AVR.

Conclusion: In patients with varying degree of AS severity in Study 1, lower myocardial contractility and higher arterial stiffness were both independently associated with lower EF1. In Study 2, higher AT/ET ratio was associated with increased CV morbidity and mortality independent of traditional risk markers. Higher AT/ET ratio seemed especially useful in patients with discordantly graded AS, beyond conventional grading. Lastly, in Study 3, obesity was found to be independently associated with higher prevalence of LV hypertrophy, an important prognostic marker in postoperative AS patients.

6. List of Publications

I. **Einarsen E**, Hjertaas JJ, Gu H, Matre K, Chowienczyk PJ, Gerdts E, Chambers J, Saeed S. Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis. Eur Heart J Cardiovasc Imaging. Epub 2020/08/13.

II. **Einarsen E,** Cramariuc D, Bahlmann E, Midtbo H, Chambers J, Gerdts E. Higher acceleration ejection time ratio predicts outcome in non-severe aortic valve stenosis – Under review.

III. **Einarsen E**, Saeed S, Cramariuc D, Chambers JB, Midtbo H, Gerdts E. Impact of Obesity on Persistent Left Ventricular Hypertrophy After Aortic Valve Replacement for Aortic Stenosis. Am J Cardiol. 2019;123(6):942-7.

Related papers (not included in the thesis presentation)

I. **Einarsen E**, Gerdts E, Waje-Andreassen U, Naess H, Fromm A, Saeed S. Association of increased arterial stiffness with diastolic dysfunction in ischemic stroke patients: the Norwegian Stroke in the Young Study. J Hypertens. 2020;38(3):467-73.

II. **Einarsen E**, Cramariuc D, Lonnebakken MT, Boman K, Gohlke-Barwolf C, Chambers JB, Gerdts E. Comparison of Frequency of Ischemic Cardiovascular Events in Patients With Aortic Stenosis With Versus Without Asymmetric Septal Hypertrophy (from the SEAS Trial). Am J Cardiol. 2017;119(7):1082-7.

7. Introduction

The aetiology of aortic valve calcification as a cause of aortic valve stenosis (AS) was first described by Mönckeburg in 1904.[1] He proposed that pathologically calcium depositions on the aortic cusps would lead to valve sclerosis. AS denotes the narrowing of the aortic valve opening. Since Mönckeburg the cause of AS has been known to be either congenital or acquired. The latter being further classified into rheumatic or degenerative. Even though sequelae from rheumatic fever constitute a considerable portion of AS in developing countries, the decline in rheumatic fever and increasing life expectancy has made degenerative calcification by far the most common cause of AS worldwide.[2-4] The current work is focused on degenerative AS, and further mentioning of AS will thus not include rheumatic or congenital AS.

7.1 Prevalence of AS

Aortic valve sclerosis represents focal thickening of the valvular cusps without significant obstruction of blood flow. Aortic valve sclerosis is fairly common in the general population, with an expected prevalence around 25% in those 65 years or older and almost 50% in those 85 years or older.[5,6] From population based studies it has been estimated that only a minority, approximately 9%, of subjects with aortic valve sclerosis progress to AS over a five year period.[7,8] Like valve sclerosis, AS is mainly a disease encountered among the elderly, and the prevalence increases sharply with age.[9] Different studies have reported a frequency of approximately 3-5% in those over 65 years, and in 10% of octogenarians in the Tromsø study.[5,6,9,10] After coronary artery disease and hypertension, AS is the third most frequent cardiovascular (CV) disease.[11] Additionally, AS has become the most common valve disease requiring surgical intervention.[3] Also, the prevalence of AS is expected to rise in the coming years due to the aging population in the Western world.[10]

7.2 Progression of AS

Based on a observational study by Otto et al. it has been estimated that the yearly progression rate of valve severity increases by approximately 0.3 m/s in transaortic velocity, by 7 mm Hg in mean transaortic pressure gradient and with a reduction of 0.1cm^2 in aortic valve area(AVA).[12] However, there are significantly individual differences and some subgroups may experience either a faster or slower progression.[13] In the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, investigating mild and moderate AS patients without overt CV disease, the yearly progression rate was found to be lower; increase in transaortic velocity by 0.15 m/s, in mean transaortic pressure gradient by 2.8 mm Hg/year and a reduction in AVA by 0.03 cm^2/year.[14]

AS patients are usually asymptomatic for many years. Symptom-onset may represent an arbitrary timepoint as initial symptoms may be vague and unspecific due to the progressive nature of the disease. Additionally, many patients may adhere to a sedentary lifestyle due to aging or comorbidities, which may conceal apparent symptoms such as exertional dyspnea and reduced exercise capacity. However, the onset of cardinal symptoms such as dyspnea, angina and syncope have a grim prognosis without intervention.[15] With no pharmacological treatment proven to attenuate or prevent the sclerotic process, the only available treatment options are either surgical aortic valve replacement(AVR) or transcatheter valve replacement.[16,17] Left untreated symptomatic patients face a two-year mortality rate of up to 50% when treated conservatively.[18,19] The effect of development of symptoms on mortality was first documented by Braunwald and Ross in their seminal paper from 1968.[15] Even today, the presence or absence of symptoms are critical for appropriate management of patients. The current guidelines recommend valvular intervention mainly in patients with severe symptomatic AS, in patients with severe AS and reduced LV function, or in moderate AS when presence of other cardiac diseases requires open heart surgery.[16,17]

Whilst older studies implied that non-severe AS should be regarded as benign, contemporary findings suggest that even mild or moderate AS may have poor long-

term prognosis.[20] Rosenhek et al. demonstrated that mortality was 1.8 times higher in patients with mild to moderate AS compared to an age and gender matched population.[13] The Cardiovascular Health Study reported that even individuals with aortic sclerosis, without known coronary artery disease, had 1.4 times higher risk of myocardial infarction than those without aortic sclerosis.[21] Recent studies challenge current practice by demonstrating that subgroups of AS patients, currently not deemed eligible for valvular intervention by the current guidelines, may have similarly prognosis as severe symptomatic AS without valvular replacement.[22,23] New and better tools for identification of the optimal timing of valvular replacement are necessary to improve patient outcomes. The challenge remains to better identify high-risk patients where the risk of valve replacement outweighs the risk of conservative treatment for long-term prognosis. Thus, novel markers of early LV systolic dysfunction, additional measures to accurately grade AS and integrated CV risk factor management are needed.

7.3 LV systolic function in AS

Ejection fraction (EF) is the most commonly used measure of left ventricular (LV) systolic performance in AS. Assessment of transvalvular flow by stroke volume index (SVi) by Doppler is used to subdivide into different flow gradient patterns based upon a low flow state ($SVi<35ml/m^2$). The current guidelines regard EF<50% as a class 1 indication for valvular replacement in patients with severe symptomatic AS,[16,17] although the lower gender-specific values for normal LV EF is 52% in men and 54% in women, respectively.[24] In truly asymptomatic patients the prevalence of EF<50% may be as low as below 1%, despite reduced LV systolic function when assessed by other methods.[25,26] Furthermore, a particular ambiguity exist in patients with EF >50% and a flow gradient pattern of low gradient severe AS with either reduced or normal flow, which may have increased risk compared to other subtypes of AS with EF >50%.[27] These patients may have severely elevated afterload, but also reduced LV function when assessed by global longitudinal strain.[28] An EF >50% with reduced myocardial contractility may occur due to LV geometric remodelling,

recruitment of preload reserve or a compensatory increase in circumferential shortening which may maintain SV and EF even with reduced long-axis function.[29-31] This underlines that the traditional 50% EF cut-off is not sufficient to detect subtle changes in LV function which may portray early systolic dysfunction. Some have proposed using a EF threshold of 60%,[32] whereas other highlight the limitation of EF as a marker of contractility in LV hypertrophy.[33,34] Additional measures of systolic function, like midwall fractional shortening and myocardial strain, have been developed and documented to be more sensitive in detection of early LV systolic dysfunction.[35-37] In patients with severe AS and preserved EF(>50%), lower global longitudinal strain was shown to be more sensitive in predicting CV events compared to EF.[38] Recently, lower global longitudinal strain was also associated with higher mortality rates in patients with moderate AS and preserved EF.[39] However, global longitudinal strain is, similar to EF, significantly afterload dependent.[40] This represents an inherent problem in AS which is characterized by a high afterload. There is also lack of a universal cut-off value which may be used to discriminate between high-and low risk individuals, mainly due to inter-vendor variabilities in strain algorithms, and a wide range between proposed cut-offs in different studies.[41,42] Measures of peak systolic function, such as strain rate, may also be measured by speckle tracking echocardiography. Strain rate is more related to contractility than strain and less influenced by changes in cardiac load. However, it is not widely used in clinical practice, mainly because of limited temporal resolution.[43,44] In clinical practice, measurement of strain rate may be considered time consuming. A marker of LV function that relates more to peak systolic function and is easy to measure would therefore be of interest.

7.4 Peak LV systolic function

Given the prognostic implications on development of LV systolic dysfunction, detection of early myocardial dysfunction may offer the potential to optimize timing of intervention and thereby improve patient outcomes. The first-phase EF (EF1) has in this regard been proposed as a novel marker of peak systolic function, and has been

described as the “FEV1 of the heart”.[45] EF1 represents the LV EF measured at the time of peak aortic jet velocity.[46] Biophysics of cardiomyocytes suggests that regulation of myocyte contraction through mechanosensing may preserve overall contraction but at the expense of a slower and sustained contraction.[47,48] Previous studies have shown that EF1 is impaired in patients with hypertension and diastolic dysfunction and in patients with AS with preserved EF.[46,49] EF1 was also shown to predict adverse outcome in patients with AS better than end-systolic markers, including global longitudinal strain.[49]

EF1 as a measure of peak systolic function may therefore be a more sensitive measure of early dysfunction than end-systolic markers like EF and global longitudinal strain in patients with AS. Theoretically, EF1 should occur at the time of maximal myocardial contraction. However, the association between EF1 and other markers of peak systolic function have not been reported. *In particular, more knowledge about the association between EF1 and strain rate, a measure closely related to myocardial contractility,[43] would be of interest.*

7.5 Ejection dynamics

Current markers of AS severity are clearly insufficient to identify all high-risk individuals. In particular, evaluation of AS severity remains challenging when conventional grading by peak aortic jet velocity, mean transaortic pressure gradient and AVA results in discordant grading, i.e. graded as moderate AS by peak jet velocity and mean valve gradient, but graded as severe by AVA. Often this situation occurs in patients with a reduced LV EF (<50%), which is termed low-flow low-gradient AS when SVi is <35 ml/m^2. A discordant grading in patients with normal EF (>50%), termed paradoxical low gradient severe AS (PLGAS), is a particularly challenging entity.[50] Accurately assessing AS severity in patients with moderate AS, and especially in patients with PLGAS, remains difficult when adhering to the current guidelines. Doppler measurements of peak aortic jet velocity and transaortic pressure gradient are highly angle-dependent, and the use of the continuity equation is prone to significant measurement errors which can lead to an underestimation or

overestimation of the orifice area.[51] Ejection dynamics on the other hand, are less angle-dependent and reliable measurements which may provide incremental information in patients with native AS. It is well known from older studies that severe AS has a slow up stroke and an aortic jet with a rounded contour.[52] However, the utility of the acceleration/ejection time (AT/ET) ratio was first evaluated in patients with prosthetic valves by Zekry et al., and is currently implemented in the evaluation of prosthetic valve function.[53,54] In smaller studies on native severe AS, an increased AT/ET ratio has been independently associated with increased mortality.[55,56] *The associations between higher AT/ET ratio and LV systolic function and prognosis have not been reported in patients with non-severe AS. Furthermore, whether assessment of ejection dynamics may improve identification of high-risk individuals among patients with PLGAS needs further exploration*.

7.6 Obesity and LV hypertrophy after AVR

Worldwide the prevalence of obesity has nearly doubled from the 1980 to 2017 and is expected to rise further in the coming years, especially in women.[57] With an inevitably higher prevalence of AS due to longer life expectancies and an aging population, the potential importance of obesity on AS management and outcome will increase.

Following AVR an abrupt alleviation of the LV overload leads to a reduction in LV pressure and afterload. Normalization of LV geometry is expected after successful AVR in AS, but does not occur in all patients despite appropriately sized aortic valve prostheses.[58] Lack of normalization of LV hypertrophy has been documented to be associated with poor long-term postoperative prognosis.[59] In a prospective study following LV mass regression in patients operated with AVR for AS, regression of LV hypertrophy was dependent on the preoperative risk profile.[60] This highlights that understanding the underlying factors contributing to lack of normalization of LV hypertrophy is of utter importance. It is well known that severe patient-prosthetic mismatch, uncontrolled blood pressure and systemic hypertension are associated with a lack of mass regression and symptom relief after AVR.[61-63]

Previous data from our group have shown that obesity increases LV mass during progression of AS.[64] Obesity has also been implicated as a risk factor for many predisposing conditions for CV disease such as hypertension, diabetes and atherosclerosis.[65]. Interestingly, new data from large epidemiologic studies with mendelian randomization design suggests that obesity might be causally associated with higher risk of developing AS.[66,67] In similar studies with over 100.000 participants from the general population, plasma triglycerides, remnant cholesterol and low-density lipoprotein, important components of the metabolic syndrome, have been associated with higher risk of incident and symptomatic AS.[68,69] Even though obesity has been extensively studied as a risk marker for CV disease in general and during progression of AS, less is known about the effect of obesity on normalization of LV structure and function after AVR. *Thus, more knowledge on the influence of obesity on post-AVR normalization of LV mass is spoken for.*

8. Hypothesis and study aims

8.1.1 Hypothesis

We hypothesized that measures of peak systolic function and LV ejection dynamics could be useful in detection of high-risk AS patients beyond conventional measures. Secondly, we hypothesized that obesity would be associated with a lack on normalization of LV mass and myocardial function after AVR.

8.1.2 Specific aims

1. Identify covariates of peak LV systolic function measured by EF1 in patients with mild, moderate and severe AS.

2. Assess the impact of LV ejection dynamics measured by AT/ET ratio on CV outcome in patients with non-severe AS.

3. Investigate the effect of preoperative obesity on persistent LV hypertrophy after AVR for severe AS.

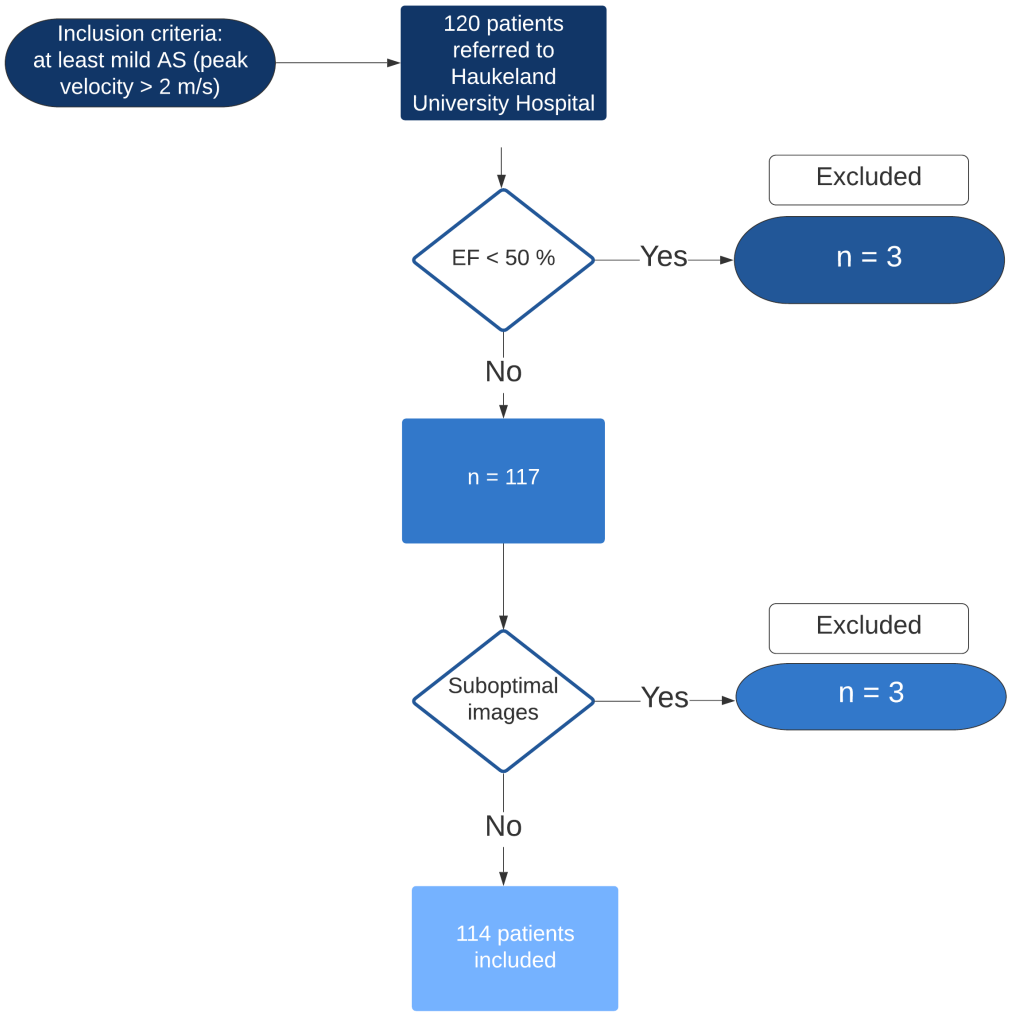
9. Methods

9.1 Study design and patient population

9.1.1 Study 1

Study 1 is a prospective cross-sectional study which was conducted to test the associations between EF1, myocardial contractility and arterial function. A total of 120 study participants were recruited from the Department of Heart Disease, Haukeland University Hospital between October 2015 and December 2017. Inclusion criteria were aortic valve thickening on echocardiography and at least mild AS, defined in accordance with the current AHA/ACC guidelines at the time of inclusion.[17] Patients were excluded if they met one of the predefined exclusion criteria: cardiac arrhythmias, prior pacemaker implantation, other concomitant valvular disease of more than moderate grade, known coronary artery disease (myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention) or previous cardiac surgery. For the present study, three patients were excluded from the analysis due to EF <50% and another three patients due to poor image quality not suited for reliable analysis of EF1. Thus, 114 patients with mild, moderate or severe AS were included in the final analysis (Figure 1). Written informed consent was obtained from all study participants. The study was approved by the local Regional Committee for Medical and Health Research Ethics (approval number 2014/1895/REK Nord) and was conducted in accordance with the Declaration of Helsinki.

Figure 1. Flow chart of patients included in Study 1.



9.1.2 Study 2 and 3

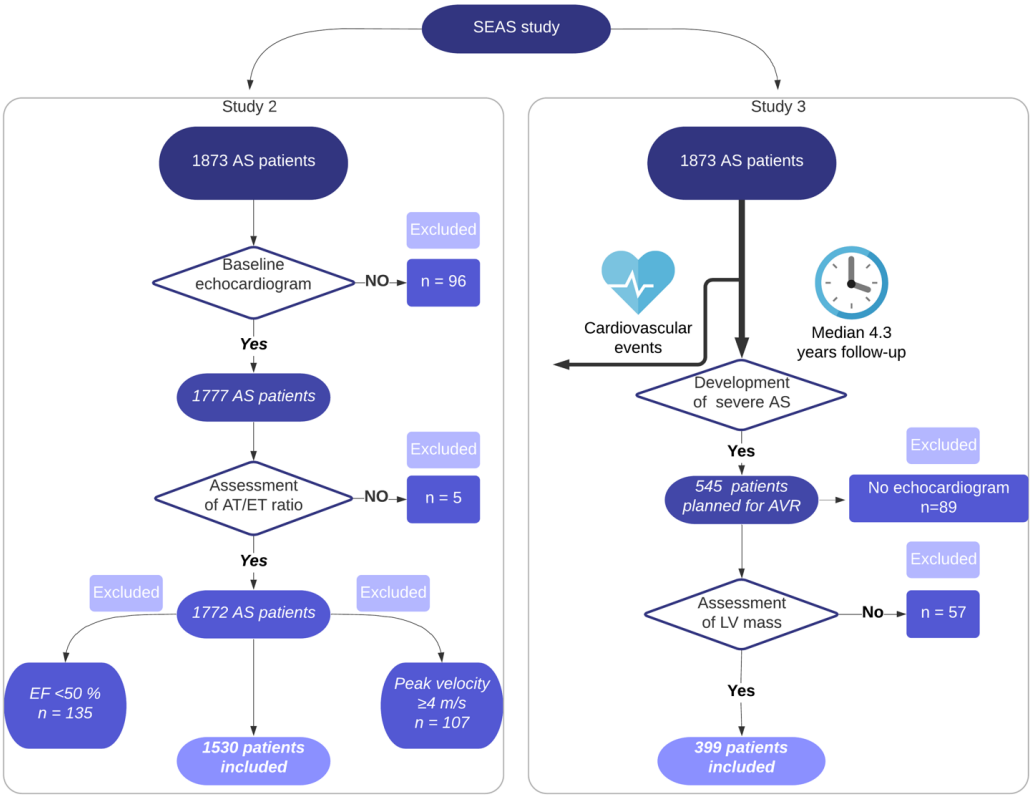
Study 2 and 3 were based on data from the SEAS study. The SEAS study included 1873 participants aged 45-85 years with asymptomatic mild-and moderate AS (thickened aortic valve cusps and peak aortic jet velocity ≥ 2.5 and ≤ 4 m/s).[14] Patients were randomized to double blind, placebo-controlled lipid lowering treatment with combined simvastatin 40 mg and 10 mg ezetimibe. Study participants were enrolled from 173 different study sites from seven European countries between

2002-4 and were followed up at a minimum of 4 years (median 4.3 years). Patients with coronary artery disease, peripheral vascular disease, previous stroke, history of diabetes, systolic heart failure (HF), other significant valvular disease, renal insufficiency or any other condition requiring lipid lowering treatment were excluded from the study.[70] A detailed description including study protocol, design and patient's recruitment has been previously published.[70] The study protocol was approved by regional ethics committees in all participating countries, and informed consent was obtained from all patients. The study was registered online at www.clinicaltrials.gov with identifier NCT00092677.

In SEAS, a total of 1772 patients had data on AT/ET ratio on the baseline echocardiogram (95%). Some of the patients included in SEAS as moderate AS by their attending physician were documented to have severe AS after core laboratory reading of the images (peak aortic jet velocity $\geq$ 4.0 m/s). For Study 2, these patients were excluded (n=107). Additionally, patients with EF < 50% were excluded from the final analysis (n=135)(Figure 2). Study 2 therefore included 1530 patients.

Study 3 was a post hoc analysis of data from SEAS patients who underwent AVR during a median of 4.3 years follow-up. A total of 545 SEAS patients developed severe AS and were referred to AVR by the local study site physician. Among these patients, post-AVR echocardiograms were sent for expert interpretation at the core laboratory in 456 patients. 57 of these patients were excluded due to poor acoustic window in parasternal views, on either the pre-or post AVR echocardiogram. This yielded 399 SEAS patients with measurements of LV mass both at the pre-and post AVR echocardiogram (Figure 2).

Figure 2. Flow chart of study participants in Study 2 and *3.*



9.2 Echocardiography

9.2.1 Protocol and analyses

In Study 1, all patients were examined with two-dimensional transthoracic echocardiography following a standardized protocol using a Vivid E9 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway). All images were digitally stored and analyzed using an offline digital workstation (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). All readings were done blinded to clinical and demographic data. Examinations were first read by the first author (EE) and later proof read by a highly experienced reader (EG).

For Study 2 and 3, echocardiograms were obtained at the 173 local SEAS study sites with second harmonic imaging following a standardized protocol. All images were recorded and submitted to the Echocardiography Core Laboratory either by Video Home System videotapes, compact discs or magnetic optical disks for blinded expert interpretation. The inclusion of patients were decided by the local study site according to local measurements. Consequently, the study included some participants deemed outside the initial inclusion criteria (peak aortic jet velocity ≥ 2.5 and ≤ 4.0 m/s) by the echocardiography core laboratory analysis. In Study 2, all baseline examinations were initially read by a junior member of the staff, and thereafter proof read by an experienced reader (EG). In Study 3, all post-AVR examinations were first read by the first-author (EE) and quality assured by the last-author (EG). In both studies, all readings were performed offline using a digital workstation equipped with Image Arena (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) software. In Study 1, we assessed global longitudinal strain and strain rate by speckle tracking echocardiography. Global longitudinal strain and strain rate were measured offline on a dedicated workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway) software, following current recommendations.[71] The analyses were performed by a single investigator (EE) and later quality assured by experienced readers (KM, SS).

9.2.2 Evaluation of LV mass and geometry

LV dimensions and wall thicknesses were measured in two-dimensional parasternal long-axis views following the current guidelines.[72] LV mass was calculated by the Devereux's formula that was validated against necropsy findings in a wide range of cardiac conditions:[73]

$$\text{LV mass(g)} = 0.8 \times (1.04[(\text{LVEDD} + \text{PWTD} + \text{IVSDD})^3 - (\text{LVEDD})^3]) + 0.6\text{g}$$

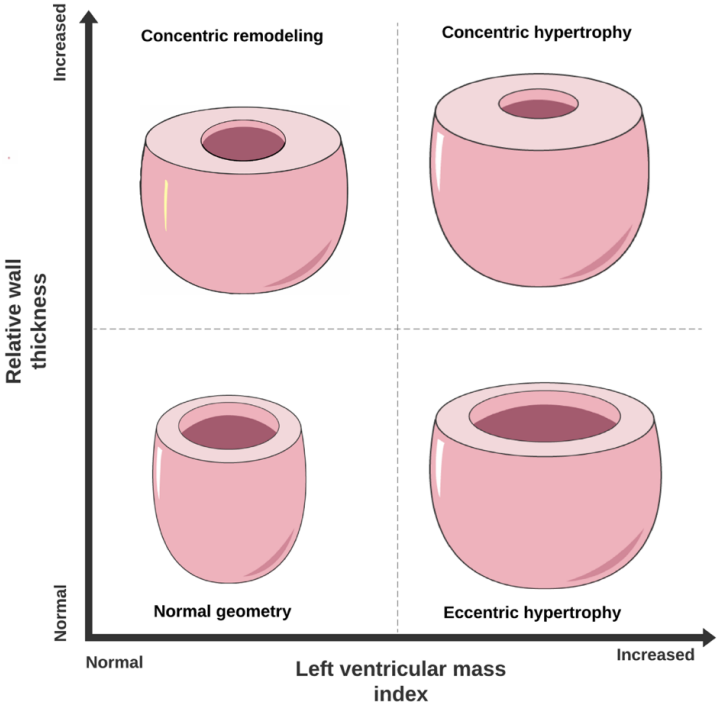
in which LVEDD = LV end-diastolic inner diameter, PWTD = posterior end-diastolic wall thickness, IVSDD = interventricular septum end-diastolic wall thickness. LV mass was indexed for height in the allometric power of 2.7 to account for the influence of disproportionally increased body weight in relation to body height in

overweight and obese subjects.[74] LV hypertrophy was considered present if LV mass index exceeded the gender-specific, prognostically validated cut-off values of >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men, respectively.[74] Relative wall thickness (RWT) was defined by the following equation:

$$\mathrm{RWT} = \frac{2 \times \mathrm{PWTD}}{\mathrm{LVEDD}}$$

and considered increased if ≥ 0.43.[72] LV geometry was classified based on combined assessment of LV RWT and LV mass index into four different LV geometric groups in accordance with the guidelines.[72] Normal LV geometry was defined as normal LV mass index by the aforementioned gender-specific values, and RWT <0.43. Concentric remodeling was considered present if LV mass was normal and RWT was abnormal (≥ 0.43). Eccentric hypertrophy was defined by the presence of LV hypertrophy and RWT <0.43, while concentric hypertrophy by presence of LV hypertrophy and abnormal RWT (≥ 0.43) (Figure 3).

Figure 3. Patterns of LV geometry.



9.2.3 Systolic function

Conventional LV EF was assessed at the endocardial level by the modified Simpsons' biplane method of discs.[72] In all studies, EF was considered low if <50% in both sexes in accordance with guidelines on AS.[75] Additionally, LV systolic function was assessed at the myocardial level by calculation of midwall shortening (MWS).[35] MWS considers the epicardial migration of the midwall during systole, and is measured in two-dimensional parasternal images as follows:

$$\text{MWS} = \frac{\left(\text{LVEDD} + \frac{\text{PWTD}}{2} + \frac{\text{IVSDD}}{2}\right) - (\text{LVESD} + \frac{\text{Hs}}{2})}{\left(\text{LVEDD} + \frac{\text{PWTD}}{2} + \frac{\text{IVSDD}}{2}\right)} \text{ x } 100$$

In the equation, Hs is the estimated LV inner myocardial thickness at end-systole.

$$\text{Hs} = 2\text{x}[(\text{LVEDD} + \frac{\text{IVSDD}}{2} + \frac{\text{PWTD}}{2})^3 - \text{LVEDD}^3 + \text{LVESD}^3]^{\frac{1}{3}} - \text{LVESD}$$

To account for afterload dependent systolic function, midwall shortening was adjusted for circumferential end-systolic stress, as validated in hypertensive patients.[76] Circumferential end-systolic stress was estimated at midwall assuming a cylindrical model as described by Gaasch et al.[77,78] In the calculation of circumferential end-systolic stress, the mean aortic transvalvular pressure gradient was added to the brachial systolic blood pressure in the equation to allow for a more precise estimation of LV systolic pressure. Stress-corrected midwall shortening was then derived by the ratio of predicted to observed midwall shortening, adjusted for end-systolic stress. Stress-corrected midwall shortening was thus regarded as a relatively afterload independent marker of LV systolic function in Study 1 and 2.

$$\text{predicted MWS} = 20.01 - 0.022 \text{ x CESS (mmHg)}$$

$$\text{ScMWS} = \frac{\text{actual MWS}}{\text{predicted MWS}} \text{ x } 100$$

CESS = Circumferential end-systolic stress, ScMWS = stress-corrected midwall shortening.

Systolic flow status was estimated by Doppler stroke volume, corrected for body surface area. Low-flow was defined as a SVi (<35 ml/m^2), and normal-flow when above this threshold. [75]

Global longitudinal strain and strain rate

Myocardial deformation can be assessed by the concept of strain.[79] Strain is defined as the fractional change of tissue length compared to its original length. It is usally expressed as negative percentage shortening.[80] Longitudinal strain during systole(ε) is assumed to be approximately linear and can be defined by the Lagrangian formula:

$$\varepsilon = \frac{L - L0}{L0}$$

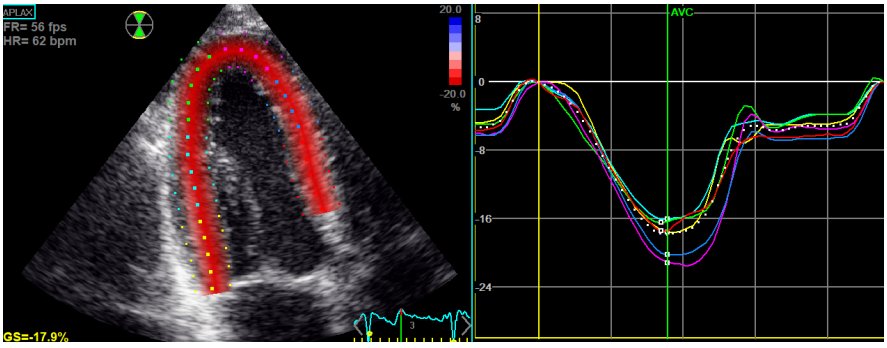
Where L is the length at a given point in time, and L0 is the reference length at end-diastole.

Myocardial deformation can be measured in the 3 chamber directions, longitudinal, circumferential and radial direction, as well as twist and rotation. Longitudinal strain is an index of the long axis function of LV. Strain rate (s^{-1}) on the other hand, is the first derivative of strain with respect to time, and describes the speed of deformation in the myocardium during the cardiac cycle.[81]

A method to measure strain is by the use of Speckle Tracking Echocardiography.[80,82] Briefly, speckles are the results of random scattering from small reflectors and the interference between this scattering from several ultrasound beams. Speckles are relatively stable during the cardiac cycle and can be grouped into kernels within a region of interest. These kernels can then be tracked during the cardiac cycle. Speckle tracking echocardiography has been validated against both microsonometry and magnetic ressonance imaging.[83] Global longitudinal strain is the most widely used and reproducible measure of strain, and is less affected by geometrical assumptions compared to circumferential or radial strain.[36,84]

In Study 1, global longitudinal strain was defined as the average of peak systolic negative longitudinal shortening from 18 LV segments from the apical four-chamber, two-chamber and long-axis views (Figure 5). The onset of contraction was defined as the first deflection of the QRS-complex on the electrocardiogram recording. End-diastole was defined from aortic valve closure from a pulsed wave Doppler recording with similar heart rate as the images used for strain analyses. All images were carefully optimized to achieve an adequate frame rate / heart rate ratio >1(median 74 frames/s, mean 73 frames/s). Strain rate was derived automatically from the strain curves as the first derivative in each segment, and then averaged to obtain peak systolic strain rate

Figure 5. Typical example of global longitudinal strain by speckle tracking measured from a apical three-chamber view.

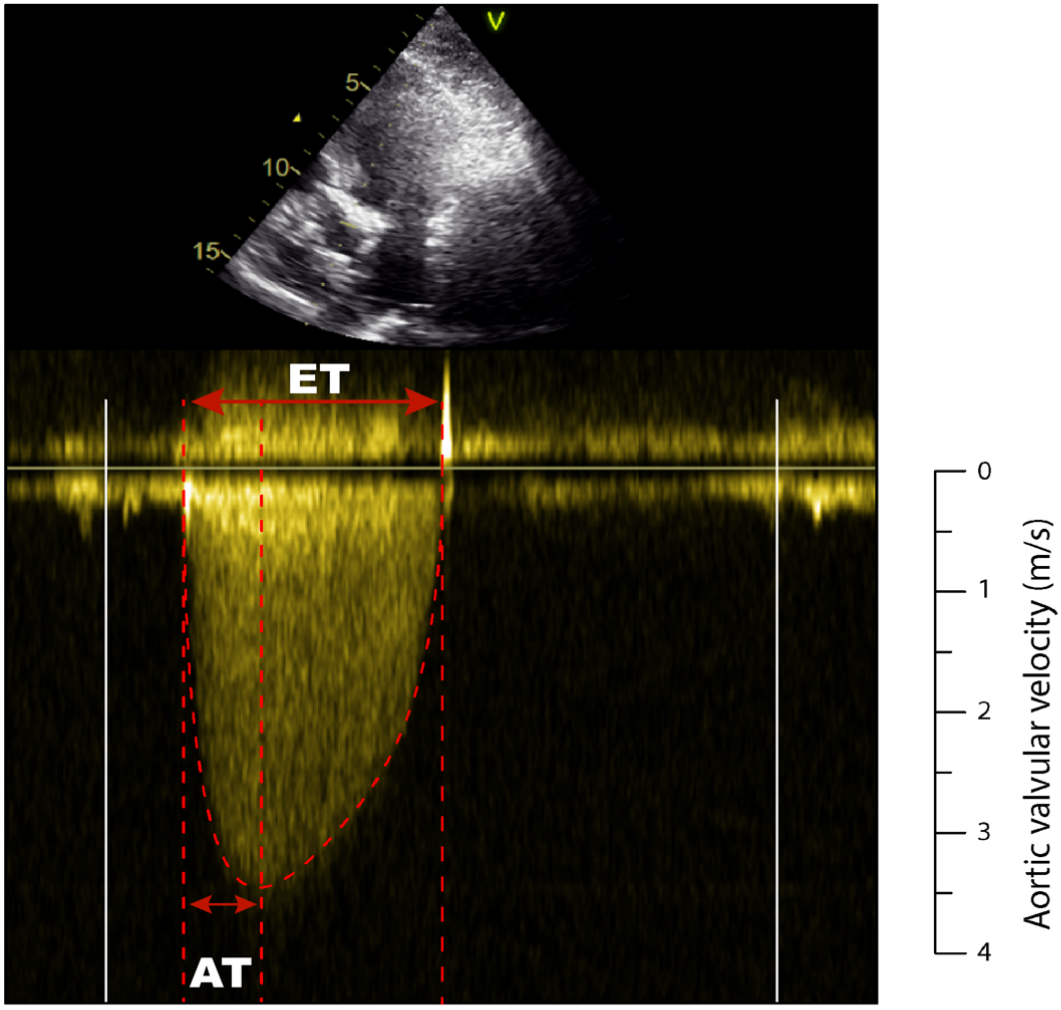


Acceleration/Ejection time ratio

In Study 1 and 2, AT/ET ratio was calculated by assessment of the timing intervals from a continuous spectral Doppler recording of the aortic jet velocity. AT time was defined as the time in milliseconds from aortic valve opening to peak aortic jet velocity. The ET was defined as the time in milliseconds from opening to closure of the Doppler signal (Figure 6). The AT/ET ratio was then calculated by the following formula:

$$\frac{\text{AT}}{\text{ET}} = \frac{\text{Acceleration time}}{\text{Ejection time}}$$

Figure 6. Measurement of AT/ET ratio from a continuous wave Doppler recording of the aortic jet velocity.



EF1

In Study 1, EF1 was measured manually by the biplane method of discs by measuring the volume change from end-diastole to the time that corresponded to peak aortic jet velocity.[46] EF1 was thus derived by the following equation:

$$EF1\ (\%) = \frac{EDV - V1}{EDV}\ x\ 100$$

EDV= end-diastolic volume. V1 = volume at the peak aortic jet velocity (Figure 7).

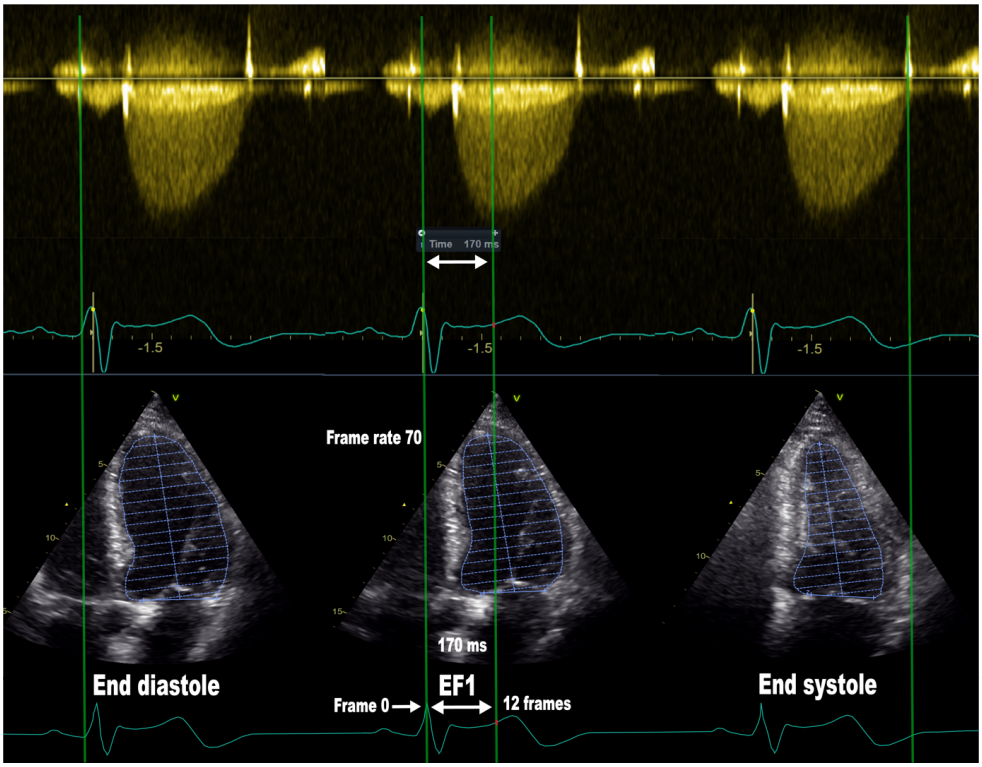
We calculated the exact frame in which to measure EF1. This was done by first measuring the time in milliseconds(ms) from the R-wave on electrocardiogram recordings from the Doppler signal to peak aortic jet velocity. With a simple in custom-made program, the exact frame of EF1 on B-mode images was derived by multiplying the frame-rate with the time to peak aortic jet velocity (Figure 7):

$$Frame\ EF1 = Frame\ 0 + \frac{Framerate\ x\ time\ to\ peak\ (ms)}{1000}$$

Frame 0= the starting frame that matches the peak of the R-wave on the B-mode image.

Due to the importance of timing for exact EF1 analysis, images with inadequate quality or frame rate were discarded. Adequate framerate was defined as framerate/heartrate ratio equivalent to or above one. Only images with a heartrate with equal or ± 10% difference between Doppler and B-mode images were chosen. EF1 was measured separately on a workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway) sofware. All measurements were performed by the same reader (EE).

Figure 7. *Measurement of EF1*



9.3 LV diastolic function

In Study 2, diastolic dysfunction was defined in accordance with the current guidelines,[85] if at least three of the following parameters were present: reduced annular è velocity by tissue Doppler (septal é <7 cm/s or lateral é <10cm/); filling pressure >14, defined as early transmitral E-wave/average mitral annular velocity ratio (E/è); biplane left atrial volume index >34mL/m^2; tricuspid regurgitant jet velocity >2.8m/s.

9.4 Assessment of AS

In Study 2 and 3, AS severity was graded in accordance with the joined European Association of Echocardiography and American Society of Echocardiography guidelines on management of valvular heart disease at the time of the SEAS study completion (Table 1).[86] In Study 1, the current American College of Cardiology/American Heart Association guidelines was used, which includes those with a peak velocity of 2.0-2.9 m/s as mild AS.[17]

Table 1. European guideline recommendations for grading of AS by echocardiography.

Grading of aortic stenosis severity

	Mild	Moderate	Severe
Peak velocity (m/s)	2.5-2.9	3.0-3.9	≥4.0
Mean gradient(mm/Hg)	<20	20-40	≥40
AVA (cm^2)	>1.5	1.0-1.5	<1.0

Peak aortic jet velocity was measured by continuous wave Doppler in several acoustic windows (apical, right parasternal and suprasternal view). The highest aortic jet velocity acquired from any acoustic window was used for the tracing of the time velocity integral. The mean transaortic pressure gradient was obtained from the velocity time integral curve by tracing the outer edge of the Doppler flow. In patients with irregular heart rhythms, five beats were averaged. AVA was calculated by using the continuity-equation.

$$AVA = \frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_{AS}}$$

AVA=aortic valvular area. CSA=cross sectional area. LVOT=left ventricular outflow tract. VTI= velocity-time integral. AS= aortic valve stenosis.

Patients with discordant grading (mean transaortic pressure gradient<40mmHg and AVA<1.0 cm^2) were in Study 3 further assessed by low flow (SVi<35 ml/m^2), which yielded two different flow gradient patterns, low flow low gradient and normal flow low gradient. In Study 3 these were grouped together as PLGAS. This was not assessed in Study 1 due to insufficient statistical power to investigate differences between flow gradient patterns.

Arterial stiffness and global LV load

Arterial stiffness was estimated by the ratio from a central pulse pressure (PP)/SVi. Central PP was estimated from brachial PP using a validated formula: brachial PP x 0.49 + age x 0.30 +7.11.[87]

Valvulo-arterial impedance (Zva) has been proposed as a surrogate measure of combined valvular and arterial load imposed on the LV during ejection. As appropriate, we calculated Zva as the sum of systolic blood pressure and mean transaortic pressure gradient divided by SVi.[88]

9.5 Cardiovascular risk factors

9.5.1 Blood pressure and hypertension

In all studies, clinic blood pressure was measured as recommended by the current guidelines.[89] Clinic and post-echocardiography blood pressure were measured both at baseline and at the last study visit before AVR in the SEAS study. Data were forwarded to the SEAS echocardiography core laboratory after study completion by the SEAS sponsor, Merck Schering Plough. Clinic blood pressure was measured by a standardized procedure with an appropriate cuff for the individual patient. Blood pressure measurement was performed with the patient in sitting position after five minutes initial rest. Blood pressure was measured in triplicates by a calibrated aneroid sphygmomanometer by trained study nurses. The average of the last two

measurements was taken as the clinic blood pressure. Supine blood pressure was measured immediately after completion of the echocardiographic examination when the room was still dark, and with the patient in a supine position. Post-echocardiographic blood pressure was used for calculations of hemodynamic variables. In all studies, hypertension was defined as combined history of hypertension, elevated clinic blood pressure (≥140/90 mmHg) and/or use of antihypertensive treatment.

9.5.2 Overweight and obesity

Body mass index (BMI) was derived from body weight in kilograms divided by height in meter squared in all studies. The criteria from the World Health Organization were used to classify patients into normal weight (BMI <25.0 kg/m^2), overweight (BMI 25.0 kg/m^2 – 29.9 kg/m^2) and obesity (BMI ≥30.0 kg/m^2)

9.6 Endpoints in the SEAS study.

All study endpoints in the SEAS study were adjudicated by an independent committee.[70] The primary endpoint in the SEAS study was major CV events, a composite which included AS-related events (AVR, death from CV causes and congestive HF due to AS progression) and ischemic CV events (combined death from CV causes, non-fatal myocardial infarction, coronary artery revascularization, hospitalization for unstable angina and non-hemorrhagic stroke). All-cause mortality was considered as a tertiary endpoint. In Study 2, we assessed the associations between higher AT/ET ratio with the primary study endpoint, with CV death and HF hospitalization and with all-cause mortality. The latter endpoints were considered harder, or more objective endpoints compared to the primary study endpoint which was driven mainly by referral for AVR, based upon decision at local study sites. In Study 2 the endpoints CV death and HF hospitalization were combined to achieve sufficient statistical power in multivariable analysis

9.7 Statistics

Statistical analyses were performed using Statistical Package for Social Sciences version 24.0-25.0 (IBM Corporation, Armonk, NY, USA) and R version 3.6.1(The R Foundation for Statistical Computing, Vienna, Austria). Normal distributed data are expressed as mean ± standard deviation and non-normally. In Study 1, the participants were grouped according to AS severity by peak aortic jet velocity. In Study 2, according to the quartiles of AT/ET ratio. In Study 3, BMI was used to define obesity, and to divide the study population into BMI classes: normal weight (BMI < 25 kg/m^2), overweight (BMI ≥25 kg/m^2 and <30 kg/m^2) and obesity (BMI ≥30 kg/m^2). Comparisons between groups were done with analysis of variance (ANOVA) with Scheffes`s post-hoc test for continuous variables. Categorical variables were compared with a general linear model with Sidak´s post hoc test or Cochrane Armitage trend test.

Univariable associations were tested in univariable logistic and linear regression analyses. In linear regression, variables were entered into the multivariable models if $p<0.10$ in univariable analysis and removed by a stepwise procedure if $p>0.10$. Some variables were forced into the model if deemed either clinically or statistically relevant by an enter procedure. Collinearity tools were used in multivariable linear regression, with assessment of variance of inflation factor and tolerance. Model assumptions were tested by assuring that normality of the error distribution, linearity and homoscedasticity were not violated. The goodness of fit was expressed as the adjusted R^2. Logistic regression analysis followed a similar procedure, but goodness of fit was tested by the Hosmer-Lemeshow test.

In Study 2, survival analysis was performed using Cox proportional hazard regression and results are presented as hazard ratio (HR) with 95% confidence interval (CI). Proportional hazard assumptions were tested by Schoenfeld residuals for each independent continuous variable and by visual examinations of log-log plots.

Nested models were compared using Akaike`s information criterion (AIC), which is based on the gold-standard likelihood ratio test but penalizes the addition of non-explanatory variables. The statistical difference between AIC values were

compared with the likelihood ratio test. The continuous net reclassification improvement (NRI) and Harrell C statistics were calculated to evaluate the discriminatory power between models with and without AT/ET ratio. Kaplan-Meier curves with log rank statistics visualized the unadjusted rate of event free-survival between high and low AT/ET ratio. Receiver operating characteristic curves were plotted to calculate the optimal cut-off to discriminate between high and low risk individuals with regards to AT/ET ratio. Non-linear relations between AT/ET ratio and the outcome variables were visualized in adjusted generalized additive models (GAM) with restricted cubic splines.

Intra- and inter-observer reliabilities were reported as intraclass correlation coefficient with 95% CI in Study 1. Intra-observer reliability of EF1 was calculated by reanalyzing 18 randomly selected participants analyzed twice by the same reader (EE) three months after initial reading. Inter-observer reliability was calculated by comparing baseline EF1 measurements between two readers (EE and SS) in 18 randomly selected participants.

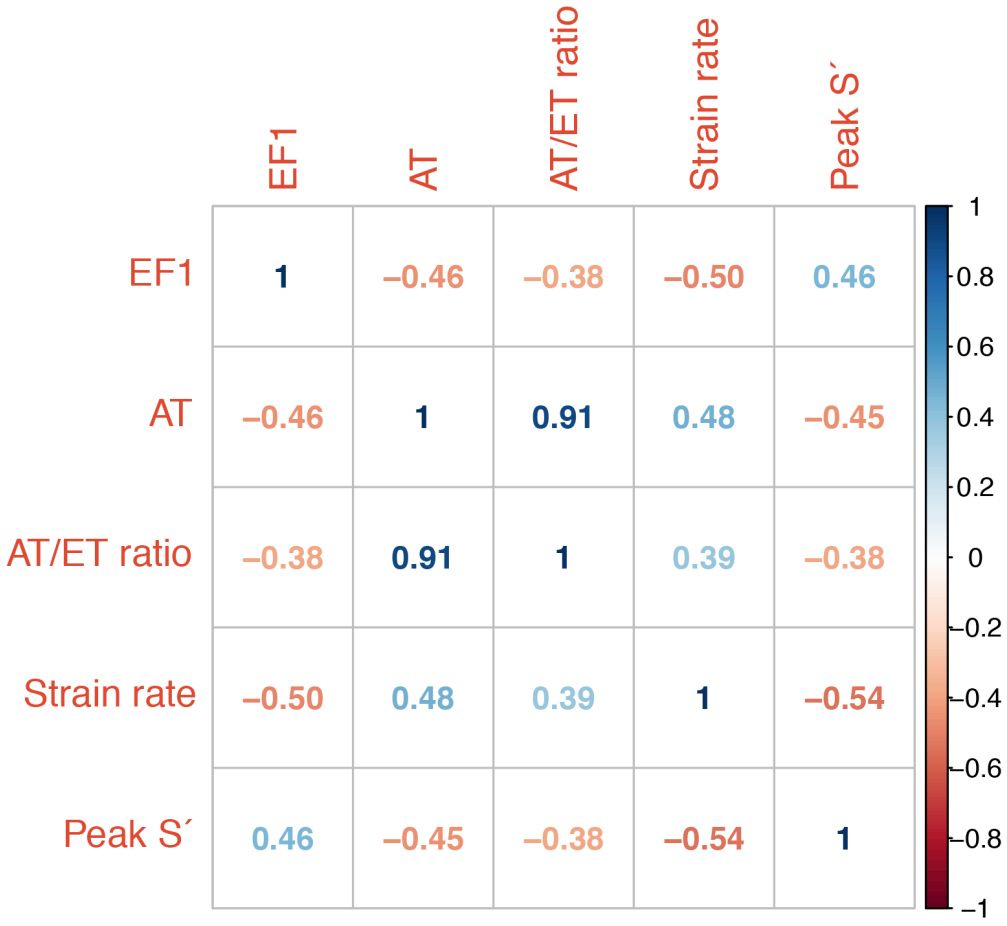
10. Summary of results

10.1 Study 1: Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis.

The aim of this study was to identify covariates of EF1 across the spectrum of AS severity. A total of 114 patients (48% women) with AS and LV EF≥50% were studied. In the study population, 38 patients had mild, 44 moderate and 32 severe AS, respectively. Median age was 73 years (age range 31-94 years), while the prevalence's of hypertension were 89.5%, diabetes 11.4% and hypercholesterolemia 46.5%, respectively. Patients with severe AS had significantly higher LV mass index and RWT ($p<0.05$). Measures of end-systolic function such as global longitudinal strain, EF and SVi did not differ between groups ($p>0.05$). Indices of peak LV systolic function, including AT, strain rate, and EF1 all progressively declined from mild to severe AS (all $p<0.05$). All measures of peak systolic function were significantly correlated with each other (Figure 9).

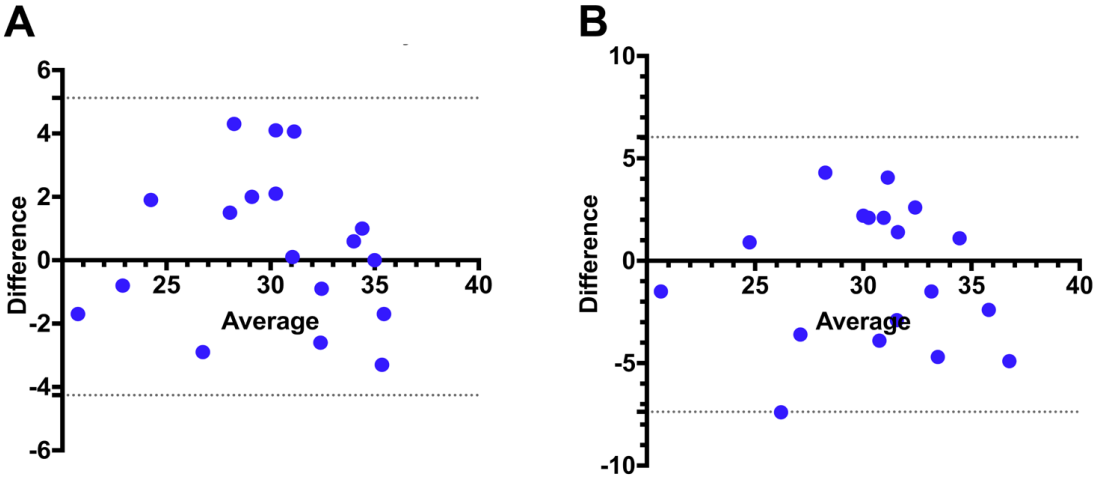
Intra-observer and inter-observer agreement of EF1 measurements were good, with intraclass correlation coefficient 0.94 (95% CI [0.85-0.98]) and 0.88 (95% CI [0.67-0.95]), respectively (Figure 10). When analyzing the covariates of EF1 in univariable linear regression, EF1 was significantly associated with strain rate (β -0.50), PP/SVi (β -0.29), peak aortic jet velocity (β -0.41), AT/ET ratio (β -0.38), filling pressure (β -0.27), LV mass index (β -0.24), in which higher values of all variables lowered EF1(all $p<0.05$). The correlation between EF and EF1 did not reach statistical significance (β 0.18, $p=0.059$). In multivariable linear regression analysis, the association between EF1 and strain rate, peak jet velocity and PP/SVi remained significant ($R^2=0.40$, $p<0.001$), while the association between EF1 and other variables were attenuated**.**

Figure 9. Correlation plot showing the bivariate correlations between measures of peak systolic function.



In a separate analysis, EF1 was analyzed as a dichotomous variable (≥25% or <25%). This cut-off was based on a previous study which found that a cut-off of <25% was associated with worse prognosis in patients with moderate and severe AS.[49] In logistic regression analysis, EF1 shared the same covariates as EF1 in a continuous scale. Diastolic dysfunction was highly associated with EF1 <25% in univariable analysis (OR 4.36, 95% CI [1.74-10.90], p=0.002), but this association was non-significant in multivariable analysis.

Figure 10. Bland Altman plots showing the variation between repeated measures of first-phase ejection fraction for intra-observer (A) and inter-observer (B) analyses.



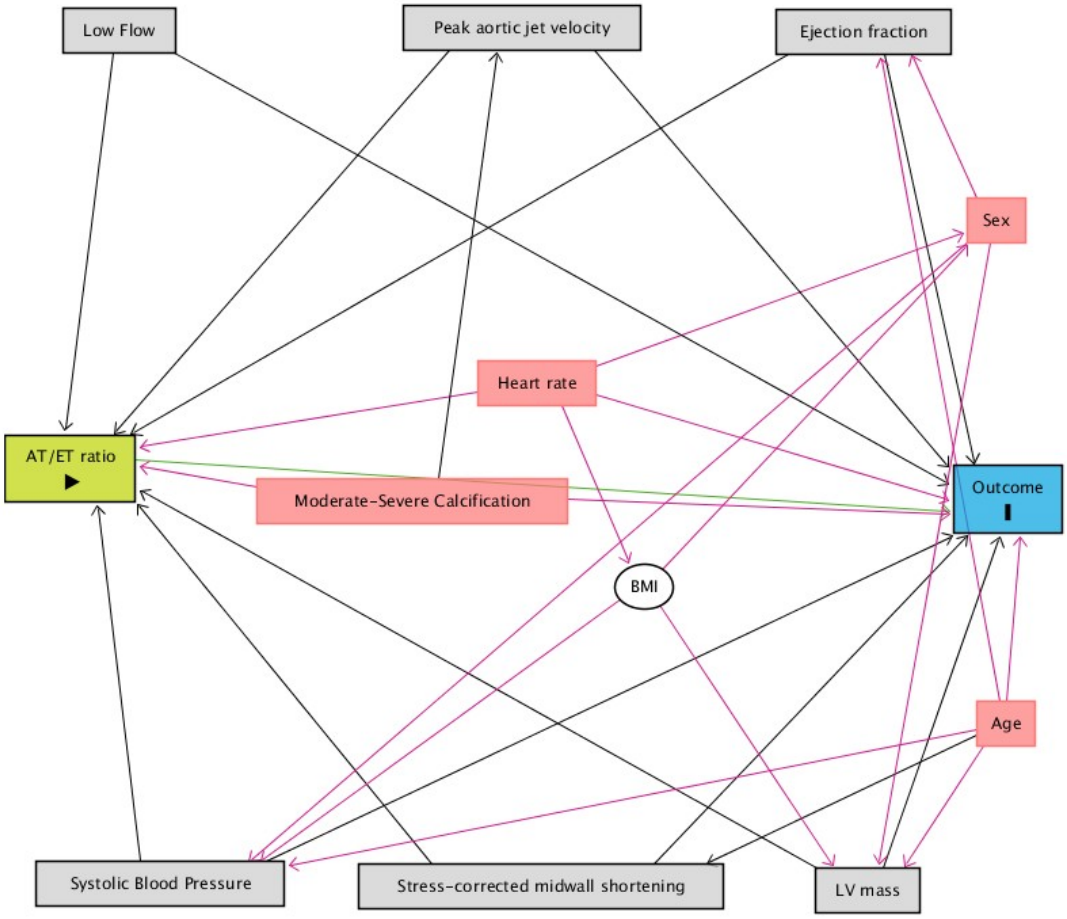
10.2 Study 2: Higher acceleration ejection time ratio predicts impaired outcome in non-severe aortic valve stenosis.

The aim of this study was to assess the association between higher AT/ET ratio and outcome during follow-up in non-severe AS participating in the SEAS study. The total study population included 1530 patients (38% women) with a mean age of 67 years and mean peak aortic jet velocity of 3.02 m/s. Patients were grouped into quartiles of AT/ET ratio at baseline, with the 1st quartile as the reference group. There was a significant trend of increasing AS severity by all conventional echocardiographic measures with increasing AT/ET ratio quartile (all $p<0.05$). The 4th quartile had significantly lower LV EF, stress-corrected midwall shortening and higher prevalence of low SVi (all $p<0.05$).

The covariates of AT/ET ratio were investigated in linear regression. In univariable analysis, higher AT/ET ratio correlated with lower values of stress-corrected midwall shortening, LV EF, systolic blood pressure and presence of low SVi, and with higher LV mass, aortic jet velocity, heart rate and RWT, with male sex and more extensive aortic valve calcification (all $p<0.05$). In multivariable analysis,

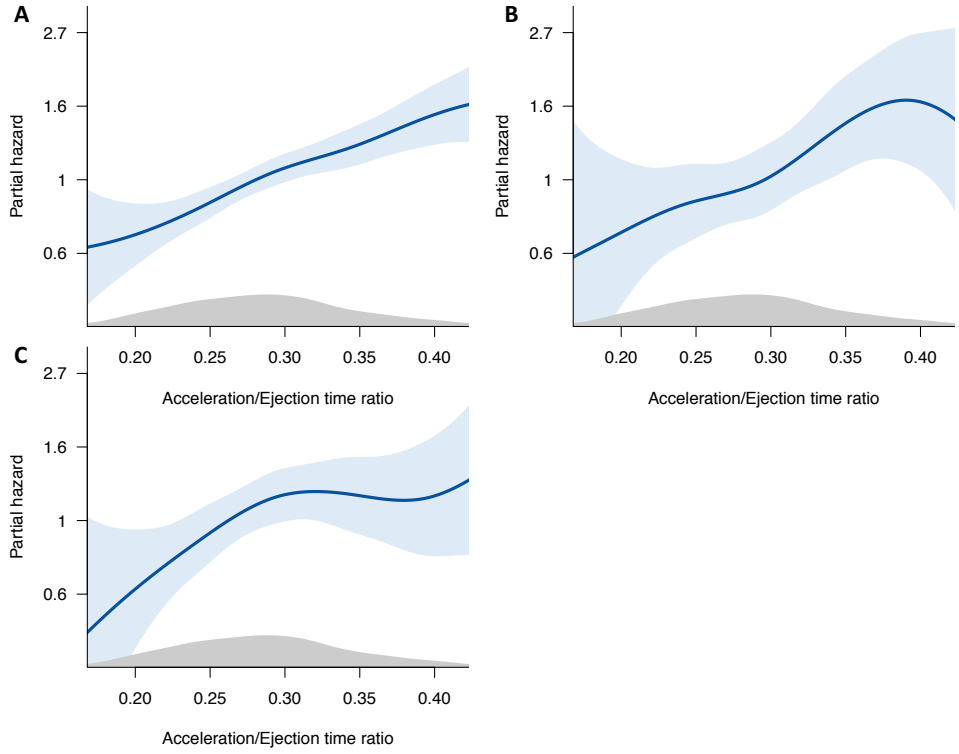
higher AT/ET ratio remained significantly correlated with higher peak aortic jet velocity and LV mass, and with lower LV EF, stress-corrected midwall shortening, and systolic blood pressure, and with presence of low SVi (multiple R^2=0.124, all P<0.05) (Figure 11).

Figure 11. Directed acyclic graph showing the complexity between correlates and confounders of higher AT/ET ratio. The grey boxes indicate the confounders which are adjusted for in multivariable analysis, blue boxes indicate variables which may influence outcome but is not associated directly with increased AT/ET ratio Pink boxes indicate variables which may or may not be associated with outcome, but their association with AT/ET ratio are explained through other variables.



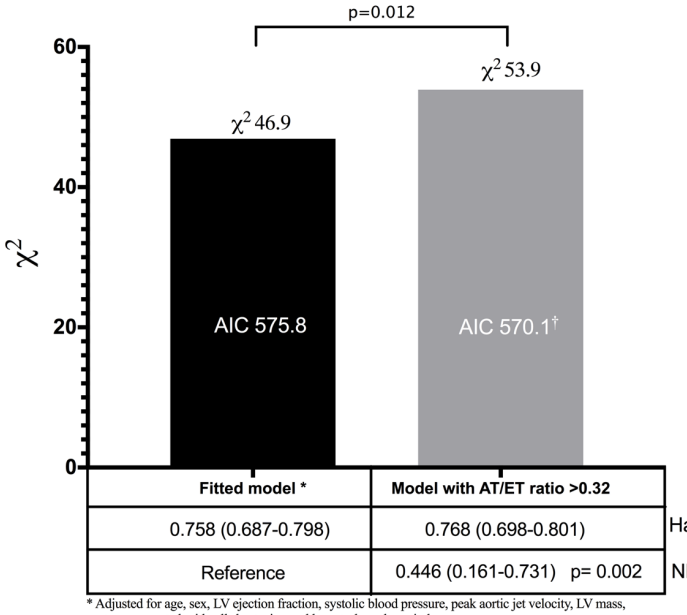
In the total study population, the 4th quartile had a 2-fold higher HR of major CV events (P<0.001), a 2.5-fold higher HR of CV death and HF hospitalizations (P=0.005) and 2-fold higher HR for all-cause mortality (P=0.011) compared to the 1st quartile. All models were adjusted for covariates of AT/ET ratio identified in multivariable linear regression. Additionally, age and sex were forced into the models for adjustment. GAM curves showed an increasing rate of events for higher values of AT/ET ratio but also a lower partial hazard for lower values of AT/ET ratio (Figure 12).

Figure 12. GAM plots showing the partial hazard per value of AT/ET ratio in the total study population for major CV events (A), combined CV death and hospitalization for HF (B) and all-cause mortality (C). All plots are adjusted for peak aortic jet velocity, ejection fraction, left ventricular mass, low SVi, systolic blood pressure, sex and age.



Among the 1530 patients in Study 2, 28.3% (n=433) were found to have PLGAS. Restricting analysis only to include patients with PLGAS, the optimal cut-off for predicting CV death and HF hospitalizations was an AT/ET ratio >0.32. Adding AT/ET ratio >0.32 to a Cox regression model assessing CV death and HF hospitalizations, fitted with the same covariates as mentioned above, yielded a better model-fit by a lower AIC and a significant loglikelihood-ratio test (Figure 13). Model discrimination was assessed by Harrell C-statistics, which yielded slightly higher concordance-value for the model including AT/ET ratio >0.32 (0.758 – 0.768). Additionally, AT/ET ratio >0.32 improved reclassification of patients at risk for CV death and HF hospitalizations (NRI improvement > 0, NRI=0.446 (95% CI 0.161-0.731) in the PLGAS group (Figure 13).

Figure 13. *Bar-plot showing the effect of adding AT/ET >0.32 ratio to a nested Cox regression model assessing CV death and HF hospitalizations among patients with PLGAS. The y-axis shows the overall chi-square distribution for the likelihood ratio test compared to an intercept model. The x-axis shows the fitted model and the model including AT/ET ratio >0.32.*



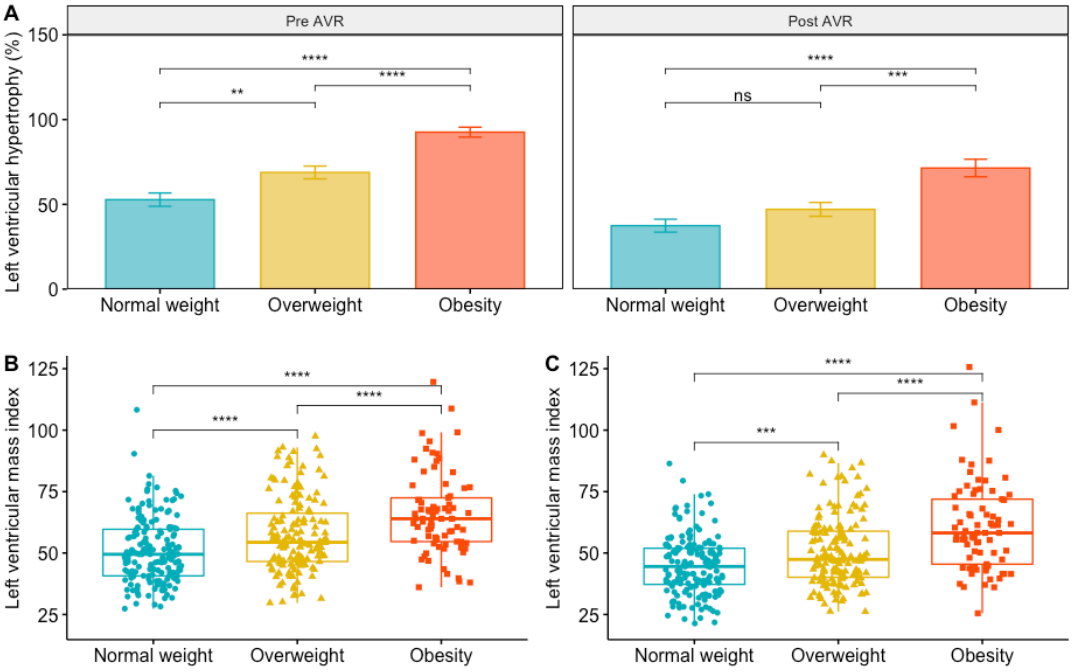
Fitted model *	Model with AT/ET ratio >0.32	
0.758 (0.687-0.798)	0.768 (0.698-0.801)	Harrell´s Concordance ‡ (95% CI)
Reference	0.446 (0.161-0.731) p= 0.002	NRI (95% CI)

* Adjusted for age, sex, LV ejection fraction, systolic blood pressure, peak aortic jet velocity, LV mass, stress-corrected midwall shortening and low stroke volume index.
†Lower values indicate better model.
‡Higher values indicate better model.
AIC=Akaike´s information criterion, NRI=net reclassification improvement.

10.3 Study 3: Impact of obesity on persistent left ventricular hypertrophy after AVR for aortic stenosis

The aim Study 3 was to assess the effect of preoperative obesity on presence of LV hypertrophy following AVR in severe AS patients. A total of 399 patients were included, mean age was 64 years and 64% were male. The participants were grouped according to BMI groups as either normal weight (BMI<25.0 kg m^2), overweight (BMI 25.0-29.9 kg m^2) or obese (BMI ≥30 kg/m^2). Preoperatively, 163 patients were normal weight, 154 were overweight 85 were considered obese. Age, blood pressure, heart rate and serum creatinine were similar across BMI groups (all ANOVA p>0.05). In contrast, the prevalence of hypertension was significantly higher among obese patients (77% in normal weight, 84% in overweight and 89% in obesity, ANOVA p=0.043). Additionally, serum HDL cholesterol level was lower and serum triglyceride level higher in the obese group (ANOVA p <0.001). Obese patients were also less likely to be smokers (26% in normal weight, 21% in overweight and 11% in obesity, ANOVA p=0.038). Patients with obesity had higher LV mass and higher prevalence of LV hypertrophy both pre-and postoperatively (p<0.05) (Figure 14). Obese subjects also and lower prevalence of normal LV geometry compared to normal weighted subjects (p<0.001). Post-AVR, the prevalence of hypertrophy decreased in all groups, but eccentric LV hypertrophy was significantly higher in obese subjects (p=0.006). The prevalence of concentric LV hypertrophy was numerically higher in obese patients post-AVR but did not reach statistical significance (p=0.057) (Figure 15). Mean LV mass reduction post-AVR was similar in all groups. We observed a 11% reduction in LV mass among obese patients, a 10% reduction among overweight patients and a 10% among those with normal weight (p=0.945). Peak aortic jet velocity and mean transaortic pressure gradient across the prosthetic valve did not differ between groups (ANOVA p=0.565 and p=0.281, respectively). The prevalence of patient-prosthesis mismatch was also similar across groups (ANOVA p=0.599).

Figure 14. Prevalence of LV hypertrophy preoperatively and postoperatively (A) and LV mass index preoperatively (B) and postoperatively (C).



In univariable logistic regression analyses, persistent LV hypertrophy post-AVR was significantly associated with presence of obesity, lower midwall shortening and higher systolic blood pressure (all $p < 0.05$). In multivariable logistic regression analysis, persistent LV hypertrophy remained associated with obesity (OR 3.75, 95% CI [2.04 – 6.91], $p < 0.001$), lower pre-AVR midwall shortening (OR 0.90, 95% CI [0.83 – 0.97], $p=0.008$) and higher pre-AVR systolic blood pressure (OR 1.02, 95% CI [1.01 – 1.03], $p=0.003$). Factors which could influence LV mass regression such as age, sex, patient-prosthesis mismatch, post-AVR mean transaortic gradient or duration of days from AVR to follow-up echocardiography were not associated with persistent LV hypertrophy in univariable analyses (all $p>0.05$), and therefore not included in the multivariable model. However, if these variables were forced into the multivariable model, the results remained unchanged. Higher BMI pre-AVR was significantly associated with post-AVR LV mass (Pearson's $r=0.36$, $p<0.01$) (Figure 16).

Figure 15. Prevalence of different types of geometry pre- and post-AVR in obesity, overweight and normal weight.

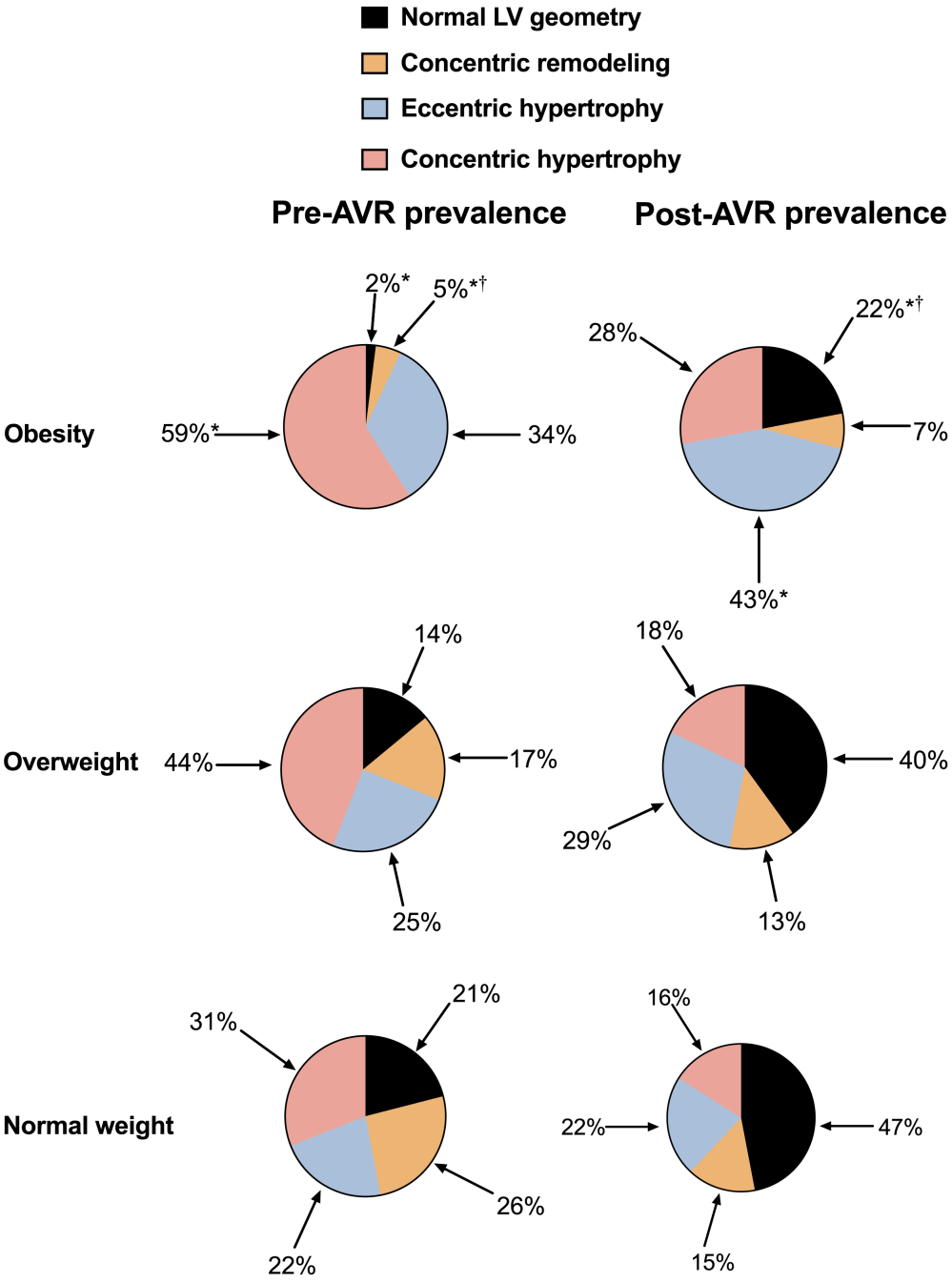
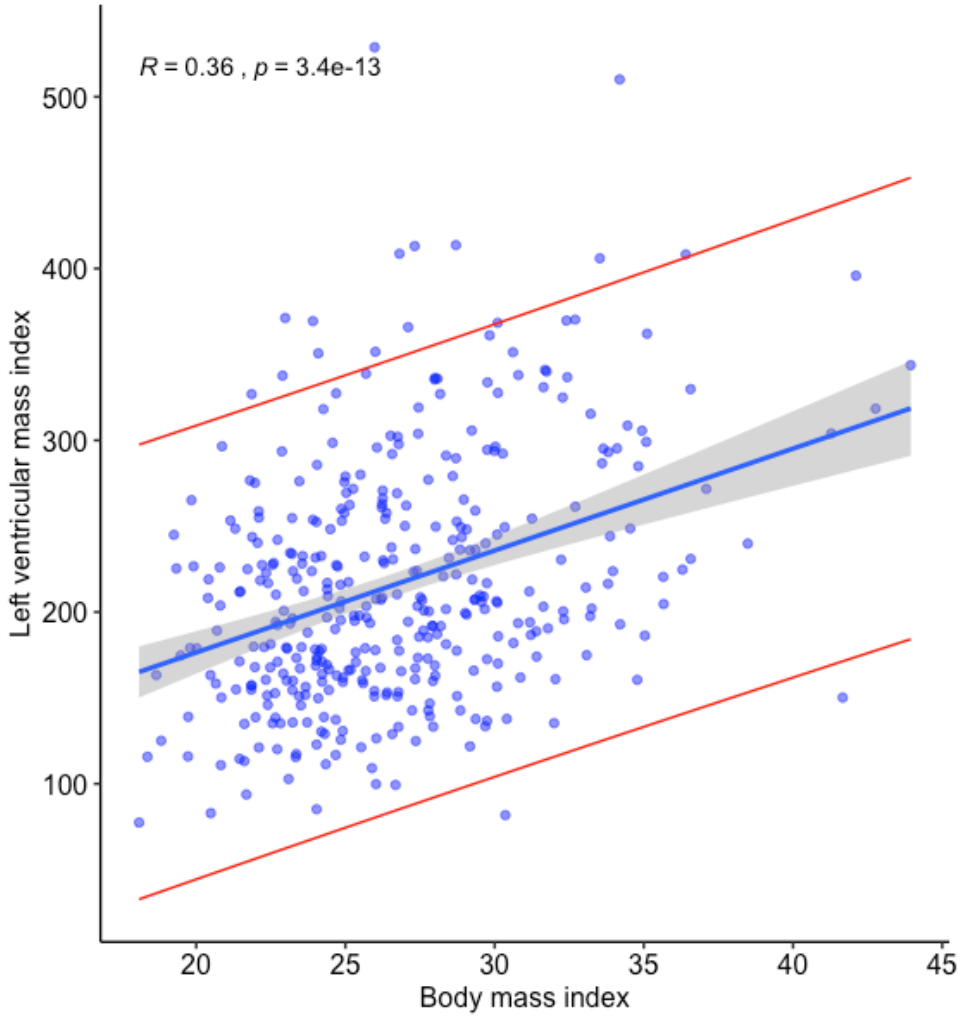


Figure 16 . Correlation between pre-AVR BMI on post-AVR LV mass.



11. Discussion

Optimal risk stratification and therapeutic decision making in AS require early detection of LV dysfunction, accurate grading of AS severity and an integrated assessment of CV risk factors for proper management and referral for timely intervention. The current PhD project studied peak systolic LV function, LV ejection dynamics and obesity in this context. In Study 1, our aim was to investigate if an impairment in EF1 could be detected in patients with preserved EF, and as such be regarded as a marker of early systolic dysfunction. In Study 2, we assessed whether higher AT/ET ratio could identify high-risk subjects among those with non-severe AS, thus providing additional insight in grading of AS severity independent of conventional measures. In Study 3, our aim was to investigate whether obesity could negatively influence lack of improvement in postoperative LV mass regression. The studies included in this thesis have added to current knowledge in several aspects. First, we demonstrate that EF1, a marker of peak systolic function, progressively declines from mild to severe AS and is closely related to myocardial contractility and arterial stiffness. Secondly, higher AT/ET ratio was independently associated with an increased risk of CV death and HF hospitalizations in non-severe AS and in patients with PLGAS. Lastly, we demonstrate that obesity is associated with persistent LV hypertrophy after valvular replacement, a factor known to influence post-AVR morbidity and mortality in these patients.

11.1 EF1 in AS

In AS EF may remain preserved until late in the disease progression. It should be noted that the occurrence of EF<50% in asymptomatic AS patients is rare, with a prevalence of only 0.4%.[25] Indeed, approximately one third of patients with AS and preserved EF have significant evidence of LV systolic impairment when assessed by other methods.[26] Importantly, recent studies have called into question the tradional 50% cut-off proposed by the guidelines. Studies in severe AS have pointed out that those with EF between 50-59% have increased mortality compared to those with EF ≥60%.[90] Capoulade et al. found that the optimal cut-off value for EF to predict all-

cause mortality was 55%, clearly contrasting the threshold of <50% for valvular intervention.[91] Further, gender-specific cut-off values for normal LV EF values (52% in men and 54% in women) are promoted in the general recommendations for echocardiographic chamber quantification.[72] Although these studies show that EF may inherit prognostic value, the current threshold value seems incorrect and may be improved. In this regard, EF1 has emerged as a novel marker of myocardial function that represents the early phase of EF measured at the time of peak aortic jet velocity, reflecting peak systolic function.[46] A previous study has demonstrated the feasibility of EF1 measurements in AS, proposing a cut-off <25% as a predictor of poor prognosis, assessed from combined AVR, HF and all-cause mortality.[49] Importantly, EF1 was a better predictor of outcome than LV myocardial long-axis function measured by global longitudinal strain, which has been shown to be a better predictor of outcome than LV EF in both severe and moderate AS.[38,39] The rational of measuring EF1 early in systole as opposed to EF at end-systole, is that at peak myocardial contraction occurs predominantly in the first part of systole. As demonstrated by our results the most important correlate of EF1 was strain rate, a marker closely related to myocardial contractility. Even though strain rate may not directly measure myocardial contraction per se, a close relationship between strain rate and load independent markers of contractility have been demonstrated in experimental studies in animals.[92,93] EF1 was also closely related to AT, as expected, since it has been demonstrated that strain rate and peak aortic jet velocity are almost simultaneous events during the cardiac cycle.[94] These events coincide with peak myocardial wall stress which occur in early systole to fascilitate LV relaxation.[95] EF1 was more related to all measures of peak systolic function such as peak systolic annular velosity (S`), AT and strain rate compared to end-systolic markers such as EF, global longitudinal strain and SV. Taken together this suggest that EF1 should be regarded as a marker of peak systolic function in AS. This is of importance as events in early systole may be less load dependent, and thus more sensitive to contractile changes in the myocardium. It has been demonstrated in healthy subjects that peak systolic indices, such as strain rate and peak S`, are considerably more affected by inotropic alterations than end-systolic measures.[96] Events at end-systole, on the other

hand, are measures of the total systolic workload performed by the LV during ejection. This may not represent peak systolic function since maximal load is reached at end-systole.

Weideman et al. showed in a porcine model that global longitudinal strain was more related to SV and EF, while strain rate was more related to invasive measures of contractility.[97] In the same study, the authors showed that strain rate remained constant during an increase in heart rate, suggesting that it is relatively independent of heart rate variations.[97] Similarly, we found no correlation between heart rate and EF1 or strain rate, while SV and ET where were negatively associated with higher heart rate. In cases of high heart rate, these findings might be explained by the Bowditch effect or force-frequency relation.[98] This implies that a faster stimulation may increases the force of contraction, which may maintain EF1 but decrease SV due to a decreased ejection duration and reduced venous return.

Strain rate has been shown to be affected by pre-and afterload,[99] but to a considerably lesser degree than global longitudinal strain.[43] Thus, the same is to be expected of EF1. In a study by Dahle et al. strain rate was significantly associated with changes of the time of maximum rate of LV pressure rise (dP/dt max) during isovolumetric contraction time.[43] dP/dt max is considered a reasonable marker of contractility largely independent of afterload, although effected by preload by length dependent activation of myocardial fibers. With reduced contractility, a diminished rate of dP/dt max results in a prolongation of isovolumic contraction time and the pre-ejection period.[100] One would expect that reduced force generating capabilities in the isovolumetric phase may continue in early systole, prolonging AT and reducing EF1. Some of the unexplained variance in EF1 from our study could therefore be explained by the systolic timing events occuring prior to ejection.

In our study, EF1 was not significantly correlated with overall EF in univariable analysis. Even though they both primarily represent cavity deformation and endocardial displacement during systole, EF1 seem to decline at an earlier stage than overall EF. This suggest that EF1 in early systole may differ from overall EF. It is well known that geometrical remodeling, a frequent occurrence in AS, may

preserve overall EF despite reduced contractility.[29] In a mathematical model, EF was shown to be unaffected by a reduction in longitudinal shortening by compensatory changes in circumferential strain or wall thickness.[30] In the same study, Stokke et al. demonstrated that higher wall thickness and smaller LV chamber volumes may maintain EF >50% despite significantly reduced longitudinal and circumferential shortening.[30] In line with this, other have also shown that circumferential strain contributes twice as much to EF compared to longitudinal strain.[101] This may explain the clinical finding that some AS patients with low flow low gradient display pronounced concentric remodeling with small cavity size and impaired longitudinal function by peak S`, despite preserved EF.[102] In line with this, we found that both peak S` and EF1 were lower in patients with severe compared to mild AS, despite preserved EF. Patients with a low EF1 had visually less displacement of the mitral annulus in early systole, explaining the correlation between a higher EF1 and higher peak S'. In contrast, we were unable to demonstrate a significant difference between global longitudinal strain across groups of AS severity, although there was a trend towards lower strain in patients with severe AS. In larger studies, lower global longitudinal strain has been reported in asymptomatic severe AS.[103] Thus, our finding should be interpreted with caution and in the context of the existing body of literature. A reduction in longitudinal shortening prior to a reduction in circumferential shortening may be observed in AS because the subendocardial fibers of the LV, which are mainly oriented in the longitudinal direction, are more sensitive to ischemia. This may occur due to the increasing mismatch between subendocardial blood flow and oxygen demand as a results of increasing wall thickness and wall stress.[104] Subsequently, fibrotic changes may first appear in the subendocardium and affect longitudinal shortening at an earlier stage of the disease.[104] Events in early systole may therefore be more related to longitudinal rate of shortening, while end-systolic events and EF may be more related to circumferential shortening in the midmyocardium and LV geometric remodeling.

In two retrospective studies, EF1 was the most powerful predictor of combined AVR and all-cause mortality independently of global longitudinal strain.[49,105] Taken together, these results suggest that EF1 may be a more sensitive marker of early

systolic dysfunction, but the results need to be validated in prospective studies in the future.

The association between EF1 and arterial function

In Study 1, an important covariate of EF1 was PP/SVi, a measure of arterial stiffness, which has documented prognostic value in AS patients.[106] Experimental studies have suggested that arterial stiffness could lead to reduced coronary flow and subendocardial fibrosis even in the absence of coronary artery disease.[107] Furthermore, arterial wave reflections have been associated with greater extracellular mass in patients with severe AS.[108] In a magnetic resonance study by Bing et al. lower EF1 was significantly associated with more fibrosis detected by late gadolinium enhancement and higher indexed extracellular volume, representing focal replacement fibrosis and diffuse interstitial fibrosis, respectively.[105] In their study, the main determinant of a low EF1 following AVR was infarct-related, non-reversible replacement fibrosis.[105]

Similar to crude measures of arterial stiffness, backward traveling reflection waves arrive earlier in patients with higher central PP compared to those with lower central PP.[109] In patients with arterial stiffness backward wave reflections may arrive in mid-to late systole rather than in diastole, further boosting central systolic blood pressure, increasing the myocardial oxygen consumption and lowering the ischemic threshold of the myocardium.[110] A loss of diastolic pressure may further contribute to myocardial oxygen mismatch due to reduced coronary perfusion. It is therefore possible that the observed association between PP/SVi and EF1 might be mediated through early wave reflection induced ischemia which facilitates development of fibrosis when persisting over time.[108]

However, since PP/SVi is derived from a Windkessel model it does not explicitly account for wave propagation and reflections.[87] In our study, the association between EF1 and PP/SVi was primarily driven by a higher central PP. In the population based Strong Heart Study of 3,520 individuals, noninvasively determined central PP was a better predictor of vascular hypertrophy, atherosclerosis, and CV events than brachial blood pressure.[111] For this reason we estimated the central PP by a validated formula,[87] and found a better correlation between EF1 and

central PP compared to brachial PP. Several large studies in non-AS patients have documented the importance of increased PP as a risk factor for CV events.[112,113] Central PP has been thought to be mainly determined by stiffness of the aorta, which is amplified by age-related arterial stiffening.[114] In hypertensive patients increased aortic stiffness, measured as aortic characteristics impedance, was the major determinant of higher PP.[115] Because most of the central pressure rise is achieved during early systole, attributable to the forward pressure wave, aortic impedance and not wave reflections may influence peak wall stress and EF1 to a larger degree.[108] Since the first shoulder of the forward pressure wave coincide with peak aortic flow, the correlation between EF1 and PP/SVi could be mediated through the interaction between these two phenomena. However, the determinants of the forward pressure wave and central PP are not only influenced by arterial stiffness and aortic stiffness, but also by time-dependent LV ejection and SV.[116,117]

In a recent study by Li et al., investigating the hemodynamic effects of age-related increases in central PP among women, the authors measured time-dependent LV ejection volumes at the peak of the first shoulder of the forward pressure wave, equivalent to EF1, and LV volume at the peak of the second shoulder, compromising the sum of the forward and backward reflecting pressure waves. They found that a substantial component of the increase in central PP with age was due to an increase in augmentation pressure. The increase in augmentation pressure was best explained by the ratio of the LV ejection volume at the time of the second pressure wave to the aortic jet velocity at the first shoulder.[117] This would be equivalent of a change in the ejection pattern similar to what is observed for EF1 in our study, with a lower ejected volume at EF1 in early systole and a greater proportion of ejected volume occurring later in systole, after the time of EF1. The authors propose that this could be explained by a reduction in EF1, which could sustain ejection to maintain overall EF and SV in cases with afterload excess through a reverse of the shortening deactivation phenomenon.[46,117] The independent association between EF1 and PP/SVi in our study could therefore be mediated through reverse causality, where a lower EF1 would influence central PP by the aforementioned mechanism. However, since both our

study and the study by Li et al. were cross-sectional and observational by nature, these studies are merely hypothesis generating.

An association between EF1, arterial stiffness and ischemia could arise by the fact that myocardial wall stress has been shown to be a time-dependent phenomenon.[95] Peak oxygen consumption is thought to relate most to peak myocardial wall stress which occur in early systole.[118,119] This may correspond to the time of EF1, especially when AT is significantly prolonged. Peak wall stress is also more dependent on the impedance of the aorta and systemic vasculature than wave reflections.[120] Since myocardial wall stress is dependent both on pressure, wall thickness and LV cavity size, as expressed by the law of Laplace, a less dynamic reduction of LV cavity size in early systole, or a lower EF1, will fail to reduce wall stress relative to pressure. This may further contribute to increased myocardial oxygen demand independent of wave reflections. Arterial stiffness in itself contributes to higher end-systolic wall stress, which increases LV remodeling, fibrosis, and impairs LV relaxation.[110] A lower EF1 was in our study was significantly correlated with higher end-systolic wall stress, but when adjusting for PP/SVi this association was attenuated. This suggests that increased wall stress may be associated with lower EF1 downstream from the deleterious effects of increased arterial stiffness. Interestingly, increased arterial stiffness or reduced systemic arterial compliance have been associated with increased mortality both in hypertension and in patients with AS.[87,106] One may speculate that EF1 might yield prognostic information in AS patients with concomitant arterial stiffness.

EF1, global LV load and diastolic dysfunction

In AS, hypertension and arterial stiffness are highly prevalent, especially in elderly subjects.[121] Zva estimates the overall LV afterload caused by the combined valvular obstruction and arterial load.[122,123] Increased Zva predicts impaired outcome in several studies involving AS.[122,123] A high global LV load increases maladaptive LV remodeling and has been associated with a low flow state.[124] Similar to our findings, the study by Bing et al. found that a lower EF1 was significantly associated with higher Zva.[105] Taken together, EF1 does show some afterload dependency. With a similar stepwise regression procedure as us, Bing et al. found in their study that Zva,

indexed extracellular volume and infarct-related late gadolinium enhancement only explained 25 % of the variance in EF1. In our study, strain rate was the major determinant of EF1 and our model in total predicted considerably more of the variance in EF1 (40%). This suggest that a low EF1 is not only caused by an afterload mismatch, but also reflects an impairment in intrinsic myocardial systolic contractility. This may explain why some patients with mild and moderate AS also had lower values of EF1. Known coronary artery disease was an exclusion criterion by design in our study. However, since coronary angiography was not conducted as a part of the study protocol and concomitant coronary artery disease is common in AS patients, we cannot exclude the possibility that subclinical coronary artery disease could contribute to reduced EF1 in mild and moderate AS.

Gu et al. have documented that EF1 may be impaired in hypertensive patients with diastolic dysfunction.[46] We corroborate these findings by demonstrating a linear relationship between higher filling pressure, estimated by the E/e' ratio, and lower EF1. When we analyzed EF1 as a dichotomous variable with a previous proposed cut-off of <25%, there was a univariable association between diastolic dysfunction and lower EF1. However, this association was attenuated when we adjusted for strain rate and peak aortic jet velocity. This may partly be explained by the fact that only 25 patients in Study 1 had low EF1. It may be difficult to retain significant associations in multivariable adjustments when the numbers are low.

The association between EF1 and diastolic function could occur as a consequence of impaired shortening deactivation. In the normal heart, shortening deactivation refers to the reduced capacity of activated myocytes to further develop force after shortening. Shortening deactivation increases relaxation after onset of contraction and allows for early filling of the LV in diastole. Only sustained force development may allow for continued fiber shortening. Increased tension during systole may therefore prolong ejection but slow shortening velocity.[125] With an increase in late systolic load, sustained force development may preserve overall EF, but at the expense of impaired diastolic relaxation.[126] In AS, ejection duration usually increases with AS severity. In our data, higher ET was significantly associated with higher SV, but lower EF1, strain rate and peak S`. By contrast, EF and global

longitudinal strain remained unchanged by a longer ET. A lower EF1 and events in early systole could therefore be closely related to end diastolic events. In our study, there was a significant relationship between higher left atrial volume index and lower EF1, which persisted after adjustment for aortic jet velocity, arterial stiffness, global longitudinal strain, age, LV mass and gender, but not when adjusting for strain rate.

11.2 Ejection dynamcis in AS

The natural history and poor prognosis of severe AS have been well documented. However, moderate AS may also inherit poor prognosis.[20] Patients with moderate AS usually present with many CV risk factors, and have significantly increased mortality compared to the general population.[127] Most recently, in a large study of 122,809 male (mean age 61 ± 17 years) and 118,494 female patients (mean age 62 ± 19 years) from Australia, Strange et al. reported a 5-year mortality of 56% in untreated moderate AS.[22] In a Veterans Affairs cohort, 63 deaths were observed among 104 individuals with moderate AS during a mean follow-up period of 1.8 years.[128] Coexistence of moderate AS and LV dysfunction is not uncommon and heralds poor outcome and high risk of clinical events.[129] In a French population including patients with moderate AS and EF ≥50%, mortality rates were 13%, 28%, and 47% at 1, 3, and 6 years, respectively.[127] Similar results were shown in patients with moderate AS and EF ≥50% in a study by Zhu et al., which demonstrated that impaired global longitudinal strain was associated with worse survival outcomes in both those who underwent AVR and in those who received conservative treatment.[39]
Recent evidence suggests that a decline in EF may start before the AS becomes severe, with the decline accelerating after the AVA reaches 1.2 cm. [90] Taken together, this underlines the importance of detecting early LV dysfunction, and demonstrates that the prognosis in some patients with moderate AS is poor, despite an EF above 50%.

This provokes the idea that some AS patients might benefit from AVR at an earlier stage than currently recommended by the guidelines.[16,17] Kang et al. showed that in patients with asymptomatic severe AS (peak aortic jet velocity≥4.5), currently

deemed outside the guideline recommendations for valvular intervention, those who received early AVR had significantly lower CV mortality compared to those who received conservative care.[23] Moreover, in patients with normal flow and low transvalvular pressure gradient, a phenotype classified as moderate AS by the European guidelines, AVR significantly improved survival compared to conservative treatment.[130] Accordingly, it might be time to reconsider its indication in selected patients with moderate AS.

Recent studies suggest that AT/ET ratio may be an angle independent marker that correlates with AS severity. In smaller studies, higher AT/ET ratio predicts mortality in patients with moderate-severe AS and in patients with low-gradient severe AS.[55,56] LV ejection dynamics may therefore improve detection of high-risk individuals among patients with discordantly graded AS or moderate AS with subclinical systolic dysfunction.

It is well known from early studies that a prolongation of the ET occurs with increasing AS severity.[131] In more recent times, two different studies reported that AT increases in parallel with AS severity,[132,133] which is consistent with the well-recognized physical finding of a late peaking murmur in severe AS. Bermejo et al. who studied Doppler spectrograms in 15 patients with AS and 10 control subjects, suggested that a slow end-systolic opening of the aortic valve was more often observed in patients with AS than in controls.[52] This may be visualized by a rounded contour of the systolic aortic flow waveform by Doppler with the peak moving towards mid-systole in severe AS, compared to a more triangular shape in less severe AS. The current guidelines on native AS state that the shape of the aortic flow waveform may be helpful when assessing AS severity.[16] However, the AT/ET ratio quantifies this relationship, making it considerably more useful in clinical practice. So far, the AT/ET ratio has been incorporated in the echocardiographic evaluation of prosthetic aortic valve function, but not in the assessment of native valve AS.[134] The clinical application of the AT/ET ratio was first demonstrated by Ben Zekry et al., in their study an AT> 100 milliseconds and an AT/ET ratio >0.37 was predictive of prosthetic valve obstruction.[53] In a study of 108 patients with native mostly severe symptomatic AS, an AT/ET>0.35 had a sensitivity of 77% and a specificity of 100%

to discriminate between symptomatic and asymptomatic patients.[135] The same optimal AT/ET cut-off of >0.35 was also able to reasonably differentiate severe AS from mild or moderate AS (sensitivity 59%, specificity 86%) in a small AS population.[136] The association of higher AT/ET ratio with increased mortality in native severe AS was reported by Ringle Griguer et al.[55] In their study of 456 patients, higher AT/ET ratio was associated with symptoms and an AT/ET ratio >0.36 predicted increased mortality. In contrast to the population in paper 2, their study included patients with high co-morbidity, including diabetes, atrial fibrillation and coronary artery disease. Thus, our study extends their findings into a large cohort of AS patients without diabetes and overt CV disease and presumably non-severe AS. The finding of a lower prognostic threshold value for AT/ET ratio in our study, compared to previous studies, probably reflects that our study population had less severe AS, as AT/ET ratio increases in parallel with AS severity. Interestingly, the optimal prognostic threshold value of AT/ET ratio >0.32 identified in our cohort, corresponds to the recommended cut-off value to distinguish between mild and moderate prosthetic valve obstruction.[134] Further, the threshold of an AT/ET ratio >0.36 proposed by Ringle Griguer et al. is rather similar to the recommended threshold value of >0.37 used to discriminate between moderate and severe prosthetic valve obstruction.[134] Taking a closer look at the GAM plots from Study 2, it is apparent that not only higher AT/ET ratio is associated with an increased risk, but also lower values seems to be associated with a lower rate of all endpoints investigated. In light of previous work, it may seem that an AT/ET ratio <0.32 is highly suggestive of milder AS severity, while an AT/ET ratio >0.36 may be used to identify high-risk subjects among those with severe AS.

ET is not only increased in AS, but also increases in relation with higher age, hypertension, arterial stiffness and diastolic dysfunction.[125,137,138] Increased ET (≥ 320 ms) by impedance cardiography was shown to be a reasonable screening tool for diastolic dysfunction with a sensitivity of 90.2% and positive predictive value of 76.6% among patients with hypertension.[139] Weber et al. observed a prolongation of the ET indexed for heart rate patients with diastolic dysfunction.[125] In a study

investigating LV adaptations during ageing in healthy subjects, there was an increase in ET with higher age. In this study age and diastolic E/A ratio by Doppler were the independent determinants of increased ET indexed for heart rate.[140] In animal studies of senescence the duration of contraction and relaxation is prolonged.[141,142] An increase in afterload during active contraction may prolong the duration of systole and slow relaxation.[143] Considering that the first phase of diastole is dependent on active relaxation, the duration of diastole depends not only on heart rate but also to some extent on the duration of systole. Sustained contraction must imply a relative abundance of calcium. Accumulation of calcium at the onset of diastole may impair LV diastolic relaxation and early diastolic filling. This may maintain SV, but at the expense of diastolic filling.[144,145] An increase in ET may therefore be an adaptive mechanism in the early phases of AS. Since ET varies inversely with heart rate and directly with SV,[146] estimation of transvalvular flow rate (SV/ET) rather than SVi may be more appropriate to identify low flow in AS. Transvalvular flow rate has been shown to predict outcome in several AS populations.[147-149] This has the advantage of representing the systolic flow across the valve, which could be reduced in the setting of a prolonged systolic ejection period, even with a normal SV. This underlines the importance of evaluating timing of systolic events in AS.

LV ET is sensitive to inotropic alterations and preload. It can be observed that there is a delayed onset of ejection and that ET shortens when systolic failure occurs.[150,151] Similarly, in patients with severe AS who develop LV systolic dysfunction, the ET tends to be less prolonged compared to patients with AS and preserved LV systolic function.[152] This suggests that both shortening as well as a prolongation of the ET is associated with an impaired prognosis, which may explain the u-shaped relationship between mortality and ET observed in a large study of patients with coronary artery disease.[138] In our cohort of presumably non-severe AS, ET was significantly lower in those with higher AT/ET. Higher AT/ET ratio was also significantly associated with lower stress-corrected midwall shortening, suggesting that both lower ET and a higher AT/ET ratio may imply early systolic dysfunction. This may partly explain why those with higher AT/ET ratio had higher rate of CV death and HF hospitalizations independent of AS severity.

Deterioration of LV systolic function is characterized by a decreased rate of LV pressure rise (dP/dt) during the isovolumetric contraction period.[100] When preload reserve is exhausted and progressive systolic dysfunction occurs, SV declines and cardiac output becomes heart-rate dependent. This may not only shorten the ET, but may increase the pre-ejection period.[153] The pre-ejection period is defined as the time interval from the Q-wave of the electrocardiogram until the onset of ejection. This is equal to the electromechanical delay plus the isovolumic contraction time. Therefore, changes in the pre-ejection period are largely dependent on isovolumic contraction time, which increases in HF. Weissler and colleagues demonstrated in 1968 that patients with HF had significantly shorter ET and longer pre-ejection periods compared to normal individuals at any given heart rate.[153] More recent studies have confirmed that the pre-ejection period/ET may be a useful index of overall LV performance that correlates well with overall EF, global longitudinal strain and dP/dt max.[100] Even though we did not measure the pre-ejection period but rather the AT, one would expect that a diminished rate of LV pressure rise during the isovolumetric contraction period could continue in the early phases of systole and prolong the AT. A prolongation of the AT is likely to occur as a direct effect of valve obstruction, but may also reflect systolic dysfunction with reduced ability of the LV to generate force. An early peak of AT is found in healthy individuals, with the peak occurring before mid-systole as opposed to patients with severe AS. Higher AT may therefore be considered as a combined marker of reduced contractility and valve obstruction. This might be of particular relevance in low-flow states, where AT and the AT/ET ratio may be increased in non-severe AS because of the lack of LV ejection force to open the valve despite only mild or moderate calcification. From a hemodynamic standpoint, an early peak of AT may reduce energy dissipation compared to a late peak, as demonstrated in vitro by Hatoum et al.[154] Ejection dynamics may in itself control some of the energy efficiency of the aortic valve. When acceleration is slower, more energy dissipation occurs. This may to some degree determine the formation and strength of vortices in the aorta, which suggest that a delayed AT in AS is not compensatory.[154,155] In some patients with discordantly graded AS, and often small aortic roots, kinetic energy loss may occur downstream from the valve

due to the pressure recovery phenomenon. In these patients one would expect that AT would be longer, since a late peak is associated with higher energy dissipation.

In Study 2, we observed that the AT/ET ratio was directly correlated with higher AS severity. Across quartiles there was a larger difference in AT between groups compared to the difference in ET which was lower in the higher quartiles. On the other hand, in Study 1, we found no difference in ET across mild to severe AS. In Study 1, we also observed that AT in itself was significantly increased from mild to moderate and severe AS, confirming previous observations.[133] This suggests that since both AT and ET is prolonged in compensated AS, the observation of a higher AT/ET ratio with increasing AS severity is explained by a longer AT relative to the ET.

An important limitation of both AT and ET is that they are both heart rate dependent. A faster heart rate implies shorter AT, regardless of AS severity. The AT/ET ratio may to a certain degree reduce this limitation by dividing the AT by the ET, canceling out the effect of heart rate. In Study 2, there was a low but significant association between higher heart rate and lower AT/ET ratio in univariable analysis. When we adjusted for possible confounders this association became non-significant. However, since heart rate was within normal limits in our study, the AT/ET ratio should be interpreted with caution in patients with tachycardia.

In linear regression in Study 2, higher AT/ET ratio was correlated with several risk factors that have been shown to predict outcome both in severe and non-severe AS. These included higher LV mass, systolic blood pressure and markers of LV myocardial dysfunction. Importantly, higher LV mass has been shown be an important predictor of outcome in the SEAS population.[156] The link between higher AT/ET ratio and increased LV mass is likely to be mediated through increased midwall fibrosis in the non-contractile component of the myocardium, which contributes to LV dysfunction when LV hypertrophy progresses.[157,158] Usually, development of LV hypertrophy may in the early stages of AS adapt to the increased afterload to maintain wall stress and cardiac output, but largely reflects co-morbidities like hypertension, arterial stiffness or obesity rather than the valvular stenosis itself.[159,160] However, in some patients a disproportionate increase in LV

mass relative to wall stress may occur, a condition called inappropriately high LV mass. In a study by Cioffi et al., inappropriately high LV mass shared many of the same covariates as higher AT/ET ratio, including lower stress-corrected midwall shortening.[161] Interestingly, the coexistence of hypertension did not influence either the prevalence nor magnitude of inappropriate LV mass in a cross-sectional study from the SEAS population, possibly reflecting the high prevalence of hypertension in this study cohort.[162] In those with inappropriately high LV mass, indices of afterload and contractility were actually lower while RWT was higher, despite similar degrees of AS severity.[162] This makes an argument that structural changes may explain reduced contractility in these patients. This offer an explanation to why higher AT/ET ratio was associated with higher LV mass independent of AS severity.

In accordance with previous results,[163] higher AT/ET ratio was associated with lower systolic blood pressure in Study 2. The occurrence of either systemic hypertension or reduced arterial compliance have in a combined experimental and clinical study shown to reduce the transaortic mean pressure gradient and peak aortic jet velocity independent of flow status.[164] With regards to AT/ET ratio, higher afterload and wave reflections during the systolic phase could induce compensatory lengthening of the ET, which would lower the AT/ET ratio.[125,165] This may also result in systolic flow deceleration and induce shortening of AT, as observed in a study measuring AT during exercise and rest in healthy subjects.[166] A study in healthy young and elderly subjects showed that there exists an inverse relation between higher carotid-femoral pulse-wave velocity and ET, which persist through all age-categories independent of heart rate.[167] However, in their study, the contribution of ET explained only 2-5% of the variance in pulse-wave velocity. Additionally, mean systolic blood pressure in all age-categories were within the normotensive range. This suggests that these results cannot be extrapolated to our elderly hypertensive AS patients. Further studies are therefore needed to elucidate the mechanisms behind lower systolic blood pressure and higher AT/ET ratio.

Kadem et al. showed that hypertension may reduce the transaortic mean pressure gradient and peak aortic jet velocity, contributing to discordant AS grading.[168] An increase in LV afterload may lower mean transvalvular gradient

through a decrease in LV contractility, SV and transvalvular flow.[169] However, a lower AT/ET ratio due to afterload driven decrease in SV is unlikely, as low flow was associated with higher AT/ET ratio independent of systolic blood pressure in our cohort. Kadem et al. offer a different explanation by speculating that in AS the aortic root may expand as aortic pressure increase, resulting in an increase in AVA irrespective of flow rate.[168,170] A slight increase in AVA due to aortic root expansion might offer less resistance to the aortic flow, easing acceleration, lowering AT and thus the AT/ET ratio. In our study, there is a possibility that study site physicians recognized those with higher AT/ET ratio as more high-risk individuals. These patients tended to have more severe AS by conventional measurements, higher prevalence of low flow and higher burden of moderate-severe valve calcification. As such these patients might have been treated more aggressively with antihypertensive treatment. To some degree this was accounted for, since we adjusted for AS severity in multivariable analysis. Despite this, we cannot exclude that hypertension treatment bias may partly explain the association between higher systolic blood pressure and lower AT/ET ratio, since we did not have detailed information on in-study changes in hypertension management.

As recommended by the guidelines AS severity, and probably also AT/ET ratio, should be reassessed when systolic blood pressure is normalized.[16] However, antihypertensive treatment may often fail to normalize arterial compliance or blood pressure in elderly subjects despite appropriate treatment. An important finding from our study is therefore that higher AT/ET ratio seems to predict increased risk of CV events independent of systolic blood pressure or hypertension. Consequently, AS patients with hypertension and high AT/ET ratio may be a particular high-risk group.

The role of increased AT/ET ratio in patients with PLGAS

Therapeutic decision making remains difficult in discordantly graded AS like PLGAS. The 2014 American Heart Association/ American College of Cardiology (AHA/ACC) valvular disease guidelines acknowledges that there exists a high prevalence (5% to 25%) of low-gradient severe AS in patients with preserved LV EF. This low-gradient entity may raise uncertainty regarding the actual severity of the AS and the potential indication for AVR if the patient is symptomatic. Precise grading is

of particular importance if the patient presents with dyspnea, which alternatively may originate from comorbidities such as chronic obstructive pulmonary disease, obesity, hypertension or coronary artery disease, and not from the AS itself. At present, the current European guidelines regard patients with normal flow-low gradient as moderate AS.[16] Studies focusing on the natural progression and risk in patients with paradoxical low flow-low gradient or normal flow-low gradient (together comprising the entity of PLGAS) have shown conflicting results. One study suggested that during follow-up, most patients with PLGAS may develop adverse concentric remodeling and low-flow before the development severe AS.[171] In the SEAS study, PLGAS patients showed the same rate of outcome as patients with moderate AS.[172] On the contrary, some propose that PLGAS should be considered a more advanced disease stage, more akin to HF with preserved EF.[173,174] Even though the debate on how to manage these patients is still ongoing, a meta-analysis from Dayan et al. concluded that PLGAS was associated with increased risk of mortality compared to other subtypes of AS.[27] Improved identification of high-risk patients among those with PLGAS is therefore of utter importance. However, conflicting results have been noted, with some studies reporting no benefit of AVR among patients with PLGAS. These studies suggested that those with normal flow low gradient should be regarded as low risk patients.[102,175,176] On the contrary, recent data from the PARTNER 2 trial, consisting of 3511 patients with AS, found that outcomes after AVR were equally good in patients with PLGAS as in those with high-gradient severe AS.[177] In the same study, similar rates of the primary outcome was observed among PLGAS and high-gradient severe AS.[177] However, the PARTNER 2 trial included symptomatic AS patients, and a direct comparison between our asymptomatic population should be done with caution. In line with previous literature, patients with PLGAS in our cohort included more women with smaller LV cavities, more concentric LV remodeling, lower LV myocardial function and higher prevalence of low flow compared to the total study population. Of note, an AT/ET ratio>0.32 improved identification of high-risk patients among those with PLGAS, independent of these prognostic factors. Our results expand previous observations in symptomatic PLGAS patients with multimorbidity into asymptomatic PLGAS patients without diabetes or CV disease.[56]

In our cohort of PLGAS patients, both those with normal flow and low flow were included. Since low flow is a strong predictor of worse outcome in AS,[178,179] an important finding from our results is that an AT/ET ratio >0.32 predicted increased risk of CV death and HF hospitalizations independent of low flow. It is well known that discrepancies between AVA and mean transaortic pressure gradient may arise because of low flow.[180] Hence, in the presence of low flow there may not be sufficient power to generate a pressure difference that exceeds the threshold of severe AS despite a low effective orifice area. Estimation of AT/ET ratio may improve identification of high-risk subjects since it increases with low flow. Consideration of systolic ET in AS may be of importance in patients with discordant AS grading, as a study by Kadem et al. found that a modification of ET could translate into a difference in mean transvalvular gradient of 15 mmHg independent of SV.[181]

Other possible mechanisms for discordant grading may include measurement errors, small body size, but also inherent inconsistencies in the guideline criteria. In a large study by Minners et al., the current threshold of an AVA of 1.0cm^2 as a cut-off to define severe AS, corresponded more precisely to a mean transaortic pressure gradient of 30-35 mmHg rather than the currently used threshold of 40 mmHg as a definition of severe AS.[182] Compared to measurement of transvalvular gradients, AT/ET ratio may be less angle-dependent, as the absolute values of peak and mean pressure gradients may be lowered by incorrect angulation, but the timing of events (AT and ET) may remain the same.

Other approaches to classify high-risk PLGAS patients may include evaluation of serum biomarkers,[183] low-dose dobutamine echocardiography,[184] and aortic valve calcium score by multidetector computed tomography.[185] In our study population computed tomography was not included as a part of the study protocol. Several studies have validated a simpler approach by assessing aortic valve calcification by echocardiography, which was used in the present study.[13,186] As demonstrated by Cramariuc et al., moderate-severe calcification by echocardiography was associated with higher CV event rate in both sexes, and with higher all-cause mortality in men.[187] In the present study, higher AT/ET ratio was significantly associated with

presence of moderate-severe calcification by echocardiography in univariable analysis. In multivariable analysis, this relationship became non-significant, probably due to high collinearity between peak aortic jet velocity and calcium score. Nonetheless, an independent correlation between higher AT/ET ratio and higher calcium score by computed tomography has been reported by others.[163] Since calcium score is a flow-independent marker of AS severity, a correlation between higher AT/ET ratio and higher calcium burden may contribute to the prognostic value of higher AT/ET ratio.

11.3 Obesity and persistent LV hypertrophy after AVR

During progression of AS, an increase in LV mass is due both to cellular hypertrophy and development of myocardial fibrosis. While cellular hypertrophy and diffuse fibrosis may regress after valvular replacement, midwall replacement fibrosis on the other hand seems irreversible, and may hinder cardiac remodeling after AVR.[188,189] Myocardial replacement fibrosis in patients with severe AS has been proposed as a cause of persistent LV diastolic dysfunction and symptoms after AVR, and is closely linked to increased mortality during postoperative follow-up.[104,190,191] Lack of normalization of LV mass after AVR is likely to involve presence of replacement fibrosis, but also residual diffuse interstitial fibrosis which may take longer time to regress than cellular hypertrophy. Residual fibrosis also predicts outcomes during progression of AS.[192,193] A proportion of those with persistent LV hypertrophy after AVR in our study are likely to have irreversible fibrosis to some extent. This is supported by the finding that higher amount of fibrous tissue in myocardial biopsies at the time of AVR is associated with residual LV hypertrophy also after AVR.[194] In line with this, sequential biopsy findings from Krayenbuehl et al. proposed that an early regression of LV mass after AVR is predominately driven by a reduction of cellular hypertrophy, whereas a decrease in myocardial fibrosis (albeit incomplete) may be observed 6-7 years later.[195] This is consistent with more contemporary studies focusing solely on regression of LV mass by echocardiography or magnetic resonance imaging. These findings indicate that mass regression may continue as

long as up to 5-10 years, but with the majority of the reduction occurring within the first six months up to a year following AVR.[60,196-200] In our study, the post-AVR echocardiogram was taken after a median of 196 days(mean 208 days). This may explain why the duration of days from AVR to follow-up echocardiography in our study did not seem to influence the extent of LV mass regression. Most of the regression of LV mass is therefore likely to have occurred in the early phases of the postoperative period. Similarly, in a study in AS patients with severe LV hypertrophy treated with transcatheter AVR, 50% of the first year LV mass regression occurred within the first 30 days.[58]

The importance of LV hypertrophy regression for long-term prognosis after AVR for AS have been well documented.[60,201] In a recent study by Gonzales et al. severe LV hypertrophy at one year after transcatheter AVR was associated with a 16% increased risk of all-cause death, 26% increased risk of CV death and a 45% increase in the risk of rehospitalizations during a median of 3 years follow-up.[202] Greater LV mass regression at one year was independently associated with lower rates of death and hospitalization up to five years after transcatheter AVR.[200] Taken together, AVR tend to promote regression of LV mass and improve LV function.[203] However, this might not always occur, and many patients fail to experience LV mass regression despite appropriately sized aortic valve prosthesis.[200]

As the correlation between LV mass and myocardial fibrosis is only modest, it may be that patients with persistent LV hypertrophy have more myocardial fibrosis, which may explain the discrepancies between preprocedural hypertrophy and outcomes.[194] Furthermore, only a modest correlation between the degree of AS severity and LV mass exists.[204,205] The remodeling process of the LV during progression of AS is determined by numerous factors which may not resolve following AVR. The presence of concomitant hypertension, obesity, metabolic syndrome and arterial stiffness have been shown to influence LV mass and geometry in patients independent of AS severity.[160,206,207] Understanding of the factors contributing to persistent LV hypertrophy after AVR is of importance. Knowledge of these factors could help to identify when it may be optimal to intervene, or provide targets to increase LV mass regression after AVR. A noteworthy finding from our

study is that obese patients had significantly higher prevalence of persistent LV hypertrophy during the first 6 months after surgical AVR. Obese patients had considerably higher LV mass before AVR, but a similar reduction in LV mass after AVR compared to normal weight and overweight. This suggests that the effect of valve replacement on the LV was equal across BMI classes. A more adverse remodeling during progression of AS, thus seems to translate to more residual hypertrophy also after AVR. This finding is supported by studies in obese subjects without AS, where there is positive correlation between severity of obesity and higher LV mass. Prior to our study, documentation regarding the effect obesity on LV hypertrophy after surgery for AS was scarce. However, two smaller studies primarily focusing on circulatory levels of micro-ribonucleic acids had noted a negative impact of higher preoperative BMI on less LV mass regression following AVR.[208,209]

Obesity may induce or maintain LV hypertrophy in AS patients through a number of hemodynamic and non-hemodynamic mechanisms.[210] From a hemodynamic perspective, obesity may impose a residual overload on the LV caused by a hyperdynamic circulation and increased blood volume.[211] This may explain the higher prevalence of eccentric hypertrophy observed in obese patients after AVR in our study, as LV overload usually induce eccentric hypertrophy. At baseline in the SEAS study, eccentric LV hypertrophy was more common in obese patients than in their leaner counterparts. However, during progression of AS the LV geometry changed considerably, and at the last study visit concentric LV hypertrophy was the predominant type of abnormal LV geometry irrespective of BMI class. This suggests that after AVR the effect of obesity on LV remodeling reverts to that observed in the milder stages of AS. Afterload may also be elevated in obese subjects after AVR due to large artery stiffening,[211] which may negatively influence regression of myocardial fibrosis.[108]

With respect to metabolic effects, obesity may induce cardiac steatosis through accumulation of epicardial and pericardial fat, which has been shown to increase myocardial fibrosis and lead to more pathological remodeling during progression of AS.[212] This epicardial fat may stimulate reactive fibrosis in the myocardium,

subsequently leading to reduced LV function.[210] Results from magnetic resonance imaging suggest a pathophysiological role of myocardial steatosis in the development of systolic dysfunction in AS, independent of obesity.[213] Marfella et al., showed that in severe AS patients with metabolic syndrome, systolic function decreased as myocardial steatosis increased in myocardial biopsies.[214] In patients without obesity this steatosis seems to reverse after AVR, facilitating improvement in LV strain measured by magnetic resonance tagging.[213] In the presence of obesity, alterations in cardiac fatty acid metabolism may favor lipid accumulation within the myocardium also after AVR. Because increased myocardial triglyceride content has been shown to increase LV mass and reduce LV function,[44,215] one may speculate if the observed relationship between persistent LV hypertrophy and obesity could occur as an epiphenomenon since triglyceride levels significantly increased across BMI classes in our cohort. Elevated levels of serum triglycerides are a component of atherogenic dyslipidemia, common in those with metabolic syndrome. The metabolic syndrome is associated with a cluster of metabolic risk factors beyond obesity, such as hypertension, impaired glucose regulation and dyslipidemia which could influence both pre-and postoperative LV mass. When our study was published, there had been less focus on the effect metabolic syndrome on LV mass regression following AVR. Later, Guzzetti et al. showed that those with metabolic syndrome had less LV mass regression and higher prevalence of persistent LV hypertrophy after AVR.[216] However, in a re-analysis done after publication, forcing any component of the metabolic syndrome into the multivariable model in Study 3, such as serum-triglycerides or high-density lipoproteins, did not change the association between obesity and persistent LV hypertrophy. This suggests a crude effect of obesity on increased LV mass beyond dyslipidemia.

Progressively lower LV myocardial function, assessed by midwall shortening, was found with increasing BMI class. This trend was evident both before and after AVR. This effect was also found throughout the SEAS study.[159] Previous studies on midwall mechanics in obese patients indicate that lower midwall shortening is related to abnormalities in LV geometry, particularly concentric LV hypertrophy.[217,218] In Study 3, lower midwall shortening was independently correlated with persistent LV

hypertrophy, despite EF being >60% in the majority of patients. This finding is in accordance with other authors who also found that worse systolic function, measured by peak S´, was an independent predictor of persistent LV hypertrophy after AVR for AS.[194]

Other potential mechanisms that may link obesity to LV hypertrophy are insulin resistance, activation of the renin-angiotensin system and sympathetic nervous system, low-grade inflammation and a high prevalence of comorbidities such as hypertension and obstructive sleep apnea. Even though we could not account for all of these potential confounders in our dataset, the relationship between persistent LV hypertrophy and obesity was independent of higher systolic blood pressure. This is of importance as higher systolic blood pressure may impose a residual load on the LV and hamper LV mass regression.[63,219] Cramariuc et al. identified hypertension, together with AS severity and male sex, as the main baseline determinants of LV hypertrophy in the SEAS population.[220] Our findings shows that the detrimental effect of higher systolic blood pressure also continues after AVR. Other factors of residual load include patient-prosthesis mismatch, which has been identified as an important factor associated with lack of LV hypertrophy regression after surgical AVR.[221,222] In our cohort, the prevalence of patient-prosthesis mismatch did not differ between groups, and there was no association between persistent LV hypertrophy and severe patient-prosthesis mismatch.

Our results have implications for the timing of AVR in obese patients, as it may be suggested to intervene at an earlier timepoint as these patients have adverse remodeling which may not adequately regress after AVR. However, our study demonstrate that LV mass reduction was comparable in obese and non-obese subjects. Thus, weight reduction in these patients may be beneficial to normalize LV mass after AVR, while earlier AVR will not. Even a modest weight loss is almost invariably associated with a reduction in LV mass.[217,223] This effect also appears to be stronger than the decrease in LV mass associated with a concomitant reduction of blood pressure.[217] Voluntary weight loss induced by bariatric surgery or life-style modifications may therefore produce favorable changes in cardiac structure and function both pre-and post-AVR in AS.[224]

11.4 Limitations

The results reported in this thesis should be considered in the light of some limitations. The main statistical limitations in Study 1 are the cross-sectional study design and small sample size. This precludes evaluation of causal effects, and some of the observed correlations might be bi-directional. It should be emphasized that results from cross-sectional studies are mainly hypothesis generating. Prospective studies are needed to confirm the impact of increased arterial stiffness and myocardial contractility with EF1. Further, the small sample size may also increase the risk of type-II statistical errors. This limited the possibility of investigating how EF1 might have been distributed across different flow gradient patterns. However, the sample size of 120 patients was calculated beforehand in order to have 90% power with statistical level of 0.05 to find a 20% difference in myocardial function between AS severity groups, including an anticipated dropout rate of 10%.

In general, a single center observational design reduce external validity as the analysis may be subject to referral bias. However, since patients were recruited prospectively this strengthens that our results may be generalizable to other AS patients. Furthermore, we cannot exclude that coronary artery disease may have been present in some patients, since computed tomography angiography was not a part of the study.

The SEAS study population, investigated in Study 2 and 3, was a multinational population of patients with initially asymptomatic mild to moderate AS without known CV diseases, diabetes mellitus, kidney disease, HF or other significant heart valve diseases. Our results are therefore not directly comparable to other AS groups expressing any of these comorbidities. Nevertheless, this population allowed us to investigate the impact of increased AT/ET ratio in AS, and the association between concomitant obesity and persistent LV hypertrophy, without many confounding factors. The SEAS study was a randomized clinical trial designed to assess the impact of lipid-lowering treatment on AS progression. The main limitation in Study 2 and 3 is therefore the post-hoc study design which does not conform to the randomization model of statistical inference. The probability that the apparent associations

discovered herein might occur by coincidence increase as the SEAS study was not originally planned for these studies. A post-hoc study design may also increase the risk of type-II statistical errors, due to the fact that no a priori power-analyses were done with these research questions born in mind. However, our results are clearly in line with previous results and generates hypotheses that should be formally investigated in future prospective studies.

11.4.1 Methodological considerations

General considerations

In all three papers, magnetic resonance imaging assessment of fibrosis, computed tomography assessment of calcium-score, dobutamine stress-testing or venous blood samples with measurement of cardiac biomarkers such as B-natriuretic peptides were not available due to resource constraints. We cannot exclude that assessment of any of these modalities could have provided additional information regarding underlying disease mechanisms beyond the tools investigated in the present thesis. However, echocardiography remains the main tool for management of AS patients.

Accuracy of cine-magnetic resonance imaging may allow for identification of alterations in cardiac structure and function that may be missed using two-dimensional echocardiography. Three-dimensional echocardiography is available and may also measure cardiac volumes and LV mass directly. Three-dimensional echocardiography have several advantages compared to two-dimensional echocardiography. It does not require image plane positioning to avoid apical foreshortening and eliminates the need of geometrical assumptions. This provides a more precise representation of chamber quantification. Accuracy of three-dimensional LV volumes and EF have demonstrated superiority compared to two-dimensional echocardiography. Improvement of LV mass estimation due to better endocardial and epicardial visualization may explain why three-dimensional echocardiography is more closely related to the of gold-standard by magnetic resonance imaging. However, three-dimensional echocardiography is more dependent on image quality, which is a prerequisite for accurate volume and LV mass assessment. This error may be further amplified in obese patients, who more often

present with poor acoustic windows. The application of magnetic resonance imaging is limited by increased time to acquire and analyze images, and its accessibility is restricted compared to echocardiography.

The Devereux`s necropsy method for LV mass calculation was used in all studies. This assumes a fixed geometric shape, which may be a source of error, especially with major distortions of LV geometry. The calculation of LV mass is based on the modeling of the LV as a prolate ellipsoid, and any error in linear measurements can results in significant inaccuracies because the measurements are cubed in the formula. This may be of particular importance, especially in Study 3, where the main variable of interest was LV mass and LV hypertrophy. The impact of these potential technical pitfalls may be partly limited by the large number of observations, which reduce the error. Despite the limitations noted, two-dimensional echocardiographic assessment of LV mass is recommended in AS follow-up, and the majority of the existing prognostic data are from studies using two-dimensional detection of LV hypertrophy.

Several methods have been proposed to normalize LV mass to body size. We chose to index LV mass to height$^{2.7}$ as it gives the most accurate estimation of LV mass and the most sensitive cut-off for LV hypertrophy, particularly in obesity. Additionally, core laboratory readings were done in all studies, following the recommendations for utility of echocardiography in clinical studies. All clinical and demographic data were collected prior to echocardiography and all imaging analyses were done blinded, as recommended for clinical trials.

Specific limitations

Study 1

In Paper 1, we measured strain rate by speckle tracking echocardiography as a surrogate of contractility. However, strain rate is load-dependent and not a perfect measure of contratility. The main methodological limitation in Paper 1 is therefore the lack of a load-independent marker of contractility. Ideally, EF1 should be compared against contractility indices derived from invasive pressure volum loops such as the slope of the linear preload recruitable stroke work, which is insenstive to preload by defintion, but also remarkably insensitive to changes in afterload.

Alternatively, comparing EF1 to the end-systolic pressure-volume relation or dP/dt max during different loading conditions would be a more appropriate assessment of EF1 as a marker of contractility. There are several advantages with speckle tracking derived strain rate compared to other methods such as Tissue Doppler Imaging. Speckle tracking allows for a faster post-processing because it is automatic/semiautomatic and is less angle dependent compared to Tissue Doppler Imaging. However, speckle tracking achieves significantly lower frame rate than Tissue Doppler imaging, which may cause an underestimations of peak strain and especially peak strain rate in subjects with high heart rate. This may to a certain degree have influenced strain rate in our population.

Although intra- and inter observer reliability for measurements of EF1 was good, EF1 was measured by the two-dimensional bi-plane Simpson's method. As previously stated this method is limited by geometrical assumptions and measurements made in a routine clinic may exhibit more variability. Automated three-dimensional analysis may provide a more reliable measurement of EF1 without geometrical assumptions, and would be the preferred method for future studies. However, the current commercially available software for three-dimensional echocardiography is limited by low temporal resolution and stitching artefacts. Low volume rates (10-30 volumes per second) implies that it may be difficult to identify the exact frame of EF1, as there may be large discrepancies between frames with three-dimensional echocardiography compared to high-frame rate two-dimensional images.

Study 2

In the SEAS study deformation analysis including strain and strain rate was not investigated, as this was not a part of the SEAS study protocol. Adding deformation analysis may have elucidated important confounders which could not be adjusted for in our cohort. In multivariable Cox regression analyses, we did not adjust for AVA which is recommended in the guidelines when assessing AS severity. The rational for this was that AVA was not significantly associated with higher AT/ET ratio in the multivariable models. However, if AVA was forced into the Cox regression models the results remained unchanged.

Since we excluded patients with EF<50%, our results should be interpreted with caution in AS patients with classical low flow low gradient. Even though we found a non-significant association between higher AT/ET ratio and heart rate in multivariable analyses, it's likely that AT/ET ratio could be more affected in cases with higher heart rates. Similar to most measures of systolic function, measurement of AT/ET ratio seems dependent on loading conditions. Precautions must be considered for interpretation of AT/ET ratio in AS patients with coexistence of other valvular heart disease that alters LV hemodynamics.

Study 3

The selection of patients referred for AVR were done by local study personell, which may favour patients with certain features. The specific indications for surgery were not forwarded to the core laboratory, and thus information regarding development of sympomts were not collected in our database. However, the collection of data from several independent hospitals, analysed by the core laboratory, significantly reduces the risk of referal bias. In the SEAS study echocardiography protocol, only LV filling and atrial volumes were assesed, while no data on mitral annular plane velocites or tricuspid reguritation were included in this study that was performed in 2002-2008. This limited the evaluation of diastolic function. It is known that obesity is associated with worse LV diastolic function independent of LV mass and other risk factors.[225] Also, LV diastolic dysfunction may persist in AS patients even after transcatheter AVR, and is an independent predictor of outcomes.[226] Lastly, BMI may be inferior to other measures of fatness like waist circumference or waist-to-hip ratio, which were not collected in the SEAS study. The rational of using BMI dependends on the assumptions that anthropometric measures correlates with more direct measures of adiposity such as excess fat mass, subcutanous fat or visceral fat which are more metabolic active. This may not always be the case and some studies support the notion of addition of waist circumference or waist-to-hip ratio when assessing BMI.[227] However, other suggest that most of the variance in obesity-related anthropometrics is captured by BMI which makes an argument for the use of BMI in the present study.[228]

11.5 Clinical implications and future perspectives

The present project demonstrates that EF1 is a marker of peak systolic function while ejection dynamics may improve identification of high-risk individuals among presumable non-severe AS patients, including PLGAS patients. Our results indicate that EF1 may be a promising marker of early systolic dysfunction that incorporates the effect of both arterial and ventricular function. Although retrospective studies suggest that EF1 may inherit predictive value, future prospective longitudinal studies are needed to confirm whether EF1 has true prognostic value in both AS patients and other heart disease cohorts. If these results are confirmed, EF1 may be an easy echocardiographic marker that could effortlessly be implemented in clinical practice.

Higher AT/ET ratio seems to be a promising angle-independent marker of AS severity that could be especially useful in patients with discordant graded AS. In the same matter, future studies with addition of deformation analysis and computed tomography assessment of calcium score should assess the prognostic value of higher AT/ET ratio. The present project also demonstrates that obesity has a pronounced association with persistent LV hypertrophy and higher LV mass also after AVR for severe AS. Since higher BMI did not influence the magnitude of LV mass regression, interventions to induce weight-loss in a safe manner both pre-and postoperatively may be warranted to reduce the obesity-related effect of adverse LV remodeling.

12. Conclusions

The present thesis investigated several pre-specified aims and found the following answers related to the scientific questions asked:

Study 1

The purpose of Study 1 was to identify the covariates of EF1 in patients with mild, moderate and severe AS. Especially, the associations between EF1, myocardial contractility and arterial stiffness were of interest. This paper suggests that EF1 is a promising marker of peak systolic function that may detect early systolic dysfunction among AS patients before end-systolic markers. Our results show that lower strain rate as a surrogate of myocardial contractility and higher PP/SVi as a surrogate of arterial stiffness are important covariates of lower EF1.

Study 2

The purpose of Study 2 was to assess the impact of LV ejection dynamics measured as AT/ET ratio on CV outcome in patients with non-severe AS. The present study shows that higher AT/ET ratio may improve identification of high-risk subjects among patients with mild, moderate and inconsistently graded AS. In the subgroup of asymptomatic patients with PLGAS, an AT/ET > 0.32 improved identification of patients at high-risk for combined CV death and HF hospitalization.

Study 3

The purpose of Study 3 was to investigate the effect of preoperative obesity on persistent LV hypertrophy after AVR for severe AS. Our study show that obesity has a strong association with residual LV hypertrophy that is independent of known prognostic factors such as patient-prosthesis mismatch, higher systolic blood pressure and lower myocardial function.

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Impact of arterio–ventricular interaction on first-phase ejection fraction in aortic stenosis

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Aims First-phase ejection fraction (EF1), the EF at the time to peak aortic jet velocity, has been proposed as a novel marker of peak systolic function in aortic stenosis (AS). This study aimed to explore the association of myocardial contractility and arterial load with EF1 in AS patients.

Methods and results Data from a prospective, cross-sectional study of 114 patients with mild, moderate, and severe AS with preserved left ventricular EF (>50%) were analysed. EF1 was measured as the volume change from end-diastole to the time that corresponded to peak aortic jet velocity. Myocardial contractility was assessed by strain rate measured by speckle tracking echocardiography. Arterial stiffness was assessed by central pulse pressure/stroke volume index ratio (PP/SVi). The total study population included 48% women, median age was 73 years, and mean peak aortic jet velocity was 3.47 m/s. In univariable linear regression analyses, lower EF1 was associated with higher age, higher peak aortic jet velocity, lower global EF, lower global longitudinal strain, lower strain rate, and higher PP/SVi. There was no significant association between EF1 and heart rate or sex. In multivariable linear regression analysis, EF1 was associated with lower strain rate and higher PP/SVi, independent of AS severity. Replacing PP/SVi by valvular impedance did not change the results.

Conclusion In patients with AS, reduced myocardial contractility and increased arterial load were associated with lower EF1 independent of the severity of valve stenosis.

Keywords aortic stenosis • ejection fraction • myocardial function • arterial stiffness

Introduction

Aortic stenosis (AS) is the most common cause of aortic valve replacement in developed countries.[1,2] Once symptoms occur or there is a reduction in left ventricular ejection fraction (LVEF) <50%, the current guidelines recommend aortic valve intervention.[3,4] The transition to symptoms partly reflects maladaptive compensatory mechanisms,[5] particularly characterized by myocardial fibrosis which may not reverse following aortic valve replacement.[6]

Experimental research has suggested that when systolic function is impaired in early systole an intrinsic mechanism may exist to preserve LVEF, but at the expense of a slower and sustained contraction.[7,8] However, in AS it is well known that LVEF may be preserved by compensatory remodelling and hypertrophy,[9] despite reduced myocardial contractility.[10] Recently, the first-phase EF (EF1), a measurement of the LVEF at the time of peak aortic jet velocity, has emerged as a novel marker of early LV systolic impairment both in hypertension and AS patients.[11,12] Early and accurate recognition of subclinical LV systolic dysfunction offers the potential to optimize the timing of intervention in AS. In patients with moderate or severe AS, lower EF1 showed incremental prognostic value compared with LVEF and global longitudinal strain.[12] However, more information on the underlying factors influencing EF1 is needed. In particular, the interaction between EF1 with myocardial contractility and increased

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arterial load needs further exploration. Increased arterial load is highly prevalent in AS patients due to higher age, hypertension, and large arterial stiffening. Previous studies have documented the association of arterial stiffness with impaired myocardial function.[13] This study aimed at exploring the associations between myocardial contractility and arterial load with EF1 in AS.

Methods

Study population

We prospectively recruited 120 patients with AS from the outpatient clinic, Department of Heart Disease, Haukeland University Hospital, Bergen, Norway, between October 2015 and December 2017. Patients were considered eligible if they had at least mild AS defined as aortic valve thickening and peak aortic jet velocity >2 m/s. Exclusion criteria were cardiac arrhythmias, prior pacemaker implantation, other concomitant valvular disease of more than moderate grade, known coronary artery disease (myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention), or previous cardiac surgery. Patients with reduced LVEF (<50%) ($n = 3$) were excluded from the present analysis. The study was approved by the local Regional Committee for Medical and Health Research Ethics, and was conducted in accordance with the Declaration of Helsinki. All patients signed a written informed consent prior to study examinations.

Cardiovascular risk factors

Following inclusion, all participants underwent a clinical examination at the outpatient clinic. Before the echocardiographic examination, brachial blood pressure (BP) was measured in triplicate with 1-minute intervals after an initial 5 minute rest in the seated position using a regularly calibrated aneroid sphygmomanometer and appropriate cuff size.[14] The average of the last two measurements was taken as the clinic BP. Hypertension was defined as use of antihypertensive medication, history of hypertension, or clinical BP ≥140/90 mmHg. Self-reported health was recorded on a standardized questionnaire including information on cardiovascular risk factors, medication, and known diseases and was quality assured by study personnel.

Echocardiography

A standardized transthoracic echocardiogram was performed in all patients using a Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). Digital images were stored and analysed at the Bergen Echocardiographic Core Laboratory using TomTec workstations equipped with Image Arena 4.6 soft-ware (TomTec, Unterschleissheim, Germany). Conventional measurements in all studies were first analysed by the same reader (E.E.) and later proof-read by an experienced reader (E.G.). Quantitative assessment of the LV and AS severity were performed according to the joint European Association of Echocardiography and American Society of Echocardiography recommendations.[3,15] LV mass was calculated using the Devereux formula, and indexed to body height in the allometric power of 2.7 to obtain LV mass index.[16] LV hypertrophy was defined by the prognostically validated cut-off values of LV mass index >49.2 g/m$^{2.7}$ in men and LV mass index >46.7 g/m$^{2.7}$ in women.[16] LVEF was calculated using the Simpson biplane method. Peak aortic jet velocity was measured from different acoustic windows including the use of a stand-alone probe, and the highest velocity was used for tracing of the time-velocity integral. The effective aortic orifice area was calculated by the continuity equation. Mild AS was defined as peak aortic jet velocity of 2.0–2.9 m/s, moderate AS as peak aortic jet velocity of 3.0–3.9 m/s, and severe AS as peak aortic jet velocity ≥4.0 m/s.

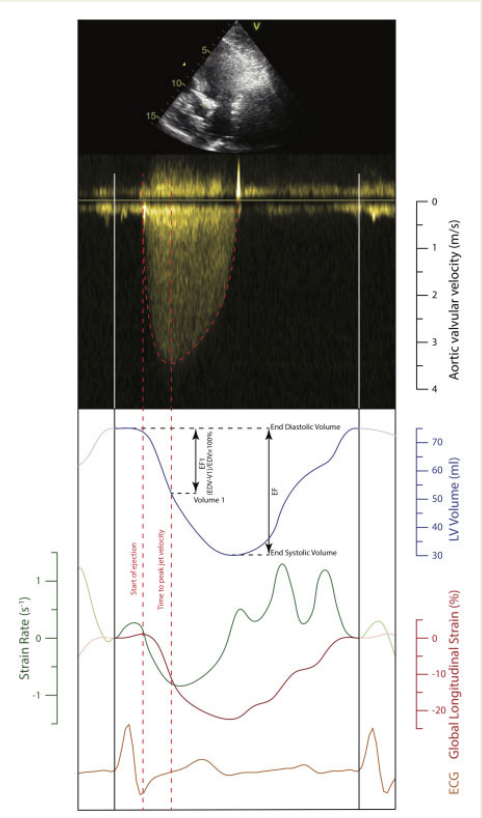

Figure 1 Measurement of first-phase ejection fraction, and its relation with global ejection fraction, global longitudinal strain, and strain rate.

Stroke volume (SV) was assessed by Doppler and indexed for body surface area, as recommended by the guidelines.[4] Central pulse pressure (PP) was estimated using a validated formula: brachial PP × 0.49 + age × 0.30 + 7.11.[17,18] Arterial stiffness was estimated by the ratio from central PP/SV index (PP/SVi).[17] Global LV load was assessed from valvuloarterial impedance (Zva), calculated as systolic BP + mean aortic pressure gradient/SVi.[19] Peak systolic annular velocities were measured by tissue Doppler imaging at the medial and lateral annulus, and averaged to obtain peak *S'*.

EF1 was measured by the biplane method of discs by measuring the volume change from end-diastole to the time that corresponded to peak aortic jet velocity by spectral Doppler. EF1 was thus derived by:

$$EF1 = \frac{(EDV - V1)}{EDV}$$

where EDV is the LV volume at end-diastole and V1 is the LV volume at the time corresponding to peak aortic jet velocity in the cardiac cycle (*Figure 1*).[12] EF1 was measured manually at the exact frame of peak aortic

Table 1 Clinical characteristics across patients with mild, moderate, and severe AS

	Mild (*n* = 38)	Moderate (*n* = 44)	Severe (*n* =32)	*P* (ANOVA)
Age (years)	72 ± 10	71 ± 12	76 ± 9	0.133
Sex (male)	45%	57%	47%	0.513
Systolic blood pressure (mmHg)	153 ± 25	146 ± 18	143 ± 15	0.063
Diastolic blood pressure (mmHg)	84 ± 11	83 ± 7	79 ± 9*	0.036
Heart rate (bpm)	66 ± 10	68 ± 9	71 ± 12	0.119
Body surface area (m^2)	1.89 ± 0.19	1.91 ± 0.24	1.84 ±0.23	0.278
Weight (kg)	78 ± 14	78 ± 18	72 ± 16	0.159
Height (cm)	170 ± 10	171 ± 9	170 ± 9	0.803
Body mass index (kg/m^2)	26.9 ± 4.1	26.6 ± 4.6	25.0 ± 3.8	0.066
Hypertension, *n* (%)	33 (90)	40 (91)	29 (88)	0.912
Diabetes, *n* (%)	5 (13)	6 (14)	2 (6)	0.563
Current smokers, *n* (%)	1 (3)	4 (9)	3 (9)	0.109
Symptoms, *n* (%)	0 (0)	7 (16)	9 (28)*	0.011
NYHA functional class, *n* (%)				
2	0 (0)	6 (14)	8 (25)	
3	0 (0)	1 (2)	1 (3)	
Hypercholesterolaemia, *n* (%)	7 (18)	9 (20)	7 (22)	0.938

NYHA, New York Heart Association; bpm, beats per minute.
*$P < 0.05$ vs. mild AS.

jet velocity by taking into account the frame rate and time in milliseconds from aortic valve opening to peak aortic jet velocity.

Two-dimensional speckle tracking echocardiography and EF1 analyses were performed offline on a dedicated workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway), using apical two-, three-, and four-chamber views with frame rate optimized to 60–90 frames/s (median 74 frames/s, mean 73 frames/s). The endocardial border of the LV was traced, and the region of interest was adjusted at the epicardial border per segment, as appropriate. After software processing, tracking quality was checked visually, and all segments were adjusted manually if needed. The time of aortic valve closure was measured from a pulsed wave Doppler recording in the LV outflow tract, and was defined as the end of systole. Drift compensation was used during analysis, and smoothing parameters were kept at default. Global longitudinal strain was calculated as the average peak negative longitudinal shortening from the 18 LV segments. Longitudinal strain rate values from the 18 LV segments were averaged to obtain peak systolic strain rate.

Diastolic function was defined in accordance with current guidelines,[20] if at least three of the following parameters were present: reduced annular e' velocity by tissue Doppler (septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s); early transmitral E-wave/average mitral annular velocity ratio (E/e') >14; biplane left atrial volume index >34 mL/m^2; tricuspid regurgitant jet velocity >2.8 m/s.

Statistical analyses

Statistical analyses were performed using IBM SPSS version 25.0 (IBM, Armonk, NY, USA). The study population was divided into three groups: mild, moderate, and severe AS. Findings are reported as mean ± standard deviation for continuous variables and as percentages for categorical variables. Normal distribution was checked prior to analyses by *Q–Q* plots and normality tests (Kolmogorov–Smirnov). Groups were compared by analysis of variance (ANOVA) with Scheffe's post-hoc test for continuous variables and by general linear model with Sidak's post-hoc test for categorical variables, respectively. Covariates of EF1 were identified in univariable and multivariable linear regression analyses using an enter or stepwise procedure. The core assumptions of normality of the error distribution, homoscedasticity, and linearity were tested and not violated. Multicollinearity was assessed by the variance of inflation factor. Results are presented as standardized β-coefficients and *P* values. Goodness of fit is expressed as the adjusted R^2. Independent covariates of EF1 <25% were tested in univariable and multivariable binary logistics regression analyses. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Goodness of fit was tested with Hosmer–Lemeshov's test. For intra- and interobserver variability, intraclass correlation coefficients were calculated to assess agreement between EF1 measurements. Intra- and interobserver variability of EF1 measurements were assessed in 18 randomly selected subjects by repeated analyses 3 months after initial reading. A two-tailed *P* value <0.05 was considered statistically significant in all analyses.

Results

A total of 120 patients (48% women) were recruited and median age was 73 years (age range 31–94 years). Six patients were excluded, three because of suboptimal echocardiographic images, and three due to reduced LVEF (<50%), leaving 114 patients eligible for the inclusion in the present analysis. 16 patients (nine with severe AS and seven with moderate AS) had mild symptoms. Among those with symptomatic severe AS, six patients received aortic valve intervention, one patient was offered aortic valve replacement but declined, while two patients were considered not eligible for valve replacement due to severe comorbidities including cancer. The prevalence

Table 2 Echocardiographic characteristics across patients with mild, moderate, and severe AS

	Mild (*n* = 38)	Moderate (*n* = 44)	Severe (*n* = 32)	*P* (ANOVA)
Peak aortic jet velocity (m/s)	2.5 ± 0.3	3.5 ± 0.3*	4.6 ± 0.5**	<0.001
Mean aortic gradient (mmHg)	13 ± 3.5	26 ± 4.1*	50 ± 13**	<0.001
Aortic valve area (cm^2)	1.83 ± 0.34	1.26 ± 0.32*	0.91 ± 0.21**	<0.001
Zva ($mmHg/mL/m^2$)	2.9 ± 0.8	3.3 ± 0.9	3.6 ± 0.8*	0.001
LV end-diastolic diameter (mm)	47 ± 6	47 ± 6	45 ± 6	0.246
LV end-systolic diameter (mm)	31 ± 5	31 ± 5	29 ± 5	0.116
Septal wall thickness (mm)	13 ± 2	13 ± 3	16 ± 3**	<0.001
Posterior wall thickness (mm)	9 ± 1	10 ± 2	11 ± 2*	0.014
Relative wall thickness	0.41 ± 0.08	0.42 ± 0.09	0.48 ± 0.10**	0.003
LV hypertrophy (%)	34	39	56	0.151
LV mass (g)	195 ± 59	198 ± 65	235 ± 90	0.040
LV mass index ($g/m^{2.7}$)	46.2 ± 11.9	45.6 ± 11.6	54.8 ± 16.0**	0.006
PP/SVi ($mmHg/mL/m^2$)	1.19 ± 0.29	1.17 ± 0.34	1.20 ± 0.28	0.922
Meridional end-systolic stress ($dyne/cm^2$)	179 ± 37	184 ± 42	192 ± 41	0.376
Systolic function				
Global ejection fraction (%)	63 ± 4	62 ± 5	64 ± 5	0.216
Global longitudinal strain (%)	-20.5 ± 2.0	-20.0 ± 2.3	-19.1 ± 3.2	0.061
Peak *S′* (cm/s)	8.1 ± 1.6	7.8 ± 1.2	7.0 ± 1.2**	0.002
Stroke volume index (mL/m^2)	55 ± 10	52 ± 10	55 ± 11	0.319
Global longitudinal strain rate (s^{-1})	-1.05 ± 0.16	-1.03 ± 0.15	-0.94 ± 1.17*	0.017
Mechanical dispersion (ms)	44 ± 12	43 ± 17	57 ± 21**	0.001
First-phase ejection fraction (%)	31 ± 4	30 ± 4	27 ± 4**	<0.001
Diastolic function				
Filling pressure (*E*/*e′*)	11.1 ± 5.5	12.4 ± 5.2	13.9 ± 4.6*	0.010
Peak *e′* (cm/s)	6.9 ± 1.6	6.9 ± 1.5	5.7 ± 1.2**	<0.001
Tricuspid jet (m/s)	2.47 ± 0.47	2.59 ± 0.33	2.54 ± 0.38	0.460
Left atrial volume index (mL/m^2)	33.5 ± 8.5	36.0 ± 12.3	38.9 ± 11.6	0.139
Diastolic dysfunction, *n* (%)	5 (11)	13 (30)	11 (36)*	0.036
Ejection dynamics				
Acceleration time (ms)	78 ± 17	93 ± 18*	111 ± 15**	<0.001
Ejection time (ms)	314 ± 31	313 ± 27	323 ± 36	0.353
Acceleration/ejection time ratio	0.25 ± 0.05	0.30 ± 0.05*	0.35 ± 0.05**	<0.001

LV, left ventricular; ms; milliseconds; PP/SVi, pulse pressure/stroke volume index; Zva, valvuloarterial impedance.
*$P < 0.05$ vs. mild AS
**$P < 0.05$ vs. mild and moderate AS.

of hypertension was 89.5%, diabetes 11.4%, hypercholesterolemia 46.5%, and diastolic dysfunction 25.4%. Clinical characteristics between groups of mild, moderate, and severe AS did not differ, except for diastolic BP which was lower in patients with severe AS (*Table 1*).

Patients with severe AS had significantly higher LV mass index and relative wall thickness (both $P < 0.05$). Global longitudinal strain, LVEF, and SVi did not differ between groups (*Table 2*). Indices of peak LV systolic function, including acceleration time, strain rate, and EF1 all progressively declined from mild to severe AS (all $P < 0.05$) (*Table 2* and *Figure 2*). Filling pressure (*E*/*e′*) increased in parallel with the increasing AS severity grade ($P < 0.05$).

The intraclass correlation coefficient for EF1 was 0.94 (95% CI 0.85–0.98) for intra-observer variability and 0.88 (95% CI 0.67–0.95) for interobserver variability, reflecting excellent reproducibility. In univariable linear regression analyses in the total study population, lower EF1 was associated with higher LV mass index, older age, and end-systolic wall stress (*Table 3*). Lower EF1 was also associated with lower global longitudinal strain, lower strain rate, and with higher peak aortic jet velocity. Higher EF1 was associated with a higher peak *S′*. In bivariate analyses, EF1 was negatively correlated with higher Zva ($r = -0.33$, $P < 0.001$), PP/SVi ($r = -0.29$, $P = 0.002$), higher central PP ($r = -0.29$, $P = 0.002$), higher brachial PP ($r = -0.25$, $P = 0.009$), and with symptoms ($r = -0.34$, $P < 0.001$). No association between hypertension and EF1 was detected ($P = 0.123$). In multivariable linear regression, lower EF1 was associated with lower strain rate independent of age, peak aortic jet velocity, LV mass index, diastolic dysfunction, and LVEF (*Table 3*, Model 1). In Model 2, lower EF1 was associated with higher PP/SVi independent of age, peak aortic jet velocity, LVEF, and global longitudinal strain (*Table 3*). Replacing PP/SVi by Zva did not change the results. In Model 3, we included all

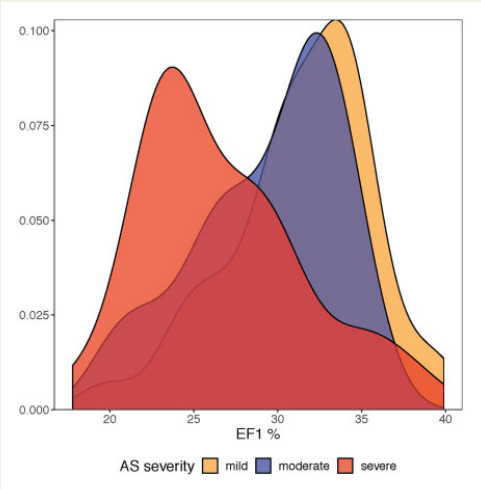

Figure 2 Distribution of first-phase ejection fraction (EF1) in subgroups of AS.

significant variables from the univariable analyses in a stepwise procedure. Lower strain rate, higher peak aortic jet velocity and higher PP/SVi all remained as significant and independent covariates of EF1 (all $P < 0.05$) (*Table 3*). Higher acceleration time was also associated with lower EF1 in univariable analysis ($\beta = -0.46$, $P < 0.001$). Due to a strong collinearity between peak aortic jet velocity and acceleration time, these two variables were not included in the same multivariable model. However, replacing peak aortic jet velocity with acceleration time in secondary models, did not change the results, and the association between EF1 and acceleration time remained significant in all multivariable models (data not shown). When restricting analyses only to moderate and severe AS groups, the association between PP/SVi and EF1 in multivariable stepwise regression became stronger ($\beta = -0.35$, $P < 0.001$), the association between peak velocity and EF1 slightly attenuated ($\beta = -0.27$, $P = 0.006$), while the association between EF1 and strain rate remained unchanged ($\beta = -0.39$, $P < 0.001$).

In univariable logistic regression analysis, EF1 <25% was associated with higher mechanical dispersion (OR = 1.03, $P = 0.022$), but after multivariable adjustment the association was attenuated ($P > 0.05$). In multivariable logistic regression analysis, EF1 <25% shared the same covariates as for EF1 in a continuous scale (*Table 4*).

Discussion

The detection of early myocardial dysfunction in AS may be challenging. After the development of symptoms, there is a sharp increase in the risk of irreversible myocardial damage and mortality. Irreversible myocardial damage is often referred to as midwall fibrosis on late gadolinium enhanced cardiac magnetic resonance imaging, which is common in AS and reduces the survival benefit of aortic valve replacement.[21] EF1, a measure of peak systolic LV function, has been shown to predict outcome more precisely than the traditional markers of end-systolic LV function like LVEF and global longitudinal strain in patients with AS.[12] The present study adds to previous knowledge by demonstrating that EF1 progressively declined with increasing AS severity, and that lower EF1 was associated with lower global longitudinal strain rate and higher PP/SVi independent of AS severity.

The association between EF1 and strain rate

Cardiomyocyte contraction occurs predominantly in the first part of systole and peaks approximately at the time of peak aortic jet velocity. It has been demonstrated that strain rate and peak aortic jet velocity are almost simultaneous events in the cardiac cycle,[22] and their respective timing intervals in early systole corresponds well with peak force development in individual cardiomyocytes.[23] In line with these findings, we observed a closer association between EF1 and peak strain rate than with global longitudinal strain and EF1 in the present study.

Even though strain rate does not directly measure peak myocardial contraction *per se*, the relationship between strain rate and contractility has been shown in an experimental pig model.[24] Weidemann *et al.* demonstrated that while strain rate was related to contractility, global longitudinal strain was more closely related to SV and LVEF.[25] EF1 and strain rate are measures of peak systolic performance, and are therefore less load dependent, and more closely related to contractility, which is in line with our findings. In contrast, end-systolic measures, such as LVEF and global longitudinal strain, are more associated with maximal LV load which is reached in late systole. As demonstrated by our results, EF1 showed a progressive reduction from mild to severe AS while LVEF remained within the normal range across all grades of AS severity. Similarly, EF1 was also closely related to peak *S'*, a reliable marker of systolic function that has been closely related to contractility.[26]

Peak systolic indices are also better markers of changes in inotropic alterations.[26] Strain rate often remains constant during an increase in heart rate, suggesting that it is relatively independent of heart rate variations.[25] Similarly, no correlation between heart rate and EF1 was detected in this study.

Strain rate has been shown to be affected by both preload and afterload, but to a lesser degree than end-systolic markers.[27] In this regard, it is inevitable that EF1 to a certain degree is load dependent due to its close correlation with strain rate. This is reflected by our findings, as EF1 remained associated with peak strain rate independent of both PP/SVi and AS severity, together representing the total arterial- and valvular load on the LV. Thus, lower EF1 is not just a consequence of afterload excess, but reflects impairment in intrinsic myocardial systolic contractility. These results are in line with previous research demonstrating that in severe AS patients, the ratio between wall stress and LVEF is significantly reduced, indicating reduced contractility.[28] This highlights the fact that watchful waiting for spontaneous symptoms in some patients with severe AS may lead to irreversible damage in LV myocardium. As recommended by the guidelines, valve replacement is recommended in patients with asymptomatic very severe AS (peak jet velocity > 5.5 m/s).[3,29] We

Table 3 Linear regression analyses of covariates of first-phase ejection fraction

	Univariable		Multivariable model 1		Multivariable model 2		Multivariable model 3	
	Standardized β coefficient	*P* value	Standardized β coefficient	*P* value	Standardized β coefficient	*P* value	Standardized β coefficient	*P* value
Global longitudinal strain rate (s^{-1})	-0.50	<0.001	-0.38	<0.001			-0.40	<0.001
PP/SVi (mmHg/mL/m^2)	-0.29	0.002			-0.27	0.003	-0.28	<0.001
Peak aortic jet velocity (m/s)	-0.41	<0.001	-0.26	0.003	-0.36	<0.001	-0.33	<0.001
Age (years)	-0.28	0.003	-0.20	0.021	-0.11	0.241	NS	NS
Global ejection fraction (%)	0.18	0.059	0.13	0.106	0.15	0.059	NS	NS
Left ventricular mass index (g/$m^{2.7}$)	-0.24	0.011	-0.02	0.833			NS	NS
Diastolic dysfunction (yes/no)	-0.29	0.002	-0.09	0.284			NS	NS
Filling pressure (*E*/*e*′)	-0.27	0.004					NS	NS
Global longitudinal strain (%)	-0.40	<0.001			-0.28	0.001	NS	NS
Peak *S*′ (cm/s)	0.46	<0.001					NS	NS
End-systolic wall stress (dyne/cm^2)	-0.26	0.005					NS	NS
Acceleration time (ms)	-0.46	<0.001					NS	NS
Body mass index (kg/m^2)	0.18	0.060					NS	NS
Heart rate (bpm)	-0.07	0.469					NS	NS
Hypertension (yes/no)	-0.15	0.123					NS	NS
Mechanical dispersion (ms)	-0.15	0.127					NS	NS
Systolic blood pressure (mmHg)	-0.15	0.077					NS	NS
Zva (mmHg/mL/m^2)	-0.33	<0.001					NS	NS
Relative wall thickness ratio	-0.12	0.188					NS	NS
Posterior wall thickness (mm)	-0.20	0.033					NS	NS
Septal wall thickness (mm)	-0.21	0.027					NS	NS
Acceleration/ejection time ratio	-0.38	<0.001					NS	NS

Model 1, multiple R^2 0.37, $P < 0.001$; Model 2, multiple R^2 0.37, $P < 0.001$; Model 3, multiple R^2 0.40, $P < 0.001$. Model 1: multivariable model of the association between EF1 and global longitudinal strain rate. Model 2: multivariable model of the association between EF1,global longitudinal strain and PP/SVi. Model 3: multivariable stepwise regression model, including all significant variables from univariable analyses.
ms, milliseconds; NS, not significant; bmp, beats per minute; PP/SVi, pulse pressure/stroke volume index; Zva, valvulo-arterial impedance.

hypothesize that EF1 could be particular useful in this setting as a sensitive and prognostically validated tool to guide treatment decisions in patients with asymptomatic severe AS and normal LVEF in the future.

The association between EF1 and arterial stiffness

In AS, increased LV load is caused by combined arterial and valvular resistance. Increased arterial load in AS is commonly caused by hypertension and/or increased arterial stiffness.[19,30] Interestingly, in this study higher PP/SVi, a surrogate of arterial stiffness, was identified as an important covariate of EF1. In patients with arterial stiffness, the reflected-wave reaches the proximal aorta in early systole, boosting systolic BP and increasing myocardial oxygen demand.[20] Early wave reflections increase the pulsatile load in mid-systole, and may occur at the time corresponding to EF1. This underlines the importance of time-varying systolic load on LV function. The increased tension in early systole might prolong contraction, preserving LVEF at the expense of an impaired early systolic function and diastolic relaxation. We corroborate previous findings by demonstrating a significant univariable relationship between EF1 and filling pressure.[11]

In our data, EF1 correlated better with the estimated central PP than with brachial PP. This is in line with previous findings which showed that central aortic PP was a better predictor of target organ damage.[31] Higher PP/SVi has also been demonstrated as an independent predictor of cardiovascular events and all-cause mortality in hypertensive patients.[32] Furthermore, one could speculate that the arterio–ventricular coupling demonstrated in the current study, could contribute to the observed impaired prognosis in AS patients with reduced arterial compliance.[18]

Limitations

This study was small and performed in AS patients with acceptable image quality, and assessment may be less feasible and reproducible in patients with poor acoustic windows. In addition, cause–effect relations cannot be determined due to the cross-sectional study design. PP/SVi is an echocardiographic surrogate of arterial stiffness. The relationship between EF1 and a more direct and accurate measure of arterial stiffness, such as the gold standard pulse wave velocity, should be tested in larger outcome studies in the future.

EF1 was significantly associated with self-reported symptoms. However, the true prevalence of symptoms in our study cohort may have been underestimated since a treadmill exercise test was not

Table 4 Uni- and multivariable logistic regression analyses of covariates of first-phase ejection fraction <25%

	Univariable		Multivariable	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
PP/SVi (mmHg/mL/m^2) (per 1SD)	1.61 (1.05–2.48)	0.029	1.89 (1.08–3.31)	0.026
Strain rate (s^{-1}) (per 1SD decline)	2.74 (1.59–4.77)	<0.001	2.56 (1.57–5.54)	0.003
Peak aortic jet velocity (m/s)	3.08 (1.74–5.44)	<0.001	2.95 (1.57–5.54)	0.001
Diastolic dysfunction (yes/no)	4.36 (1.74–10.90)	0.002	NS	NS
Left ventricular mass index (g/m$^{2.7}$)	1.04 (1.01–1.07)	0.014	NS	NS
Global longitudinal strain (%)	1.32 (1.09–1.60)	0.004	NS	NS
Mechanical dispersion (ms)	1.03 (1.04–1.05)	0.022	NS	NS
Age (per year)	1.09 (1.04–1.15)	0.001	NS	NS
Ejection fraction (%)	0.94 (0.86–1.03)	0.172	NS	NS
Relative wall thickness (per 0.01)	1.05 (1.00–1.09)	0.048	NS	NS
Systolic blood pressure (mmHg)	1.01 (0.99–1.03)	0.262	NS	NS

CI, confidence interval; ms, milliseconds; NS, not significant; OR, odds ratio; PP/SVi, pulse pressure/stroke volume index; SD, standard deviation.

performed to assess revealed symptoms. In our study, there was some overlap in EF1 across mild, moderate and severe AS , which might limit its application in patients with less severe AS. This needs to be studied in larger studies with less severe AS. Coronary artery disease is common in AS patients. Although known coronary artery disease was an exclusion criterion by design, we cannot exclude that asymptomatic coronary artery disease may have been present in some participants with reduced EF1. In severe AS, higher serum B-type natriuretic peptide has been independently associated with lower global longitudinal strain.[33] However, B-type natriuretic peptide was not measured in the present study, and the relation to EF1 could therefore not be assessed. Lastly, both EF1 and strain rate values were derived from the B-mode frame rate. This could lead to inaccuracies in the measurement of EF1 and underestimation of strain rate. However, we have carefully optimized the frame rate and achieved an acceptable frame rate which is above the recommended frame rate threshold for strain rate measurements.

Conclusions

In patients with varying degree of AS, severity, lower myocardial contractility and higher arterial stiffness were both associated with lower EF1, a marker of peak systolic function, independent of AS severity.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: none declared.

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Impact of Obesity on Persistent Left Ventricular Hypertrophy After Aortic Valve Replacement for Aortic Stenosis

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Normalization of left ventricular (LV) hypertrophy is expected after successful aortic valve replacement (AVR) in patients with aortic valve stenosis (AS), but is not always observed. We tested the impact of body mass index (BMI) ≥30 kg/m^2 on persistent post-AVR LV hypertrophy. In the present subanalysis of Simvastatin Ezetimibe in Aortic Stenosis study, clinical and echocardiographic data of 399 patients with severe AS who underwent surgical AVR were analyzed. All patients had a standardized pre- and post-AVR echocardiogram. Patients were grouped by BMI categories into BMI <25 kg/m^2, BMI 25 to 29.9 kg/m^2, and BMI ≥30 kg/m^2. LV hypertrophy was defined as LV mass/height$^{2.7}$ >49.2 g/m$^{2.7}$ in men and >46.7 g/m$^{2.7}$ in women. Predictors of persistent LV hypertrophy after AVR were identified in logistic regression analysis. After a median follow-up of 196 days after AVR, LV hypertrophy was more prevalent in patients with BMI ≥30 kg/m^2 compared with those with BMI 25 to 29.9 kg/m^2 and those patients with BMI <25 kg/m^2 (71% vs 47% and 37%, p <0.01). BMI ≥30 kg/m^2 patients also remained with lower LV midwall shortening post-AVR compared with patients with normal weight (p <0.01), independent of patient prosthesis mismatch. In multivariable logistic regression analysis, the presence of BMI ≥30 kg/m^2 before AVR was associated with an almost fourfold higher prevalence of post-AVR LV hypertrophy independent of significant associations with higher systolic blood pressure and lower LV midwall shortening preoperatively (odds ratio 3.75 [95% confidence interval 2.04 to 6.91], p <0.001). In conclusion, the presence of BMI ≥30 kg/m^2 before AVR in patients with severe AS was strongly and independently associated with persistent post-AVR LV hypertrophy. **(Am J Cardiol 2019;123:942−947)**

Aortic valve stenosis (AS) is a progressive disease that causes chronic pressure overload on the left ventricle, and induces structural and functional changes in the left ventricular (LV) myocardium.[1,2] Concomitant hypertension, obesity, and metabolic syndrome have all been shown to increase myocardial fibrosis and LV hypertrophy during progression of AS.[3−6] LV hypertrophy has been documented as an independent risk factor for impaired prognosis both during AS progression and after aortic valve replacement (AVR) in AS patients.[7−9] Following a successful AVR in AS patients, regression of LV hypertrophy is expected but may not always occur. Systemic hypertension and male gender have both been associated with reduced post-AVR regression of LV hypertrophy in AS patients.[10−12] In smaller studies focusing on the association of preoperative myocardial gene expression with post-AVR regression of LV hypertrophy, a negative impact of higher preoperative body mass index (BMI) on the postoperative LV hypertrophy regression was noted.[13,14] However, the influence of BMI ≥30 kg/m^2 on postoperative LV hypertrophy regression in AS patients has not been reported from larger clinical studies. Thus, the aim of the present study was to assess the association of overweight (BMI 25 to 29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) with persistent post-AVR LV hypertrophy in symptomatic severe AS patients treated with surgical AVR.

Methods

The present post hoc substudy was based on clinical and echocardiographic data from patients enrolled in the large prospective Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study who developed severe symptomatic AS during the study follow-up period, and subsequently underwent surgical AVR. The SEAS study was a randomized clinical control trial investigating the effect of combined treatment with Simvastatin 40 mg and ezetimibe 10 mg/day on progression of AS and associated cardiovascular events in patients with initially mild-to-moderate AS. Patients with preexisting coronary heart disease, heart failure, diabetes mellitus, or other severe preexisting conditions were not

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See page 946 for disclosure information.

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included in the SEAS study.[15] Ethical committees in all participating countries approved the SEAS study protocol, and patients signed written informed consent.[16]

Of the 1,873 patients enrolled in the SEAS study in 173 study centers within Europe, 545 patients underwent surgical AVR. Among these, a post-AVR follow-up echocardiogram was sent for blinded expert analysis at the SEAS core echocardiography laboratory in Haukeland University Hospital, Bergen, Norway in 456 patients. In a total of 57 patients, LV mass could not be assessed both on the pre- and post-AVR echocardiograms due to poor image quality in parasternal views. The remaining 399 patients were included in the present analysis. Patients were grouped according to BMI values measured at the pre-AVR clinical visit into normal weight (BMI <25 kg/m^2), overweight (BMI ≥25 kg/m^2 and <30 kg/m^2) and obesity (BMI ≥30 kg/m^2). Hypertension was defined as a history of hypertension, use of antihypertensive treatment, or clinical brachial blood pressure ≥140/90 mm Hg measured at the baseline clinical SEAS study visit.[4]

All echocardiograms used in the present study were first read by the same junior investigator (EE), and later proofread by an experienced investigator (EG).[15,16] Quantitative assessment of LV structure and function and AS severity was performed in accordance with current guidelines.[1,17] LV hypertrophy was defined using the prognostically validated cut-off values LV mass/height$^{2.7}$ >49.2 g/m$^{2.7}$ in men and >46.7 g/m$^{2.7}$ in women.[7] LV relative wall thickness was calculated as posterior wall thickness × 2/LV internal diameter in end-diastole, and considered increased if ≥0.43. LV geometry was categorizing from LV relative wall thickness and LV hypertrophy in combination, identifying concentric remodeling as increased LV relative wall thickness in patients with normal LV mass, and patients with LV hypertrophy as having eccentric and concentric hypertrophic patterns, respectively, depending on normal or increased LV relative wall thickness. Severe patient prosthesis mismatch was defined as an indexed effective orifice area ≤0.65 cm^2/m^2.[18]

Statistical analysis was performed using IBM SPSS version 24.0 (IBM, Armonk, New York). Findings are reported as mean with standard deviation for continuous variables and as percentages for categorical variables. Analysis of variance (ANOVA) with Scheffe's post hoc test for continuous variables and Sidak post hoc test for categorical variables was used to compare BMI groups, as appropriate. Covariates of persistent LV hypertrophy at the post-AVR echocardiogram were identified in uni- and multivariable logistic regression analyses, and reported as odds ratio (OR) and 95% confidence interval. A 2-tailed p value <0.05 was considered statistically significant in all analyses.

Results

Mean age in the total study population was 66 ± 9 years and 64% were male. BMI groups did not differ in blood pressure, age, or gender, but prevalence of hypertension increased in parallel with BMI (Table 1). The post-AVR echocardiogram was taken after a median of 196 days (mean 208 ± standard deviation 157 days). The post-AVR follow-up time did not differ between BMI groups. The prevalence of LV hypertrophy decreased in all groups from the pre-AVR to the post-AVR echocardiogram, but remained significantly higher in patients with BMI ≥30 kg/m^2 (p <0.01; Figure 1). In particular, eccentric hypertrophy was more prevalent among patients with BMI ≥30 kg/m^2 at the post-AVR echocardiogram (Table 2). Both patients with BMI 25 to

Table 1
Pre-AVR clinical characteristics of the BMI <25, BMI 25 to 29.9, and BMI ≥30 groups

	Body mass index (kg/m^2)			
Variable	<25 (n = 163)	25–29.9 (n = 154)	≥30 (n = 82)	ANOVA p
Age (years)	67 ± 10	65 ± 9	65 ± 9	0.052
Women	40%	34%	35%	0.525
Systolic blood pressure (mm Hg)	139 ± 20	140 ± 18	141 ± 18	0.358
Diastolic blood pressure (mm Hg)	78 ± 10	80 ± 10	80 ± 10	0.141
Heart rate (beats/min)	69 ± 12	70 ± 12	71 ± 13	0.567
Body surface area (m^2)	1.78 ± 0.16	1.95 ± 0.18*	2.01 ±0.19*,†	<0.001
BMI (kg/m^2)	22.8 ± 1.6	27.4 ± 1.4*	33.3 ± 3.1*,†	<0.001
Height (meters)	1.71 ± 0.1	1.72 ± 0.1	1.70 ± 0.1	0.243
Weight (kg)	68 ± 10	81 ± 11	95 ± 14	<0.001
Hypertension	77%	84%	89%	0.043
Serum creatinine (mg/dl)	1.0 ± 0.2	1.04 ± 0.2	1.0 ± 0.2	0.308
Total cholesterol (mg/dl)	181 ± 54	185 ± 54	178 ± 46	0.586
HDL cholesterol (mg/dl)	66 ± 15	58 ± 15*	50 ± 15*,†	<0.001
LDL cholesterol (mg/dl)	101 ± 50	104 ± 50	101 ± 46	0.376
Triglycerides (mg/dl)	88 ± 35	106 ± 53*	133 ± 53*,†	<0.001
Concomitant CAD requiring CABG	37%	30%	26%	0.185
Smoking	26%	21%	11%*	0.038

AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

* p <0.01 vs normal weight group.

† p <0.05 vs overweight group.

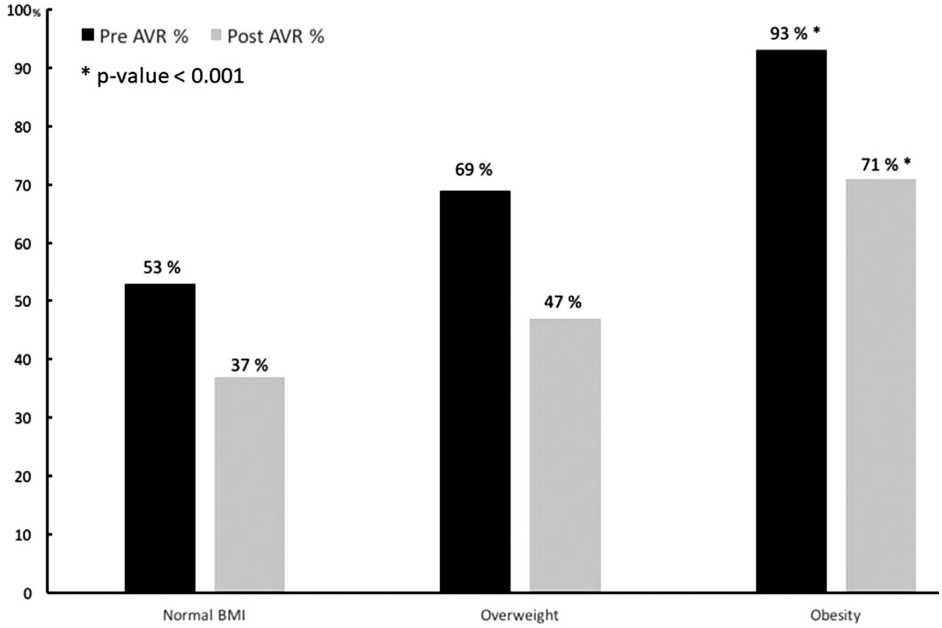

Figure 1. Prevalence of LV hypertrophy in obese, overweight, and normal weight groups at the pre- and post-AVR echocardiograms.

29.9 kg/m^2 and patients with BMI ≥30 kg/m^2 had significantly higher LV mass at the post-AVR echocardiogram compared with those with normal BMI. Patients with BMI ≥30 kg/m^2 also had significantly lower midwall shortening compared with patients with normal weight (Table 2). The mean change in LV mass after AVR did not differ between groups (11% reduction in the BMI ≥kg/m^2 30 group, 10% reduction in the BMI 25 to 29.9 kg/m^2 group and 10% reduction in the BMI <25 kg/m^2 group, p = 0.945). The prevalence of severe patient prosthesis mismatch did not differ between BMI groups (Table 2). The prevalence of persistent post-AVR LV hypertrophy did not differ by gender (46.2% for women and 48.8% for men, p = 0.67).

In univariable logistic regression analyses, persistent post-AVR LV hypertrophy was significantly associated with presence of BMI ≥30 kg/m^2, lower midwall shortening, and higher systolic blood pressure (all p <0.05), but not with gender, age, mean transprosthetic gradient, duration of days post-AVR follow-up echocardiography or presence of severe patient-prosthesis mismatch (all p >0.05; Table 3). In a multivariable logistic regression analysis, BMI ≥30 kg/m^2, but not BMI 25 to 29.9 kg/m^2, was associated with persistent post-AVR LV hypertrophy independent of significant associations with higher pre-AVR systolic blood pressure and lower midwall shortening (all p <0.05; Table 3). Multicolinearity was ruled out in a parallel linear regression model with post-AVR LV mass as a dependent variable and including the same independent variables. All variables had a high tolerance >0.96 and variance of inflation factor was <1.1 for all variables. Replacing pre-AVR with post-AVR BMI class in an alternative model yielded similar results (data not shown).

Discussion

The present post hoc substudy from the SEAS study focused on the impact of preoperative BMI ≥30 kg/m^2 on persistent LV hypertrophy after surgical AVR for severe AS. As demonstrated, BMI ≥30 kg/m^2 was strongly associated with LV hypertrophy and lower LV systolic myocardial function postoperatively, even after adjustment for important confounders including systolic blood pressure, and lower midwall shortening. These findings add to previous knowledge focusing on the impact of obesity on LV remodeling in preoperative studies in AS patients.[3,5,6,19]

Previous studies have documented the importance of LV hypertrophy regression for long-term postoperative prognosis.[9,20] The present study expands previous findings from smaller studies by documenting that BMI ≥30 kg/m^2 may independently impair normalization of LV mass during the first 6 months after surgical AVR for AS.[13,14] Biederman et al demonstrated using cardiac magnetic resonance imaging that although LV mass regression may continue up to 4 years after surgical AVR, it primarily may occur within the first 6 postoperative months.[21]

Obesity is associated with cardiac steatosis and induces LV hypertrophy through a number of hemodynamic and nonhemodynamic mechanisms.[22] In patients with AS, obesity has been shown to increase myocardial fibrosis and lead to more pathological remodeling during progression of AS.[3,6] The extent of myocardial fibrosis whether quantified

Table 2
Findings in BMI <25, BMI 25 to 29.9, and BMI ≥30 groups on the pre- and postaortic valve replacement echocardiogram

	Body mass index (kg/m^2)								
Pre-AVR variable	<25 (n = 163)	25-29.9 (n = 154)	≥30 (n = 82)	ANOVA p	Post-AVR variable	<25 (n = 163)	25-29.9 (n = 154)	≥30 (n = 82)	ANOVA p
Aortic annulus (cm)	2.26 ± 0.30	2.32 ± 0.30	2.33 ± 0.27	0.087	Aortic annulus (cm)	2.17 ± 0.25	2.21 ± 0.28	2.21 ± 0.24	0.241
LV end-diastolic diameter (cm)	4.72 ± 0.68	4.87 ± 0.71*	4.88 ± 0.69*	0.094	LV end-diastolic diameter (cm)	4.64 ± 0.58	4.90 ± 0.63*	4.95 ± 0.67*	<0.001
LV end-systolic diameter (cm)	3.11 ± 0.67	3.20 ± 0.68*	3.28 ± 0.72*	0.163	LV end-systolic diameter (cm)	3.08 ± 0.54	3.33 ± 0.59*	3.38 ± 0.64*	<0.001
Septal wall thickness (cm)	1.35 ± 0.28	1.43 ± 0.27	1.56 ± 0.30*,†	<0.001	Septal wall thickness (cm)	1.34 ± 0.28	1.36 ± 0.30	1.51 ± 0.35*,†	<0.001
Posterior wall thickness (cm)	1.07 ± 0.17	1.13 ± 0.20	1.21 ± 0.23*,†	<0.001	Posterior wall thickness (cm)	0.91 ± 0.20	0.95 ± 0.19	1.04 ± 0.22*,†	<0.001
LV mass index (g/m$^{2.7}$)	50.1 ± 13.5	57.6 ± 15.0*	67.1 ± 17.9*,†	<0.001	LV mass index (g/m$^{2.7}$)	44.8 ± 11.9	50.6 ± 14.2*	60.7 ± 18.3*,†	<0.001
Midwall LV shortening (%)	13.7 ± 2.9	13.5 ± 2.9	12.3 ± 2.4*,†	0.001	Midwall LV shortening (%)	12.5 ± 2.3	12.2 ± 2.2	11.5 ± 2.1*	0.003
Relative wall thickness	0.46 ± 0.10	0.48 ± 0.13	0.51 ± 0.14*	0.015	Relative wall thickness	0.40 ± 0.10	0.40 ± 0.10	0.43 ± 0.12	0.036
Ejection fraction (%)	63 ± 8	63 ± 8	62 ± 10	0.154	Ejection fraction (%)	61 ± 6	60 ± 6	60 ± 7	0.333
Peak aortic jet velocity (m/s)	4.20 ± 0.63	4.06 ± 0.62	4.13 ± 0.63	0.174	Peak aortic jet velocity (m/s)	2.23 ± 0.47	2.22 ± 0.52	2.28 ± 0.51	0.565
Mean transaortic gradient (mm Hg)	44 ± 13	41 ± 13	43 ± 13	0.066	Mean transaortic gradient (mm Hg)	10 ± 5	11 ± 5	11 ± 5	0.281
Aortic valve area (cm^2)	0.92 ± 0.37	1.04 ± 0.42*	0.99± 0.39	0.039	Aortic valve area (cm^2)	1.84 ± 0.91	1.87 ± 0.75	1.86 ± 0.66	0.949
Normal LV geometry	21%	14%	2%*	<0.001	Normal LV geometry	47%	40%	22*,†	0.001
Concentric remodeling	26%	17%	5%*,†	<0.001	Concentric remodeling	15%	13%	7%	0.232
Eccentric hypertrophy	22%	25%	34%	0.131	Eccentric hypertrophy	22%	29%	43%*	0.006
Concentric hypertrophy	31%	44%	59%*	<0.001	Concentric hypertrophy	16%	18%	28%	0.057
					Severe patient prosthesis mismatch	17%	20%	18%	0.599

AVR = aortic valve replacement; LV = left ventricular.
* p <0.01 vs normal weight group.
† p <0.05 vs overweight group.

Table 3
Impact of BMI ≥30 on persistent post-AVR LV hypertrophy, uni- and multivariable logistic regression analyses

	Univariable		Multivariable	
Variable	OR (95% CI)	p	OR (95% CI)	p
BMI ≥ 30	4.18 (2.32-7.52)	< 0.001	3.75 (2.04-6.91)	<0.001
BMI 25-29.9	1.48 (0.95-2.33)	0.086	1.47 (0.93-2.35)	0.102
Pre-AVR systolic blood pressure (mm Hg)	1.02 (1.01-1.03)	0.003	1.02 (1.01-1.03)	0.003
Pre-AVR midwall shortening	0.89 (0.83-0.96)	0.002	0.90 (0.83-0.97)	0.008
Baseline hypertension	1.47 (0.87-2.49)	0.149		
Post-AVR days	1.00 (0.99-1.00)	0.963		
Mean trans-prosthetic gradient (mm Hg)	1.02 (0.98-1.07)	0.256		
Age (years)	1.00 (0.98-1.02)	0.965		
Men	1.11 (0.74-0.68)	0.615		
Severe patient prosthesis mismatch	0.66 (0.38-1.14)	0.133		

BMI = body mass index.

by magnetic resonance imaging or histopathology has been associated with less LV functional improvement as well as increased late mortality after AVR for AS.[23] A nonlinear relation with BMI and 30-day and long-term mortality was reported by Roberts et al, demonstrating that patients treated with AVR for AS with BMI >40 kg/m^2 and in the mid-20s had significantly higher mortality rates compared with patients with BMI in the early 30s.[24] Recently, it was demonstrated by cardiac magnetic resonance spectroscopy also that severe AS is associated with myocardial steatosis.[25] This cardiac steatosis may saturate the beta-oxidative system, and fatty acids may by nonoxidative pathways lead to myocardial fibrosis and altered myocardial structure and function.[6] While post-AVR pressure-overload relief leads to reduction of the cardiomyocyte hypertrophy, nonmuscular myocardial components, including the obesity associated interstitial fat infiltration and accumulation of triglycerides in the contractile elements, will not be reduced, leading to persistent LV hypertrophy in these patients, as demonstrated by the present findings.[22] Our findings are in line with a recent report by Treibel et al demonstrating by cardiac magnetic resonance imaging that post-AVR regress of nonmuscular myocardial LVH in AS mainly took place after the first 6 postoperative months.[26]

In the SEAS-study, BMI ≥30 kg/m^2 was associated with higher LV mass, LV systolic dysfunction, and increased mortality during progression of AS.[3,19] The Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin study also linked obesity and metabolic syndrome with presence of impaired LV diastolic and systolic function, and reported that patients with obesity had significantly more concentric LV hypertrophy.[5] In contrast, BMI ≥30 kg/m^2 was particularly associated with persistent eccentric LV hypertrophy in the present post-AVR study. The contrasting findings may reflect that AVR effectively reduce pressure overload caused by the valvular obstruction in AS, whereas LV effects of concomitant obesity or hypertension are not influenced. Our findings expand previous knowledge by demonstrating the influence of BMI ≥30 on persistent LV hypertrophy and myocardial LV dysfunction after surgical AVR for severe AS.

Previous data from our group demonstrated that uncontrolled hypertension is associated with lack of improvement in postoperative exercise capacity in AS patients.[10] Imanaka et al also reported the importance of postoperative blood pressure control on regression of LV mass.[27] In the present study, no association between hypertension and post-AVR LV hypertrophy was found, but higher pre-AVR systolic blood pressure was associated with persistent post-AVR LV hypertrophy independent of presence of BMI ≥30 kg/m^2.

Prosthesis-patient mismatch is commonly found after surgical AVR for AS and associated with impaired post-AVR LV hypertrophy regression and prognosis, in particular in patients with impaired preoperative LV function.[18,28] In the present study, the prevalence severe prosthesis-patient mismatch did not differ between groups, and no significant association with persistent post-AVR LV hypertrophy was found.

Circulating female estrogens have been proposed to influence micro ribonucleic acid expression in collagens synthesis,[29] explaining the previous reported gender difference in LV remodeling during progression of AS.[2] In the present study, no association between gender and persistent post-AVR LV hypertrophy was observed, in line with previous findings by Dobson et al assessing LV structure by cardiac magnetic resonance imaging.[30] In contrast, among AS patients treated with transcatheter AVR (TAVR) in the PARTNER (Placement of Aortic Transcatheter Valves) study, women were reported to have significantly better post-TAVR reduction in LV mass compared with men which translated into lower incidence of rehospitalization for heart failure.[12] However, the majority of these patients had persistent LV hypertrophy at the 30-day post-TAVR echocardiogram.

In conclusion, the present findings expand current knowledge by demonstrating that preoperative BMI ≥30 in AS patients without known diabetes or cardiovascular disease is an independent and important contributor for persistent post-AVR LV hypertrophy.

Disclosures

JBC and EG were members of the scientific steering committee of the SEAS study and received honoraria for this work in the period 2002 to 2008. EE, DC, HM and SS have no conflicts of interest to disclose.

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