Influence of obesity on left ventricular adaptation, grading and outcome in aortic valve stenosis

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Scientific environment

The present project was undertaken within the Bergen Hypertension and Cardiac Dynamics group at Department for Clinical Science, University of Bergen through the years 2007-2014.The Bergen Hypertension and Cardiac Dynamics group is chaired by professor Eva Gerdts and currently includes 2 professors, 1 professor emeritus, 3 post-doctoral fellows, 4 Ph.D. fellows and 5 research medical students. One of the main activity areas of the research group is post-processing echocardiographic images by data programs in large clinical studies focusing on changes in myocardial structure and function in cardiovascular disease, in particular during chronic pressure overload.

The present project was undertaken as a prospectively planned substudy of the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study which was based on collaboration with 173 hospitals in 7 European countries. The Bergen Hypertension and Cardiac Dynamics Group was in charge of the echocardiography core laboratory in the SEAS study which included analysis of serial echocardiograms of 1873 patients with aortic valve stenosis. The candidate Barbara Rogge was one of the primary readers of echocardiograms in this landmark study during the years 2007-8.

The research group has national collaborations with the Cardiovascular Research Group at the Arctic University of Tromsø (Professor Kirsti Ytrehus) and the Norwegian PhD School for Cardiac Research anchored at University of Oslo (Professor Geir Christensen) and a large international network with repeated exchange of junior and senior researchers creating a pulsating international environment. The main international partners are Weill Medical College, Cornell University, New York, USA (Professor Richard B. Devereux) and Federico II University, Naples, Italy (Professor Giovanni de Simone). The research activities in the group are funded by the Norwegian Research Council, the University of Bergen, The Western Norwegian Regional Health Authorities (Helse-Vest), MedViz and the Grieg Foundation, and from echocardiography core laboratory activity in studies funded by pharmaceutical industry.

The Echocardiography Research Laboratory at Department of Clinical Science, University of Bergen is DICOM based and fully digitalized with up-to-date equipment for analyses of all echocardiographic modalities including conventional echocardiography, deformation analysis by speckle tracking and three-dimensional echocardiography. Dedicated equipment for tissue Doppler analysis of myocardial mechanics is also available. The Echocardiography Research Laboratory is well integrated within the Unit for Non-invasive Cardiac Imaging at Department of Heart Disease, Haukeland University Hospital, providing an excellent basis for integrated training in clinical echocardiography and scientific utilization of echocardiographic images.

The research group gives courses in echocardiography for medical students twice a year. The research fellows are included as teachers on these courses. An annual course for fellows under specialization in internal medicine or cardiology is also given. The latter is compulsory for obtaining board certification as cardiologist.

Acknowledgements

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First of all I would like to thank my principal mentor Professor Eva Gerdts. In autumn 2007, she made me an offer I could not resist, and I started in a 4 year combined research and clinical position at the Department of Heart Disease. She found the skills in me I did not know I had, and inspired me with her enthusiasm for echocardiography and clinical research. Her never ending willingness to use her time for advice and support is astonishing and without her, this thesis would have never happened.

I am very thankful to my associated mentors Dana Cramariuc and Mai Tone Lønnebakken for their friendly encouragement and guidance.

I wish to thank Chandru Punwani for not only teaching me to perform, but also to love echocardiography.

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I am very grateful to my parents, Hana and Ivan, who taught me and my brother Martin that everything worth doing should be done properly. Thank you and the rest of my family for all your love and for believing in me.

Finally, deepest thanks to my husband Thomas for his love, support, steadiness and patience with my temper and for our two children, Elisabeth and Mathias. You make me happy.

Abbreviations

AS = Aortic valve stenosis

AVA = Aortic valve area

AVAI = Aortic valve area index

BMI = Body mass index

CI = Confidence interval

CV = cardiovascular

EL = energy loss

ELI = energy loss index

HR = hazard ratio

LV = Left ventricular

MetS = Metabolic syndrome

SEAS = Simvastatin Ezetimibe in aortic stenosis study

WHO = World Health Organization

Abstract

Background/Aim: Obesity is associated with hemodynamic changes characterized by volume overload adding to the progressive pressure overload induced by aortic valve stenosis (AS). This thesis investigated whether concomitant obesity in patients with AS independently impacts left ventricular (LV) adaptation, grading and outcome during progression of the valve stenosis.

Methods: The project was a planned substudy of the Simvastin Ezetimibe in Aortic Stenosis study (SEAS), a prospective, double-blind, placebo-controlled trial of the effect of statin treatment over 4.3 years in 1873 patients with initially mild to moderate AS. Body mass index (BMI) 25.0-29.9 kg/m^2 defined overweight and BMI > 30 kg/m^2 defined obesity.

Results: In the first study, increasing BMI was associated with higher LV mass and lower LV systolic function in AS patients, independent of age, AS severity and presence of hypertension. In the second study, progression rate of AS did not differ between BMI classes. However, increased BMI predicted higher total mortality and combined rate of hospitalization for heart failure and death from any cause independent of AS severity and other confounders. Study 3 demonstrated that indexing aortic valve area (AVA) for body surface area in obesity was associated with high prevalence of discordant grading (severe AS by aortic valve area index (AVAI), but non-severe AS by AVA).

Conclusions: The thesis demonstrates that overweight and obesity significantly influence LV response, grading and outcome in AS patients independent of other known confounders.

List of publications

1. Lund B.P., Gohlke-Bärwolf C., Cramariuc D., Rossebø A.B., Rieck Å.E., Gerdts E. Effect of obesity on left ventricular mass and systolic function in patients with asymptomatic aortic stenosis (a SEAS Substudy). Am J Cardiol 2010;105:1456-1460.

2. Rogge B.P., Cramariuc D., Lønnebakken M.T., Gohlke-Bärwolf C., Chambers J.B., Boman K., Gerdts E. Effect of overweight and obesity on cardiovascular events in asymptomatic aortic stenosis. A SEAS Substudy. J Am Coll Cardiol 2013;62:1684-1690.

3. Rogge B.P., Gerdts E., Cramariuc D., Bahlmann E., Jander N., Gohlke-Bärwolf C., Pedersen T.R., Lønnebakken M.T. Impact of obesity and nonobesity on grading the severity of aortic valve stenosis. Am J Cardiol 2014;113:1532-1535.

Contents

1. Introduction

1.1 The obesity epidemic

The existence of overweight and obesity is surprisingly not just a phenomenon of the modern world. Already in ancient Greece, Hippocrates (c.460-c.375 BC) expressed that 'corpulence is not only a disease itself, but the harbinger of others'. In the last decades, the epidemic of obesity has grown worldwide. In the World Health Organization (WHO) document on obesity published in 2000, body mass index (BMI) $\geq$ 25 kg/m^2 was defined as abnormal, classifying overweight as BMI $\geq$25 but < 30 kg/m^2 and obesity as BMI $\geq$ 30 kg/m^2.[1] The estimates of regional prevalence of obesity showed already in 2004 that the only area where obesity is not common are parts of sub-Saharan Africa,[2] but also in Sub-Saharan Africa obesity is on the rise in urban regions. In the adult population of the United States, the prevalence of obesity in 2009-2010 was 35.8% among women and 35.5% among men.[3] When it comes to overweight, WHO data from 2008 are even more alarming: global prevalence of overweight in persons older than 20 years is 34.5% (54.8% in Europe and 61.9% in North and South America) (http://www.who.int/gho/ncd/ risk_factors/overweight/en/). Also in Norway, the obesity problem is emerging. The Nord-Trøndelag Health Study, HUNT, showed increased obesity prevalence between surveys performed in 1984 and 2008 from 13.3 % to 23.1% in women and from 7.7% to 22.1% in men, while the prevalence of overweight increased from 29.9 to 37.7% in women and from 42.1 to 52.4% in men, respectively.[4]

1.2 Obesity-associated morbidity and mortality

Excess body weight has many adverse health effects. Complex changes in body metabolism in obesity are directly related to development of several diseases. Increasing insulin resistance leads to glucose intolerance and type 2 diabetes mellitus and release of angiotensinogen from adipocytes, which together with increased blood volume and viscosity cause hypertension. These changes, together with dyslipidemia, predispose to atherosclerosis with clinical manifestations as coronary artery disease and stroke. Hyperinsulinemia has been associated with colon cancer, while increase in free estrogen and reduction in sex-steroid-binding globulin is thought to dispose to breast, endometrial and prostate cancer.[2] Furthermore, also respiratory disorders, non-alcoholic steatohepatitis, gout and psychic health problems are well known consequences of obesity.[2 5] Overall obesity is associated with increased all-cause mortality, reducing median survival by up to 10 years in presence of BMI $\geq$ 40 kg/m^2.[6-8] Death from CV disease has the strongest, linearly shaped association with obesity.[6 9] The relation between obesity, CV risk factors, morbidity and mortality is obvious, but still not satisfactory explained. The term metabolic syndrome (MetS) has been introduced to express clustering of CV metabolic risk factors (excess weight, dyslipidemia, impaired glucose metabolism and hypertension).[10] Several studies have proven an association between MetS and increased risk of diabetes and CV disease,[11-13] also in patients with hypertension.[14] However, it is still unclear if MetS itself is associated with increased CV morbidity and mortality beyond what is attributable to the effect of individual risk factors.

1.3 Obesity and heart disease

Increased total blood volume in obesity contributes to larger stroke volume and thus higher cardiac output. Increased cardiac output together with lower total peripheral vascular resistance leads over the time to dilatation of heart chambers.[15]

[16] Increasing wall stress leads to increased left ventricular (LV) mass and development of LV hypertrophy and abnormal LV geometry.[17 18] The strong association of increased BMI to LV wall thickness, mass and chamber size was previously demonstrated in the population based Strong Heart Study.[17 19 20] Also left atrium enlarges as the result of increased blood volume and partly due to reduced myocardial compliance. These changes together with fat infiltration in and around myocytes impairing their function predispose to diastolic and systolic dysfunction and subsequent development of clinical heart failure.[21 22]

1.4 Aortic valve stenosis

Degenerative aortic valve stenosis (AS) is a progressive disease. Multiple factors, such as mechanical damage, inflammation, hemodynamic shear stress and genetic factors may over time facilitate progressive changes of the valve tissue leading to progressive fibrosis and calcification of the valve cusps.[23] Changes in aortic valve are usually asymptomatic over a long period of time, until the calcification process causes severe narrowing of the valve orifice and increased pressure gradients across the valve. The progressive AS leads to increased workload of the left ventricle and results in LV hypertrophy, subsequent cardinal symptoms being angina, exercise induced syncope and dyspnea. When severe, symptomatic AS is present, the only treatment available is aortic valve replacement. After the onset of symptoms, if untreated, patient will usually die within 5 years.[24]

In developed countries, degenerative AS is the most common valve diseases requiring open heart surgery. The prevalence of AS is increasing with age. A pooled analysis of large population-based studies from USA have found the prevalence of AS to rise from <0.2% under age of 64 to 2.8% in those older than 75 years.[25] A recent publication from the Tromso Study reported similar results, with prevalence increasing from 0.2% in the age group of <60 years to 3.9 % in the group aged 70-79 years and up to 9.8% in those ≥80 years old.[26] No significant

difference in mortality in asymptomatic patients was found, but in symptomatic patients treated conservatively, the mean survival was 2.3 years.[26]

1.5 Obesity in aortic valve stenosis

At the time when the present project on obesity in AS was launched, few studies had reported on the impact of concomitant obesity on the course of AS.[27-30] Given the general obesity epidemic, an increasing prevalence of obesity is to be expected also among patients with degenerative AS. However, an age-gradient of obesity is evident in most populations, obesity still being more prevalent in younger and middle aged population. In contrast, degenerative AS is primarily a disease of the elderly in Western societies. With increasing life expectancy the prevalence of degenerative AS will increase and together with the emerging epidemic of obesity, combined AS and obesity is expected to become a new health care challenge. Both conditions, obesity and AS, are often related to the same comorbidities, and their interaction may have implications both for the course of AS and for its CV consequences. This interaction was the focus of the present project.

2. Hypothesis and aims

2.1 Hypothesis

The hypothesis of this thesis was that in patients with AS, obesity independently influences LV geometry and systolic function, is associated with faster progression and worse outcome of AS, and influences the accuracy of grading of AS severity.

2.2 Specific aims

- Evaluate the impact of obesity on LV mass and systolic function in patients with asymptomatic AS

- Assess the relation of obesity to progression of AS and outcome in initially asymptomatic AS patients

- Evaluate the impact of obesity on grading of AS in patients with asymptomatic, mild to moderate AS

3. Methods

3.1 Patient population

All analyses in this thesis are based on the data from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, a randomized, multicenter, double-blind trial designed to study the effects of the cholesterol lowering treatment on outcomes in patients with asymptomatic, mild-to-moderate AS. In 2003-2004, a total of 1873 patients were recruited and randomized to either combined simvastatin 40 mg and ezetimibe 10 mg daily or placebo treatment in a double blind procedure, to be followed up for a minimum of 4 years. Study participants were women and men aged 45 to 85 years with initially asymptomatic, mild-to-moderate AS with peak aortic jet velocity of 2.5 to 4 m/s, recruited and followed up in 173 centers in 7 European countries (Figure 1).

Figure 1: *Countries participating in the SEAS trial*

Patients with other significant valvular disease, diagnosis or symptoms of coronary artery disease, systolic heart failure, cerebrovascular disease, peripheral arterial diseases, diabetes mellitus, renal insufficiency or any condition requiring lipid lowering therapy were excluded from the study.[31 32] The study protocol was approved by ethical committees in all participating countries and all patients signed informed consent. The study was registered at www.clinicaltrials.com (NCT00092677).

Study I

In the first study, 1719 patients in whom baseline echocardiogram recordings allowed determination of the LV geometry and BMI could be calculated were included in the analysis. BMI was used to define obesity and to divide patients into four weight groups: underweight with BMI <18.5 kg/m^2, normal weight with BMI 18.5-24.9 kg/m^2, overweight with BMI 25-29.9 kg/m^2 and obese with BMI ≥30 kg/m^2.[33 34] Only16 patients had BMI <18.5 kg/m^2, and these were excluded for statistical reasons. Thus, the study population included 1703 patients.

Study II

For the second study, 1664 patients with registered body stature and complete study echocardiogram at baseline and at least one follow-up study visit before occurrence of any study endpoint were included. The patient population was divided into BMI classes: normal weight, overweight and obese. A total of 19 underweight patients with BMI <18.5 were excluded from the study due to small group size.

Study III

A total of 1561 patients had complete echocardiographic data allowing assessment of aortic valve area (AVA), aortic valve area index (AVAI), energy loss (EL) and energy loss index (ELI) at baseline. Of these, 13 patients with BMI <18.5 kg/m^2, 15 patients with combined AVA < 1.0 cm^2 and AVAI >0.6 cm^2/m^2 and 9 patients with

combined EL <1.0 cm^2 and ELI >0.6 cm^2/m^2 were excluded for statistical reason, leaving 1524 patients for this analysis. Obesity was defined as BMI ≥30 kg/m^2, and the study population was grouped as either obese or non-obese.

3.2 Metabolic syndrome

In study II, patients were also grouped according to presence or absence of metabolic syndrome (MetS) in a subanalysis. The international definition of MetS has changed several times during the past 2 decades and various criteria are being used by different organizations.[35-37] To facilitate comparison of results from previous publications on MetS in patients with AS, MetS in study II was defined by the modified American Heart Association/National Heart, Lung, and Blood Institute[36] as present when at least 3 of 5 of the criteria detailed in Table 1 were fulfilled at baseline.

Table 1: *Criteria for clinical diagnosis of MetS used in study II*

Variables	Cut-off values (SI system)	Cut-off values
Body mass index	≥ 30 kg/m^2	
Blood pressure	≥ 130/85 mmHg	
Fasting serum glucose	≥ 5.5 mmol/L	≥ 100 mg/dl
Serum triglycerides	≥ 1.7 mmol/L	≥ 150 mg/dl
Serum high density lipoproteins	< 1.3 mmol/L in women < 1.03 mmol/L in men	< 50 mg/dl < 40 mg/dl

3.3 Hypertension

Sitting blood pressure was measured in triplets at each clinic study visit following international guidelines on blood pressure management.[38] The average of the 2 last measurements was recorded as the clinic blood pressure in individual patients on study forms. In study I, hypertension was defined as history of hypertension as reported by the patient's attending physician, while in study II and III hypertension was defined as combined history of hypertension and elevated blood pressure at the clinic baseline visit. Blood pressure was also measured at the end of each echocardiography and reported on the echocardiography study form sent together with the echocardiographic images to the SEAS Echocardiography Core laboratory. The post-echocardiography blood pressure was used for calculation of hemodynamic variables.

3.4 Echocardiography

All echocardiograms were performed by specially trained physicians or sonographers using a standardized SEAS scanning protocol. All echocardiograms were stored on VHS-tapes, magnetic optical disks or computer discs and sent for interpretation at the SEAS echocardiography core laboratory.[39] Transthoracic echocardiography was done at baseline and then annually and before scheduled aortic valve surgery. The last study echocardiogram was defined as the final study echocardiogram in patients who did not experience CV events and the last echocardiogram taken before a study endpoint. At the SEAS Echocardiographic Core Laboratory, interpretation blinded to randomized study medication was first performed by a junior investigator, and thereafter quality assured by a senior investigator at off-line digital workstations (Image Arena, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). 95% of all echocardiograms were read by the same senior investigator.

All echocardiographic measurements were performed according to European Association of Echocardiography and American Society of Echocardiography guidelines for quantitative echocardiography and evaluation of AS.[40 41]

3.4.1 Evaluation of LV geometry and function

LV wall thickness, end-diastolic and end-systolic diameters were determined in parasternal long-axis view using 2-D linear measurements. LV mass was calculated by an autopsy-validated formula[42]

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

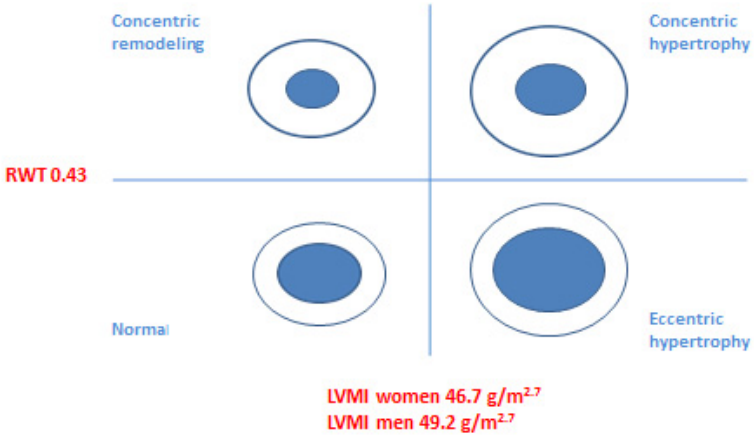
(LVEDD= LV end-diastolic inner diameter, PWTD= posterior end-diastolic wall thickness, IVSDD interventricular septum end-diastolic diameter) and indexed for height in the allometric power of 2.7. Indexing for height$^{2.7}$ has proven to be more accurate in obese subjects and is recommended for testing of the independent impact of obesity.[43 44] LV hypertrophy was defined as the LV mass indexed for height$^{2.7}$> 46.7 g/m$^{2.7}$ in women and > 49.2 g/m$^{2.7}$ in men. Relative wall thickness (RWT) was calculated by the formula

$$\text{RWT} = (2 \times \text{PWTD}) / \text{LVEDD}$$

and considered increased when ≥ 0.43.[45]

LV geometry was assessed from LV mass/height$^{2.7}$ and RWT in combination, grouping patients with normal LV mass index into normal or concentric remodeling geometry, and patients with increased LV mass index into eccentric or concentric hypertrophy patterns, as depicted in Figure 2.

Figure 2: *Four LV geometry patterns identified from relative wall thickness (RWT) and LV mass index (LVMI) in combination*



LV endocardial systolic function was expressed by ejection fraction using linear measurements from 2-D images and calculated by the Teichholz method.[46] Ejection fraction was considered low when < 50%. Fractional shortening was calculated as the difference between LVEDD and LVESD (LVESD = LV end-systolic inner diameter) divided by LVEDD.

LV myocardial systolic function was assessed by midwall shortening (MWS) calculated from 2-D images in parasternal long axis,[47]

$$MWS = \frac{(LVEDD + PWTD/2 + IVSDD/2) - (LVESD + Hs/2)}{(LVEDD + PWTD/2 + IVSDD/2)} \times 100$$

This equation takes into account migration of midwall during systole, which is caused by thickening of the inner layer formed by longitudinal fibers (Hs/2 is the estimated thickness of the inner layer in end-systole).

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

Circumferential end-systolic stress (CESS) was estimated at midwall according to a validated equation.[48] To estimate the LV systolic pressure, the mean aortic valve gradient was included in the equation. Estimation of stress-corrected midwall shortening (ScMWS*)* in study I and II allowed us even more precisely to estimate myocardial function in conditions of increased pressure overload. ScMWS was calculated as the ratio of predicted to actual midwall shortening for the actual CESS.

$$\text{predicted MWS} = 20.01 - 0.022 \times \text{CESS}$$

$$\text{ScMWS} = (\text{actual MWS} / \text{predicted MWS}) \times 100$$

ScMWS < 90% in women and < 87% in men was considered low, indicating LV systolic dysfunction.[49] Stroke volume was assessed by the Teichholz derived LV volumes.[50] Cardiac output was calculated by multiplying stroke volume by heart rate.

3.4.2 Grading of AS

Grading of AS was performed in accordance with current guidelines on management of valvular heart disease and included a number of different measures detailed in Table 2.[41 51 52]

Table 2: *Grading of AS according to current guidelines*

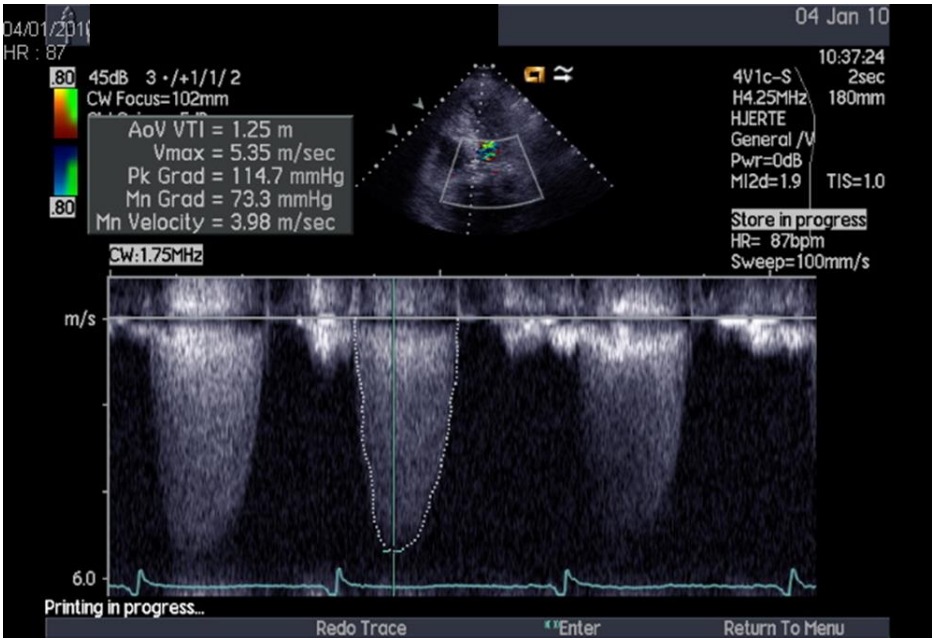
	Mild stenosis	Moderate stenosis	Severe stenosis
Peak aortic jet velocity (m/s)	2.6-2.9	3.0-4.0	>4.0
Mean pressure gradient (mmHg)	<30* (<20#)	30-50* (20-40#)	>50* (>40#)
AVA (cm^2)	>1.5	1.0-1.5	<1.0
AVAI (cm^2/m^2)	>0.85	0.6-0.85	<0.6
EL (cm^2)			<1.0[41,50]
ELI (cm^2/m^2)			<0.6[50]
*ESC guidelines, #AHA/ACC guidelines			

Peak aortic jet velocity was measured by continuous-wave Doppler. Measurements were done in several acoustic windows, including apical 3- and 5-chamber views and stand-alone Doppler recordings, and the highest velocity acquired was taken into account. Peak pressure gradient (pressure drop across the narrowed aortic valve) was calculated using the simplified Bernoulli equation:

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

(ΔP= pressure gradient, V_{max}=peak aortic jet velocity) (Figure 3).

Figure 3: *Assessment of AS severity using continuous-wave ultrasound*



Mean transaortic pressure gradient was obtained from velocity time integral by tracing the continuous wave Doppler velocity curve, thus averaging the instantaneous gradients over the whole ejection period. Aortic valve annulus diameter was measured at the hinging point of aortic valve leaflets from 2-D parasternal long-axis images at end-diastole. The aortic valve area (AVA) was calculated using the continuity equation:

$$AVA = (A_{LVOT} \times VTI_{LVOT}) / \ VTI_{aortic\ valve}$$

where $VTI_{aortic\ valve}$ = peak velocity time integral, recorded by continuous- wave Doppler, A_{LVOT} = area in left ventricle outflow tract, derived from aortic valve annulus diameter and VTI_{LVOT} = peak jet velocity time integral in LV outflow tract, obtained from pulsed-wave Doppler recording. To relate valve area to the body size of each patient, AVA was indexed by body surface area (AVAI). In an attempt to

further improve assessment of severity and prognosis of AS, energy loss (EL) and energy loss indexed for body size, energy loss index (ELI) were used. EL enables us to take into account the pressure recovery behind the stenosis:

$$EL = (AVA \times Aa)/ (Aa \times AVA),$$

where Aa is the aortic area at the sinotubular junction.[50 53]

3.5 AVAI/AVA and ELI/EL discordance

According to current guidelines, indexing of AVA and EL for body surface area is recommended to avoid overestimation of AS severity, especially in patients with small body surface.[51-53] Body surface area is calculated by the DuBois formula: body surface area = $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$. In obesity, body surface area is increasing disproportionately to body height, and indexing for body surface area may therefore lead to overestimation of the severity of AS in obese patients. Discordant grading was considered present when different measures of AS stenosis severity lead to different grading of the stenosis, i.e. grading by AVA as non-severe AS, while grading by AVAI yielding severe AS was considered AVAI/AVA discordance. Similarly, ELI/EL discordance was defined when AS was graded as severe by ELI, but non-severe by EL.

3.6 Endpoints

The pre-specified primary study endpoint in the SEAS trial was major CV events, a composite of AS-related events (aortic valve replacement, CV death and congestive heart failure due to progression of AS) and ischemic CV events (CV death, nonfatal myocardial infarction, hospital stay for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention and non-hemorrhagic stroke). Pre-specified secondary endpoints were AS-related events and ischemic CV events

analyzed separately. Total mortality was a tertiary study endpoint. In study II we also considered the post-hoc defined combined endpoint of hospitalization for heart failure and death from any cause. An independent endpoint classification committee blinded to study drug randomization, adjudicated all outcomes in the SEAS trial.[31]

3.7 Statistics

All statistical analyses and data management were performed with Statistical Package for Social Sciences (SPSS, IBM Corporation, Armonk, New York) version 15.0, 20.0 and 21.0 in study I-III, respectively. Data were presented as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. The number of antihypertensive drugs in study I was not normally distributed, and thus reported as median and range. Comparisons between patient groups were performed with independent samples t-tests and analysis of variance (ANOVA) for repeated measurements with Sidaks or Scheffe's post-hoc tests for continuous variables and chi-square test for categorical variables as appropriate. Bonferroni adjustment for multiple comparisons and Kruskal-Wallis ANOVA were used in study II. Univariate correlations were tested using Pearson's correlation coefficient. In study II and III, calculation of the cumulative proportions of endpoint events during a follow-up period was performed by Kaplan-Meier curves, and reported as percentage ± standard error of the mean. In study I, the effect of BMI on LV hypertrophy was assessed by multiple regression analysis. The impact of BMI on different types of events in study II and the association of AVAI/AVA and ELI/EL discordances with different endpoints in study III were evaluated by Cox regression analyses adjusting for known covariates. Two-tailed $p<0.05$ was considered significant in all analyses.

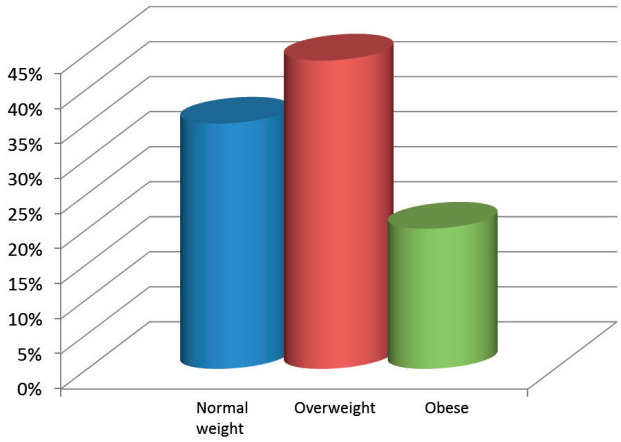
4. Summary of results

4.1 Study I

Effect of obesity on left ventricular mass and systolic function in patients with asymptomatic aortic stenosis (a SEAS substudy)

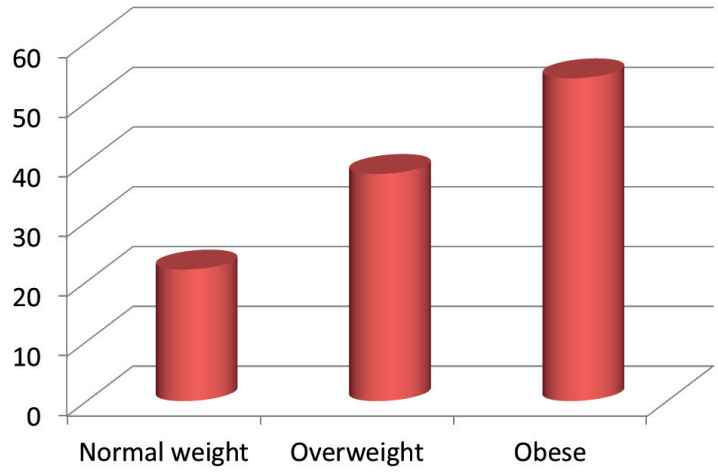
In the 1703 patients included, 660 women and 1043 men, mean BMI was 26.9 ± 4.3 kg/m^2 (Figure 4), age 67 ± 10 years, mean blood pressure measured at baseline 145/82 ± 20/10 mmHg and peak aortic velocity 3.1 ± 0.5 m/sec.

Figure 4: *Prevalence of normal weight (n=605), overweight (n=752) and obesity (n=346) in the study population of 1703 patients.*



Compared to normal weight group, LV mass index, as well as prevalence of LV hypertrophy, increased with increasing BMI ($p<0.001$) (Figure 5).

Figure 5: *Prevalence of LV hypertrophy (%) in normal weight, overweight and obese groups of asymptomatic AS patients (p<0.01)*



Peak aortic velocity did not differ between BMI classes, however, hypertension and the number of antihypertensive drugs (in particular use of angiotensin-converting enzyme inhibitors, but not angiotensin II receptor blockers) increased with increasing BMI class (all p<0.05). LV ejection fraction and prevalence of mitral regurgitation was reduced with increasing BMI class (p<0.01 and 0.05, respectively). LV systolic dysfunction, measured by lower stress-corrected midwall shortening, was more prevalent in obesity.

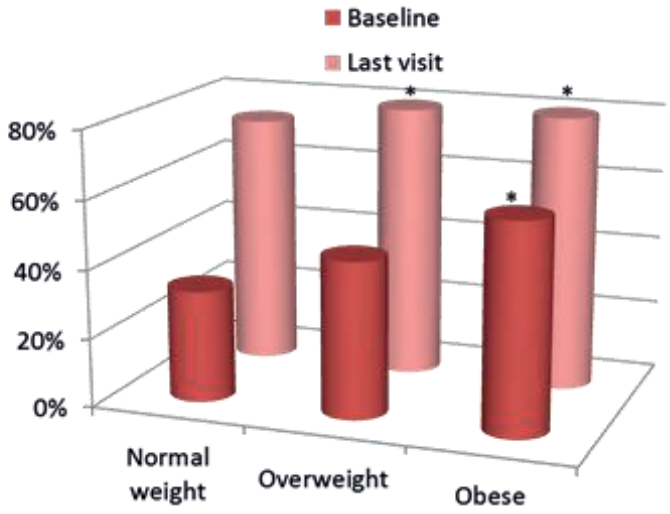
LV geometry differed significantly between the 3 BMI classes. Obesity was associated with presence of eccentric LV hypertrophy (p<0.05). When tested together with other known covariates of LV hypertrophy like age, sex, AS severity, mitral regurgitation and hypertension in multiple regression analysis, BMI was independently associated with presence of LV hypertrophy (odds ratio 1.15 per unit of increased BMI, 95% confidence interval [CI] 1.12-1.18, p< 0.001). Adding the use of antihypertensive medication in a second model did not change the results.

4.2 Study II

Effect of overweight and obesity on cardiovascular events in asymptomatic aortic stenosis. A SEAS substudy

Data from 1664 patients (593 normal weight, 737 overweight and 334 obese) enrolled in the SEAS trial were analyzed in this study. The prevalence of hypertension increased in parallel with BMI class, as did fasting serum glucose and serum triglycerides, while high-density lipoprotein cholesterol and total serum cholesterol fell progressively. During a mean follow-up of 3.4 ± 1.4 years, obesity was associated with development of more abnormal LV geometry (Figure 6).

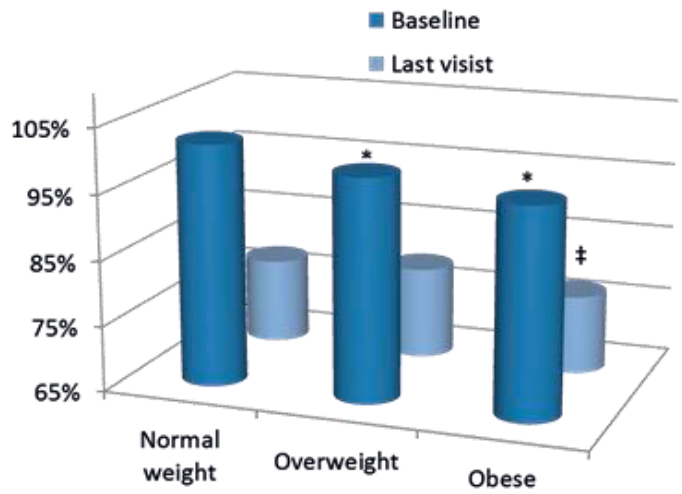
Figure 6: *Prevalence of abnormal LV geometry in normal weight, overweight and obese groups of AS patients during follow-up (* p<0.01 vs. normal weight group)*



Eccentric LV hypertrophy (39% in obese, vs. 27% in overweight and 14.5 % in normal weight groups, p<0.001) was the most common abnormal geometric pattern

at baseline, while at final study visit concentric LV hypertrophy was the most common LV geometric pattern (present in 49% in obese, 39% in overweight and 30% in normal weight groups, p<0.001). LV systolic dysfunction measured by stress-corrected midwall shortening was also markedly reduced in parallel with increasing BMI and progression of AS particularly in obese patients (Figure 7). On the other hand, ejection fraction remained normal in most of the patients (97.2%) during the study period.

Figure 7: *Stress-corrected midwall shortening in the 3 weight groups: compared with normal weight group, stress-corrected midwall shortening decreased significantly in obese group during follow-up (*p<0.01, ‡p<0.05)*



The presence of MetS was 27% in overall study population and increased exponentially with increasing BMI (9.9% in normal weight group, 20.7 % in overweight group and 71.2 % in obese group of patients, p< 0.001 vs. normal

weight group). Increasing BMI or presence of MetS did not have any influence on the progression of AS. Progression rate was 0.21 ± 0.34 m/s/year and 0.19 ± 0.30 m/s/year in overweight and obese groups vs. 0.19 ± 0.24 m/s/year in normal weight group (p= 0.55 between groups) and 0.19 ± 0.23 m/s/year in patients without MetS and 0.22 ± 0.43 m/s/year in patients with MetS (p= 0.21 between groups). Furthermore, the severity of AS evaluated at the preoperative echocardiogram before aortic valve replacement did not differ between the BMI classes.

In univariate Cox regression, overweight patients had lower rate of ischemic CV and AS-related events (22 % and 17%, respectively, both p≤ 0.05), but comparable rate of CV death, total mortality and combined hospitalization for heart failure and death from any cause compared to normal weight patients. The same results were confirmed when adjusting for smoking, hypertension, LV geometry, LV ejection fraction, sex, mean aortic gradient and randomized study treatment in multivariate Cox regression models, showing overweight to be associated with lower rates of ischemic CV (hazard ratio [HR] 0.69, 95% CI 0.53-0.90, p= 0.007) and AS-related events (HR 0.82, 95% CI 0.68-0.99, p= 0.04). In similar models, obesity had no significant influence on any of the study endpoints. Of note, overweight patients experienced ischemic CV event earlier (on average 2 years) than normal weight patients. When age was added to the covariates in a second Cox regression model, the positive association between overweight and lower ischemic CV and AS-related events became non-significant (p= 0.073 and 0.072, respectively). In addition, overweight and obesity had higher rates of total mortality in the aged-adjusted model (HR 1.46, 95% CI 1.02-2.10, p= 0.041 for overweight and HR 1.67, 95% CI 1.07-2.63, p= 0.026 for obese patients) and higher rates of combined hospitalization for heart failure and death from any cause (HR 1.42, 95% CI 1.03-1.97, p= 0.033 for overweight and HR 1.69, 95% CI 1.14-2.50, p= 0.009 for obese patients). Presence of MetS at baseline did not have any influence on the outcome.

4.3 Study III

Impact of obesity on grading the severity of aortic valve stenosis

In the 1524 SEAS patients available for this analysis, AS severity at baseline did not differ between obese (n=321) and non-obese (n=1203) groups when measured by peak aortic velocity, mean aortic gradient, AVA or EL. In contrast, the obese group had significantly smaller AVAI and ELI, suggesting more severe AS. In the total study population, 15% of the patients were identified with AVAI/AVA discordance and 9% of the patients with ELI/EL discordance. Discordance, whether measured by AVAI/AVA or ELI/EL, was more common in the obese group compared to the non-obese group (23% and 13% vs.13% and 9%, respectively, both $p< 0.05$). Patients with discordant grading were more likely to be men, with larger aortic sinus diameter, higher LV mass, stroke volume and mean aortic gradient (all $p<0.05$). Also in multivariate analyses obesity was associated with a 2.4 fold higher prevalence of AVAI/AVA discordance and a 1.6 fold higher prevalence of ELI/EL discordance also when adjusted for sex, stroke volume, mean aortic gradient, aortic sinus diameter and LV mass.

To test if discordant grading influenced the management of the AS patients, we tested the association of presence of AVAI/AVA and ELI/EL discordance with the study outcomes aortic valve replacement and combined death from any cause and hospitalization for heart failure. In univariate Cox regression analysis AVAI/AVA discordance was associated with 28% higher incidence of aortic valve replacement surgery (95% CI 1-65%, $p<0.05$), while ELI/EL discordance was associated with 68% higher rate of aortic valve replacement (HR 1.68, 95% CI 1.27-2.24, $p<0.01$). In contrast, AVAI/AVA discordance was not associated with reduced combined death from any cause and hospitalization for heart failure (HR 1.04, 95% CI 0.69-1.57, $p=0.846$) in univariate analysis or when adjusted for aortic valve replacement. In multivariate Cox models, no influence of AVAI/AVA or ELI/EL discordance on the rate of aortic valve replacement (HR 1.02, 95% CI 0.78-1.34, $p= 0.890$ for AVAI/AVA and HR 1.26, 95% CI 0.94-1-67, $p=0.120$ for ELI/EL), nor the rate of

combined death from any cause and hospitalization for heart failure (HR 0.99, 95% CI 0.65-1.53, p= 0.993 for AVAI/AVA and HR 1.40, 95% CI 0.90-2.19, p= 0.139 for ELI/EL) was found when adjusted for obesity, sex, mean aortic gradient and hypertension.

5. Discussion

Few studies have previously assessed the impact of increased BMI on LV response, grading, disease progression or outcome in AS patients. The current thesis has therefore substantially advanced current knowledge on the impact of obesity on management and prognosis in AS. In particular, the studies included in this thesis have demonstrated that overweight and obesity influenced LV adaptation during progression of AS, predisposing to myocardial dysfunction and higher mortality, and that indexing valve area for body surface area in obese patients was associated with higher frequency of discordant grading, leading to premature referral to aortic valve replacement without any documented improvement in prognosis. Presence of increased BMI did not influence the progression rate of the AS. However, overweight and obesity were associated with increased total mortality and combined hospitalization for heart failure and death from any cause.

5.1 Prevalence and covariates of obesity and MetS in AS

As demonstrated, increased BMI was common in the study population: 44 % of the study population was overweight, while 1/5 of patients were obese. These prevalences are in concordance with recent findings on body stature in the Nord-Trøndelag Health Study, HUNT, from 2008 which demonstrated 23.1% of Norwegian women and 22.1% of Norwegian men to be obese, while the prevalence of overweight was 37.7% in women and 52.4% in men, respectively,[4] reflecting that body stature in the SEAS population was representative also for the general Norwegian population.

In the general population, an inverse relation between age and presence of obesity has been reported, with obesity being more common among young and middle-aged persons.[54] In the present study population, overweight patients were slightly younger than normal weight patients, but there was no difference in age between obese and normal weight or non-obese groups of patients suggesting that among AS patients participating in the SEAS study, obesity was more evenly distributed. Of note, in the SEAS study, the patients were on average 67 years, and eligible patients were also free of any other major disease, including diabetes, heart failure or renal insufficiency. From this it may be argued that the SEAS population was healthier, younger and heavier than the typical AS patient population managed at today's cardiology units.[55]

Hypertension was strongly associated with increased BMI in our study population, found in >80% of overweight and >90% of obese patients. This confirms the close link between hypertension and overweight and obesity reported from general population, with about 75% of obese subjects having hypertension.[6 56 57] Also other studies in AS patients have found high prevalence of hypertension, without pointing out the association with increased BMI. In a retrospective study of statin treatment on the progression of aortic valve sclerosis and stenosis in1046 patients with mild to moderate AS, Antonini-Canterin et al. found hypertension in 78% of patients.[58] Also Briand et al, in a study investigating the influence of MetS on progression and prognosis in AS, documented an 81% prevalence of hypertension.[30] The present study adds to previous findings by demonstrating the parallel increase in prevalence of hypertension with increasing BMI class in AS patients.

Our results also demonstrated the clustering of metabolic risk factors with increasing BMI. The presence of MetS increased exponentially from normal weight to obesity. It is somewhat difficult to compare the prevalence of MetS in the present study population to previous studies due to the different definitions used. However, in the few reports on Mets in AS, prevalence of MetS was similar to our results.[30 59]

5.2 Effect of obesity on LV geometry in patients with asymptomatic AS

The present results demonstrate that higher BMI was associated with significantly higher prevalence of LV hypertrophy in asymptomatic AS patients, in particular of the eccentric type. Moreover, greater BMI predicted increased prevalence of LV hypertrophy in patients with asymptomatic AS independently of concomitant hypertension and independently of the AS severity. Of note, during the progression of AS the LV geometry changed considerably, and at the last study echocardiogram concentric LV hypertrophy was the predominant type of abnormal LV geometry in all BMI classes. However, LV mass and prevalence of LV hypertrophy remained higher in overweight and obese groups also during follow-up.

Previous research has demonstrated that the increasing LV systolic pressure during progression of AS results in LV hypertrophy and remodeling.[60] These changes, resulting mainly in concentric hypertrophy, maintain LV systolic function and cardiac output.[61 62] If the increased systolic load is not relieved, ultimately the compensatory mechanism will fail, and LV geometry change to eccentric, the left ventricle dilates and the rise of filling pressures will result in end-stage heart failure. LV hypertrophy is known to be closely related to adverse outcome in different conditions, including severe asymptomatic AS.[63-65] The time to appearance of symptoms, adverse events and the need of surgery are all determined not only by the mere valve narrowing, but also by the changes of myocardium.[64 66] Both these processes are of clinical importance and although connected, they are influenced by different pathophysiological factors.[23] The variation of the grade of hypertrophic response in patients with AS, and the understanding of the factors and mechanisms of these changes of the left ventricle are therefore of great clinical importance.

In the hypertensive population, prevalence of LV hypertrophy is known to be 30-50%, the most common geometric pattern being eccentric hypertrophy and concentric remodeling. [45 67] The importance of concomitant hypertension for presence of LV hypertrophy in patients with asymptomatic mild-moderate AS, has been documented in several previous publications from our group. Cramariuc et al.

identified hypertension, together with AS severity and male gender to be 3 main determinants of LV hypertrophy at baseline in the SEAS population of patients with asymptomatic, mild to moderate AS.[39] Rieck et al. added to this knowledge by the follow-up study which demonstrated that during the progression of disease, concentric hypertrophy was the most common type of hypertrophy in both normotensive and hypertensive patients, but higher LV mass and abnormal LV geometry were still more prevalent in patients with concomitant hypertension.[68 69]

Although obesity has been traditionally associated with LV dilatation and eccentric LV hypertrophy, recent research has demonstrated that co-presence of diabetes and myocardial effects of cytokines excreted from abdominal and pericardial fat cells leads to cell proliferation in the myocardial interstitium resulting in increased LV wall thickness and concentric LV geometry.[70] Storage of lipids in the cytosol of the cardiomyocytes as a consequence of excessive caloric intake and subsequent maximal expansion of adipocytes leads to reduced mitochondrial function and reduced energy production resulting in LV systolic dysfunction, often referred to as cardiac lipotoxicity.[71 72] LV hypertrophy is a well known predictor of adverse CV outcomes independent of other known risk factors in general as well as in hypertensive populations, and recently the impaired prognostic impact of excessive LV hypertrophy in patients with asymptomatic, severe AS was demonstrated.[63 64 73 74]

In the present project, eccentric LV hypertrophy was the most common type of abnormal LV geometry associated with obesity at baseline, while at the last visit the dominating abnormal geometric pattern was concentric LV hypertrophy, in obese subjects as well as in the total study population. These findings probably reflect that although comorbidities like hypertension and obesity had as strong an influence on LV geometry as the AS itself when the AS was mild to moderate at baseline in the SEAS study, the LV geometry was predominantly influenced by pressure overload caused by the severe AS at the end of the SEAS study. However, recent echocardiographic[75-77] and magnetic resonance imaging studies[78] on LV remodeling

in obesity have demonstrated that obesity may often be associated with concentric LV hypertrophy. Our findings add to this previous knowledge by demonstrating that obesity, in addition to and independent of hypertension, plays an important role in the LV response during progression of AS.

5.3 Obesity and changes in LV systolic function

In the SEAS study, patients with known LV ejection fraction < 40% and high-risk subjects for development of LV dysfunction, like patients with known coronary artery disease, diabetes or renal impairment were excluded from participation. Consequently, LV systolic function, whether expressed by LV ejection fraction, fractional shortening, midwall shortening or stress-corrected midwall shortening, was normal at baseline in all weight groups. However, even within the SEAS study population with normal systolic LV function, a progressively lower LV myocardial function, reflected by midwall shortening and stress-corrected midwall shortening, was found with increasing BMI class, and this trend was evident throughout the duration of the study. These findings are consequent with previous research on AS, describing reduced LV ejection fraction and cardiac output only in end-stage disease.[79] Reduction in systolic midwall performance is documented to be independently associated with the presence of symptoms in AS.[80] Dweck et al. observed in a cardiac magnetic imaging study using late gadolinium enhancement technique, that midwall fibrosis was present in 38% of patients with moderate or severe AS, and particularly associated with more pronounced hypertrophy and a subsequent 8-fold higher mortality.[81] Adverse prognosis is likely to reflect subclinical LV dysfunction, and current European Society of Cardiology guidelines for management of AS recommends aortic valve replacement in asymptomatic severe AS if reduced LV ejection function (<50%) is found.[82] However, in the present study population, LV ejection fraction did not differ between BMI classes. Similarly, overweight and obesity did not show significant association with low systolic LV

function in the MESA study (Multi-Ethnic Study of Atherosclerosis), suggesting that ejection fraction is an insensitive marker of myocardial changes in obesity.[78] Of note, previous studies on midwall mechanics in obesity indicated that impairment of LV systolic function detected by midwall shortening is closely related to the abnormalities in LV geometry, concentric hypertrophy in particular.[83-85] Our results are in line with these observations in other patient populations, adding that lower stress-corrected midwall shortening was particularly common in obese patients with asymptomatic, mild to moderate AS. In addition to LV ejection fraction and midwall shortening, longitudinal systolic strain is another measure of LV systolic function. Reduced longitudinal systolic strain is known to be associated with increased myocardial fibrosis,[86] abnormal exercise test and higher rate of adverse cardiac events in AS patients.[87] Our group has also demonstrated the relation between lower longitudinal strain and higher LV mass, concentric LV geometry and more severe AS.[88] However, in the large SEAS study based on echocardiograms from the period 2002-8 from 173 hospitals in 7 different European countries at a time when many still stored echocardiograms on video tapes, strain assessment was not included in the protocol.

5.4 Progression and grading of AS in obesity

Our study is the first prospective study investigating the effect of overweight and obesity on the progression of asymptomatic, mild to moderate AS. During a mean follow-up of 4.3 years, we found no relation between increased BMI and progression of AS, and although elevated BMI was associated with clustering of cardiometabolic risk factors, presence of MetS was not related with the AS progression rate. Furthermore, among the 459 patients who underwent aortic valve replacement during the conduct of the study, pre-operative AS severity did not differ between the BMI groups, reflecting that BMI did not influence referral to surgical treatment.

There are only few studies that have tested the influence of MetS on AS progression. In a substudy from the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin) study including 272 patients with mild to moderate AS free from hypercholesterolemia and diabetes mellitus, Pagé et al. found no difference in AS severity between groups of AS patients with and without MetS.[89] In contrast, from the same research group, Briand et al.[30] reported a 2-fold increased progression rate of AS in a retrospective analysis of 105 patients with at least moderate AS. Furthermore, Capoulade et al.,[59] in another substudy of 243 patients from the ASTRONOMER population found a positive association between MetS and faster AS progression. In particular, presence of MetS was associated with an adverse outcome in patients < 57 years, but not in older patients during a mean 3.4 year follow-up. The latter finding is in concordance with our results in the SEAS population which was on average 67 years old. In the general population, a clear association of higher prevalence of MetS with higher age has been noted,[10] making the clinical implication of the results by Capoulade difficult to interpret. Of note, the retrospective study by Briand et al. also included AS patients with diabetes and hypercholesterolemia and had a higher prevalence of smokers than the SEAS population. Finally, in the cohort of 5723 participants of MESA (Multi-Ethnic study of Atherosclerosis), prevalence of new aortic valve calcium and progression of established valve calcium were assessed by cardiac computer tomography. In this study, presence of MetS was associated with new onset aortic valve calcification, but not with faster progression of established calcific valve disease.[29] Taken together, the largest studies reported to date using both echocardiography and cardiac computer tomography imaging have both concluded that presence of obesity or MetS in AS is not associated with more rapid progression of the valve disease, suggesting that such patients do not warrant a closer follow-up management than that recommended by current guidelines.

Echocardiography plays a key role in the diagnosis as well as grading and management of patients with AS. Following current guidelines on management of AS, several measures are recommended for grading of the AS, including peak aortic

jet velocity, mean transvalvular gradient, AVA and AVAI. In obesity, an increase in body surface area disproportional to body height occurs when DuBois formula is used for calculation of body surface area. From this, we hypothesized that using AVAI in obese subjects would lead to more discordant grading and overestimation of the AS severity. Thus, our study questioned the common clinical practice of indexing AVA for body surface area (AVAI) when evaluating the severity of the AS in obese patient. As demonstrated by our findings, when unindexed AVA was used, the prevalence of severe AS was similar in non-obese and obese groups of patients, while when AVAI was used, a 2-fold higher prevalence of severe AS was found in obese patients, suggesting overestimation of valve stenosis severity when indexation of valve area by body surface was used. Previous publications from our group by Bahlmann et al. have demonstrated that using ELI, i.e. AVA corrected for the pressure recovery in the aortic root, gives more accurate grading of AS in particular in milder severity and in patients with small aortic root.[50 90] However, applying this principle reduced, but did not remove the increased prevalence of discordant grading in the obese group as higher prevalence of severe AS was found also when ELI was used. As demonstrated, the overestimation of AS severity in patients with asymptomatic AS using indexing AVA to body surface area was associated with increased referral to surgical treatment, without improving the prognosis measured by death from any cause and hospitalization for heart failure. Our results thus support those recently published by Jander et al. that indexing AVA to body surface area in patients with asymptomatic AS increases significantly the prevalence of severe stenosis without improving the predictive accuracy of AS-related events.[91] This new knowledge show, in line with Minners et al., the limited advantage of adjusting AVA for body surface area, but also indicate the need for adjusting current cut-off values for severe AS by different measures to improve hemodynamic consistency and concordance between commonly used measures.[92]

5.5 Impact of obesity on outcome in AS

The impact of overweight and obesity on CV outcome in patients with AS has not been reported from a large, prospective study before. Our results showed no association between excess weight and the rate of AS-related or ischemic CV events, also when adjusted for confounders including age. But overweight and obesity were associated with higher mortality and combined hospitalization for heart failure and death. The question whether overweight and obesity play any role for the morbidity and mortality in the general population have been studied with increasing interest during the last decades, in accord with growing epidemic of obesity. Several large studies have confirmed that CV diseases, diabetes and some cancers are closely related to overweight and obesity and are also main causes of death related to excess body weight.[93 94] Generally, risk of obesity associated mortality is increasing in parallel with BMI. This added risk is decreasing with age, but is still significant at the age of 75 years.[95] At the age of 40 years, obesity decreases life expectancy by 7 years.[96] In the large study by Flegal et al. using data from National Health and Nutrition Survey (NHANES) I-III from 1971 to 2002 in the United States, analysis of death information from 2.3 million adults 25 years and older demonstrated that overweight was associated with significantly increased mortality from diabetes and kidney disease combined, but significantly decreased mortality from other non-cancer, non-CV disease causes, and showed no association with mortality from cancer or CV disease. On the other hand, obesity was associated with increased mortality from CV disease, some cancers, diabetes and kidney disease combined and increased mortality overall, caused mainly by CV mortality.[9] The unexpected association of overweight and obesity with better prognosis in patients with CV disease,[5 97 98] heart failure,[99 100] hypertension[101 102] as well as in patients undergoing percutaneous coronary intervention,[103 104] coronary artery bypass grafting[97 105] or aortic valve replacement,[106] is known as the obesity paradox. However, in a recent review of 46 articles, Chrysant and Chrysant did not find a convincing evidence of this phenomenon.[107] This controversy has several possible explanations. BMI as an indicator of overweight and obesity may be insufficient, as

it expresses relation between body weight and height, but gives no information of total body fat, or fat distribution. Furthermore, in observational studies, overweight and obese patients may have been treated earlier or more aggressively for CV risk factors than normal weight patients.[108] Since the prevalences of overweight and obesity are decreasing with age, patients with excess weight experience adverse events at in younger age, probably with less comorbidity and better exercise capacity which may also play the role in better outcome. Age was also strong predictor of adverse events in our population, and an important mediator of the association between overweight and lower rate of ischemic AS-related and CV events, as demonstrated in the multivariate analyses. However, both overweight and obesity remained associated with reduced survival and with hospitalization for heart failure. Our findings indicate that although excess weight in asymptomatic AS patients without known CV disease, diabetes or hyperlipidemia has no significant influence on incident ischemic CV disease or AS-related events, overweight and obese patients experienced these outcomes at an earlier age than normal weight AS patients. Furthermore, increased BMI had an adverse impact on total mortality and combined hospitalization for heart failure and death from any cause, challenging the obesity paradox reported from observational studies and registries.

5.6 Limitations

The SEAS study population, investigated in this thesis, was a selected population of patients with initially asymptomatic mild to moderate AS without diabetes mellitus, known CV disease, heart failure, kidney disease, peripheral arterial disease or other significant heart valve disease. Our population of AS patients was therefore not directly comparable to general AS population with mostly elderly patients with more comorbidity or younger AS patients with bicuspid aortic valve or predominant aortic regurgitation. However, this selected SEAS population allowed us to study the

impact of concomitant overweight or obesity in AS without many confounding factors.

BMI is excessively used as a simple tool of estimating excess weight in medical practice as well as in research studies. Recently, other indices of fatness like waist circumference or waist-to-hip ratio have been demonstrated to better reflect presence and distribution of fat in the body and to identify central or visceral obesity, which is a more metabolic active fat tissue and more closely associated with increased incidence of CV disease and all-cause and CV mortality.[109 110] In the SEAS study, height and weight were the only registered anthropometric parameters. The original WHO 1998 definition of MetS included body weight assessment either by waist-to-hip ratio or by BMI.[111] The method used for identification of presence of MetS in the present project is in concordance with this approach. This definition has since then been changed several times, waist circumference being the currently preferred criterion of body stature.[36] However, since previous retrospective and smaller studies in AS had reported conflicting results on the impact of MetS on progression of AS, it was clearly of interest to test this hypothesis also in the present prospective, much larger study population, although somewhat different measures of central obesity were used to identify MetS in these studies.

Impairment of LV diastolic function is known to be associated with obesity and suggested as one of the earliest obesity-associated changes of the left ventricle.[112] It has been suggested that obese patients without comorbidities may first present with diastolic LV dysfunction without impaired LV systolic function or LV hypertrophy.[113] Increased LV filling pressure is commonly found in patients with chronic pressure overload including AS.[62] However, in the SEAS study echocardiography protocol, only LV filling and left atrial antero-posterior diameter were captured, while no data on pulmonary venous flow or mitral annular plane velocities were included, resulting in a very limited capture of diastolic functional parameters. For this reason assessment of LV diastolic function was not included in the present project.

Increased inflammatory state and abnormal endothelial function are important consequences of visceral obesity predisposing for premature atherosclerosis beyond clustering of traditional CV risk factors in obesity, including hypertension, dyslipidemia and type 2 diabetes, and in turn affecting myocardial structure and function.[114] However, these parameters were not recorded in the SEAS study.

As recently demonstrated in several studies, cardiorespiratory fitness is related to better survival in obesity, and alters thus the obesity paradox.[115 116] Exercise testing in patients with AS facilitates objective assessment of functional capacity and symptoms, and can be helpful in evaluation and risk stratification especially in asymptomatic patients with severe AS, as indicated in the current European Society of Cardiology guidelines on management of AS.[82] Testing of fitness would be an interesting and relevant additional measure for the evaluation of the impact of excess weight on LV response and outcomes in asymptomatic patients with AS, but was not possible since exercise testing was not included in the SEAS study protocol, mainly because of concern that findings during exercise testing could have influenced referral to aortic valve replacement and thereby interfere with the main study hypothesis that aggressive lipid lowering treatment would reduce AS progression rate and consequently the CV event rate.

5.7 Clinical implications and perspectives

The obesity epidemic and increasing life expectancy in the general population are reflected also in the changing characteristics of patients with AS. Results of this thesis demonstrate the changes of the LV geometry and function in overweight and obese patients with AS, thus adding to the knowledge needed to determinate the influence of both excess weight and AS severity on the left ventricle. Our results suggest that in overweight patients with mild to moderate AS, and without diabetes mellitus, hypercholesterolemia, history of CV disease or impaired renal function,

closer follow-up is not indicated. On the other hand, management of other CV risk factors in these patients should be followed according to established guidelines. We have demonstrated that increased BMI predisposes to hospitalization for heart failure and increased mortality, therefore weight control in these patients is recommended. However, the impact of excess weight on prognosis in AS patients needs further investigations in a prospective, longitudinal study.

Our findings have also demonstrated that in obese patients, indexing AVA and EL for body surface area in grading of AS leads to overestimation of the AS severity, causing premature aortic valve replacement without improving rates of mortality or hospitalization for heart failure. In our opinion, our results thus indicate that indexing of AVA and ELI to body surface area in obese patients should not be recommended.

6. Conclusions

The present thesis found the following results related to the pre-specified aims:

- **Study I: To evaluate the impact of obesity on LV mass and systolic function in patients with asymptomatic AS**

  In patients with asymptomatic, mild to moderate AS, overweight and obesity are associated with increased LV mass. Prevalence of LV hypertrophy is increasing with higher BMI, and obesity is associated with higher prevalence of LV hypertrophy independently of AS severity or concomitant hypertension. LV systolic function, whether measured as LV ejection fraction or stress-corrected midwall shortening, decrease in accord with increasing BMI. However, the prevalence of low LV function does not differ between the weight groups.

- **Study II: To assess the relation of obesity to progression of AS and outcome in initially asymptomatic AS patients**

  In patients with initially asymptomatic, mild to moderate AS without known diabetes mellitus or CV disease , overweight and obesity do not influence the progression of AS or the rate of AS-related or ischemic CV events, but both overweight and obesity are associated with increased total mortality and combined hospitalization for heart failure and death from any cause.

- **Study III: To evaluate the impact of obesity on grading of AS in patients with asymptomatic, mild to moderate AS**

  In grading of AS severity, indexing of AVA and EL for body surface area leads in obese patients to overestimation of AS severity, higher prevalence of discordant

grading and premature referral to aortic valve replacement without any positive influence on total mortality or combined hospitalization for heart failure and death from any cause.

References

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization technical report series* 2000;894:i-xii, 1-253.
2. Haslam DW, James WP. Obesity. *Lancet* 2005;366(9492):1197-209.
3. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012;307(5):491-7.
4. Midthjell K, Lee CM, Langhammer A, Krokstad S, Holmen TL, Hveem K, et al. Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study, Norway. *Clinical obesity* 2013;3(1-2):12-20.
5. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;53(21):1925-32.
6. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373(9669):1083-96.
7. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363(23):2211-9.
8. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309(1):71-82.
9. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007;298(17):2028-37.
10. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365(9468):1415-28.
11. Grundy SM, Hansen B, Smith SC, Jr., Cleeman JI, Kahn RA, American Heart A, et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation* 2004;109(4):551-6.
12. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, et al. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 2004;164(10):1066-76.
13. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288(21):2709-16.
14. de Simone G, Olsen MH, Wachtell K, Hille DA, Dahlof B, Ibsen H, et al. Clusters of metabolic risk factors predict cardiovascular events in hypertension with target-organ damage: the LIFE study. *J Hum Hypertens* 2007;21(8):625-32.
15. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *The American journal of the medical sciences* 2001;321(4):225-36.
16. Messerli FH. Cardiopathy of obesity--a not-so-Victorian disease. *N Engl J Med* 1986;314(6):378-80.
17. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension* 1994;23(5):600-6.

18. de Simone G, Izzo R, De Luca N, Gerdts E. Left ventricular geometry in obesity: Is it what we expect? *Nutr Metab Cardiovasc Dis* 2013;23(10):905-12.
19. Chinali M, de Simone G, Roman MJ, Lee ET, Best LG, Howard BV, et al. Impact of obesity on cardiac geometry and function in a population of adolescents: the Strong Heart Study. *J Am Coll Cardiol* 2006;47(11):2267-73.
20. Devereux RB, Roman MJ, de Simone G, O'Grady MJ, Paranicas M, Yeh JL, et al. Relations of left ventricular mass to demographic and hemodynamic variables in American Indians: the Strong Heart Study. *Circulation* 1997;96(5):1416-23.
21. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Progress in cardiovascular diseases* 2014;56(4):369-81.
22. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113(6):898-918.
23. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol* 2012;60(19):1854-63.
24. Saikrishnan N, Kumar G, Sawaya FJ, Lerakis S, Yoganathan AP. Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. *Circulation* 2014;129(2):244-53.
25. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368(9540):1005-11.
26. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromso study. *Heart* 2013;99(6):396-400.
27. Chambers J, Takeda S, Rimington H, Lambert-Hammill M, Shetty C, Wierzbicki A. Determinants of left ventricular mass in aortic stenosis. *J Heart Valve Dis* 2004;13(6):873-80.
28. Ngo MV, Gottdiener JS, Fletcher RD, Fernicola DJ, Gersh BJ. Smoking and obesity are associated with the progression of aortic stenosis. *Am J Geriatr Cardiol* 2001;10(2):86-90.
29. Katz R, Budoff MJ, Takasu J, Shavelle DM, Bertoni A, Blumenthal RS, et al. Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes* 2009;58(4):813-9.
30. Briand M, Lemieux I, Dumesnil JG, Mathieu P, Cartier A, Despres JP, et al. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. *J Am Coll Cardiol* 2006;47(11):2229-36.
31. Rossebo AB, Pedersen TR, Allen C, Boman K, Chambers J, Egstrup K, et al. Design and baseline characteristics of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. *Am J Cardiol* 2007;99(7):970-3.
32. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359(13):1343-56.
33. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998;68(4):899-917.

34. WHO. World Health Organization - Department of Noncommunicable Disease Surveillance: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. WHO/NCD/NCS/99.2. Geneva, 1999. Avaliable at: http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf. Accessed December 16, 2012.
35. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine : a journal of the British Diabetic Association* 1998;15(7):539-53.
36. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112(17):2735-52.
37. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabetic medicine : a journal of the British Diabetic Association* 1999;16(5):442-3.
38. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009;27(11):2121-58.
39. Cramariuc D, Rieck AE, Staal EM, Wachtell K, Eriksen E, Rossebo AB, et al. Factors influencing left ventricular structure and stress-corrected systolic function in men and women with asymptomatic aortic valve stenosis (a SEAS Substudy). *Am J Cardiol* 2008;101(4):510-5.
40. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18(12):1440-63.
41. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009;10(1):1-25.
42. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57(6):450-8.
43. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992;20(5):1251-60.
44. Foppa M, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? *Cardiovascular ultrasound* 2005;3:17.
45. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992;19(7):1550-8.
46. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976;37(1):7-11.

47. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. *J Am Coll Cardiol* 1994;23(6):1444-51.
48. Gaasch WH, Zile MR, Hoshino PK, Apstein CS, Blaustein AS. Stress-shortening relations and myocardial blood flow in compensated and failing canine hearts with pressure-overload hypertrophy. *Circulation* 1989;79(4):872-83.
49. Bella JN, Palmieri V, Roman MJ, Paranicas MF, Welty TK, Lee ET, et al. Gender differences in left ventricular systolic function in American Indians (from the Strong Heart Study). *Am J Cardiol* 2006;98(6):834-7.
50. Bahlmann E, Gerdts E, Cramariuc D, Gohlke-Baerwolf C, Nienaber CA, Wachtell K, et al. Prognostic value of energy loss index in asymptomatic aortic stenosis. *Circulation* 2013;127(10):1149-56.
51. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;28(2):230-68.
52. Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008;118(15):e523-661.
53. Garcia D, Pibarot P, Dumesnil JG, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: A new index based on the energy loss concept. *Circulation* 2000;101(7):765-71.
54. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating G. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;360(9343):1347-60.
55. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29(3):630-4.
56. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 1978;240(15):1607-10.
57. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, et al. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 2000;8(9):605-19.
58. Antonini-Canterin F, Hirsu M, Popescu BA, Leiballi E, Piazza R, Pavan D, et al. Stage-related effect of statin treatment on the progression of aortic valve sclerosis and stenosis. *Am J Cardiol* 2008;102(6):738-42.
59. Capoulade R, Clavel MA, Dumesnil JG, Chan KL, Teo KK, Tam JW, et al. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. *J Am Coll Cardiol* 2012;60(3):216-23.
60. Burwash IG, Forbes AD, Sadahiro M, Verrier ED, Pearlman AS, Thomas R, et al. Echocardiographic volume flow and stenosis severity measures with changing flow rate in aortic stenosis. *Am J Physiol* 1993;265(5 Pt 2):H1734-43.

61. Ozkan A, Kapadia S, Tuzcu M, Marwick TH. Assessment of left ventricular function in aortic stenosis. *Nature reviews. Cardiology* 2011;8(9):494-501.
62. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. *Circulation research* 2013;113(2):223-37.
63. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004;292(19):2350-6.
64. Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart* 2011;97(4):301-7.
65. de Simone G, Izzo R, Chinali M, De Marco M, Casalnuovo G, Rozza F, et al. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? *Hypertension* 2010;56(1):99-104.
66. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;111(24):3290-5.
67. Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Relation of arterial structure and function to left ventricular geometric patterns in hypertensive adults. *J Am Coll Cardiol* 1996;28(3):751-6.
68. Rieck AE, Cramariuc D, Staal EM, Rossebo AB, Wachtell K, Gerdts E. Impact of hypertension on left ventricular structure in patients with asymptomatic aortic valve stenosis (a SEAS substudy). *J Hypertens* 2010;28(2):377-83.
69. Rieck AE, Cramariuc D, Boman K, Gohlke-Barwolf C, Staal EM, Lonnebakken MT, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. *Hypertension* 2012;60(1):90-7.
70. Malavazos AE, Corsi MM, Ermetici F, Coman C, Sardanelli F, Rossi A, et al. Proinflammatory cytokines and cardiac abnormalities in uncomplicated obesity: relationship with abdominal fat deposition. *Nutr Metab Cardiovasc Dis* 2007;17(4):294-302.
71. Szczepaniak LS, Victor RG, Orci L, Unger RH. Forgotten but not gone: the rediscovery of fatty heart, the most common unrecognized disease in America. *Circulation research* 2007;101(8):759-67.
72. Niemann B, Chen Y, Teschner M, Li L, Silber RE, Rohrbach S. Obesity induces signs of premature cardiac aging in younger patients: the role of mitochondria. *J Am Coll Cardiol* 2011;57(5):577-85.
73. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322(22):1561-6.
74. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Annals of internal medicine* 1991;114(5):345-52.
75. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. *Am J Cardiol* 2007;100(9):1460-4.
76. Woodiwiss AJ, Libhaber CD, Majane OH, Libhaber E, Maseko M, Norton GR. Obesity promotes left ventricular concentric rather than eccentric geometric remodeling and hypertrophy independent of blood pressure. *Am J Hypertens* 2008;21(10):1144-51.

77. Khouri MG, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the Dallas heart study. *Circulation. Cardiovascular imaging* 2010;3(2):164-71.
78. Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). *JACC. Cardiovascular imaging* 2010;3(3):266-74.
79. Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol* 2006;47(11):2141-51.
80. Ballo P, Mondillo S, Motto A, Faraguti SA. Left ventricular midwall mechanics in subjects with aortic stenosis and normal systolic chamber function. *J Heart Valve Dis* 2006;15(5):639-50.
81. Dweck MR, Joshi S, Murigu T, Alpendurada F, Jabbour A, Melina G, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2011;58(12):1271-9.
82. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2012;42(4):S1-44.
83. Avelar E, Cloward TV, Walker JM, Farney RJ, Strong M, Pendleton RC, et al. Left ventricular hypertrophy in severe obesity: interactions among blood pressure, nocturnal hypoxemia, and body mass. *Hypertension* 2007;49(1):34-9.
84. Sadler DB, Aurigemma GP, Williams DW, Reda DJ, Materson BJ, Gottdiener JS. Systolic function in hypertensive men with concentric remodeling. *Hypertension* 1997;30(4):777-81.
85. Aurigemma GP, de Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. *Circulation. Cardiovascular imaging* 2013;6(1):142-52.
86. Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* 2009;120(7):577-84.
87. Lafitte S, Perlant M, Reant P, Serri K, Douard H, DeMaria A, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. *Eur J Echocardiogr* 2009;10(3):414-9.
88. Cramariuc D, Gerdts E, Davidsen ES, Segadal L, Matre K. Myocardial deformation in aortic valve stenosis: relation to left ventricular geometry. *Heart* 2010;96(2):106-12.
89. Page A, Dumesnil JG, Clavel MA, Chan KL, Teo KK, Tam JW, et al. Metabolic syndrome is associated with more pronounced impairment of left ventricle geometry and function in patients with calcific aortic stenosis: a substudy of the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin). *J Am Coll Cardiol* 2010;55(17):1867-74.
90. Bahlmann E, Cramariuc D, Gerdts E, Gohlke-Baerwolf C, Nienaber CA, Eriksen E, et al. Impact of pressure recovery on echocardiographic assessment of asymptomatic aortic stenosis: a SEAS substudy. *JACC. Cardiovascular imaging* 2010;3(6):555-62.
91. Jander N, Gohlke-Barwolf C, Bahlmann E, Gerdts E, Boman K, Chambers JB, et al. Indexing aortic valve area by body surface area increases the prevalence of severe aortic stenosis. *Heart* 2013.
92. Minners J, Gohlke-Baerwolf C, Kaufmann BA, Bahlmann E, Gerdts E, Boman K, et al. Adjusting parameters of aortic valve stenosis severity by body size. *Heart* 2014.

93. Katzmarzyk PT, Reeder BA, Elliott S, Joffres MR, Pahwa P, Raine KD, et al. Body mass index and risk of cardiovascular disease, cancer and all-cause mortality. *Can J Public Health* 2012;103(2):147-51.
94. Global Burden of Metabolic Risk Factors for Chronic Diseases C, Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;383(9921):970-83.
95. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338(1):1-7.
96. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of internal medicine* 2003;138(1):24-32.
97. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368(9536):666-78.
98. Azimi A, Charlot MG, Torp-Pedersen C, Gislason GH, Kober L, Jensen LO, et al. Moderate overweight is beneficial and severe obesity detrimental for patients with documented atherosclerotic heart disease. *Heart* 2013.
99. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38(3):789-95.
100. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of Obesity and the Obesity Paradox on Prevalence and Prognosis in Heart Failure. *JACC. Heart failure* 2013;1(2):93-102.
101. Stamler R, Ford CE, Stamler J. Why do lean hypertensives have higher mortality rates than other hypertensives? Findings of the Hypertension Detection and Follow-up Program. *Hypertension* 1991;17(4):553-64.
102. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007;120(10):863-70.
103. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *Eur Heart J* 2010;31(2):222-6.
104. Lancefield T, Clark DJ, Andrianopoulos N, Brennan AL, Reid CM, Johns J, et al. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. *JACC. Cardiovascular interventions* 2010;3(6):660-8.
105. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol* 2005;95(4):439-44.
106. Roberts WC, Roberts CC, Vowels TJ, Ko JM, Filardo G, Hamman BL, et al. Effect of body mass index on survival in patients having aortic valve replacement for aortic stenosis with or without concomitant coronary artery bypass grafting. *Am J Cardiol* 2011;108(12):1767-71.

107. Chrysant SG, Chrysant GS. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. *Journal of the American Society of Hypertension : JASH* 2013;7(1):85-94.
108. Schenkeveld L, Magro M, Oemrawsingh RM, Lenzen M, de Jaegere P, van Geuns RJ, et al. The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study. *BMJ open* 2012;2:e000535.
109. Ammar KA, Redfield MM, Mahoney DW, Johnson M, Jacobsen SJ, Rodeheffer RJ. Central obesity: association with left ventricular dysfunction and mortality in the community. *Am Heart J* 2008;156(5):975-81.
110. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes (Lond)* 2012.
111. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998;6 Suppl 2:51S-209S.
112. Chakko S, Mayor M, Allison MD, Kessler KM, Materson BJ, Myerburg RJ. Abnormal left ventricular diastolic filling in eccentric left ventricular hypertrophy of obesity. *Am J Cardiol* 1991;68(1):95-8.
113. Iacobellis G, Ribaudo MC, Leto G, Zappaterreno A, Vecci E, Di Mario U, et al. Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. *Obes Res* 2002;10(8):767-73.
114. Madala MC, Franklin BA, Chen AY, Berman AD, Roe MT, Peterson ED, et al. Obesity and age of first non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2008;52(12):979-85.
115. McAuley PA, Smith NS, Emerson BT, Myers JN. The obesity paradox and cardiorespiratory fitness. *Journal of obesity* 2012;2012:951582.
116. Zafrir B, Salman N, Amir O. Joint impact of body mass index and physical capacity on mortality in patients with systolic heart failure. *Am J Cardiol* 2014;113(7):1217-21.